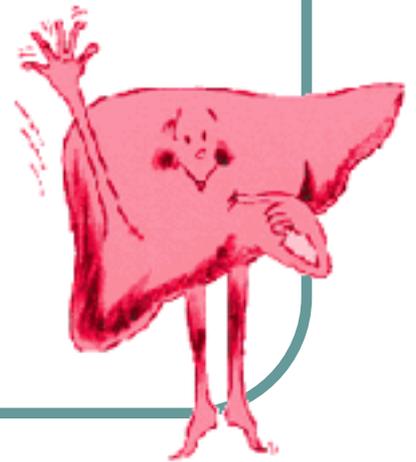


# Drug use in patients with liver disease

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# Aim

- To illustrate some of the problems encountered regarding the use of medicines in patients with liver dysfunction
- To demonstrate a strategy for finding solutions to these queries

# Plan for session

- **Presentation**
  - Types of liver related MI enquiries and why it is so hard to answer them
  - Basic hepatology
  - Interpreting laboratory tests
  - Pharmacokinetics and dynamics
  - Pulling together an answer
- **Interactive workshop**

# Types of liver enquiry – Leeds MI

Until 2012 Leeds was the UK MI centre for liver enquiries

- 152 enquiries from Apr 10 to Mar 11
  - 109 choice/dose of drug in a liver patient
  - 20 requests for protocol information
  - 9 for ADR/hepatotoxicity information
  - Others incl. compatability, general background

# Types of liver enquiry – choice/dose

- Antimicrobials 34
- Analgesia 11
- Psychotropics 11
- Antiepileptics 6
- Antidepressants 6
- Chemotherapy 6
- Hormones 4
- Others incl. antihistamines, antiemetics

# Why the problem?

- Lack of information in regular sources e.g BNF, SPC (misinformation/lack of data)
- Lack of research, small numbers of patients
- No easy equation to use
- Poor understanding of liver dysfunction

# Where to start

- Taking in an enquiry
  - Liver Enquiry proforma

# LIVER ENQUIRIES - Patient Considerations

## Gathering the Information

LFT	Range	Date	Date	Date	Date
ALT	<40iu/L				
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Alk Phos	30-300iu/L				
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PT	9-14.5 secs				
Creat	80-115 µmol/L				

**Check enquirers range** - ranges may vary, particularly Alk Phos

## What is the liver diagnosis?

Over what timescale has this occurred?

Acute - could this be hepatotoxicity?

Chronic - Is the pt cirrhotic?

Any signs or symptoms?

Encephalopathy -present or previous

Jaundice or Pale stools/Dark urine

Ascites - present or previous

Varices - present or previous

Do you have results of any tests?

Ultra Sound Scan

Biopsy

ERCP/HIDA

Endoscopy

Is there known Portal Hypertension

Does the patient have any other conditions or medications that need to be considered?

What is the ideal choice of agent(s)?

## Applying the Information

Effect on kinetics/dynamics	Risk factors for side effects
Ascites (A/D)	Varices
Cholestasis (A/E)	Coagulopathy or low platelets
Low albumin (D)	Encephalopathy
Portal hypertension (M)	Pruritus
Acute liver failure (M)	Alcoholism
Cirrhosis - compensated (M)	Ascites
Cirrhosis - decompensated (M)	Renal impairment/hepatorenal
Encephalopathy (P)	Cirrhosis

Key A: Absorption D: Distribution M: Metabolism E: Elimination P: Pharmacodynamics

# LIVER ENQUIRIES - Drug Considerations

Pharmacokinetics		Considerations
Absorption		Lipid solubility (Absorption affected by ascites)
Distribution		Water/fat Protein binding % Displaced by bilirubin or displaces bilirubin
Metabolism		First pass effect Hepatocyte dependent Prodrug CYPs Active metabolites Genetics
Elimination		Biliary excretion Alternative mechanisms Enterohepatic recirculation (Renal impairment)

## Adverse Effects :

### Hepatotoxicity

Does the drug affect LFTs?

What is the incidence of this reaction?

Is this a transient effect?

Is it known how long it will take for the LFTs to recover?

Is the drug associated with causing hepatitis or cholestasis?

What type of reaction does it cause?

What is the incidence of this reaction?

How long does it take to recover from this effect?

Is the drug associated with any more serious or long-term hepatotoxic reactions?

eg hepatic necrosis, vanishing bile duct syndrome?

What is the incidence of this reaction?

## Other Relevant Adverse Effects

### Dermatological

eg. pruritus and urticaria

What is the incidence of this reaction?

Is it a common, uncommon or rare effect?

### Endocrine/Metabolic

eg. fluid & electrolyte imbalance

What is the incidence of this reaction?

Is it a common, uncommon or rare effect?

### Gastrointestinal

eg. constipation

What is the incidence of this reaction?

Is it a common, uncommon or rare effect?

### Haematological

eg. Thrombocytopenia, effects on clotting, increased risk of bleeding

What is the incidence of this reaction?

Is it a common, uncommon or rare effect?

### Neurological

eg.confusion, seizures, sedation

What is the incidence of this reaction?

Is it a common, uncommon or rare effect?

### Renal

eg. renal toxicity

What is the incidence of this reaction?

Is it a common, uncommon or rare effect?

**Are there any drug interactions or drug-disease interactions that need to be considered?**

# Why so much information?

## *Back to first principles*

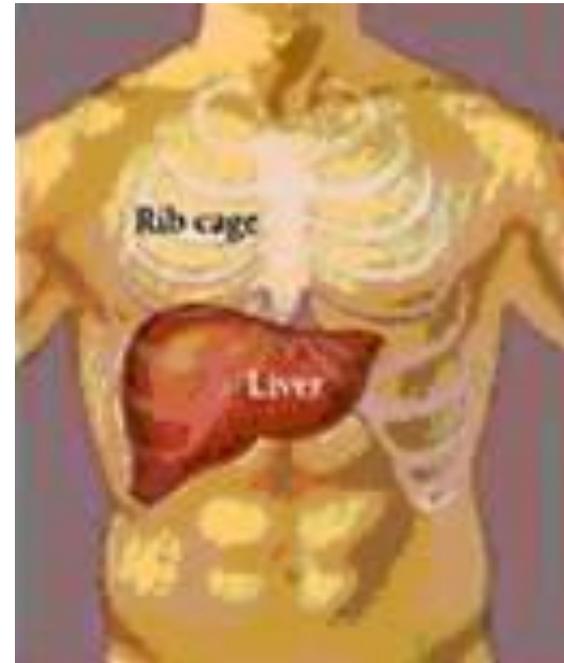
- Identify extent and type of liver dysfunction
- Consider how this will affect drug handling
- Consider how the drug may affect the patient – side effects, pharmacodynamic effects
- Remembering the whole patient

# Plan for session

- Types of liver related MI enquiries and why it is so hard to answer them
- Basic hepatology
- Interpreting laboratory tests
- Pharmacokinetics and dynamics
- Pulling together an answer

# Where is the liver?

- In a child it can be felt 1-2cm below the ribcage.
- In adults it can only be felt if it is enlarged
- RUQ pain if enlarged



# What does the liver do?

## **Synthesis**

(e.g. albumin & clotting factors)

## **Homeostasis**

e.g. glucose



## **Lipid Metabolism**

e.g. cholesterol

## **Bile production and secretion**

## **Filtration**

e.g. antigens

**Metabolism** e.g drugs, oestrogens, toxic products such as ammonia

# Terminology – time frame

- **Acute**

Sudden onset – jaundice to encephalopathy in less than 7 days (hyperacute), 28 days (acute), 6 months (sub-acute)

- **Chronic**

Extended duration – months/years

# Terminology – type of picture

- **Hepatocellular**

- Fatty infiltration (steatosis) e.g. alcohol
- Inflammation (hepatitis) e.g. viral
- Cell death (necrosis) e.g. POD

- **Cholestasis**

- Static bile flow (not specifically bilirubin)

# Terminology - Hepatocellular

- **Hepatitis**

- Inflammation of hepatocytes

- **Fibrosis**

- An increase in connective tissue in the liver  
– reversible



# Terminology - Hepatocellular

- **Cirrhosis**

Widespread disorganised nodules in the liver combined with fibrosis

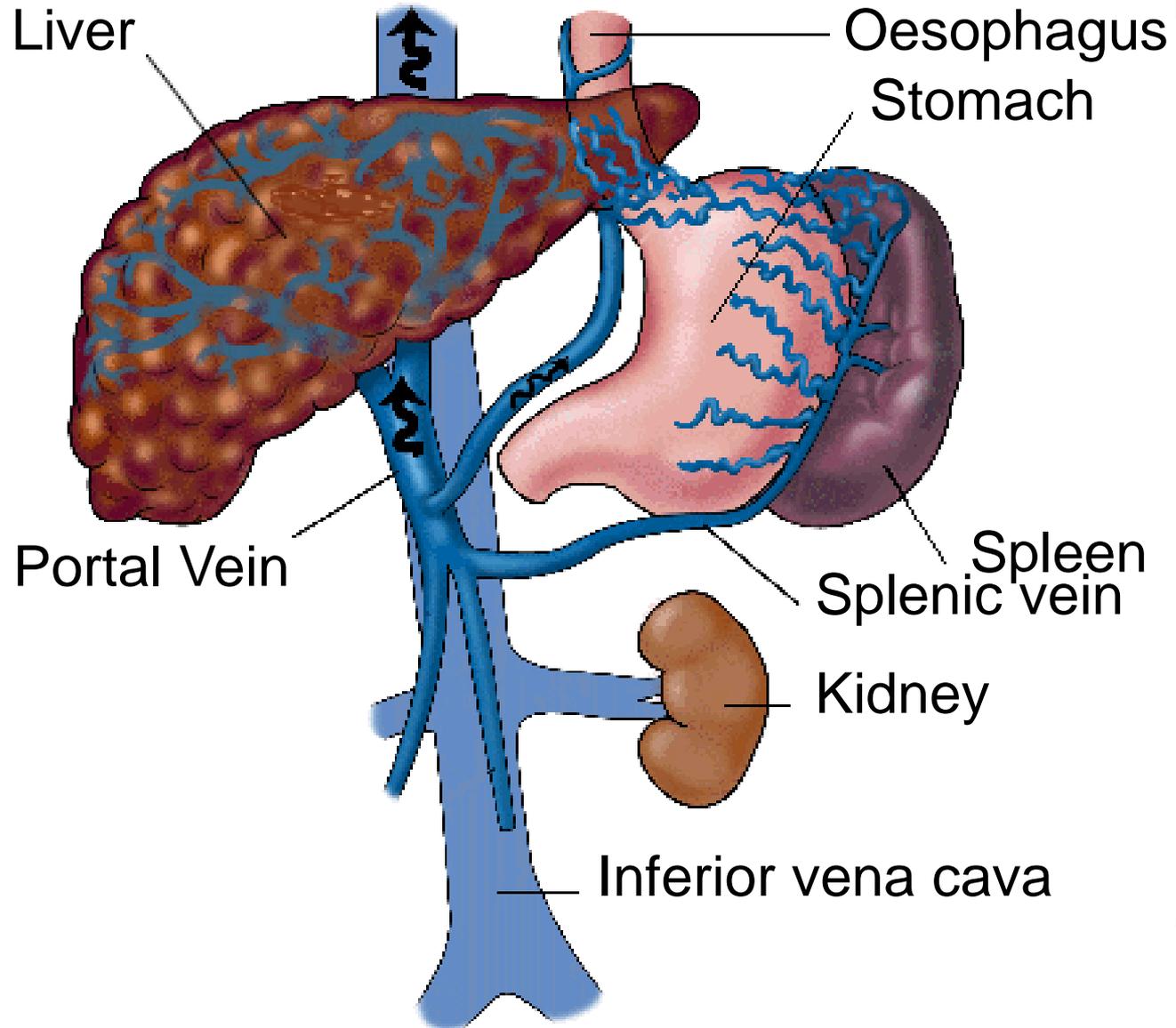
- **Compensated cirrhosis**

When a cirrhotic liver continues to function

- **Decompensated cirrhosis**

When a cirrhotic liver can no longer function adequately – signs eg coagulopathy occur

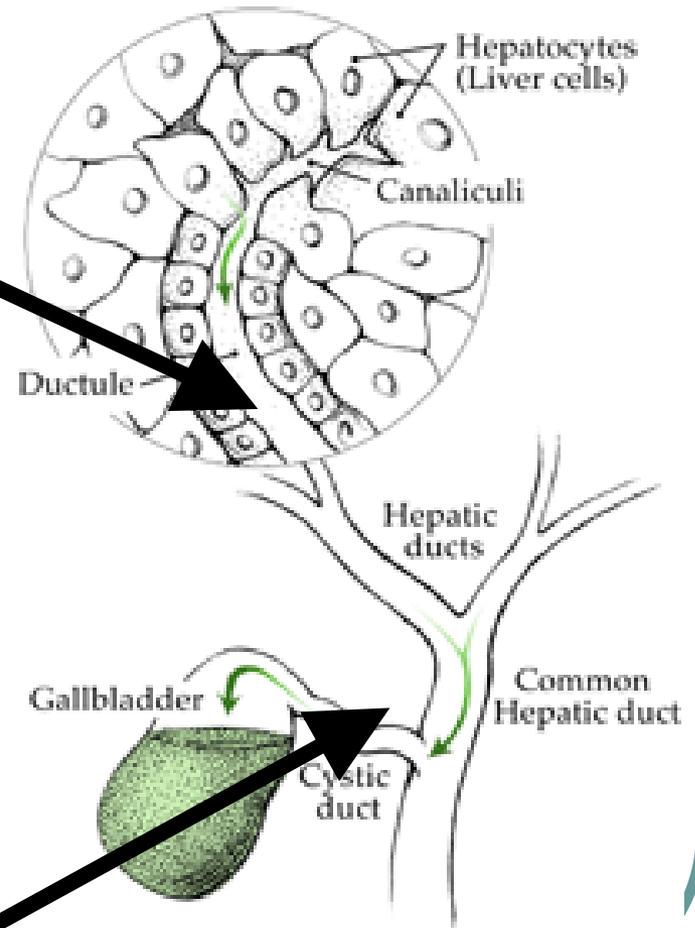
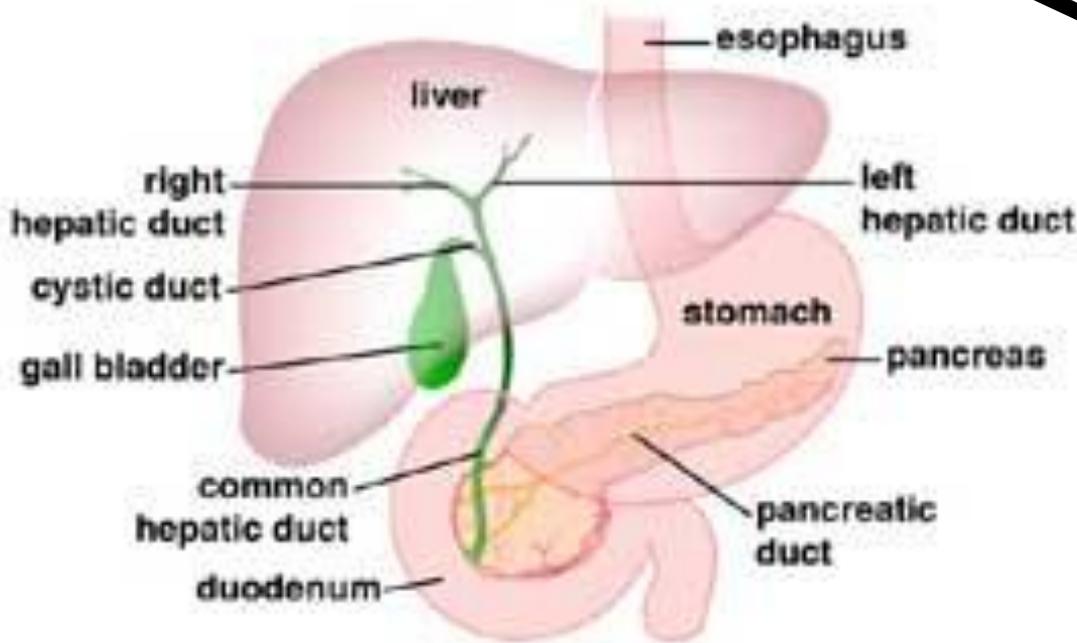
# - Portal hypertension



# Terminology - Cholestasis

## Intrahepatic

### Biliary System



## Extrahepatic

# Causes of liver **disease**

- Metabolic & inherited – CF, Alagille, tyrosinaemia, Wilson's
- Autoimmune – AIH, PSC, PBC
- Structural – biliary atresia, choledochal cysts
- Infection – hepatitis B, C
- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Primary cancer – usually in cirrhotics

# Causes of liver dysfunction

- Ischaemia
- Infection – H1N1, CMV, EBV, malaria...
- Multi-organ failure
- Drugs, parenteral nutrition
- Trauma
- Oncological – metastases
- Gallstones, pancreatitis

## Need to know:

- the type of dysfunction your patient has - hepatocellular or cholestatic
- diagnosis
- the degree of dysfunction

# Why?

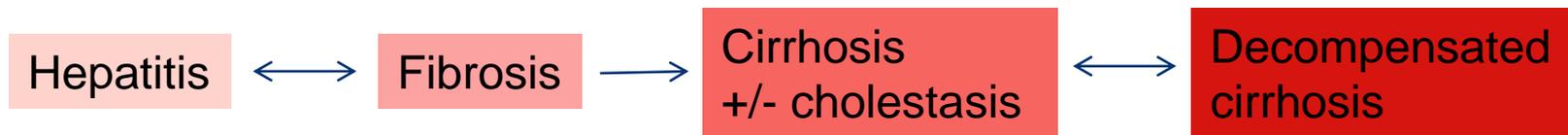
## Cholestasis

- Impaired elimination of biliary cleared drugs, malabsorption of fat soluble drugs
  - Extent dependent on degree of cholestasis
- Diagnosis e.g. gallstones may be partial or complete block of bile ducts. Normal hepatocyte function

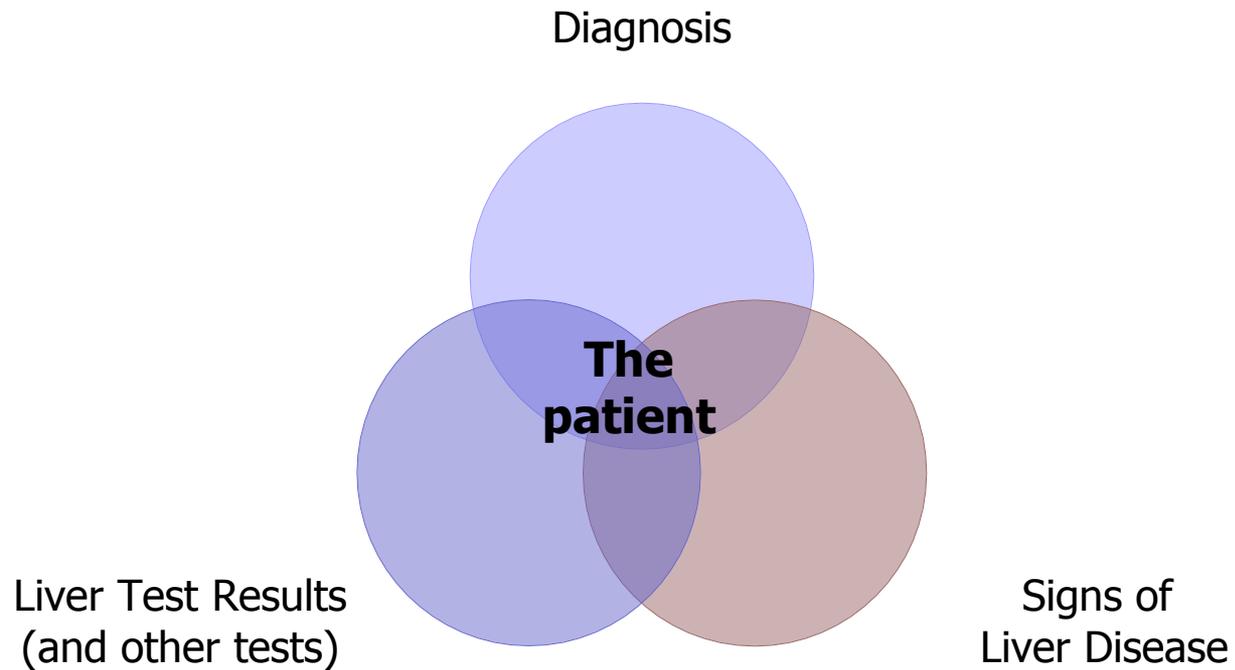
# Why?

