Analgesics

Euan Sandilands BSc MRCP, Specialist Registrar, *National Poison Information Service (Edinburgh Unit), Royal Infirmary of Edinburgh, Edinburgh*

D Nick Bateman BSc MD FRCP FBPharmacolS FBTS, Professor in Clinical Toxicology and Consultant Physician; Director, *Scottish Poisons Information Bureau*

Clin Med 2008;8:96–99

Analgesics are one of the most common groups of drugs prescribed, are freely available over the counter in pharmacies and other general outlets and are a common cause of deliberate self-harm. This article outlines the clinical features and management of self-poisoning with the analgesic agents most frequently seen in hospitals in the UK.

Paracetamol

Paracetamol (acetaminophen) is the drug most commonly used for self-poisoning in the UK. It results in a significant number of deaths every year[1] and is a frequent cause of acute liver failure that potentially will require transplantation.[2] Since the first reports of hepatotoxicity in 1966,[3,4] our knowledge and understanding of the toxicity of paracetamol and methods of treating it have improved, but management difficulties persist, particularly when dealing with staggered overdoses, delayed presentations and patients with risk factors for hepatoxicity.

Paracetamol toxicity

In therapeutic doses, up to 90% of paracetamol is metabolised by formation of glucuronic acid and sulphate conjugates.[5] A small fraction (<5%) is excreted unchanged. The remaining 5–10% is catalysed by the cytochrome P450 system to produce the highly reactive N-acetyl-p-benzoquinoneimine (NAPQI). Under normal conditions, detoxification of NAPQI occurs through conjugation with glutathione and urinary excretion. After an overdose, this conjugation pathway becomes saturated, leaving glutathione stores depleted. The NAPQI accumulates and covalently binds and arylates hepatic cell proteins, which ultimately leads to cell death.

Clinical manifestations

Many patients remain asymptomatic after a paracetamol overdose. Clinical features are non-specific and include nausea and vomiting, anorexia, malaise and abdominal pain. Metabolic acidosis and a high level of lactate in the blood are associated with a poor prognosis.[6] Although liver damage is usually undetectable on initial blood tests, abnormalities are normally apparent by 36 hours, with maximal hepatotoxicity occurring 72–96 hours after ingestion. This is shown by increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and prolonged prothrombin time and, clinically, through the presence of jaundice, encephalopathy and coagulopathy. Renal failure secondary to acute tubular necrosis can also occur –independently or in the context of hepatic failure.[7] Fatalities after paracetamol overdose generally occur 3–5 days after ingestion because of the complications of fulminant hepatic failure.

Management of paracetamol overdose

Activated charcoal should be considered in any patient who presents within one hour of ingestion in an attempt to reduce absorption of paracetamol. Integral to the assessment of patients who have taken a paracetamol overdose, however, is measurement of the levels of paracetamol in plasma. It is impossible to interpret levels measured within the first four hours after ingestion, so they cannot be plotted on the treatment nomogram (Fig 1). This nomogram, which was originally devised through observation of untreated patients before the development of antidotes, identifies patients with potentially hepatotoxic levels of paracetamol.

Acetylcysteine is the preferred antidote in paracetamol poisoning. It acts primarily by replacing the glutathione stores depleted in the detoxification process of NAPQI and has an additional antioxidant role.[5] Oral methionine was used formerly but lacks this additional property. All patients with levels of paracetamol above the treatment line at four hours should receive intravenous acetylcysteine (Box 1), with an alternative lower treatment line for those who fulfil the 'high-risk' criteria for hepatotoxicity (Box 2).