## Hepatocellular damage

- Impaired metabolism, reduced protein binding, deranged distribution ...
  - Extent depends on stage of damage
- Diagnosis e.g. Auto-immune hepatitis:



# Where on the continuum?



# Transaminases (0-35iu/L) (ALT & AST) [GPT]

- Enzyme released from hepatocytes when damaged
- Markers of hepatocellular injury
  - High elevations in acute injury (in several thousands)
  - Can be **normal** in severe chronic liver disease (cirrhosis)
- Also found in heart, muscle and kidney
- ALT more specific to liver than AST

# Alkaline Phosphatase

(normal range varies for age and hospital)

- Biliary enzyme – raised with bile duct damage
  - Increased in cholestasis
- Less raised in hepatocellular disease
- Not specific to the liver
  - also found in bone (eg raised in Paget's disease/bone metastases/hepatic osteodystrophy – vitamin D deficiency)
  - small quantities in the intestine and placenta

# Gamma glutamyl transferase (GGT) (0-30u/l)

- Enzyme in biliary tract
  - Increased in cholestasis
- Increased by enzyme inducing drugs  
e.g. rifampicin and alcohol
- Useful to determine if isolated raised alkaline phosphatase is liver related

# Bilirubin ( $\leq 1 \text{ mg/dL}$ ) (3-17 micromol/L)

- **Unconjugated**

- Increased production (haemolysis)
- Decreased conjugation (Gilberts, neonate, cirrhosis)

- **Conjugated**

- Intrahepatic cholestasis
- Extrahepatic cholestasis (gall stones, BA)



# Albumin (3,5 – 5g/dL)

- Synthesised in liver
- Half-life approx 20 days
- Good indicator of chronic liver disease
- Low specificity
  - Decreased intake e.g. malnutrition
  - Increased loss e.g. enteropathy

# Prothrombin Time (~13 secs) or INR (0.9-1.2)

- Decreased synthesis of clotting factors (cirrhosis/ALF)  
OR
- Vitamin K malabsorption (in cholestasis)
  
- Elevation > 3 seconds significant
- Prolonged in acute & chronic liver disease
- Useful prognostic indicator of impending liver failure e.g. acute liver failure or decompensated chronic liver disease

# Other useful tests

- Ultrasound – liver texture, dopplers for blood flow in hepatic artery, portal vein
- Liver biopsy – fibrosis, cirrhosis, intrahepatic cholestasis
- OGD – varices
- HIDA – bile flow (cholestasis)
- Blood glucose, creatinine

# Signs of liver dysfunction

- Jaundice
- **Pale stools/dark urine**
- Palmar erythema
- White nails
- Gynaecomastia/testicular atrophy
- Spider naevi
- **Ascites**
- Bruising and bleeding
- **Splenomegaly**
- **Oesophageal and gastric varices**
- **Encephalopathy**



**Jaundice**



**“Spiders”**



**Ascites**

# Symptoms of liver dysfunction

- Pruritus
- Lethargy
- Abdominal pain
- Bruising and bleeding
- Anorexia

# Categorising patients

Helps to decide how to modify drug therapy if categorise patient into one of the following types:

- Hepatitis
- Cholestasis
- Cirrhosis – compensated
- Cirrhosis – decompensated
- Acute liver failure

# LIVER ENQUIRIES - Patient Considerations

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Effect on kinetics/dynamics	Risk factors for side effects
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Key A: Absorption D: Distribution M: Metabolism E: Elimination P: Pharmacodynamics

# Next stage - drug considerations

- Pharmacokinetics
- Pharmacodynamics
- Adverse drug reactions

# Absorption

- **Ascites** may impair absorption e.g. diuretics
  - Bigger doses or IV
- **Cholestasis** may impair absorption of fat soluble drugs e.g. fat soluble vitamins
  - Bigger doses

# Distribution

- **Ascites** will increase volume of distribution for water soluble drugs
  - Bigger doses *per kg*
- **Low albumin** will alter amount of free drug if highly protein bound
  - Reduced doses

# Metabolism

- **Decompensated cirrhosis** - reduced number of functioning hepatocytes
  - Reduce dose or increase interval
- **Portal hypertension** - reduced first pass metabolism if highly extracted drug e.g. propranolol, lidocaine
  - Reduce dose

# Metabolism

- Prodrugs that need to be metabolised to the active form in the liver may need bigger doses! E.g. enalapril

# Elimination

- **Cholestasis** – biliary cleared drugs may accumulate
  - Caution if active/toxic metabolites are produced, possibly not important if inactive
  - Compensatory pathways e.g. renal if reduced biliary clearance?

# Pharmacodynamics

- Increased receptor sensitivity
  - More permeable BBB
  - Increased respiratory depression with opioids

# Side Effect Profile

Some side effects may be harmful to liver patients:

- GI ulceration – *varices, coagulopathy*
- Constipation – *cirrhosis, encephalopathy*
- Pruritus - *cholestasis*
- Sedation – *encephalopathy, cirrhosis*
- Coagulation defects - *coagulopathy*
- Effects on electrolytes – *cirrhosis, encephalopathy*
- Effects on fluid balance – *ascites, cirrhosis*
- Renal toxicity - *cirrhosis*

# Hepatotoxicity

- Dose dependent (intrinsic e.g. paracetamol, methotrexate)
- Dose independent (idiosyncratic)
- Usually acute, can be chronic
- Acute is usually 5 to 90 days of starting drug
- Can occur after stopping causative drug
- Existing liver dysfunction does not increase risk of hepatotoxic reaction

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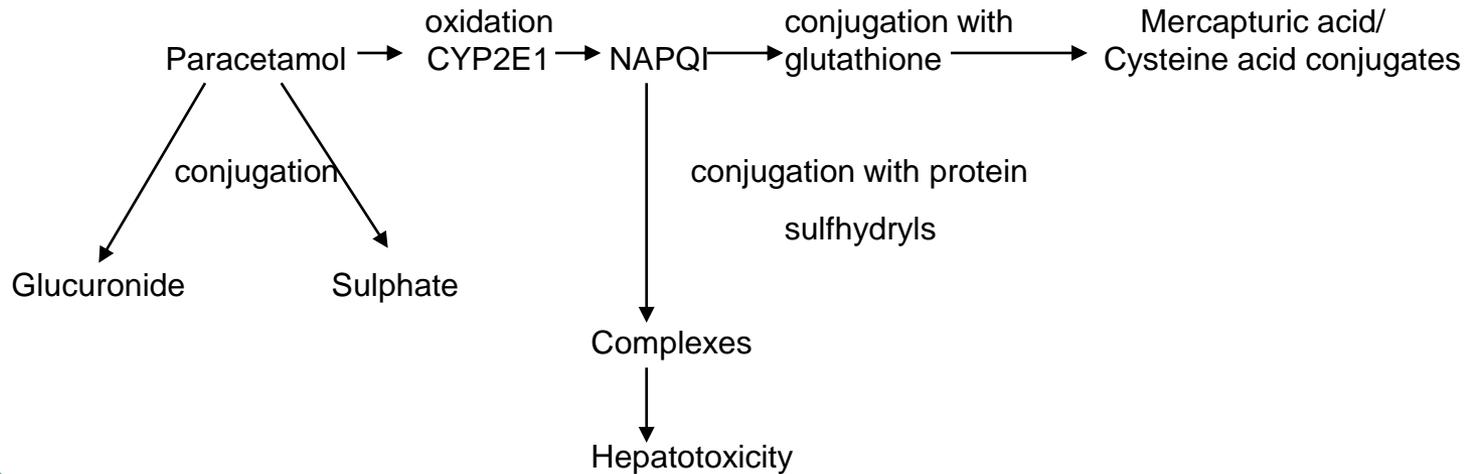
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# Workshop

- Review patient details to establish:
  - What type and extent of liver dysfunction
  - How pharmacokinetics/dynamics may be affected
  - What side effects of drugs do you need to consider
  - Which analgesic is safest for this patient – review ibuprofen and consider paracetamol and morphine

# Paracetamol

- Hepatic metabolism (multiple pathways)
  - Need glutathione – stores may be reduced in the severely malnourished
- Hepatotoxic in overdose



# Ibuprofen

- Lipid soluble
- 99% protein binding
- Extensive hepatic metabolism
- Side effects?
  - GI ulceration
  - Inhibition of platelet aggregation
  - Renal impairment
  - Fluid retention and electrolyte abnormalities
  - Hepatotoxicity

# Morphine

- Low protein binding
- Extensive hepatic metabolism, first pass >50%
- Biliary excretion and enterohepatic recirculation
- Half life 1-5 hrs
- Side effects
  - Sedation, respiratory depression
  - Constipation
  - Pruritus

# Summary

- Work out what is wrong with your patient's liver and how bad it is
- See if the pharmacokinetics of the drug you want to use could be affected
- Check the drug doesn't have side effects which could harm the patient

Advise accordingly

# Sources of further information

- Medicines Q&As on NELM
- Drug PK data – Dollery, micromedex, SPC
- Drugs and the Liver
  
- Caution with interpreting references



**ANY QUESTIONS?**



# Child-Pugh score – cirrhosis only

Score	1	2	3
SBr	<34	34-51	>51
Albumin	>35	30-35	<30
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Minimal	Advanced

A = 5-6 (*mild*),    B = 7-9 (*moderate*),    C ≥ 10 (*severe*)

# Ibuprofen

Date of monograph review: latest modification: 14-Jan-2014)

**Ph. Eur. 8** (Ibuprofen). A white or almost white, crystalline powder or colourless crystals. M.p. 75 degrees to 78 degrees. Practically insoluble in water; freely soluble in acetone, in dichloromethane, and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides and carbonates.

**USP 36** (Ibuprofen). A white to off-white crystalline powder having a slight characteristic odour. Practically insoluble in water; very soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ethyl acetate. Store in airtight containers.

## Uses and Administration (Latest modification: 01-Mar-2011)

Ibuprofen, a propionic acid derivative, is an NSAID (↔📄). Its anti-inflammatory properties may be weaker than those of some other NSAIDs.

Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

Ibuprofen is also used as an alternative to indometacin in the treatment of patent ductus arteriosus.

The usual **oral** dose for painful conditions is 1.2 to 1.8 g daily in divided doses although maintenance doses of 600 mg to 1.2 g daily may be effective in some patients. If necessary the dose may be increased; in the UK the maximum recommended dose is 2.4 g daily whereas in the USA it is 3.2 g daily. Modified-release preparations of ibuprofen are available for once- or twice-daily dosing, although actual dosages vary with different preparations. Patients with rheumatoid arthritis generally require higher doses of ibuprofen than those with osteoarthritis. The recommended dose for fever reduction is 200 to 400 mg every 4 to 6 hours to a maximum of 1.2 g daily. For oral doses in children, see Administration in Children, ↔📄.

Ibuprofen may be given **parenterally** by intravenous infusion for the management of mild to moderate pain and as an adjunct to opioid analgesics for moderate to severe pain, and for reduction of fever. For painful conditions, 400 to 800 mg may be given every 6 hours as necessary. For fever reduction, an initial dose of 400 mg may be followed by 400 mg every 4 to 6 hours or 100 to 200 mg every 4 hours as necessary. Regardless of indication, infusion time must be no less than 30 minutes and a dose of 3.2 g daily should not be exceeded. Ibuprofen is also given parenterally for the treatment of patent ductus arteriosus in preterm infants; for details of doses, see ↔📄.

Ibuprofen is applied **topically** as a 5% cream, foam, gel, or spray solution; a 10% gel is also available. It is also used topically as a dressing containing 500 micrograms/cm<sup>2</sup> of ibuprofen for the management of ulcers and superficial wounds.

Ibuprofen is usually given as the base but **derivatives**, including various salts, esters, and other complexes, have also been used. These include lysine (see Patent Ductus Arteriosus,

↔📄), potassium, and sodium salts, guaiacol and pyridoxine esters, and mabuprofen (ibuprofen aminoethanol), isobutanolammonium, and meglumine derivatives.

Ibuprofen is usually given as a racemic mixture but preparations containing only the S-(+)-isomer dexibuprofen (↔📄) are available in some countries.

(last reviewed 2010-08-20; last modified 2011-03-01)

### **Cachexia** (Latest modification: 25-Oct-2006)

For reference to the use of ibuprofen with megestrol to treat cancer cachexia, see ↔📄.

(last reviewed 2010-08-20; last modified 2006-10-25)

### **Cystic fibrosis** (Latest modification: 08-Sep-2010)

In patients with cystic fibrosis (see ↔📄), the inflammatory response to chronic pulmonary infection with *Pseudomonas* organisms contributes to lung destruction. NSAIDs have been studied in patients with cystic fibrosis as an alternative to corticosteroids to reduce pulmonary inflammation. Some reviews<sup>1,2</sup> found evidence in support of using high-dose NSAIDs, most notably ibuprofen, to slow the progression of lung damage in patients with cystic fibrosis. However, there are limited data about the long-term safety of high doses<sup>1</sup> and some consider that this may have limited such use of NSAIDs;<sup>3</sup> others remain to be convinced that a benefit has been shown.<sup>4</sup> Furthermore there were sufficient data to recommend that NSAIDs be temporarily stopped when intravenous aminoglycosides or other nephrotoxic drugs are used.<sup>1</sup>

(last reviewed 2010-08-20; last modified 2010-09-08)

1. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 07/11/07). [PubMed](#)
2. Konstan MW. [Ibuprofen therapy for cystic fibrosis lung disease: revisited](#). *Curr Opin Pulm Med* 2008; **14**: 567–73. [PubMed](#)
3. Fennel PB, et al. [Use of high-dose ibuprofen in a pediatric cystic fibrosis center](#). *J Cyst Fibros* 2007; **6**: 153–8. [PubMed](#)
4. Bush A, Davies J. [Non! to non-steroidal anti-inflammatory therapy for inflammatory lung disease in cystic fibrosis \(at least at the moment\)](#). *J Pediatr* 2007; **151**: 228–30. [PubMed](#)

### **Pain** (Latest modification: 02-Jun-2010)

Findings from a long-term study<sup>1</sup> in 585 patients (mean age of 64 years) with knee pain suggested that oral and topical ibuprofen had an equivalent analgesic effect although the former was associated with more minor adverse effects; there was no difference in the rate of major adverse effects.

Single dose, oral ibuprofen is an effective analgesic for the treatment of postoperative pain.<sup>2</sup>

(last reviewed 2010-08-20; last modified 2010-06-02)

1. Underwood M, et al. [Topical or oral ibuprofen for chronic knee pain in older people: the TOIB study](#). *Health Technol Assess* 2008; **12**: 1–176. [PubMed](#)
2. Derry C, et al. Single dose oral ibuprofen for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 15/09/09). [PubMed](#)

### **Patent ductus arteriosus** (Latest modification: 04-Jun-2010)

Ibuprofen or its lysine salt may be given **parenterally** for the treatment of patent ductus arteriosus (⇒📄) in preterm infants of less than 34 weeks' gestation; doses are expressed in terms of ibuprofen. Three intravenous doses (infused over 15 minutes) are given at 24-hour intervals; the initial dose is equivalent to 10 mg/kg of ibuprofen followed by two further doses of 5 mg/kg. If, 48 hours after this course of therapy the ductus remains open, a second course may be given, but if this produces no response surgery may be necessary. Ibuprofen injection, *when given as the base*, should be used undiluted, but if necessary it may be reconstituted with sodium chloride 0.9% or glucose 5% for injection. *When given as the lysine salt*, it should be diluted with sodium chloride 0.9% or glucose 5%.

For a suggestion that ibuprofen might be a better choice than indometacin for the treatment of patent ductus arteriosus, see ⇒📄.

(last reviewed 2010-08-20; last modified 2010-06-04)

### **Adverse Effects, Treatment, and Precautions** (Latest modification: 02-Jun-2010)

As for NSAIDs in general, ⇒📄. Ibuprofen may be better tolerated than other NSAIDs.

Adverse effects that may be associated with the use of ibuprofen injection in premature **neonates** include intraventricular haemorrhage, periventricular leucomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, necrotising enterocolitis, intestinal perforation, oliguria, fluid retention, and haematuria; hypoxaemia and gastrointestinal haemorrhage have also been reported. In addition ibuprofen injection should not be given to neonates with life-threatening infection, with significant renal impairment, or with known or suspected necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should also not be given parenteral ibuprofen, and those given it should be monitored during treatment for signs of bleeding. Renal function should be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

Symptoms of nausea, vomiting, epigastric pain, and tinnitus have been reported after ibuprofen overdose. More serious toxicity is uncommon, but giving activated charcoal followed by supportive measures is recommended if the quantity ingested within the previous hour exceeds 400 mg/kg.