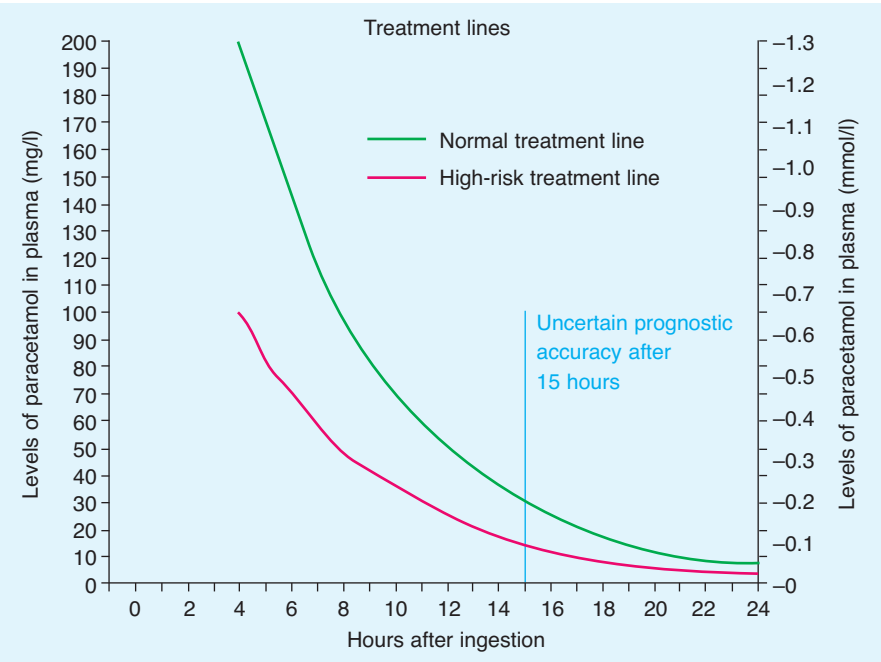

Fig 1. Paracetamol treatment nomogram.

Obtaining a history in patients who have taken a paracetamol overdose is key. Establishing time and quantity of ingestion may prove difficult, and co-ingestion of other drugs such as alcohol will serve only to complicate the clinical picture. In patients who provide an accurate time of ingestion but are delayed in presenting to hospital, there is no indication to start treatment without knowledge of the level of paracetamol in blood, as long as the level can be measured and acted on within eight hours of ingestion. Beyond eight hours, the maximum protective benefit of treatment is lost and acetylcysteine should be started immediately if there is suspicion that more than 150 mg/kg or 12 g paracetamol, whichever is smaller, has been ingested in 24 hours. For patients who fulfil the 'high-risk' criteria, treatment should be started if >75 mg/kg has been ingested. These criteria should also be followed for patients who present after a 'staggered' overdose, in whom interpretation of paracetamol levels is less reliable because the time of first ingestion may be unclear.

The frequency of adverse anaphylactoid reactions to acetylcysteine is around 15%.[8] They are most common in the first hour of treatment when the plasma levels of the antidote are high. Although nausea, flushing and urticaria are common, angioedema and cardiovascular compromise fortunately are unusual. These reactions should be treated by stopping the infusion and prescribing antihistamines and steroids as necessary before restarting the infusion at a reduced rate.

The prognostic value of the level of paracetamol in blood more than 15 hours after ingestion is less certain. Other blood markers that can be used to monitor a patient's condition and help determine prognosis are the international normalised ratio (INR), levels of ALT and creatinine in serum and venous levels of bicarbonate. After the acetylcysteine infusion is complete, these parameters should be checked and further antidote given in patients with an abnormal ALT and INR. If significant abnormalities are noted within these biochemical parameters (Box 3), consideration should be given to speaking to a consultant from the National Poisons Information Service (NPIS) or a specialist liver unit regarding assessment for transplantation. Rarely, renal failure may develop independently of liver failure, so creatinine should be checked on completion of antidote treatment. Any increase indicates that a further check is needed 12 hours later, as renal impairment is normally delayed.