(last reviewed 2010-08-20; last modified 2010-06-02)

### **Effects on the blood** (Latest modification: 28-Sep-2007)

Blood disorders including agranulocytosis, aplastic anaemia,<sup>1</sup> pure white-cell aplasia,<sup>2</sup> and thrombocytopenia<sup>3</sup> have been reported in patients taking ibuprofen. Fatal haemolytic anaemia occurred in a man taking ibuprofen and oxazepam.<sup>4</sup>

(last reviewed 2010-08-20; last modified 2007-09-28)

1. Gryfe CI, Rubenzahl S. [Agranulocytosis and aplastic anemia possibly due to ibuprofen](#). *Can Med Assoc J* 1976; **114**: 877. [PubMed](#)
2. Mamus SW, et al. [Ibuprofen-associated pure white-cell aplasia](#). *N Engl J Med* 1986; **314**: 624–5. [PubMed](#)
3. Jain S. [Ibuprofen-induced thrombocytopenia](#). *Br J Clin Pract* 1994; **48**: 51. [PubMed](#)
4. Guidry JB, et al. [Fatal autoimmune hemolytic anemia associated with ibuprofen](#). *JAMA* 1979; **242**: 68–9. [PubMed](#)

### **Effects on the cardiovascular system** (Latest modification: 28-Sep-2007)

For a discussion of the cardiovascular effects of NSAIDs, including ibuprofen, see .

(last reviewed 2010-08-20; last modified 2007-09-28)

### **Effects on the CNS** (Latest modification: 10-Aug-2010)

Aseptic meningitis has occurred in patients taking NSAIDs. A review<sup>1</sup> of NSAID-related CNS adverse effects summarised 23 literature reports of NSAID-associated aseptic meningitis; 17 reports involved ibuprofen, 4 sulindac, 1 naproxen, and 1 tolmetin. Of the 23 reports, 11 were in patients with a diagnosis of SLE. Typically the reaction is seen in patients who have just restarted NSAID therapy after a gap in their treatment. Within a few hours of restarting the NSAID the patient develops fever, headache, and a stiff neck; abdominal pain may be present. The patient may become lethargic and eventually comatose. Symptoms resolve if the NSAID is stopped. It is believed to be a hypersensitivity reaction but there does not appear to be cross-reactivity between NSAIDs.

Similar conclusions have also been reported more recently.<sup>2</sup> After experience of 2 cases, a review of the literature identified 71 episodes of ibuprofen-induced aseptic meningitis in 36 patients; 22 patients had recurrent episodes after repeated ibuprofen use. An underlying auto-immune connective tissue disorder was noted in 22 patients of whom 14 had SLE, 6 had an undifferentiated or mixed disorder, 1 had rheumatoid arthritis, and 1 had Sjögren's syndrome. In most cases, symptoms developed within 24 hours of starting ibuprofen although 1 patient had been taking ibuprofen for 2 years before the onset of symptoms. Cross-reactivity was reported in only 1 patient who had also developed aseptic meningitis with both naproxen and rofecoxib.

(last reviewed 2010-08-20; last modified 2010-08-10)

1. Hoppmann RA, et al. [Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction](#). *Arch Intern Med* 1991; **151**: 1309–13. [PubMed](#)
2. Rodríguez SC, et al. [Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature](#). *Medicine* 2006; **85**: 214–20. [PubMed](#)

### **Effects on electrolytes** (Latest modification: 02-Jun-2010)

Hyponatraemia has been described in patients taking ibuprofen;<sup>1-3</sup> other risk factors such as pre-existing renal impairment or use with desmopressin were generally present.

(last reviewed 2010-08-20; last modified 2010-06-02)

1. Blum M, Aviram A. [Ibuprofen induced hyponatraemia](#). *Rheumatol Rehabil* 1980; **19**: 258–9. [PubMed](#)
2. Rault RM. [Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs](#). *Am J Med Sci* 1993; **305**: 318–20. [PubMed](#)
3. García EBG, et al. [Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease](#). *Haemophilia* 2003; **9**: 232–4. [PubMed](#)

### Effects on the eyes (Latest modification: 02-Jun-2010)

Reversible amblyopia has been reported in patients taking ibuprofen.<sup>1,2</sup> For reference to effects on the optic nerve associated with ibuprofen, see .

(last reviewed 2010-08-20; last modified 2010-06-02)

1. Collum LMT, Bowen DI. [Ocular side-effects of ibuprofen](#). *Br J Ophthalmol* 1971; **55**: 472–7. [PubMed](#)
2. Palmer CAL. [Toxic amblyopia from ibuprofen](#). *BMJ* 1972; **3**: 765. [PubMed](#)

### Effects on the gastrointestinal tract (Latest modification: 25-Oct-2006)

Ibuprofen may be associated with a lower risk of upper gastrointestinal effects than some other NSAIDs, but nonetheless it can cause dyspepsia, nausea and vomiting, gastrointestinal bleeding, and peptic ulcers and perforation. Colitis and its exacerbation have occurred.<sup>1,2</sup>

(last reviewed 2010-08-20; last modified 2006-10-25)

1. Ravi S, et al. [Colitis caused by non-steroidal anti-inflammatory drugs](#). *Postgrad Med J* 1986; **62**: 773–6. [PubMed](#)
2. Clements D, et al. [Colitis associated with ibuprofen](#). *BMJ* 1990; **301**: 987. [PubMed](#)

### Effects on the kidneys (Latest modification: 05-Sep-2009)

Reports of adverse renal effects with ibuprofen include an increase in serum creatinine concentration,<sup>1</sup> acute renal failure,<sup>2-6</sup> and nephrotic syndrome.<sup>7</sup> Cystitis, haematuria, and interstitial nephritis may occur. Acute flank pain and reversible renal dysfunction has been reported in some patients treated with ibuprofen.<sup>8,9</sup> See also Effects on Electrolytes, .

(last reviewed 2010-08-20; last modified 2009-09-05)

1. Whelton A, et al. [Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison](#). *Ann Intern Med* 1990; **112**: 568–76. [PubMed](#)
2. Brandstetter RD, Mar DD. [Reversible oliguric renal failure associated with ibuprofen treatment](#). *BMJ* 1978; **2**: 1194–5. [PubMed](#)
3. Kimberly RP, et al. [Apparent acute renal failure associated with therapeutic aspirin and ibuprofen administration](#). *Arthritis Rheum* 1979; **22**: 281–5. [PubMed](#)
4. Spierto RJ, et al. [Acute renal failure associated with the use of over-the-counter ibuprofen](#). *Ann Pharmacother* 1992; **26**: 714. [PubMed](#)
5. Fernando AHN, et al. [Renal failure after topical use of NSAIDs](#). *BMJ* 1994; **308**: 533. [PubMed](#)
6. Moghal NE, et al. [Ibuprofen and acute renal failure in a toddler](#). *Arch Dis Child* 2004; **89**: 276–7. [PubMed](#)

7. 7. Justiniani FR. [Over-the-counter ibuprofen and nephrotic syndrome](#). *Ann Intern Med* 1986; **105**: 303. [PubMed](#)
8. 8. McIntire SC, et al. [Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use](#). *Pediatrics* 1993; **92**: 459–60. [PubMed](#)
9. 9. Wattad A, et al. [A unique complication of nonsteroidal anti-inflammatory drug use](#). *Pediatrics* 1994; **93**: 693. [PubMed](#)

### Effects on the liver (Latest modification: 02-Jun-2010)

Raised liver transaminase values were noted in 3 patients with chronic hepatitis C infection after taking ibuprofen.<sup>1</sup> Values returned to normal on stopping the drug; the effect recurred in one patient who was re-exposed. Other hepatic adverse effects reported with ibuprofen include hepatitis<sup>2</sup> and liver failure.<sup>3</sup>

See also Effects on the Skin, .

(last reviewed 2010-08-20; last modified 2010-06-02)

1. 1. Riley TR, Smith JP. [Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: a case series](#). *Am J Gastroenterol* 1998; **93**: 1563–5. [PubMed](#)
2. 2. Borel I, et al. [Hépatite aiguë sévère après prise d'ibuprofène](#). *Gastroenterol Clin Biol* 2001; **25**: 430–2. [PubMed](#)
3. 3. Rodríguez-González FJ, et al. [Orthotopic liver transplantation after subacute liver failure induced by therapeutic doses of ibuprofen](#). *Am J Gastroenterol* 2002; **97**: 2476–7. [PubMed](#)

### Effects on the skin (Latest modification: 20-Aug-2010)

Rashes may occur during hypersensitivity reactions although serious dermatological effects attributed to ibuprofen are rare. Reports of more serious effects have included Stevens-Johnson syndrome (often associated with hepatotoxicity),<sup>1-4</sup> photosensitivity,<sup>5</sup> and bullous leucocytoclastic vasculitis.<sup>6</sup>

(last reviewed 2010-08-20; last modified 2010-08-20)

1. 1. Sternlieb P, Robinson RM. [Stevens-Johnson syndrome plus toxic hepatitis due to ibuprofen](#). *N Y State J Med* 1978; **78**: 1239–43. [PubMed](#)
2. 2. Srivastava M, et al. [Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child](#). *Gastroenterology* 1998; **115**: 743–6. [PubMed](#)
3. 3. Taghian M, et al. [Acute vanishing bile duct syndrome after ibuprofen therapy in a child](#). *J Pediatr* 2004; **145**: 273–6. [PubMed](#)
4. 4. Health Canada. [Ibuprofen: Stevens-Johnson syndrome](#). *Can Adverse React News* 2005; **15** (3): 3. Also available at: [online](#) (accessed 29/08/08)
5. 5. Bergner T, Przybilla B. [Photosensitization caused by ibuprofen](#). *J Am Acad Dermatol* 1992; **26**: 114–16. [PubMed](#)
6. 6. Davidson KA, et al. [Ibuprofen-induced bullous leukocytoclastic vasculitis](#). *Cutis* 2001; **67**: 303–7. [PubMed](#)

### Hypersensitivity (Latest modification: 02-Sep-2008)

A fatal asthma attack occurred in a 65-year-old woman, with adult-onset asthma, 30 minutes after ingestion of ibuprofen 800 mg.<sup>1</sup>

For other hypersensitivity reactions or possible reactions see also Effects on the CNS (↔📄) and Effects on the Skin, ↔📄.

(last reviewed 2010-08-20; last modified 2008-09-02)

1. Ayres JG, *et al.* [Asthma death due to ibuprofen](#). *Lancet* 1987; **i**: 1082. [PubMed](#)

### **Meningitis** (Latest modification: 02-Sep-2008)

For reports of aseptic meningitis after use of ibuprofen, see Effects on the CNS, ↔📄.

(last reviewed 2010-08-20; last modified 2008-09-02)

### **Overdosage** (Latest modification: 02-Jun-2010)

There was a substantial increase in the number of cases of ibuprofen overdose reported to the National Poisons Information Service of the UK in the 2 years after its introduction as an 'over-the-counter' medication.<sup>1</sup> However, no concurrent increase in severity of poisoning was found and in only 1 of 203 cases was ibuprofen thought to have caused serious problems. It was concluded that ibuprofen appeared to be much less toxic in acute overdose than either aspirin or paracetamol. Current advice is that doses below 100 mg/kg are unlikely to cause toxicity in *children*, whereas clinical features will occur in children who have ingested more than 400 mg/kg. In *adults* the dose-response effect is less clear cut, but those who have ingested less than 100 mg/kg are unlikely to require treatment.

Nonetheless, reports illustrate the complexity of major overdosage with ibuprofen. A syndrome of coma, hyperkalaemia with cardiac arrhythmias, metabolic acidosis, pyrexia, and respiratory and renal failure was reported<sup>2</sup> in a 17-year-old man after major overdosage with ibuprofen and minor overdosage with doxepin. Hyperkalaemia was not evident until 14 hours after hospital admission and was thought to be due to a combination of potassium replacement for initial hypokalaemia, acidosis, muscle damage, and ibuprofen-induced renal failure. A 6-year-old child developed<sup>3</sup> shock, coma, and metabolic acidosis after ingestion of a dose of ibuprofen equivalent to 300 mg/kg. Treatment consisting of intubation, mechanical ventilation, fluid resuscitation, gastric lavage, and activated charcoal proved successful. In another report,<sup>4</sup> in which a 21-month-old child had ingested the equivalent of 500 mg/kg of ibuprofen, the presenting symptoms were acute renal failure with severe metabolic acidosis. The child developed tonic-clonic seizures 46 hours after ingestion, with significant hypocalcaemia and hypomagnesaemia, which may have been exacerbated by use of sodium polystyrene sulfonate and furosemide. The seizures, which could not be controlled with diazepam, phenytoin, and phenobarbital, ceased on correction of electrolyte balance.

(last reviewed 2010-08-20; last modified 2010-06-02)

1. Perry SJ, *et al.* [Ibuprofen overdose: the first two years of over-the-counter sales](#). *Hum Toxicol* 1987; **6**: 173–8. [PubMed](#)
2. Menzies DG, *et al.* [Fulminant hyperkalaemia and multiple complications following ibuprofen overdose](#). *Med Toxicol Adverse Drug Exp* 1989; **4**: 468–71. [PubMed](#)
3. Zuckerman GB, Uy CC. [Shock, metabolic acidosis, and coma following ibuprofen overdose in a child](#). *Ann Pharmacother* 1995; **29**: 869–71. [PubMed](#)
4. Al-Harbi NN, *et al.* [Hypocalcemia and hypomagnesemia after ibuprofen overdose](#). *Ann Pharmacother* 1997; **31**: 432–4. [PubMed](#)

## Porphyria (Latest modification: 14-Nov-2011)

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibuprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.<sup>1</sup>

(last reviewed 2010-08-20; last modified 2011-11-14)

1. The Drug Database for Acute Porphyria. Available at: [online](#) (accessed 23/10/11)

## Pharmacokinetics (Latest modification: 02-Jun-2010)

Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is also absorbed on rectal use. It is partially absorbed after topical application to the skin; some licensed product information state that percutaneous absorption from topical gel is about 5% of that from an oral dose form. Ibuprofen is 90 to 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in the urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. There appears to be little, if any, distribution into breast milk.

The above figures refer to racemic ibuprofen. However, ibuprofen's disposition is stereoselective and there is some metabolic conversion of the inactive *R*-(-)-enantiomer to the active *S*-(+)-enantiomer, dexibuprofen (↔).

(last reviewed 2010-08-20; last modified 2010-06-02)

References.

(last reviewed 2010-08-20; last modified 2011-01-02)

1. Davies NM. [Clinical pharmacokinetics of ibuprofen: the first 30 years.](#) *Clin Pharmacokinet* 1998; **34**: 101–54. [PubMed](#)
2. Sharma PK, et al. [Pharmacokinetics of oral ibuprofen in premature infants.](#) *J Clin Pharmacol* 2003; **43**: 968–73. [PubMed](#)
3. Gregoire N, et al. [Population pharmacokinetics of ibuprofen enantiomers in very premature neonates.](#) *J Clin Pharmacol* 2004; **44**: 1114–24. [PubMed](#)
4. Han EE, et al. [Pharmacokinetics of ibuprofen in children with cystic fibrosis.](#) *Clin Pharmacokinet* 2004; **43**: 145–56. [PubMed](#)
5. Hao H, et al. [Enantioselective pharmacokinetics of ibuprofen and involved mechanisms.](#) *Drug Metab Rev* 2005; **37**: 215–34. [PubMed](#)
6. Kyllonen M, et al. [Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration.](#) *Paediatr Anaesth* 2005; **15**: 566–73. [PubMed](#)
7. Kokki H, et al. [Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children.](#) [Abstract:](#) *Pediatrics* 2007; **120**: 882. [PubMed](#) Full version: [online](#) (accessed 15/09/09)
8. Gregoire N, et al. [Population pharmacokinetic analysis of ibuprofen enantiomers in preterm newborn infants.](#) *J Clin Pharmacol* 2008; **48**: 1460–8. [PubMed](#)

## Leber-Anfragen – Überlegungen zum Patienten

### 1. Erfassen von Informationen

Leberparameter	Normbereich*	Datum	Datum	Datum
ALT (GPT)	<35 [U/L]			
AST (GOT)	<35 [U/L]			
Alkal. Phosphatase	35-105 [U/L]			
Bilirubin	≤1 [mg/dL]			
Albumin	3,5-5 [g/dL]			
GGT	≤40 [U/L]			
INR	0,8 - 1,2			
Prothrombinzeit	23 – 35 [sec]			
Kreatinin	0,5 - 1 [mg/dL]			

\* Quelle: Institut für Klinische Chemie der LMU München Stand 17.01.2012

Vergleich der Laborwerte mit der Norm.

Cave: Die Werte können mehr oder weniger stark abweichen ohne direkt eine Leberfunktionsstörung anzuzeigen.

### 2. Was ist die Diagnose?

#### Über welchen Zeitraum trat das Ereignis ein?

Akut → Lebertoxizität?

Chronisch → Zirrhose? MELD/PELD/Childs Pugh

#### Welche Symptome liegen vor?

Enzephalopathie – derzeit oder früher?

Icterus – heller Stuhl oder dunkler Urin?

Aszites – derzeit oder früher?

Varizen – derzeit oder früher?

### Sind Testergebnisse verfügbar?

Ultraschallscan

Biopsie

Endoskop. retrograde Cholangio-Pankreatikographie/

Hepatobiliäre Szintigraphie

Endoskopie

Ist eine portale Hypertonie bekannt?

### Hat der Patient andere Einschränkungen bzw. nimmt er Medikamente über die nachgedacht werden muss?

### Was ist die Therapie der Wahl?

### 3. Anwendung der Informationen

Effekt auf die Pharmakokinetik & -dynamik	Risikofaktoren für Nebenwirkungen
Aszites (A/D)	Varizen
Cholestase (A/E)	Koagulopathie oder geringe Thrombozytenzahl
Geringe Albuminkonz. (D)	Enzephalopathie
Portale Hypertonie (M)	Pruritus
Akutes Leberversagen (M)	Alkoholismus
Zirrhose – kompensiert (M)	Aszites
Zirrhose – nicht kompensiert (M)	Zirrhose
Enzephalopathie (P)	Renales oder hepatorenales Versagen

A = Absorption; D = Distribution; M = Metabolismus; E = Eliminierung;

P = Pharmakodynamik

## Leber-Anfragen – Überlegungen zum Medikament

Pharmakokinetik		Überlegungen
Absorption		Lipid-Löslichkeit Absorption vom Aszites beeinflusst?
Distribution		Wasser/Fett Proteinbindung [%] Verdrängen von bzw. durch Bilirubin
Metabolisierung		First pass effect Durch Hepatocyten? Prodrug CYPs Aktive Metaboliten Genetische Variabilitäten
Eliminierung		Biliäre Exkretion Alternative Mechanismen Enterohepatischer Kreislauf (Niereninsuffizienz)

### **Nebenwirkungen:**

#### **Beeinflusst das Medikament die Leberfunktionswerte?**

- Wie hoch ist die Inzidenz dieser Reaktion?
- Handelt es sich um einen vorübergehenden Effekt?
- Ist bekannt wie lange es dauert bis sich die Leberfunktionswerte wieder normalisieren?