Key Points

- **Deliberate self-poisoning with over-the-counter analgesics is very common in the UK**
- **Levels of paracetamol in blood should be measured no earlier than four hours after ingestion and plotted on the treatment nomogram to guide decisions on management**
- **Acetylcysteine is the preferred antidote for paracetamol poisoning**
- **For patients who present late and those who have taken a 'staggered' overdose, treatment should be started if >150 mg/kg (>75 mg/kg in those at high risk of hepatotoxicity) has been taken in 24 hours**
- **Non-steroidal anti-inflammatory drugs are generally considered to have low toxicity, so patients normally require only routine blood tests and a period of observation**
- **Aspirin toxicity is complex and can be fatal. Management involves correcting acid–base disturbance with fluids and sodium bicarbonate. Haemodialysis may be necessary in cases of severe toxicity**

KEY WORDS: acetylcysteine, aspirin, non-steroidal anti-inflammatory drugs, paracetamol, poisoning

Box 1. Protocol for administration of intravenous acetylcysteine after paracetamol poisoning.

150 mg/kg in 200 ml of 5% dextrose over 15 minutes

followed by

50 mg/kg in 500 ml of 5% dextrose over four hours

followed by

100 mg/kg in 1,000 ml of 5% dextrose over 16 hours

Box 2. High-risk patient groups.

- Patients with chronic alcohol abuse (enzyme induction and malnutrition that causes glutathione depletion)
- Patients who take enzyme-inducing drugs (for example, anticonvulsants, isoniazid)
- Patients with eating disorders and those who are starving (glutathione depletion)
- Patients with malabsorption or significant cachexia from concurrent disease – for example, those with malignant disease or HIV with complications (potential glutathione depletion)

Box 3. Factors that identify patients with poor prognosis after paracetamol-induced liver injury.[9]

Arterial pH <7.3 (H^+ ions >50 nmol/l)

Combination of:

- international normalised ratio (INR) >6.5
- serum creatinine >300 μmol/l
- grade III/IV hepatic encephalopathy

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally considered of low toxicity, but they are frequently implicated in overdose due to their widespread availability, with most data available on ibuprofen overdose. Although no consistent relation has been found between plasma levels of ibuprofen and toxicity,[10] patients are unlikely to experience symp-

toms after ingestion of up to 100 mg/kg, while toxic effects may be evident when >400 mg/kg is consumed.[11] Clinical features typically are mild and non-specific and include nausea and vomiting, epigastric pain, headache and drowsiness. More serious effects such as acute renal failure, gastrointestinal bleeding and metabolic acidosis have been reported rarely.[12] Seizures are rare across all classes of NSAIDs in overdose, with the exception of mefanamic acid, with which they can occur in more than one third of patients.[11]

Management of poisoning with NSAIDs

The treatment of patients after an overdose with NSAIDs is entirely supportive, and there is no antidotal therapy. Although toxicity after large ingestions has been reported, survival with complete resolution is expected. Activated charcoal may be considered in those who present within one hour of ingestion, but the benefit of this is uncertain. Otherwise, patients should undergo a minimum of four hours' observation and should be kept well hydrated, and renal and liver function should be monitored. If significant respiratory or central nervous system toxicity is present, acid–base status should be assessed. Convulsions, if they occur, can be treated with diazepam.

Aspirin

Aspirin (acetylsalicylic acid) has analgesic, anti-inflammatory, antipyretic and thrombolytic properties. It is rapidly absorbed from the stomach and in therapeutic doses has a half-life of 2–4 hours.[13] Metabolism involves conjugation with glycine and glucuronides in the liver before elimination via the kidneys. In overdose, the half-life of salicylates is significantly prolonged and can be up to 20 hours.[13] As the concentration of salicylate increases, the metabolic pathways of elimination become saturated, which leads to a change from first-order to zero-order kinetics, under which salicylate excretion is constant and independent of plasma concentration.[5]