#### **Steht das Medikament im Verdacht Hepatitis oder Cholestase zu verursachen?**

- Was für eine Reaktion wird vom Medikament verursacht?
- Wie hoch ist die Inzidenz dieser Reaktion?
- Wie lange hält der Effekt an?

#### **Wird das Medikament mit anderen schweren oder langzeithepatotoxischen Reaktionen in Verbindung gebracht?**

- z.B. hepatische Nekrosen, Vanishing bile duct syndrome?
- Wie hoch ist die Inzidenz dieser Reaktion?

#### **Andere relevante Nebenwirkungen**

##### **Dermatologisch**

- z.B. Pruritus und Urticaria
- Inzidenz?

##### **Endokrinologisch/Metabolisch**

- z.B. Flüssigkeits- und Elektrolytverschiebungen
- Inzidenz?

##### **Gastrointestinal**

- z.B. Obstipation
- Inzidenz?

##### **Hämatologisch**

- z.B. Thrombozytopenie, Auswirkungen auf die Gerinnung, erhöhtes Blutungsrisiko
- Inzidenz?

##### **Neurologisch**

- z.B. Verwirrheitszustände, Anfälle, Sedierung
- Inzidenz?

##### **Renal**

- z.B. renale Toxizität
- Inzidenz?

#### **Gibt es Arzneimittelinteraktionen oder Interaktionen mit Erkrankungen, die beachtet werden müssen?**

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## Summary of Product Characteristics

### 1. Name of the medicinal product

Brufen Tablets 400mg

### 2. Qualitative and quantitative composition

Each Brufen tablet contains 400 mg Ibuprofen.

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Brufen is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies.

In the treatment of non-articular rheumatic conditions, Brufen is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain; Brufen can also be used in soft tissue injuries such as sprains and strains.

Brufen is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post-operative pain and for symptomatic relief of headache, including migraine headache.

#### 4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults: The recommended dosage of Brufen is 1200-1800 mg daily in divided doses. Some patients can be maintained on 600-1200 mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400 mg in divided doses.

Children: The daily dosage of Brufen is 20 mg/kg of body weight in divided doses.

In Juvenile Rheumatoid Arthritis, up to 40 mg/kg of body weight daily in divided doses may be taken. Not recommended for children weighing less than 7 kg.

Elderly: The elderly are at increased risk of serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. If renal or hepatic function is impaired, dosage should be assessed individually.

For oral administration. To be taken preferably with or after food, with a glass of water. Brufen tablets should be swallowed whole and not chewed, broken, crushed or sucked on to avoid oral discomfort and throat irritation.

#### 4.3 Contraindications

Brufen is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Brufen should not be used in patients who have previously shown hypersensitivity reactions (e.g. asthma, urticaria, angioedema or rhinitis) after taking ibuprofen, aspirin or other NSAIDs.

Brufen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Brufen should not be used in patients with active, or history of, recurrent peptic ulcer or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Brufen should not be given to patients with conditions involving an increased tendency to bleeding. Brufen is contraindicated in patients with severe heart failure, hepatic failure and renal failure (see section 4.4).

Brufen is contraindicated during the last trimester of pregnancy (see section 4.6).

#### 4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medication.

As with other NSAIDs, ibuprofen may mask the signs of infection.

The use of Brufen with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

##### *Elderly*

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).

##### *Gastrointestinal bleeding, ulceration and perforation*

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Brufen, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of ulcerative colitis or Crohn's disease as these conditions may be exacerbated (see section 4.8).

##### *Respiratory disorders*

Caution is required if Brufen is administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

##### *Cardiovascular, renal and hepatic impairment*

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Brufen should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with ibuprofen administration.

##### *Cardiovascular and cerebrovascular effects*

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400 mg/ daily) and in long term treatment, may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g.  $\leq 1200$ mg daily) is associated with an increased risk of arterial thrombotic events, particularly myocardial infarction.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

##### *Renal effects*

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal

prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependant reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

#### *SLE and mixed connective tissue disease*

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see below and section 4.8).

#### *Dermatological effects*

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Brufen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

#### *Haematological effects*

Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and has been shown to prolong bleeding time in normal subjects.

#### *Aseptic meningitis*

Aseptic meningitis has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

#### *Impaired female fertility*

The use of Brufen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Brufen should be considered.

## 4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Antihypertensives, beta-blockers and diuretics: NSAIDs may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers and diuretics.

Diuretics can also increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Cholestyramine; The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Lithium: Decreased elimination of lithium.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

Other analgesics and cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs, including Cox-2 inhibitors, as this may increase the risk of adverse effects (see section 4.4).

Aspirin: As with other products containing NSAIDs, concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional use (see section 5.1).

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding with NSAIDs (see section 4.4).

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare

reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

CYP2C9 Inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown.

Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

#### 4.6. Pregnancy and lactation

##### *Pregnancy*

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. In animals, the administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation losses and embryo/foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, Brufen should not be given unless clearly necessary. If Brufen is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to the following:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)

- Renal dysfunction, which may progress to renal failure with oligohydramnios.

At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the neonate to the following:

- Possible prolongation of bleeding time

- Inhibition of uterine contractions, which may result in delayed or prolonged labour.

Consequently, Brufen is contraindicated during the third trimester of pregnancy.

##### *Lactation*

In the limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

#### 4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

#### 4.8 Undesirable effects

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis has been observed. Gastrointestinal perforation has been rarely reported with ibuprofen use. Pancreatitis has also been reported very rarely.

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including Stevens- Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

Cardiac disorders and vascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg/ daily), and in long term treatment, may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke (see section 4.4). Other adverse events reported less commonly and for which causality has not necessarily been established include:

Blood and lymphatic system disorders: Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia

Psychiatric disorders: Insomnia, anxiety, depression, confusional state, hallucination

Nervous system disorders: Optic neuritis, headache, paraesthesia, dizziness, somnolence

Infections and infestations: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Eye disorders: Visual impairment and toxic optic neuropathy

Ear and labyrinth disorders: Hearing impaired, tinnitus and vertigo

Hepatobiliary disorders: Abnormal liver function, hepatic failure, hepatitis and jaundice

Skin and subcutaneous tissue disorders: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare), and photosensitivity reaction

Renal and urinary disorders: Impaired renal function and toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome and renal failure

General disorders and administration site conditions: Malaise, fatigue.

## 4.9 Overdose

### *Toxicity*

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

### *Symptoms*

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

### *Therapeutic measures*

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID is thought to result from its inhibitory effect on the enzyme cyclooxygenase, which results in a marked reduction in prostaglandin synthesis.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant

effect is considered to be likely for occasional ibuprofen use.

## 5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed from the gastrointestinal tract, peak serum concentrations occurring 1-2 hours after administration. The elimination half-life is approximately 2 hours.

Ibuprofen is metabolised in the liver to two inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Ibuprofen is extensively bound to plasma proteins.

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### Summary of Product Characteristics

#### 1. Name of the medicinal product

Morphine Sulphate 10mg/ml Solution for Injection

#### 4. Clinical particulars

##### 4.1 Therapeutic indications

The symptomatic relief of severe pain; relief of dyspnoea of left ventricular failure and pulmonary oedema; pre-operative use.

##### 4.2 Posology and method of administration

Morphine Sulphate may be given by the subcutaneous, intramuscular or intravenous route. The subcutaneous route is not suitable for oedematous patients. The dosage should be based on the severity of the pain and the response and tolerance of the individual patient. The epidural or intrathecal routes must not be used as the product contains a preservative.

##### **Adults:**

##### **Subcutaneous or intramuscular injection:**

10mg every four hours if necessary (the dose may vary from 5-20mg depending on the individual patient).

##### **Slow intravenous injection (2mg/minute):**

Quarter to half of corresponding intramuscular dose not more than four hourly.

**Elderly and debilitated patients:** The dose should be reduced because of the depressant effect on respiration. Caution is required.

**Children:** Use in children is not recommended.

##### **Hepatic impairment:**

A reduction in dosage should be considered in hepatic impairment.

##### **Renal impairment:**

The dosage should be reduced in moderate to severe renal impairment.

For concomitant illnesses/conditions where dose reduction may be appropriate see 4.4 Special Warnings and Precautions for Use.

##### 4.3 Contraindications

Acute respiratory depression, known morphine sensitivity, biliary colic (see also biliary tract disorders 4.4 Special Warnings and Precautions), acute alcoholism. Conditions in which intracranial pressure is raised, comatose patients, head injuries, as there is an increased risk of respiratory depression that may lead to elevation of CSF pressure. The sedation and pupillary changes produced may interfere with

accurate monitoring of the patient. Morphine is also contraindicated where there is a risk of paralytic ileus, or in acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated).

Phaeochromocytoma (due to the risk of pressor response to histamine release).

#### 4.4 Special warnings and precautions for use

Morphine should be given in reduced doses or with caution to patients with asthma or decreased respiratory reserve (including cor pulmonale, kyphoscoliosis, emphysema, severe obesity). Avoid use during an acute asthma attack (see 4.3 Contraindications). Opioid analgesics in general should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urethral stricture, hypotension, shock, inflammatory or obstructive bowel disorders, or convulsive disorders.

Opioids such as morphine should either be avoided in patients with biliary disorders or they should be given with an antispasmodic.

Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi. Therefore in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is a contraindication, see 4.3). In patients given morphine after cholecystectomy, biliary pain has been induced.

Caution is advised when giving morphine to patients with impaired liver function due to its hepatic metabolism (see 4.2 Posology).

Severe and prolonged respiratory depression has occurred in patients with renal impairment who have been given morphine (see 4.2 Posology).

Dependence can develop rapidly with regular abuse of opioids but is less of a problem with therapeutic use. Abrupt withdrawal from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose and the duration of drug use. Great caution should be exercised in patients with a known tendency or history of drug abuse.

Dosage should be reduced in elderly and debilitated patients (see 4.2 Posology).

Palliative care - in the control of pain in terminal illness, these conditions should not necessarily be a deterrent to use.

#### 4.5 Interaction with other medicinal products and other forms of interaction

**Alcohol:** enhanced sedative and hypotensive effects.

**Anti-arrhythmics:** There may be delayed absorption of mexiletine.

**Antibacterials:** The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The manufacturer of ciprofloxacin advises that premedication with opioid analgesics be avoided.

**Antidepressants, anxiolytics, hypnotics:** Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concurrent use of pethidine and monoamine oxidase inhibitors (MAOIs) including selegiline, moclobemide and linezolid. As it is possible that a similar interaction may occur with other opioid analgesics, morphine should be used with caution and consideration given to a reduction in dosage in patients receiving MAOIs.

The sedative effects of morphine (opioid analgesics) are enhanced when used with depressants of the central nervous system such as hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

**Antipsychotics:** possible enhanced sedative and hypotensive effect.

**Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin):** concurrent use may increase the risk of severe constipation.

**Antimuscarinics:** agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastrointestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive antimuscarinic-analgesic therapy.

**Metoclopramide and domperidone:** There may be antagonism of the gastrointestinal effects of metoclopramide and domperidone.

#### 4.6 Pregnancy and lactation

Morphine sulphate should only be used when benefit is known to outweigh risk. As with all drugs it is not advisable to administer morphine during pregnancy.

Morphine crosses the placental barrier. Administration during labour may cause respiratory depression in the newborn infant and gastric stasis during labour, increasing the risk of inhalation pneumonia. Therefore, it is not advisable to administer morphine during labour.

Babies born to opioid-dependent mothers may suffer withdrawal symptoms including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.

While morphine can suppress lactation, the quantity from therapeutic doses that may reach the neonate via breast milk is probably insufficient to cause major problems of dependence or adverse effects.

#### 4.7 Effects on ability to drive and use machines

Morphine causes drowsiness so patients should avoid driving or operating machinery.

#### 4.8 Undesirable effects

The most serious hazard of therapy is respiratory depression (see also 4.9 Overdose).

The commonest side-effects of morphine are nausea, vomiting, constipation, drowsiness and dizziness. Tolerance generally develops with long term use, but not to constipation.

Other side effects include the following:

**Anaphylaxis:** Anaphylactic reactions following intravenous injection have been reported rarely.

**Cardiovascular:** facial flushing bradycardia, palpitations, tachycardia, orthostatic hypotension.

**Central Nervous System:** mental clouding, confusion (with large doses), hallucinations, headache, vertigo, mood changes including dysphoria and euphoria.

**Gastrointestinal:** dry mouth, biliary spasm.

**Disorders of the eye:** blurred or double vision or other changes in vision, miosis.

**Sexual dysfunction:** long term use may lead to a reversible decrease in libido or potency.

**Skin:** pruritus, urticaria, rash, sweating. Contact dermatitis has been reported and pain and irritation may occur on injection.

**Urinary:** difficulty with micturition, ureteric spasm, urinary retention, antidiuretic effect. Tolerance

develops to the effects of opioids on the bladder.

The euphoric activity of morphine has led to its abuse and physical and psychological dependence may occur (see also 4.4 Special Warnings and Precautions for use).

#### 4.9 Overdose

Toxic doses vary considerably with the individual, and regular users may tolerate large doses.

The triad of respiratory depression, coma and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Death may occur from respiratory failure

Other opioid overdose symptoms include hypothermia, confusion, severe dizziness, severe drowsiness, hypotension, bradycardia, circulatory failure pulmonary oedema, severe nervousness or restlessness, hallucinations, convulsions (especially in infants and children). Rhabdomyolysis, progressing to renal failure, has been reported in overdosage.

Treatment: The medical management of overdose involves prompt administration of the specific opioid antagonist naloxone if coma or bradypnoea are present using one of the recommended dosage regimens. Both respiratory and cardiovascular support should be given where necessary.

### 5. Pharmacological properties

#### 5.1 Pharmacodynamic properties

Morphine is obtained from opium, which acts mainly on the CNS and smooth muscle.

Morphine is a potent analgesic with competitive agonist actions at the  $\mu$ -receptor, which is thought to mediate many of its other actions of respiratory depression, euphoria, inhibition of gut motility and physical dependence. It is possible that analgesia, euphoria and dependence may be due to the effects of morphine on a  $\mu$ -1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on a  $\mu$ -2 receptor subtype. Morphine is also a competitive agonist at the  $\kappa$ -receptor that mediates spinal analgesia, miosis and sedation. Morphine has no significant actions at the other two major opioid receptors, the  $\delta$ - and the  $\sigma$ -receptors.

Morphine directly suppresses cough by an effect on the cough centre in the medulla. Morphine also produces nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the area postrema of the medulla. Morphine provokes the release of histamine.

#### 5.2 Pharmacokinetic properties

Absorption:	Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.
Blood concentration:	After an oral dose of 10mg as the sulphate, peak serum concentrations of free morphine of about 10ng/ml are attained in 15 to 60 minutes.  After an intramuscular dose of 10mg, peak serum concentrations of 70 to 80ng/ml are attained in 10 to 20 minutes.  After an intravenous dose of 10mg, serum concentrations of about 60ng/ml are obtained in 15 minutes falling to 30ng/ml after 30 minutes and to 10ng/ml after three hours.  Subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following three hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the elderly.
Half-life	Serum half-life in the period ten minutes to six hours following intravenous

administration-two to three hours; serum half-life in the period six hours onwards-10 to 44 hours.

**Distribution:** Widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen; lower concentrations appear in the brain and muscles.

Morphine crosses the placenta and traces are secreted in sweat and milk.

Protein binding-about 35% bound to albumin and to immunoglobulins at concentrations within the therapeutic range.

**Metabolic reactions:** Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides. N-demethylation, O-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parental administration; the O-methylation pathway to form codeine has been challenged and codeine and norcodeine metabolites in urine may be formed from codeine impurities in the morphine sample studied.

**Excretion:** After an oral dose, about 60% is excreted in the urine in 24 hours, with about 3% excreted as free morphine in 48 hours.

After a parental dose, about 90% is excreted in 24 hours, with about 10% as free morphine, 65 to 70% as conjugated morphine, 1% as normorphine and 3% as normorphine glucuronide.

After administration of large doses to addicts about 0.1% of a dose is excreted as norcodeine.

Urinary excretion of morphine appears to be pH dependent to some extent; as the urine becomes more acidic more free morphine is excreted and as the urine becomes more alkaline more of the glucuronide conjugate is excreted.

Up to 10% of a dose may be excreted in the bile.

**Ph. Eur. 8** (Morphine Sulfate). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

**USP 36** (Morphine Sulfate). White, feathery, silky crystals, cubical masses of crystals, or a white crystalline powder. Is odourless and when exposed to air it gradually loses water of hydration. It darkens on prolonged exposure to light. Soluble 1 in 16 of water and 1 in 1 of water at 80 degrees; soluble 1 in 570 of alcohol and 1 in 240 of alcohol at 60 degrees; insoluble in chloroform and in ether. Store in airtight containers at a temperature up to 40 degrees as permitted by the manufacturer. Protect from light.

### Uses and Administration (Latest modification: 09-Jan-2014)

Morphine, a phenanthrene derivative, is the main alkaloid of opium (→📄). It is now commonly obtained from whole opium poppies (*Papaver somniferum*) which are harvested as poppy straw; a concentrate of poppy straw is known as CPS.

Morphine is an opioid analgesic (→📄) with agonist activity mainly at  $\mu$  opioid receptors and perhaps at  $\kappa$  and  $\delta$  receptors. It acts mainly on the CNS and smooth muscle. Although morphine is mainly a CNS depressant it has some central stimulant actions which result in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

Morphine may produce both physical and psychological dependence (see →📄) and should therefore be used with discrimination. Tolerance may also develop.

Morphine is used for the relief of moderate to severe pain, especially that associated with cancer, myocardial infarction, and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain and it is useful as a hypnotic where sleeplessness is due to pain. It is also used in the management of neonatal abstinence syndrome (see Administration in Children, →📄).

Morphine reduces intestinal motility but its role, if any, in the symptomatic treatment of diarrhoea is very limited. It also relieves dyspnoea associated with various conditions, including that due to pulmonary oedema resulting from left ventricular failure. It is an effective cough suppressant, but codeine is usually preferred as there is less risk of dependence; morphine may however be necessary to control intractable cough associated with terminal lung cancer. Morphine has been used pre-operatively as an adjunct to anaesthesia for pain relief and to allay anxiety. It has also been used in high doses as a general anaesthetic in specialised procedures such as open-heart surgery.

Morphine is usually **administered** as the sulfate, although the hydrochloride and the tartrate are used in similar doses. Doses are expressed as the salts. Dosage routes include the oral, subcutaneous, intramuscular, intravenous, intraspinal, and rectal routes. Subcutaneous injections are considered unsuitable for oedematous patients. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

Doses should generally be reduced in the elderly or debilitated, or in patients with hepatic or renal impairment (see also under Precautions, →📄 and →📄).

### For pain:

*Oral* doses are usually equivalent to 5 to 20 mg every 4 hours and may be given as an aqueous solution of the hydrochloride or sulfate, as modified-release granules or tablets, or as immediate-release tablets. With modified-release preparations the 24-hour dose is usually given as a single dose or in 2 divided doses; in the USA, a modified-release preparation (*MS Contin, Purdue*) that allows dosing every 8 or 12 hours is also available. With all modified-release preparations, additional doses of a conventional formulation may be needed if breakthrough pain occurs. As with the other routes, high oral doses may be required for effective analgesia in palliative care.

Morphine is sometimes given *rectally* generally as suppositories in doses of 10 to 30 mg every 4 hours. Oral modified-release preparations have also been used rectally although such use is unlicensed in the UK and is generally not recommended except, possibly, in some emergency situations.

The usual dose by *subcutaneous* or *intramuscular* injection is 10 mg every 4 hours but may range from 5 to 20 mg.

For premedication, the [BNF](#) recommends that up to 10 mg may be given by subcutaneous or intramuscular injection 60 to 90 minutes before surgery.

Doses of up to 15 mg have been given by slow *intravenous* injection, sometimes as a loading dose for continuous or patient-controlled infusion. For continuous intravenous administration maintenance doses have generally ranged from 0.8 to 80 mg/hour, although some patients have required and been given much higher doses. Similar doses have been given by continuous subcutaneous infusion.

For myocardial infarction, the [BNF](#) recommends that 5 to 10 mg may be given by intravenous injection at a rate of 1 to 2 mg/minute followed by a further 5 to 10 mg if necessary; half this dose should be used in elderly or debilitated patients.

Intraspinal doses are in the region of 5 mg for an initial *epidural* injection; if pain relief is unsatisfactory after one hour, further doses of 1 to 2 mg may be given up to a total dose of 10 mg per 24 hours. The recommended initial dose for continuous epidural infusion in opioid-naïve patients ranges from 3.5 to 7.5 mg daily; those who have some degree of opioid tolerance may be given 4.5 to 10 mg daily. However, dosage requirements may increase significantly during treatment and up to 20 to 30 mg daily may be required in some patients. A modified-release formulation of liposomal morphine sulfate for lumbar epidural use is also available for the treatment of pain after major surgery; doses range from 10 to 20 mg, depending on the type of surgery, and should be given before the operation, or after clamping of the umbilical cord if used during caesarean section. It is intended for single-use only and no other drugs should be administered into the epidural space for at least the next 48 hours.

*Intrathecal* use of morphine and its salts has tended to be less common than epidural. A single dose of 0.2 to 1 mg given by intrathecal injection may provide satisfactory pain relief for up to 24 hours. The recommended initial dose for continuous intrathecal infusion in opioid-naïve patients ranges from 0.2 to 1 mg daily; those who have some degree of opioid tolerance may be given 1 to 10 mg daily. However, dosage requirements may increase during treatment and up to 20 mg daily may be required in some patients.

For details of doses in children, see .

In **acute pulmonary oedema** 5 to 10 mg may be given by intravenous injection at a rate of 2 mg/minute; half this dose should be used in elderly or debilitated patients.

For the control of intractable **cough** associated with terminal lung cancer, morphine oral solution is given in an initial dose of 5 mg every 4 hours.

As a deterrent to abuse a combined oral preparation of morphine sulfate and naltrexone hydrochloride is available in some countries.

**Administration** (Latest modification: 17-Jun-2008)

### Continuous infusion

Both acute and chronic pain have been controlled satisfactorily by continuous intravenous or subcutaneous infusions of morphine sulfate<sup>1-3</sup> but diamorphine hydrochloride or hydromorphone hydrochloride may be preferred for subcutaneous infusion because their greater solubility in water allows a smaller dose volume. Continuous subcutaneous infusions may be preferred to continuous intravenous infusions.<sup>4</sup> Continuous subcutaneous infusion may be less effective than epidural morphine for relief of postoperative pain;<sup>5</sup> however, it was still considered to provide simple and relatively effective analgesia with a low rate of adverse effects.

See also Patient-controlled Analgesia, .

1. Waldmann CS, et al. [Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients.](#) *Anaesthesia* 1984; **39**: 768–71. [PubMed](#)
2. Goudie TA, et al. [Continuous subcutaneous infusion of morphine for postoperative pain relief.](#) *Anaesthesia* 1985; **40**: 1086–92. [PubMed](#)
3. Stuart GJ, et al. [Continuous intravenous morphine infusions for terminal pain control: a retrospective review.](#) *Drug Intell Clin Pharm* 1986; **20**: 968–72. [PubMed](#)
4. Drexel H. [Long-term continuous subcutaneous and intravenous opioid infusions.](#) *Lancet* 1991; **337**: 979. [PubMed](#)
5. Hindsholm KB, et al. [Continuous subcutaneous infusion of morphine—an alternative to extradural morphine for postoperative pain relief.](#) *Br J Anaesth* 1993; **71**: 580–2. [PubMed](#)

### Intra-articular route

Intra-articular injection of morphine into the knee at the end of arthroscopy has been reported to provide some degree of postoperative pain relief;<sup>1,2</sup> such pain relief may be more pronounced than that produced by the same dose given intravenously<sup>1</sup> or intramuscularly.<sup>2</sup> The effect appears to be due to the action of morphine on peripheral opioid receptors<sup>2</sup> although a systemic effect has not been completely excluded.<sup>1</sup>

There have been conflicting results on whether addition of morphine to intra-articular bupivacaine improves analgesia<sup>3,4</sup> and a systematic review<sup>5</sup> concluded that from the few well-controlled studies there was no evidence of an added analgesic effect of morphine compared with saline alone.

Doses of morphine reported to have been injected intra-articularly have ranged from 1 to 10 mg.

1. 1. Gupta A, et al. [A systematic review of the peripheral analgesic effects of intraarticular morphine.](#) *Anesth Analg* 2001; **93**: 761–70. [PubMed](#)
2. 2. Raj N, et al. [Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy.](#) *Eur J Anaesthesiol* 2004; **21**: 932–7. [PubMed](#)
3. 3. Laurent SC, et al. [Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy.](#) *Br J Anaesth* 1994; **72**: 170–3. [PubMed](#)
4. 4. Heine MF, et al. [Intra-articular morphine after arthroscopic knee operation.](#) *Br J Anaesth* 1994; **73**: 413–15. [PubMed](#)
5. 5. Rosseland LA. [No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review.](#) *Reg Anesth Pain Med* 2005; **30**: 83–98. [PubMed](#)

### **Intranasal route**

An intranasal formulation of morphine has been investigated for the relief of acute pain.

(last reviewed 2014-01-08; last modified 2010-04-26)

### **Intraspinal route**

Morphine is given epidurally and intrathecally to relieve both acute and chronic pain. However, reviews on the role of spinal opioids have generally concluded that they should be reserved for pain not controlled by more conventional routes.<sup>1-3</sup> When converting from conventional routes it has been suggested that 1% of the total daily dose could be tried as the daily intrathecal dose and 10% as the epidural dose.<sup>3</sup> Conversion from intrathecal to oral dosage has also been investigated.<sup>4</sup>

Intrathecal morphine may be delivered continuously via an implanted programmable infusion pump for the long-term management of chronic non-malignant and cancer pain.

See also Patient-controlled Analgesia, .

(last reviewed 2014-01-08; last modified 2008-09-03)

1. 1. Anonymous. [Spinal opiates revisited.](#) *Lancet* 1986; **i**: 655–6. [PubMed](#)
2. 2. Gustafsson LL, Wiesenfeld-Hallin Z. [Spinal opioid analgesia: a critical update.](#) *Drugs* 1988; **35**: 597–603. [PubMed](#)
3. 3. McQuay HJ. [Opioids in chronic pain.](#) *Br J Anaesth* 1989; **63**: 213–26. [PubMed](#)
4. 4. Sylvester RK, et al. [The conversion challenge: from intrathecal to oral morphine.](#) *Am J Hosp Palliat Care* 2004; **21**: 143–7. [PubMed](#)

### **Patient-controlled analgesia**

Morphine is one of the most frequently used opioid analgesics for patient-controlled analgesia (see ). Most experience has been with the intravenous route, but the intramuscular, subcutaneous, oral, pulmonary, and epidural<sup>1</sup> routes have also been used. Reasonable initial settings recommended for intravenous use have been a demand dose of 1 to 2 mg of morphine sulfate (or its equivalent) and a lockout interval of 5 to 10 minutes.<sup>2</sup>

(last reviewed 2014-01-08; last modified 2008-09-10)

1. Sjöström S, et al. [Patient-controlled analgesia with extradural morphine or pethidine](#). *Br J Anaesth* 1988; **60**: 358–66. [PubMed](#)
2. Grass JA. [Patient-controlled analgesia](#). *Anesth Analg* 2005; **101** (suppl): S44–S61. [PubMed](#)

## Pulmonary route

For reference to the use of nebulised morphine see Dyspnoea, .

(last reviewed 2014-01-08; last modified 2008-06-17)

## Topical route

Morphine has been applied topically for local analgesia in oral mucositis<sup>1,2</sup> and cutaneous ulceration<sup>3-6</sup> including epidermolysis bullosa.<sup>7</sup>

(last reviewed 2014-01-08; last modified 2008-09-10)

1. Cerchiatti LC, et al. [Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma](#). *Cancer* 2000; **95**: 2230–6. [PubMed](#) Correction. *ibid.* 2003; **97**: 1137.
2. Cerchiatti L. [Morphine mouthwashes for painful mucositis](#). *Support Care Cancer* 2007; **15**: 115–16. [PubMed](#)
3. Twillman RK, et al. [Treatment of painful skin ulcers with topical opioids](#). *J Pain Symptom Manage* 1999; **17**: 288–92. [PubMed](#)
4. Krajnik M, et al. [Potential uses of topical opioids in palliative care—report of 6 cases](#). *Pain* 1999; **80**: 121–5. [PubMed](#)
5. Zeppetella G, et al. [Analgesic efficacy of morphine applied topically to painful ulcers](#). *J Pain Symptom Manage* 2003; **25**: 555–8. [PubMed](#)
6. Zeppetella G, Ribeiro MDC. [Morphine in Intrasite gel applied topically to painful ulcers](#). *J Pain Symptom Manage* 2005; **29**: 118–19. [PubMed](#)
7. Watterson G, et al. [Peripheral opioids in inflammatory pain](#). *Arch Dis Child* 2004; **89**: 679–81. [PubMed](#)

## Cancer pain (Latest modification: 09-Aug-2010)

Morphine is the opioid of choice for moderate to severe cancer pain (); guidelines for its use issued by the European Association for Palliative Care<sup>1</sup> include:

the optimal route for use is orally. For best effect, both immediate-release (for dose titration) and modified-release (for maintenance) dosage forms are required

the simplest method of dose titration is with immediate-release morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue dose' may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take into account the amount needed for breakthrough pain

if pain returns consistently before the next dose is due the regular dose should be increased. Immediate-release formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain

if an immediate-release formulation of morphine is not available and treatment is started with modified-release morphine, changes to the regular dose should not be made more often than every 48 hours, which means that dose titration will be prolonged

for patients taking immediate-release morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep

if patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful

when converting dosage, the relative potency of oral to subcutaneous morphine is between about 1:2 and 1:3, so 20 to 30 mg of oral morphine is equianalgesic to 10 mg by subcutaneous injection

in patients who need continuous parenteral morphine the preferred route is by subcutaneous infusion. However, intravenous infusion may be preferred:

in patients who already have an indwelling intravenous line

in those with generalised oedema

if erythema, soreness, or sterile abscess develop during subcutaneous dosage

in patients with coagulation disorders

where peripheral circulation is poor

when converting dosage, the relative potency of oral to intravenous morphine is also between about 1:2 and 1:3

the buccal, sublingual, and nebulised routes of administration are not recommended in the absence of evidence for clinical advantage over more usual routes

a small proportion of patients develop intolerable adverse effects with oral morphine (with adjuvant non-opioid analgesics as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid, or a change in the route should be considered. Although switching between opioids complicates pain management, adequate pain relief for some may depend on the use of alternative drugs, the use of intraspinal routes, or non-drug methods of pain control

Similar recommendations are given in guidelines issued by the US National Comprehensive Cancer Network.<sup>2</sup>

1. Hanks GW, *et al.* [Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations.](#) *Br J Cancer* 2001; **84**: 587–93. [PubMed](#)
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: adult cancer pain (version 1.2010). Available at: [online](#) (accessed 02/08/10)

**Dyspnoea** (Latest modification: 26-Apr-2010)

In the treatment of dyspnoea (↔📄), doses of morphine tend to be smaller than those used for pain relief. Morphine hydrochloride or sulfate may be given as an oral solution in carefully titrated doses, starting at a dose of 5 mg every 4 hours; as little as 2.5 mg every 4 hours may be sufficient for opioid-naïve patients.<sup>1</sup> In acute pulmonary oedema, 5 to 10 mg may be given by slow intravenous injection. In patients already receiving morphine for pain relief the following doses have been suggested:<sup>2</sup>

mild dyspnoea: 25 to 50% of usual analgesic dose

moderate dyspnoea: 50 to 100% of usual analgesic dose

severe dyspnoea: 100% or more of usual analgesic dose

Patients have also obtained relief from subcutaneous injection.<sup>3</sup>

Although it has been reported that a low dose of nebulised morphine (mean dose 1.7 mg) improved exercise endurance in patients with dyspnoea due to advanced chronic lung disease,<sup>4</sup> several subsequent studies<sup>5-7</sup> have failed to obtain significant improvements with doses up to 40 mg. It is considered that current evidence does not support the use of nebulised morphine for breathlessness.<sup>1,8-10</sup> Furthermore, bronchospasm can be a problem, particularly at high doses, and there is no consensus on the optimal dose, schedule, or method of dose titration.

1. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.
2. Twycross R, Wilcock A. *Palliative Care Formulary*. 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 280.
3. Bruera E, et al. [Subcutaneous morphine for dyspnea in cancer patients](#). *Ann Intern Med* 1993; **119**: 906–7. [PubMed](#)
4. Young IH, et al. [Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease](#). *Thorax* 1989; **44**: 387–90. [PubMed](#)
5. Beauford W, et al. [Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patients](#). *Chest* 1993; **104**: 175–8. [PubMed](#)
6. Nosedá A, et al. [Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine](#). *Eur Respir J* 1997; **10**: 1079–83. [PubMed](#)
7. Jankelson D, et al. [Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease](#). *Eur Respir J* 1997; **10**: 2270–4. [PubMed](#)
8. Polosa R, et al. Nebulised morphine for severe interstitial lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 26/06/08). [PubMed](#)
9. Foral PA, et al. [Nebulized opioids use in COPD](#). *Chest* 2004; **125**: 691–4. [PubMed](#)
10. Brown SJ, et al. [Nebulized morphine for relief of dyspnea due to chronic lung disease](#). *Ann Pharmacother* 2005; **39**: 1088–92. [PubMed](#)

## Dependence and Withdrawal (Latest modification: 17-Jun-2008)

As for Opioid Analgesics, ↔📄.

Dependence associated with morphine and closely related  $\mu$ -agonists appears to result in more severe withdrawal symptoms than that associated with  $\kappa$ -receptor agonists. With

morphine, withdrawal symptoms usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside.

Morphine is used for substitution therapy in the management of neonatal abstinence syndrome (see Administration in Children, )

### **Adverse Effects and Treatment** (Latest modification: 21-Mar-2004)

As for Opioid Analgesics in general, .

(last reviewed 2014-01-08; last modified 2004-03-21)

References.

1. 1. Cherny N, *et al.* [Strategies to manage the adverse effects of oral morphine: an evidence-based report.](#) *J Clin Oncol* 2001; **19**: 2542–54. [PubMed](#)

### **Effects on the cardiovascular system** (Latest modification: 21-Mar-2004)

For a reference to the effects of morphine on histamine release compared with some other opioids, see under Pethidine, .

### **Effects on the muscles** (Latest modification: 17-Jun-2008)

Severe rectovaginal spasms that occurred in a patient given intrathecal morphine<sup>1</sup> were successfully controlled with midazolam.

1. 1. Littrell RA, *et al.* [Muscle spasms associated with intrathecal morphine therapy: treatment with midazolam.](#) *Clin Pharm* 1992; **11**: 57–9. [PubMed](#)

### **Effects on the nervous system** (Latest modification: 10-Sep-2008)

Myoclonus, often associated with hyperalgesia, has been reported in patients with advanced malignant disease treated with morphine.<sup>1-5</sup> It appears to be uncommon with typical oral doses of morphine and is more often associated with high intravenous and spinal doses. Neuroexcitatory metabolites of morphine are often implicated in the development of myoclonus;<sup>2,4,5</sup> however, other possible mechanisms such as drug interactions cannot be ruled out.<sup>4-6</sup>

It has been reported that myoclonus induced by morphine can be successfully controlled using a benzodiazepine such as midazolam.<sup>7</sup> Indeed, some researchers<sup>8</sup> consider benzodiazepines to be the drugs of choice: clonazepam, diazepam, and lorazepam were most frequently used. Dantrolene<sup>5,8</sup> and gabapentin<sup>9</sup> have also been tried.