Clinical manifestations

Common features after a salicylate overdose include nausea, vomiting, tinnitus, dizziness and sweating. Patients characteristically have two primary acid–base disturbances: respiratory alkalosis and metabolic acidosis.[13] The former is caused by stimulation of the brain stem respiratory centre, which results in hyperventilation, while wide anion gap metabolic acidosis results from uncoupling of oxidative phosphorylation and leads to lactic acidaemia and a reduction in production of adenosine triphosphate (ATP). A limited respiratory reserve, however, means that the dominant clinical picture in children is of metabolic acidosis. Other clinical features include electrolyte disturbances such as hypokalaemia, hyponatraemia, hypoglycaemia or hyperglycaemia and haematological effects such as hypoprothrombinaemia and platelet dysfunction. Gastrointestinal manifestations include reduced gastric motility and haematemesis. Neurological features occur with more severe salicylate toxicity and include confusion, delirium, psychosis and coma. Hyperpyrexia can occur because of the uncoupling of oxidative phosphorylation. Significant overdoses may rarely result in pulmonary oedema, acute renal failure and cardiovascular collapse.

Assessment and management of overdose

The level of salicylate in serum should be established in all cases of salicylate poisoning, as long as more than four hours have passed since ingestion. Symptoms of mild toxicity are usually observed in all patients with concentrations >350 mg/l, while concentrations >700 mg/l indicate potentially significant toxicity.[5] The severity of poisoning cannot be assessed on the basis of the levels of salicylate alone, however, and the patient's clinical status and biochemical parameters, particularly acid–base and electrolyte disturbances, must be assessed. In patients with severe toxicity, levels of salicylate in plasma should be measured every 2–3 hours, as the concentration may increase because of delayed absorption. Activated charcoal should be considered if the patient presents within one hour of ingestion. Patients who have vomiting, tachypnoea and fever can quickly become dehydrated, so renal function and fluid and electrolyte status need to be monitored accurately. Salicylic acid is a weak acid, and as acidosis increases the transfer of salicylate across the blood–brain barrier, alkalinisation of the blood with sodium bicarbonate may help to resolve any central nervous system effects of toxicity.[13] Excretion may also be enhanced through alkalinisation of the urine (not forced diuresis). In patients with severe toxicity and signs of renal failure, pulmonary oedema and severe metabolic acidosis, haemodialysis rather than haemofiltration is the preferred treatment because it more efficiently extracts salicylate and corrects electrolyte and acid–base disturbances.

Opioid analgesics

Although opioids are widely used drugs of abuse, they are also a common overdose presentation in patients with access to prescription opioids. Most act only on opioid receptors and will thus respond to naloxone. The most toxic, dextropropoxyphene (which is found in co-proxamol), is a sodium channel blocker that causes rapid death in overdose, hence recent licence changes to reduce its availability.[14] Tramadol is another analgesic with complex pharmacology, which has actions on opioid and serotonin mechanisms. The proportional effect depends on metabolism that is variable because of genetic polymorphism. Effects are variable and include convulsions and cardiovascular effects in addition to pure opioid actions. A key message in patients who ingest a mixture of analgesics is that the individual components of the overdose need to be assessed separately, particularly with respect to levels of paracetamol and monitoring for respiratory depression.

References

1 Hawton K, Townsend E, Deeks J *et al.* Effects of legislation restricting pack sizes of paracetamol and salicylate on self