1. 1. Potter JM, *et al.* [Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs.](#) *BMJ* 1989; **299**: 150–3. [PubMed](#)
2. 2. Glare PA, *et al.* [Normorphine, a neurotoxic metabolite?](#) *Lancet* 1990; **335**: 725–6. [PubMed](#)
3. 3. De Conno F, *et al.* [Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine.](#) *Pain* 1992; **47**: 337–9. [PubMed](#)
4. 4. Sjøgren P, *et al.* [Hyperalgesia and myoclonus in terminal cancer patients treated with continuous intravenous morphine.](#) *Pain* 1993; **55**: 93–7. [PubMed](#)

5. 5. Mercadante S. [Pathophysiology and treatment of opioid-related myoclonus in cancer patients](#). *Pain* 1998; **74**: 5–9. [PubMed](#)
6. 6. Quinn N. [Myoclonus associated with high doses of morphine](#). *BMJ* 1989; **299**: 683–4. [PubMed](#)
7. 7. Holdsworth MT, et al. [Continuous midazolam infusion for the management of morphine-induced myoclonus](#). *Ann Pharmacother* 1995; **29**: 25–9. [PubMed](#)
8. 8. Ferris DJ. [Controlling myoclonus after high-dosage morphine infusions](#). *Am J Health-Syst Pharm* 1999; **56**: 1009–10. [PubMed](#)
9. 9. Mercadante S, et al. [Gabapentin for opioid-related myoclonus in cancer patients](#). *Support Care Cancer* 2001; **9**: 205–6. [PubMed](#)

### **Precautions** (Latest modification: 21-Mar-2004)

As for Opioid Analgesics in general, .

### **Biliary-tract disorders** (Latest modification: 21-Mar-2004)

See under Precautions of Opioid Analgesics, .

### **Breast feeding** (Latest modification: 07-Aug-2010)

Measurable blood concentrations of morphine have been detected in 2 breast-fed infants whose mothers received oral or intrathecal morphine during and after their pregnancies; however, no adverse effects were reported in either of these infants.<sup>1,2</sup> In a group of 7 women given patient-controlled analgesia with intravenous morphine after caesarean delivery, the concentrations of morphine and its metabolite morphine-6 glucuronide in the colostrum were found to be very small.<sup>3</sup> Although no infants were breast fed during the study, it was considered that the effects of maternal morphine on breast-fed infants would be negligible.<sup>3</sup> The American Academy of Pediatrics<sup>4</sup> also states that the use of morphine is usually compatible with breast feeding.

1. 1. Robieux I, et al. [Morphine excretion in breast milk and resultant exposure of a nursing infant](#). *J Toxicol Clin Toxicol* 1990; **28**: 365–70. [PubMed](#)
2. 2. Oberlander TF, et al. [Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment](#). *J Hum Lact* 2000; **16**: 137–42. [PubMed](#)
3. 3. Baka N-E, et al. [Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia](#). *Anesth Analg* 2002; **94**: 184–7. [PubMed](#)
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Correction. [ibid.](#); 1029. Also available at: [online](#) (accessed 26/06/08)

### **Hepatic impairment** (Latest modification: 14-Jan-2014)

In view of its hepatic metabolism, caution is generally advised when giving morphine to patients with hepatic impairment (but see under Pharmacokinetics, ). The [BNF](#) advises that use should be avoided or the dose reduced because of the risk of precipitating a coma. However, it has also been noted that many patients with hepatic impairment tolerate morphine well. Others have considered that severe hepatic impairment may affect morphine metabolism but less severe impairment does not.<sup>1</sup>

The mean elimination half-life of morphine in 12 patients with cirrhosis was almost twice that in 10 healthy subjects after administration of a modified-release oral morphine preparation (*MST-Continus*; Napp, UK) and peak serum concentrations were almost three times as high.<sup>2</sup> Patients with cirrhosis had a greater degree of sedation but none developed

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encephalopathy. It was recommended that the dose for modified-release preparations should be reduced and that it be given less often when patients have cirrhosis.

In a later study<sup>3</sup> 15 patients with liver cancer were given the same oral morphine preparation and compared with 10 healthy subjects from the previous study; the area under the serum concentration-time curve of morphine was increased three- to fourfold in those with cancer. The elimination half-life of morphine was also prolonged in patients with primary cancer when compared with healthy subjects and those with secondary metastatic disease. Adverse effects were more frequent in the primary cancer group and included 2 cases of respiratory depression; the authors commented that altered blood-brain transportation may have been partly responsible for such effects.

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### **Phaeochromocytoma** (Latest modification: 21-Mar-2004)

Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma. For further details, see .

### **Porphyria** (Latest modification: 14-Nov-2011)

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies morphine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.<sup>1</sup>

1. The Drug Database for Acute Porphyria. Available at: [online](#) (accessed 22/10/11)

### **Renal impairment** (Latest modification: 03-Jul-2008)

Severe and prolonged respiratory depression has occurred in patients with renal impairment given morphine. Toxicity in 3 such patients was attributed to the accumulation of the active metabolite morphine-6-glucuronide.<sup>1</sup> Plasma concentrations of this metabolite were found<sup>2</sup> to be ten times higher than normal in a 7-year-old girl with haemolytic uraemic syndrome given morphine intravenously although the half-life of morphine was also prolonged. Plasma concentrations of morphine-6-glucuronide were also reported<sup>3</sup> to be persistently increased 19 days after stopping morphine by intravenous infusion in a 17-year-old girl with normal renal function. The authors of the report suggested that alterations in bowel flora after antibacterial therapy or inhibition of morphine-3-glucuronide glucuronidation by lorazepam might be responsible. It has also been reported<sup>4</sup> that accumulation of morphine can occur in renal failure, although to a lesser extent than accumulation of metabolites (see also under Pharmacokinetics, .

1. Osborne RJ, et al. [Morphine intoxication in renal failure: the role of morphine-6-glucuronide](#). *BMJ* 1986; **292**: 1548–9. [PubMed](#)
2. Hasselström J, et al. [Long lasting respiratory depression induced by morphine-6-glucuronide?](#) *Br J Clin Pharmacol* 1989; **27**: 515–18. [PubMed](#)

3. 3. Calleja MA, et al. [Persistently increased morphine-6-glucuronide concentrations](#). *Br J Anaesth* 1990; **64**: 649. [PubMed](#)
4. 4. Osborne R, et al. [The pharmacokinetics of morphine and morphine glucuronides in kidney failure](#). *Clin Pharmacol Ther* 1993; **54**: 158–67. [PubMed](#)

### Pharmacokinetics (Latest modification: 17-Jun-2008)

Morphine salts are well absorbed from the gastrointestinal tract but have poor oral bioavailability since they undergo extensive first-pass metabolism in the liver and gut. After subcutaneous or intramuscular injection morphine is readily absorbed into the blood. The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide. The latter is considered to contribute to the analgesic effect of morphine, especially with repeated oral doses. Morphine-3-glucuronide on the other hand can antagonise the analgesic action and might be responsible for the paradoxical pain seen in some patients given morphine. Other active metabolites include normorphine, codeine, and morphine ethereal sulfate. Enterohepatic circulation probably occurs. Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the CSF as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35% is protein bound. Mean plasma elimination half-lives of about 2 hours for morphine and 2.4 to 6.7 hours for morphine-3-glucuronide have been reported.

Up to 10% of a dose of morphine may eventually be excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90% of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

Much has been published on the metabolism and disposition of morphine and its relevance to the clinical use of morphine, in particular the analgesic effect of repeated oral doses and the relative potency of oral to parenteral doses. There has been uncertainty as to the contributions in man of first-pass metabolism in the liver and gut,<sup>1-4</sup> the possible role of renal metabolism,<sup>2,4-6</sup> the analgesic activity and clinical importance of the metabolite morphine-6-glucuronide,<sup>2,7-21</sup> and enterohepatic circulation.<sup>2,9</sup> There has also been interest in the effects of the metabolite morphine-3-glucuronide.<sup>19,22-24</sup>

1. 1. Hanks GW, Aherne GW. [Morphine metabolism: does the renal hypothesis hold water?](#) *Lancet* 1985; **i**: 221–2. [PubMed](#)
2. 2. Hanks GW, et al. [Explanation for potency of repeated oral doses of morphine?](#) *Lancet* 1987; **ii**: 723–5. [PubMed](#)
3. 3. Moore RA, et al. [Opiate metabolism and excretion](#). *Baillieres Clin Anaesthesiol* 1987; **1**: 829–58.
4. 4. Bodenham A, et al. [Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation](#). *Br J Anaesth* 1989; **63**: 380–4. [PubMed](#)
5. 5. McQuay H, Moore A. [Metabolism of narcotics](#). *BMJ* 1984; **288**: 237. [PubMed](#)
6. 6. Moore A, et al. [Morphine kinetics during and after renal transplantation](#). *Clin Pharmacol Ther* 1984; **35**: 641–5. [PubMed](#)
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## Administration (Latest modification: 20-Aug-2010)

There have been many studies on the pharmacokinetics of morphine given by various routes and methods. These include the buccal route (see ) , modified-release oral preparations,<sup>1,2</sup> the rectal route,<sup>3,4</sup> the topical route,<sup>5</sup> the pulmonary route,<sup>6,7</sup> continuous subcutaneous compared with intravenous infusion,<sup>8</sup> and the intraspinal route.<sup>9-13</sup>

Slow dural transfer of morphine and its prolonged presence in the CSF appear to correlate with its slow onset and long duration of action by epidural and intrathecal injection.<sup>14</sup> Modified release epidural preparations have further extended the duration of morphine.<sup>15</sup> More lipid-soluble opioids, such as diamorphine and pethidine, enter and leave the CSF more rapidly than morphine.

The pharmacokinetics of morphine given by 5 different routes—intravenous bolus injection and oral, sublingual, buccal, and modified-release buccal tablets—were studied<sup>16</sup> with particular reference to morphine-6-glucuronide, the active metabolite. This metabolite occurred in large quantities after intravenous doses and plasma concentrations rapidly exceeded those of morphine. After oral doses morphine-6-glucuronide and morphine-3-

glucuronide were present in quantities similar to those seen after intravenous morphine; morphine concentrations in plasma were very low and the mean morphine-6-glucuronide to morphine area under the concentration-time curve ratio was 9.7 to 1. There was delayed absorption with attenuation and delay of peak morphine and metabolite plasma concentrations after sublingual or buccal dosage.

Compared with oral doses, concentrations of morphine were higher and those of its glucuronides lower when morphine was given rectally,<sup>17</sup> suggesting avoidance of first-pass metabolism.

Morphine was not absorbed systemically when applied topically to ulcers although some absorption may occur when a large surface area is involved.<sup>5</sup>

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12. Nordberg G, et al. [Extradural morphine: influence of adrenaline admixture.](#) *Br J Anaesth* 1986; **58**: 598–604. [PubMed](#)
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## Buccal route

Conflicting results from studies on buccal morphine may reflect differences in formulation<sup>1</sup> and hence absorption. Some<sup>2</sup> reported equivalent analgesia with buccal and intramuscular morphine although others<sup>3</sup> found marked interindividual variability with mean peak serum concentrations of morphine some eight times lower after a buccal tablet than after an intramuscular injection and occurring a mean of 4 hours later. Morphine sulfate in aqueous solution has been reported to be moderately well absorbed from the buccal mucosa.<sup>4</sup> Absolute bioavailability for morphine was estimated to be 23.8% after an oral solution, 22.4% after a modified-release oral tablet (*MST Continus; Napp, UK*), and 20.2% after a modified-release buccal tablet, with peak plasma-morphine concentrations at 45 minutes, 2.5 hours, and 6 hours, respectively; mean ratios of area under the plasma concentration-time curve for morphine-6-glucuronide to morphine in plasma were 11:1 after buccal and oral morphine compared with 2:1 for intravenous morphine.<sup>5</sup> There was considerable inter-subject variation in plasma concentrations of the morphine metabolites, morphine-3-glucuronide and morphine-6-glucuronide after buccal doses of morphine as a modified-release formulation,<sup>6</sup> and lack of pain relief was subsequently reported with this buccal formulation.<sup>7</sup> Poor absorption of morphine from modified-release buccal tablets when compared with intramuscular injection was also reported;<sup>8</sup> bitterness of the tablets, leading to their premature removal, and poor dissolution may have contributed.

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8. Simpson KH, et al. [An investigation of premedication with morphine given by the buccal or intramuscular route.](#) *Br J Clin Pharmacol* 1989; **27**: 377–80. [PubMed](#)

## Children (Latest modification: 26-Apr-2010)

The pharmacokinetics of morphine in *children* are generally considered similar to those in adults,<sup>1-3</sup> in both an elimination half-life of about 2 hours has been reported after intravenous administration of morphine. In *neonates*, however, clearance is generally reduced<sup>4-7</sup> and pharmacokinetics are more variable.<sup>8-10</sup> Studies<sup>7,11</sup> have found significantly higher plasma concentrations of morphine and a significantly lower morphine-6-glucuronide to morphine ratio in neonates when compared with older infants and children; however, the morphine-6-glucuronide to morphine-3-glucuronide ratio remains constant irrespective of age.<sup>7</sup> Elimination half-lives of 6.7 and 10 hours have been reported in term

and preterm infants, respectively after a single intravenous dose of morphine, with nearly 80% of the dose remaining unbound.<sup>8</sup> The reduced clearance, which is dependent on gestational age and birth weight,<sup>12,13</sup> and higher morphine concentrations are probably due to reduced metabolism in neonates as well as immature renal function: the capacity to conjugate morphine by glucuronidation is reduced in preterm infants,<sup>6,9,10</sup> and some premature neonates may lack the capacity entirely.<sup>9</sup>

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13. 13. Saarenmaa E, et al. [Morphine clearance and effects in newborn infants in relation to gestational age](#). *Clin Pharmacol Ther* 2000; **68**: 160–6. [PubMed](#)

### **The elderly** (Latest modification: 17-Jun-2008)

The pharmacokinetics of morphine were compared<sup>1</sup> in 7 healthy elderly (60 to 69 years) and 13 healthy young (24 to 28 years) subjects, after a single intravenous injection of morphine sulfate 10 mg per 70 kg. Although the terminal rate of drug disappearance from plasma was faster in the elderly group, apparent volume of distribution at steady state was about half that of the young group and plasma clearance was reduced.

1. 1. Owen JA, et al. [Age-related morphine kinetics](#). *Clin Pharmacol Ther* 1983; **34**: 364–8. [PubMed](#)

### **Hepatic impairment** (Latest modification: 23-Jun-2008)

The liver is a major site of morphine metabolism and therefore hepatic impairment could be expected to affect elimination (see under Precautions, ). There is some evidence that in cirrhosis glucuronidation might be relatively spared compared with other metabolic processes and that some extrahepatic metabolism may occur. Several studies have served to illustrate these points:

Hepatic extraction of morphine was impaired in cirrhotic patients, but less than expected<sup>1</sup>

Morphine metabolism was minimal during the anhepatic phase of liver transplantation, but increased markedly when the new liver was reperfused<sup>2</sup>

Morphine metabolism was virtually complete after liver transplantation with only 4.5% unchanged morphine being excreted in the urine 24 hours after administration<sup>3</sup>

Morphine elimination was reduced when hepatic blood flow was impaired<sup>4</sup>

1. 1. Crotty B, et al. [Hepatic extraction of morphine is impaired in cirrhosis.](#) *Eur J Clin Pharmacol* 1989; **36**: 501–6. [PubMed](#)
2. 2. Bodenham A, et al. [Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation.](#) *Br J Anaesth* 1989; **63**: 380–4. [PubMed](#)
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4. 4. Manara AR, et al. [Morphine elimination and liver blood flow: a study in patients undergoing distal splenorenal shunt.](#) *Br J Hosp Med* 1989; **42**: 148 (abstract).

## Renal impairment (Latest modification: 10-Sep-2008)

Only a small amount of morphine is excreted unchanged in the urine. There are conflicting reports of morphine accumulation in patients with renal impairment; some for,<sup>1,2</sup> others against.<sup>3-5</sup> It does seem clear though that morphine metabolites accumulate in such patients<sup>5-9</sup> including those on peritoneal dialysis,<sup>10</sup> the half-life of the active metabolite morphine-6-glucuronide was reported to be prolonged and its clearance reduced when morphine-6-glucuronide was given to patients with renal impairment.<sup>11</sup> Opioid intoxication<sup>12</sup> and a prolonged opioid effect<sup>13</sup> in patients with renal failure has been associated with morphine-6-glucuronide (see also under Precautions, ).

1. 1. Ball M, et al. [Renal failure and the use of morphine in intensive care.](#) *Lancet* 1985; **i**: 784–6. [PubMed](#)
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8. 8. Sear JW, et al. [Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites.](#) *Br J Anaesth* 1989; **62**: 28–32. [PubMed](#)
9. 9. Peterson GM, et al. [Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration.](#) *Eur J Clin Pharmacol* 1990; **38**: 121–4. [PubMed](#)
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- [continuous ambulatory peritoneal dialysis](#). *Nephrol Dial Transplant* 1999; **14**: 903–9. [PubMed](#)
- 11.11. Hanna MH, *et al.* [Morphine-6-glucuronide disposition in renal impairment](#). *Br J Anaesth* 1993; **70**: 511–14. [PubMed](#)
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## Summary of Product Characteristics

### 1. Name of the medicinal product

Hedex or **Paracetamol** Tablets

### 2. Qualitative and quantitative composition

Each tablet contains Paracetamol Ph Eur 500.0 mg

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Hedex is a mild analgesic and antipyretic. The tablets are recommended for headaches, including migraine and tension headaches, backache, rheumatic and muscle pain, period pains, nerve pains, toothache and for relieving the fever, aches and pains of colds and flu.

#### 4.2 Posology and method of administration

Adults (including the elderly)  
2 tablets up to 4 times a day.

Children

6-12 years: ½ - 1 tablet three or four times daily as required. Not suitable for children under 6. Children should not be given Hedex tablets for more than 3 days without consulting a doctor.

These doses should not be repeated more frequently than every 4 hours and not more than 4 doses should be given in any 24 hour period.

Hedex is for oral administration.

#### 4.3 Contraindications

Hypersensitivity to paracetamol or any of the other constituents.

#### 4.4 Special warnings and precautions for use

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the stated dose.

Patients should be advised to consult their doctor if their headaches become persistent.

Patients should be advised not to take other paracetamol-containing products concurrently.

If symptoms persist consult your doctor.

Keep out of the reach and sight of children.

Pack Label:

Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Do not take with any other paracetamol-containing products.

Patient Information Leaflet:

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

#### 4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

#### 4.6 Pregnancy and lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

#### 4.7 Effects on ability to drive and use machines

None.

#### 4.8 Undesirable effects

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

##### Post marketing data

Body System	Undesirable effect
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome/toxic epidermal necrolysis
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction

\* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

#### 4.9 Overdose

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

##### Risk factors

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

### **Symptoms**

Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

### **Management**

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Paracetamol is a well established analgesic.

### **5.2 Pharmacokinetic properties**

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract.

Concentration in plasma reaches a peak in 30 - 60 minutes

Plasma half-life is 1 - 4 hours.