poisoning in the United Kingdom: before and after study. *BMJ* 2001;322:1203–7.
2 Khashab M, Tector AJ, Kwo PY. Epidemiology of acute liver failure. *Curr Gastroenterol Rep* 2007;9:66–73.
3 Davidson DG, Eastham WN. Acute liver necrosis following overdose of paracetamol. *BMJ* 1966;2: 497–9.
4 Thomson JS, Prescott LF. Liver damage and impaired glucose tolerance after paracetamol overdosage. *BMJ* 1966;2:506–7.
5 Vale A. Paracetamol (acetaminophen). *Medicine* 2007 (in press).
6 Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet* 2002;359:558–63.
7 Pakravan N, Bateman DN, Goddard J. Effect of acute paracetamol overdose on changes in serum and urine electrolytes. *Br J Clin Pharmacol* 2007;64:824–32.
8 Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; 346:547–52.
9 O'Grady JG, Wendon J, Tan KC *et al.* Liver transplantation after paracetamol overdose. *BMJ* 1991;303:221–3.
10 Seifert SA, Bronstein AC, McGuire T. Massive ibuprofen ingestion with survival. *J Toxicol Clin Toxicol* 2000;38:55–7.
11 Smolinske SC, Hall AH, Vandenberg SA, Spoerke DG, McBride PV. Toxic effects of nonsteroidal anti-inflammatory drugs in overdose. An overview of recent evidence on clinical effects and dose-response relationships. *Drug Saf* 1990;5:252–74.
12 Goddard J, Stachan FE, Bateman DN. Urinary sodium and potassium excretion as measures of ibuprofen nephrotoxicity. *J Clin Toxicol* 2003;41:747.
13 Flomenbaum NE. *Salicylates.* In: Flomenbaum NE, Howland MA, Hoffman RS. *Goldfrank's toxicologic emergencies*, 8th edn. London: McGraw-Hill Professional, 2006.
14 Afshari R, Good AM, Maxwell SR, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. *Br J Clin Pharmacol* 2005;60:444–7.

Recreational drug toxicity

Simon Hill[1] MRCP, Specialist Registrar in Clinical Pharmacology and Therapeutics

Simon HL Thomas[1,2] MD FRCP FRCPE, Consultant Physician and Reader in Therapeutics

[1]*Newcastle upon Tyne Hospitals NHS Foundation Trust*
[2]*Newcastle University*

Clin Med 2008;8:99–103

Introduction

In 2005–6, 10.5% of people aged 16–59 years who lived in England and Wales had used at least one illicit drug in the previous year and 3.4% had used a class A drug (Table 1), so it is not surprising that presentations to hospital with toxicity are common.[1] The age-standardised mortality associated with drug misuse increased between 1993 and 2000 but has declined since then. Most deaths involve men and people who are using opioids/opiates, especially heroin, methadone and dihydrocodeine, but deaths associated with cocaine and codeine have been increasing (Fig 1).[2] Recreational drug toxicity occurs in the context of other health and social problems that may also need to be addressed – for example, social and criminal justice issues, mental health problems and alcohol and tobacco abuse, as well as bloodborne virus infection, thrombosis and infections in intravenous users.

Cannabis

Smoking or ingestion of cannabis, which is derived from the plant *Cannabis sativa*, is common, but it is unusual for users to require hospital treatment. They occasionally present with disorientation, anxiety or tachycardia, and arrhythmias such as atrial fibrillation have been reported. Long-term use has been connected with psychosis and chronic lung disease.[3]

Stimulants

Sympathomimetic amines – for example, amfetamines, ecstasy, piperazines and cocaine – act by enhancing central release and inhibiting reuptake and metabolism of catecholamines and serotonin. This results in increased concentrations of norepinephrine, epinephrine, dopamine or serotonin, or their combination, within the synaptic cleft.

These substances share a number of clinical effects, although their precise mode of action and potency for causing each differs. The effects produced

Key Points

- **Toxicity associated with recreational drug use is a common reason for presentation to hospital**
- **Most deaths are associated with heroin, methadone, benzodiazepines and cocaine. Deaths due to cocaine are increasing in the UK**
- **Stimulants (for example, amfetamines and cocaine) have adrenergic effects. Serious complications of toxicity are most common with cocaine and include metabolic acidosis, convulsions, rhabdomyolysis, myocardial infarction and stroke**
- **Toxicity from opiates and opioids is exacerbated by co-ingestion of alcohol and other sedatives and those with recent abstinence. Opioid effects can be reversed by the competitive antagonist naloxone**
- **Treatment of benzodiazepine toxicity with the antidote flumezanil can increase the level of consciousness but may cause convulsions and acute benzodiazepine withdrawal**

KEY WORDS: cocaine, ecstasy, gamma hydroxybutyrate, heroin, poisoning