Paracetamol is relatively uniformly distributed throughout most body fluids.

Plasma protein binding is variable.

Excretion is almost exclusively renal, in the form of conjugated metabolites.

**Ph. Eur. 8** (Paracetamol). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

**USP 36** (Acetaminophen). A white odourless crystalline powder. Soluble 1 in 20 of boiling water, 1 in 10 of alcohol, and 1 in 15 of 1N sodium hydroxide. Store in airtight containers. Protect from light. Protect from moisture and heat.

### Uses and Administration (Latest modification: 13-May-2014)

Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain (↔📄) and for fever (↔📄). It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contra-indicated. Such patients include asthmatics, those with a history of peptic ulcer, and children.

The usual **oral** dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. Paracetamol may also be given as suppositories in a **rectal** dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Paracetamol is given by **intravenous** infusion over 15 minutes; dosage may be calculated according to body-weight as follows:

over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily

from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 3 g) daily

A maximum intravenous dose of 3 g daily should also not be exceeded in patients with chronic alcoholism, chronic malnutrition, or dehydration, regardless of their body-weight. The intravenous solution may be diluted to a minimum strength of 1 mg/mL in sodium chloride 0.9% or glucose 5%; the diluted solution should be used within 1 hour of preparation.

For doses in children, or in hepatic or renal impairment, see ↔📄, ↔📄, and ↔📄, respectively.

### References.

1. Prescott LF. *Paracetamol (acetaminophen): a critical bibliographic review*. London: Taylor & Francis, 1996.
2. Bannwarth B, Péhourcq F. [Bases pharmacologiques de l'emploi du paracétamol: aspects pharmacocinétiques et pharmacodynamiques](#). *Drugs* 2003; **63** (suppl 2): 5–13. [PubMed](#)
3. Prescott LF. [Nouvelles perspectives avec le paracétamol](#). *Drugs* 2003; **63** (suppl 2): 51–6. [PubMed](#)
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## Administration in hepatic impairment (Latest modification: 14-Jan-2014)

There is evidence to suggest that paracetamol can be safely used in patients with hepatic impairment (see under Precautions, ); however, reduced doses may be warranted to avoid accidental overdoses. The [BNF](#) recommends avoiding large doses in patients with hepatic impairment; others have suggested that doses of 2 to 3 g daily should not be exceeded in patients with cirrhosis requiring long-term use although a daily dose of 3 to 4 g may be safe for short-term or one-off use.<sup>1</sup> UK licensed product information recommends that the maximum dose of intravenous paracetamol should not exceed 3 g daily in patients with hepatic impairment or chronic alcoholism; it also states that those with severe impairment should not be given paracetamol by this route.

1. Chandok N, Watt KDS. [Pain management in the cirrhotic patient: the clinical challenge.](#) *Mayo Clin Proc* 2010; **85**: 451–8. [PubMed](#)

## Administration in renal impairment (Latest modification: 08-Jun-2011)

In renally impaired patients with a creatinine clearance of 30 mL/minute or less it is recommended that the interval between each intravenous paracetamol dose is increased to 6 hours.

## Headache (Latest modification: 13-Aug-2011)

Non-opioid analgesics such as paracetamol, aspirin, and other NSAIDs are often tried first for the symptomatic treatment of various types of headache including migraine (see ) and tension-type headache (see ). These drugs given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

### References.

1. Derry S, *et al.* Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Available in The Cochrane Database of Systematic Reviews; Issue 11. Chichester: John Wiley; 2010 (accessed 03/12/10). [PubMed](#)

## Pain (Latest modification: 04-Aug-2004)

Paracetamol is used in the management of mild to moderate pain (see Choice of Analgesic, ). It is of similar potency to aspirin, but with weak anti-inflammatory activity. Paracetamol may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (). Paracetamol is the preferred choice for pain in children () because of the association of aspirin with Reye's syndrome in this age group (see ). In the treatment of rheumatic disorders, a weak anti-inflammatory effect limits the role of paracetamol. However, it may be of benefit for simple pain control in rheumatoid arthritis () and ankylosing spondylitis (see under Spondyloarthropathies, ), although these patients usually require the additional anti-inflammatory effects provided by NSAIDs. Synovial inflammation is usually only a minor component of osteoarthritis (), and paracetamol is generally recommended as first choice of treatment before NSAIDs are tried. Paracetamol is useful for the relief of acute low back pain ().

Dependence and tolerance are not a problem with non-opioid analgesics such as paracetamol, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

### **Adverse Effects and Treatment** (Latest modification: 13-Aug-2011)

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Rashes and other hypersensitivity reactions occur occasionally.

Injection site reactions such as pain and a burning sensation are common after parenteral use; hypotension and tachycardia have been reported rarely. Application site reactions have also been noted after rectal use.

Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential and is discussed under Overdosage, ↔📄.

References.

1. 1. Graham GG, *et al.* [Tolerability of paracetamol.](#) *Drug Safety* 2005; **28**: 227–40. [PubMed](#)

### **Carcinogenicity** (Latest modification: 30-Jun-2011)

A prospective cohort study<sup>1</sup> involving over 64 000 men and women between 50 and 76 years of age found that use of paracetamol for more than 4 days a week for longer than 4 years was associated with a twofold increase in the risk of haematological malignancies. The authors considered that other prospective studies were required before any recommendations about paracetamol use could be made.

1. 1. Walter RB, *et al.* [Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective vitamins and lifestyle \(VITAL\) study.](#) *J Clin Oncol* 2011; **29**: 2424–31. [PubMed](#)

### **Effects on the cardiovascular system** (Latest modification: 16-Jun-2011)

Large cohort studies<sup>1,2</sup> have shown an association between the use of non-opioid analgesics, including paracetamol, and a significantly increased risk of hypertension in women; similar studies<sup>3,4</sup> in men have been equivocal but suggest a more moderate increase in risk. However, it has also been suggested<sup>5</sup> that the hypertension may have been caused by pain itself or more likely to be detected in patients taking more paracetamol due to a higher frequency of visits to their doctor.

1. 1. Dedier J, *et al.* [Nonnarcotic analgesic use and the risk of hypertension in US women.](#) *Hypertension* 2002; **40**: 604–8. [PubMed](#)
2. 2. Forman JP, *et al.* [Non-narcotic analgesic dose and risk of incident hypertension in US women.](#) *Hypertension* 2005; **46**: 500–507. [PubMed](#)
3. 3. Kurth T, *et al.* [Analgesic use and risk of subsequent hypertension in apparently healthy men.](#) *Arch Intern Med* 2005; **165**: 1903–9. [PubMed](#)
4. 4. Forman JP, *et al.* [Frequency of analgesic use and risk of hypertension among men.](#) *Arch Intern Med* 2007; **167**: 394–9. [PubMed](#)

5. Montgomery B. [Does paracetamol cause hypertension?](#) *BMJ* 2008; **336**: 1190–1. [PubMed](#)

### Effects on the ears (Latest modification: 30-Jun-2011)

A questionnaire study in nearly 27 000 male health professionals originally aged 40 years and over has examined the association between hearing loss and the regular use of aspirin, NSAIDs, and paracetamol.<sup>1</sup> During 369 079 person-years of follow-up, 3488 cases of hearing loss were reported; regular analgesic use (defined as 2 or more times a week) was found to be independently associated with an increased risk of hearing loss for all 3 types of analgesics. The hazard ratio of hearing loss for regular users of paracetamol was 1.22 when compared with those who used analgesics less frequently; the risk also increased with longer duration of use. Concomitant use of more than one type of analgesic also had an additive risk effect.

For reference to reports of hearing loss associated with the abuse or overuse of preparations containing paracetamol, see under Dextropropoxyphene, , and Hydrocodone, .

1. Curhan SG, *et al.* [Analgesic use and the risk of hearing loss in men.](#) *Am J Med* 2010; **123**: 231–7. [PubMed](#)

### Effects on the kidneys (Latest modification: 21-Mar-2004)

For reference to evidence that abuse or prolonged excessive use of analgesics, including paracetamol, can produce nephropathy, see under NSAIDs, .

See also under Overdosage, .

### Effects on metabolism (Latest modification: 15-Nov-2012)

Use of paracetamol, alone or with other drugs (see under Flucloxacillin, ) , has been associated with accumulation of pyroglutamic acid, resulting in pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.<sup>1-4</sup>

1. Humphreys BD, *et al.* [Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria \(pyroglutamic aciduria\) acquired in hospital.](#) *Am J Kidney Dis* 2005; **46**: 143–6. [PubMed](#)
2. Fenves AZ, *et al.* [Increased anion gap metabolic acidosis as a result of 5-oxoproline \(pyroglutamic acid\): a role for acetaminophen.](#) *Clin J Am Soc Nephrol* 2006; **1**: 441–7. [PubMed](#)
3. Alados Arboledas FJ, *et al.* [Acidosis piroglutámica asociada a paracetamol.](#) *An Pediatr (Barc)* 2007; **67**: 582–4. [PubMed](#)
4. Verma R, *et al.* [5-Oxoprolinuria as a cause of high anion gap metabolic acidosis.](#) *Br J Clin Pharmacol* 2012; **73**: 489–91. [PubMed](#)

### Effects on the respiratory tract (Latest modification: 24-Nov-2011)

The results of a case-control study<sup>1</sup> have suggested that the frequent (daily or weekly) use of paracetamol may be associated with asthma. However, the UK CSM has commented that the results of this study do not alter any advice regarding the use of paracetamol and that it remains a safe and effective pain killer for many patients including asthmatics.

Subsequently, others have found an increase in the prevalence of asthma<sup>2,3</sup> and COPD<sup>2</sup> with frequent (daily or weekly) use of paracetamol. A link between paracetamol use in pregnancy and asthma in children has also been suggested (see Pregnancy under Precautions, ↗📄). However, one review<sup>4</sup> stated that there have been very few actual reports of paracetamol causing asthma; furthermore, bronchospasm is not a recognised feature of paracetamol overdose. This review concluded that a strong link between paracetamol use and asthma was unlikely.

More recently, analysis of questionnaire data<sup>5</sup> for 205 487 children aged 6 to 7 years from 31 countries suggested that the use of paracetamol in the first year of life and later childhood was associated with an increased risk of asthma and also symptoms of rhinoconjunctivitis and eczema. In another questionnaire study<sup>6</sup> by the same group involving 322 959 adolescents aged 13 to 14 years from 50 countries, the recent use of paracetamol was also found to increase the risk of asthma, rhinoconjunctivitis, and eczema. However, after considering the first study, the UK CHM<sup>7</sup> expressed concerns over data interpretation and concluded that it did not provide strong evidence that paracetamol use in infancy can cause asthma; the CHM reiterated that paracetamol remains a safe and appropriate analgesic for children. Furthermore, a small cohort study<sup>8</sup> has also found that, although the use of paracetamol in the first 2 years of life increased the crude risk of asthma in children aged 6 to 7 years, this increase was not noted after adjustment for early respiratory-tract infections or when paracetamol use was limited to non-respiratory-tract infections.

1. Shaheen SO, et al. [Frequent paracetamol use and asthma in adults](#). *Thorax* 2000; **55**: 266–70. [PubMed](#)
2. McKeever TM, et al. [The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function](#). *Am J Respir Crit Care Med* 2005; **171**: 966–71. [PubMed](#)
3. Eneli I, et al. [Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence](#). *Chest* 2005; **127**: 604–12. [PubMed](#)
4. Nuttall SL, et al. [Does paracetamol cause asthma?](#) *J Clin Pharm Ther* 2003; **28**: 251–7. [PubMed](#)
5. Beasley R, et al. [ISAAC Phase Three Study Group. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme](#). *Lancet* 2008; **372**: 1039–48. [PubMed](#)
6. Beasley RW, et al. [ISAAC Phase Three Study Group. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three](#). *Am J Respir Crit Care Med* 2011; **183**: 171–8. [PubMed](#)
7. MHRA/CHM. [Paracetamol use in infancy: no strong evidence for asthma link](#). *Drug Safety Update* 2008; **2** (4): 9. Available at: [online](#) (accessed 13/10/09)
8. Lowe AJ, et al. [Paracetamol use in early life and asthma: prospective birth cohort study. Abridged version](#). *BMJ* 2010; **341**: 713. [PubMed](#) Full version: [online](#) (accessed 06/05/11)

## **Hypersensitivity** (Latest modification: 10-Sep-2008)

Reactions characterised by urticaria, dyspnoea, and hypotension have occurred after use of paracetamol in adults<sup>1-4</sup> and children.<sup>5,6</sup> Angioedema has also been reported.<sup>7</sup> Fixed drug eruptions, confirmed by rechallenge, have been described,<sup>8-11</sup> and toxic epidermal necrolysis has occurred.<sup>12</sup>

1. 1. Stricker BHC, *et al.* [Acute hypersensitivity reactions to paracetamol.](#) *BMJ* 1985; **291**: 938–9. [PubMed](#)
2. 2. Van Diem L, Grilliat JP. [Anaphylactic shock induced by paracetamol.](#) *Eur J Clin Pharmacol* 1990; **38**: 389–90. [PubMed](#)
3. 3. Kumar RK, Byard I. [Paracetamol as a cause of anaphylaxis.](#) *Hosp Med* 1999; **60**: 66–7. [PubMed](#)
4. 4. Bachmeyer C, *et al.* [Acetaminophen \(paracetamol\)-induced anaphylactic shock.](#) *South Med J* 2002; **95**: 759–60. [PubMed](#)
5. 5. Ellis M, *et al.* [Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry.](#) *J Pediatr* 1989; **114**: 654–6. [PubMed](#)
6. 6. Bousetta K, *et al.* [Hypersensitivity reactions to paracetamol in children: a study of 25 cases.](#) *Allergy* 2005; **60**: 1174–7. [PubMed](#)
7. 7. Idoko JA, *et al.* [Angioneurotic oedema following ingestion of paracetamol.](#) *Trans R Soc Trop Med Hyg* 1986; **80**: 175. [PubMed](#)
8. 8. Thomas RHM, Munro DD. [Fixed drug eruption due to paracetamol.](#) *Br J Dermatol* 1986; **115**: 357–9. [PubMed](#)
9. 9. Cohen HA, *et al.* [Fixed drug eruption caused by acetaminophen.](#) *Ann Pharmacother* 1992; **26**: 1596–7. [PubMed](#)
10. 10. Harris A, Burge SM. [Vasculitis in a fixed drug eruption due to paracetamol.](#) *Br J Dermatol* 1995; **133**: 790–1. [PubMed](#)
11. 11. Hern S, *et al.* [Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern.](#) *Br J Dermatol* 1998; **139**: 1129–31. [PubMed](#)
12. 12. Halevi A, *et al.* [Toxic epidermal necrolysis associated with acetaminophen ingestion.](#) *Ann Pharmacother* 2000; **34**: 32–4. [PubMed](#)

## Overdosage (Latest modification: 14-May-2014)

Acute **oral** overdose with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Toxic doses of paracetamol may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Paracetamol-induced hepatotoxicity is a major cause of acute liver failure in western countries. Hepatotoxicity may occur after ingestion of more than 150 mg/kg, or rarely, as little as 75 mg/kg, of paracetamol within a 24-hour period. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.<sup>1,2</sup>

Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at high risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia, AIDS, or cystic fibrosis. Those who have not eaten for a few days or those with a low body-weight<sup>3</sup> are also predisposed to hepatotoxicity. These factors have previously been used for risk stratification in paracetamol overdose; however, not all have been well characterised or applied consistently. Hence, the UK CHM has advised that individual risk factors should no longer be used for assessing the risk of toxicity.

Early **signs** of overdose (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured

regularly. However, as both paracetamol<sup>4</sup> and acetylcysteine<sup>5</sup> can independently affect prothrombin time in the absence of hepatic injury, the use of prothrombin time as a marker for hepatotoxicity has been questioned and it has been recommended that treatment decisions are based on the entire liver biochemistry.<sup>6</sup>

Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdose include myocardial abnormalities and pancreatitis.

The **mechanism** of toxicity in overdose with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)<sup>2</sup> in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamol overdose, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamol overdose. Acetylcysteine may also be involved in the repair of damaged tissue.

**Treatment of oral paracetamol overdose.** The management of paracetamol overdose as practised in the UK and USA has been the subject of many reviews.<sup>6-15</sup> Guidance is also available in the UK from the *National Poisons Information Service (NPIS)*. Separate consensus guidelines have been issued by clinical toxicologists in Australia and New Zealand.<sup>16</sup>

*Prompt treatment is essential, even when there are no obvious symptoms, and patients should be admitted to hospital for full supportive measures to be instituted.*

Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given orally the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.

There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.

The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used, see Figure 1 and Figure 2 ([XREF](#)). Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is on or above the reference (treatment) line.

Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatotoxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.<sup>17-19</sup> Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdose with modified-release preparations have been made.<sup>20-22</sup>

Plasma-paracetamol concentrations and the Rumack-Matthew nomogram are also of little value in patients who have taken repeated supratherapeutic doses or multiple overdoses of paracetamol over a short period of time: such patients should be considered at serious risk and given antidote treatment.

If there is any doubt about timing or the need to treat, or where the overdose is staggered, then a patient **should** be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma-paracetamol concentrations.<sup>23</sup>

Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is on or above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.

*Choice of antidote.* Acetylcysteine (↔📄) is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.<sup>6,24</sup> Intravenous use has been associated with anaphylactic reactions but is the preferred route in some countries including Australia, New Zealand, and the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is also licensed, and is clearly effective. The use of methionine (↔📄) orally has the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and has been used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting. However, it has been largely superseded by acetylcysteine.

*Acetylcysteine* is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,<sup>25</sup> and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.<sup>26,27</sup> Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.<sup>28</sup>

An initial dose of 150 mg/kg (maximum of 16.5 g) of acetylcysteine in 200 mL of glucose 5% is given intravenously over 60 minutes. This is followed by an intravenous infusion of 50 mg/kg (maximum of 5.5 g) in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg (maximum of 11 g) in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children or those with a body-weight of less than 40 kg. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate.

In the USA, acetylcysteine is also licensed for oral use as an alternative to parenteral treatment. It is given as an initial dose of 140 mg/kg as a 5% solution followed by 70 mg/kg every 4 hours for an additional 17 doses. Similar doses have been recommended by the *NPIS* in the UK when venous access is not practicable. Some<sup>29</sup> have suggested increasing the loading dose of oral acetylcysteine when it is given after activated charcoal, whereas others<sup>30</sup> have found that the efficacy of

acetylcysteine is not reduced by use of activated charcoal beforehand and consider a larger acetylcysteine dose unnecessary.

*Pretreatment.* The *NPIS* recommends pretreating patients with antihistamines (histamine H<sub>1</sub>- and H<sub>2</sub>-antagonists) if they have previously had an anaphylactoid reaction to acetylcysteine: intravenous chlorphenamine 10 mg and intravenous ranitidine 50 mg diluted to 20 mL may be given over at least 2 minutes. Pretreatment with nebulised salbutamol can be used in those with a history of acetylcysteine-associated bronchospasm. A slower initial infusion rate may be warranted in patients who have previously had a severe reaction to acetylcysteine.

*Methionine*, like acetylcysteine, is most effective when given as early as possible after paracetamol overdose. However, it is not as effective if treatment is delayed<sup>31-33</sup> and hepatic damage is more frequent and severe if treatment with methionine is started more than 10 hours after ingestion; it may also precipitate hepatic encephalopathy.

The usual oral dose of methionine in adults and children aged 6 years or older is 2.5 g every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol and provided the patient is not vomiting. Children aged under 6 years should be given 1 g every 4 hours for 4 doses.

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. Preparations containing both methionine and paracetamol (co-methiamol) have been formulated for use in situations where overdose may occur.

*Histamine H<sub>2</sub>-antagonists.* It has been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Although there have been several anecdotal reports claiming benefit for cimetidine in patients with paracetamol poisoning, there is no current evidence to support these claims.<sup>6,10,12,34</sup>

*Liver transplantation* may be considered as a last recourse in some patients.

After maternal **overdose during pregnancy** fetal metabolism of paracetamol that crosses the placenta can produce sufficient hepatotoxic metabolites to cause fetal hepatotoxicity. Limited data from case reports and a case series suggest that early treatment with oral or intravenous acetylcysteine can be safe and effective in such cases;<sup>35</sup> the *UK National Teratology Information Service* recommends the use of acetylcysteine if clinically indicated. Pre-pregnancy body-weight should be used to calculate the toxic paracetamol dose and actual pregnant body-weight to calculate the antidote dose.

Dosage errors with **intravenous** paracetamol have been reported, particularly in young children; rarely, such errors have resulted in substantial overdoses and liver damage.<sup>36,37</sup> The standard nomogram may not be appropriate in determining treatment from plasma-paracetamol concentrations after overdose by intravenous infusion, as it is based on data from acute paracetamol ingestion rather than intravenous administration. Plasma-paracetamol concentrations more than 4 hours after intravenous injection are usually lower than those predicted for the same oral dose at the same time-point after ingestion. Furthermore, patients receiving intravenous paracetamol are likely to have an increased risk of hepatotoxicity due to poor nutrition from acute fasting. The *NPIS* recommends antidote treatment with intravenous acetylcysteine (see above for doses) when 60 mg/kg or more of paracetamol in total has been given intravenously to adults and children within

24 hours. If there is uncertainty about the actual dose of paracetamol given, the standard nomogram may be used to determine the risk of liver damage. Antidote treatment (see above) is required if plasma-paracetamol concentrations, measured at least 4 hours after administration, are up to 50% below the reference line (for example—treat if the concentration is above 50 mg/L at 4 hours) (see Figure 1 and Figure 2, [XREF](#)).

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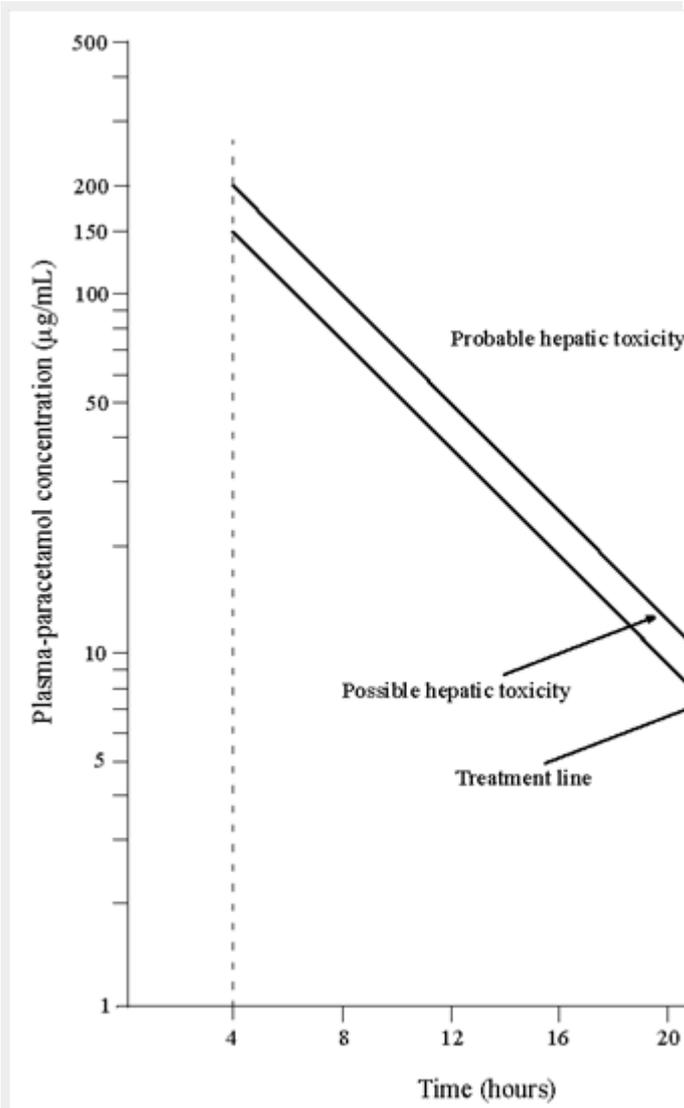
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**Figures 1 and 2. A semi-logarithmic plot and a linear plot of plasma-paracetamol concentration against hours after ingestion.**

**Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.**

**Figure 2. A linear plot of plasma-paracetamol concentration against hours after ingestion.**

**Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.**

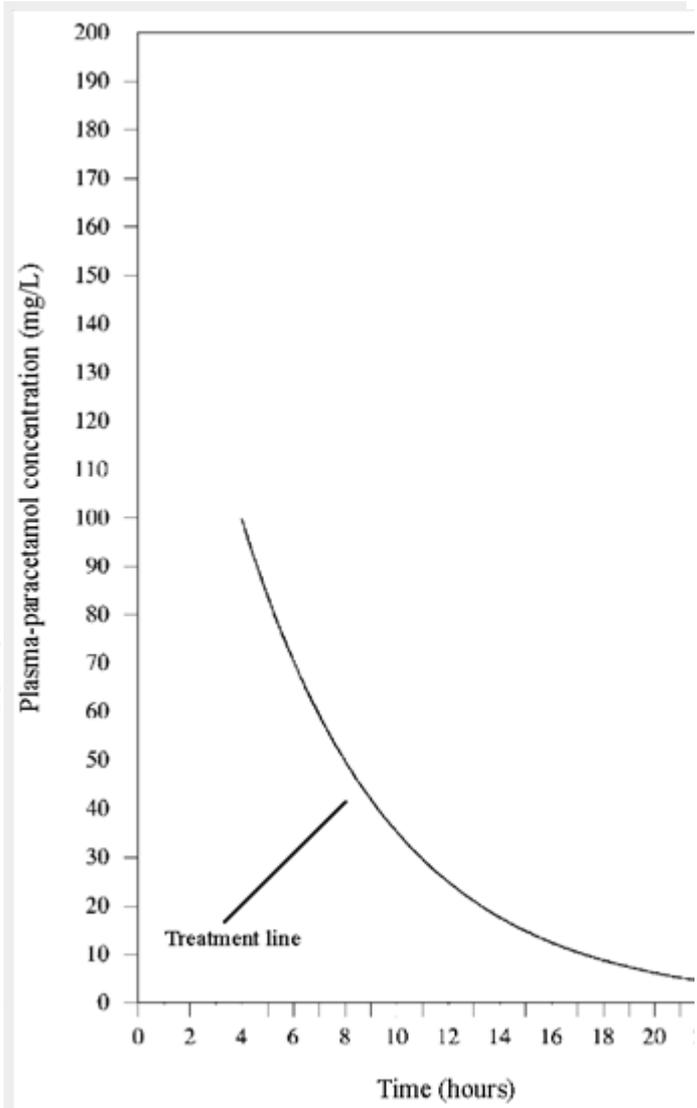


Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55**: 871–6.

Notes for the use of this chart:

1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. The solid line 25% below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose. Patients whose plasma-paracetamol concentrations are on or above this line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

**Figure 2. A linear plot of plasma-paracetamol concentration against hours after ingestion.**



Courtesy of MHRA.

Notes for the use of this chart:

1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. Patients whose plasma-paracetamol concentrations are above the normal treatment line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

## **Pancreatitis** (Latest modification: 07-Dec-2006)

Drug-induced pancreatitis associated with paracetamol was reported<sup>1</sup> to be a rare reaction only occurring in patients taking more than recommended doses. In a retrospective study of data from 814 patients who had taken paracetamol overdoses, hyperamylasaemia was detected in 246, and was more common and more severe in patients transferred to a specialist unit because of more severe poisoning.<sup>2</sup> However, acute pancreatitis was diagnosed only in 33 cases.

1. Underwood TW, Frye CB. [Drug-induced pancreatitis](#). *Clin Pharm* 1993; **12**: 440–8. [PubMed](#)
2. Schmidt LE, Dalhoff K. [Hyperamylasaemia and acute pancreatitis in paracetamol poisoning](#). *Aliment Pharmacol Ther* 2004; **20**: 173–9. [PubMed](#)

## **Precautions** (Latest modification: 14-Jan-2014)

Paracetamol should be given with care to patients with impaired kidney or liver function; the [BNF](#) recommends that large doses should be avoided in patients with hepatic impairment. It should also be given with care to patients with alcohol dependence, chronic malnutrition, or dehydration.

## **Hepatic impairment** (Latest modification: 02-Jan-2011)

Reviews<sup>1,2</sup> have concluded that there is evidence that paracetamol could be and had been used safely in patients with liver disease. Studies had also shown that although the half-life of paracetamol was prolonged in such patients, glutathione concentrations in those taking recommended doses were not depleted to the critical levels that would enable accumulation of paracetamol's hepatotoxic metabolite.

1. Benson GD, *et al.* [The therapeutic use of acetaminophen in patients with liver disease](#). *Am J Ther* 2005; **12**: 133–41. [PubMed](#)
2. Chandok N, Watt KDS. [Pain management in the cirrhotic patient: the clinical challenge](#). *Mayo Clin Proc* 2010; **85**: 451–8. [PubMed](#)

## **Porphyria** (Latest modification: 07-Nov-2011)

The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paracetamol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.<sup>1</sup>

1. The Drug Database for Acute Porphyria. Available at: [online](#) (accessed 11/10/11)

## **Renal impairment** (Latest modification: 07-Dec-2006)

Caution is recommended when giving paracetamol to patients with renal impairment. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis.<sup>1-3</sup> It has been suggested that paracetamol itself may be regenerated from these metabolites.<sup>1,2</sup> There are conflicting data on whether the conjugates of paracetamol accumulate in patients with renal impairment receiving multiple doses.<sup>2,3</sup>

1. Prescott LF, *et al.* [Paracetamol disposition and metabolite kinetics in patients with chronic renal failure](#). *Eur J Clin Pharmacol* 1989; **36**: 291–7. [PubMed](#)

2. 2. Martin U, et al. [The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure.](#) *Eur J Clin Pharmacol* 1991; **41**: 43–6. [PubMed](#)
3. 3. Martin U, et al. [The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis.](#) *Eur J Clin Pharmacol* 1993; **45**: 141–5. [PubMed](#)

### Pharmacokinetics (Latest modification: 25-Jan-2010)

Paracetamol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

### References.

1. 1. van der Marel CD, et al. [Paracetamol and metabolite pharmacokinetics in infants.](#) *Eur J Clin Pharmacol* 2003; **59**: 243–51. [PubMed](#)
2. 2. Gregoire N, et al. [Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose.](#) *Clin Pharmacol Ther* 2007; **81**: 401–5. [PubMed](#)
3. 3. Kumpulainen E, et al. [Paracetamol \(acetaminophen\) penetrates readily into the cerebrospinal fluid of children after intravenous administration.](#) *Pediatrics* 2007; **119**: 766–71. [PubMed](#)
4. 4. Palmer GM, et al. [I.V. acetaminophen pharmacokinetics in neonates after multiple doses.](#) *Br J Anaesth* 2008; **101**: 523–30. [PubMed](#)
5. 5. Liukas A, et al. [Pharmacokinetics of intravenous paracetamol in elderly patients.](#) *Clin Pharmacokinet* 2011; **50**: 121–9. [PubMed](#)
6. 6. Allegaert K, et al. [The pharmacokinetics of intravenous paracetamol in neonates: size matters most.](#) *Arch Dis Child* 2011; **96**: 575–80. [PubMed](#)
7. 7. Zuppa AF, et al. [Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever.](#) *J Pediatr Pharmacol Ther* 2011; **16**: 246–61. [PubMed](#)
8. 8. Kulo A, et al. [Pharmacokinetics of paracetamol and its metabolites in women at delivery and postpartum.](#) *Br J Clin Pharmacol* 2012. [PubMed](#) Available at: doi:10.1111/j.1365-2125.2012.04402.x

### Absorption (Latest modification: 07-Dec-2006)

The absorption of paracetamol was slow and incomplete in vegetarian subjects compared with non-vegetarian subjects.<sup>1</sup>

1. 1. Prescott LF, et al. [Impaired absorption of paracetamol in vegetarians.](#) *Br J Clin Pharmacol* 1993; **36**: 237–40. [PubMed](#)



## **Patient 1**

39 year old male with underlying ulcerative colitis. 12 month history of pruritus and increased lethargy. Recent investigations below:

### **Liver Function Tests**

	<b>Results (trend)</b>	<b>Normal range</b>
ALT	60 (↔)	< 35 U/L
Bilirubin	3.2 (↔)	≤ 1 mg/dL
Alk Phos	589 (↑ - marginally)	35-105 U/L
GGT	72 (↔)	≤ 40 U/L
Albumin	4 (↔)	3.5 - 5 g/dL
INR	1.4 (↔)	0.8 - 1.2
Creatinine	0.8 (↔)	0.5 - 1 mg/dL

### **Other investigations results**

Liver biopsy - Narrowing bile ducts with inflammation and early fibrosis, intrahepatic cholestasis

Endoscopic retrograde cholangiopancreatography (ERCP) - Diffuse biliary strictures

### **Signs and symptoms**

Fatigue  
Jaundice  
Pruritus

### **Diagnosis**

Primary sclerosing cholangitis

### **Medication history**

Ursodeoxycholic acid (improve bile flow)  
Colestyramine (bile acid sequestrant)  
Vitamins A and D (fat soluble vitamins)

- What type of liver dysfunction does the patient have?
- What is the extent of dysfunction?
- How might pharmacokinetics/dynamics may be affected?
- What side effects of drugs do you need to consider in this patient?

The patient needs analgesia and the doctor wants to give ibuprofen

- Could you use ibuprofen in this patient? If so, what dose?
- What precautions or additional advice would you give to the prescriber?
- What alternatives could you suggest? What would be your first choice?

## **Patient 2**

23 year old female with known auto-immune hepatitis diagnosed 2 years ago. Initial presentation was with hepatomegaly, abdominal pain and fatigue. Her ALT at diagnosis was 245 U/L which has fallen with immunosuppressants. Recent investigations show the picture below

### **Liver Function Tests**

	<b>Results (trend)</b>	<b>Normal range</b>
ALT	60 (↔)	< 35 U/L
Bilirubin	1 (↔)	≤ 1 mg/dL
Alk Phos	96 (↔)	35-105 U/L
GGT	37 (↔)	≤ 40 U/L
Albumin	3.4 (↔)	3.5 - 5 g/dL
INR	1.2 (↔)	0.8 - 1.2
Creatinine	0.5 (↔)	0.5 - 1 mg/dL
Platelets	75 (↔)	150-400 x 10 <sup>9</sup> /L

### **Other investigations results**

Ultrasound scan - Irregular, echogenic liver with nodular edge. Enlarged spleen and mildly dilated portal vein.

Oesophageal duodenoscopy - Single grade 1 varix, no bleeding

Liver biopsy - Fragmented biopsy showing micronodular cirrhosis

### **Signs and symptoms**

Spider naevi

Splenomegaly

Occasional fatigue

### **Diagnosis**

Auto-immune hepatitis

### **Medication history**

Prednisolone 5mg once a day

Azathioprine 150mg once a day

- What type of liver dysfunction does the patient have?
- What is the extent of dysfunction?
- How might pharmacokinetics/dynamics may be affected?
- What side effects of drugs do you need to consider in this patient?

The patient needs analgesia and the doctor wants to give ibuprofen

- Could you use ibuprofen in this patient? If so, what dose?
- What precautions or additional advice would you give to the prescriber?
- What alternatives could you suggest? What would be your first choice?

### **Patient 3**

58 year old female with a long history of excess alcohol consumption (approximately 60 units per week). Recent admissions have been for ascites, variceal bleeds and an episode of spontaneous bacterial peritonitis. Over the last 3 months she has had reduced appetite and weight loss.

#### **Liver Function Tests**

	<b>Results Last week</b>	<b>Today</b>	<b>Normal range</b>
ALT	42	41	< 35 U/L
Bilirubin	6.8	8.3	≤ 1 mg/dL
Alk Phos	119	125	35-105 U/L
GGT	111	102	≤ 40 U/L
Albumin	3.1	2.7	3.5 - 5 g/dL
INR	1.4	1.6	0.8 - 1.2
Creatinine	1.25	1.3	0.5 - 1 mg/dL

#### **Other investigations results**

Ultrasonography scan - Small echogenic, nodular liver. Ascites. Enlarged spleen.

Doppler - Patent portal vein

Liver biopsy - Cirrhosis

#### **Signs and symptoms**

Ascites

Portal hypertension with several varices and 2 previous bleeds

Encephalopathy - grade 1-2 - fluctuating

Spider naevi

Jaundice

#### **Diagnosis**

Alcoholic liver disease

#### **Medication history**

Spirolactone (ascites)

Propranolol (portal hypertension)

Ciprofloxacin (bacterial peritonitis prophylaxis)

Phytomenadione (coagulopathy)

- What type of liver dysfunction does the patient have?
- What is the extent of dysfunction?
- How might pharmacokinetics/dynamics may be affected?
- What side effects of drugs do you need to consider in this patient?

The patient needs analgesia and the doctor wants to give ibuprofen

- Could you use ibuprofen in this patient? If so, what dose?
- What precautions or additional advice would you give to the prescriber?
- What alternatives could you suggest? What would be your first choice?