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PARACETAMOL (ACETAMINOPHEN)

OVERVIEW

The major manifestation of paracetamol poisoning is hepatotoxicity, although the kidneys and heart may also be affected in severe poisoning. N-acetylcysteine prevents toxicity if given within the first eight hours but is also of benefit in patients presenting late or with established hepatotoxicity. Decisions about treatment are based on the plasma concentration in patients who present early and the dose ingested and/or clinical signs in those presenting late.

DRUGS INCLUDED IN THIS CATEGORY

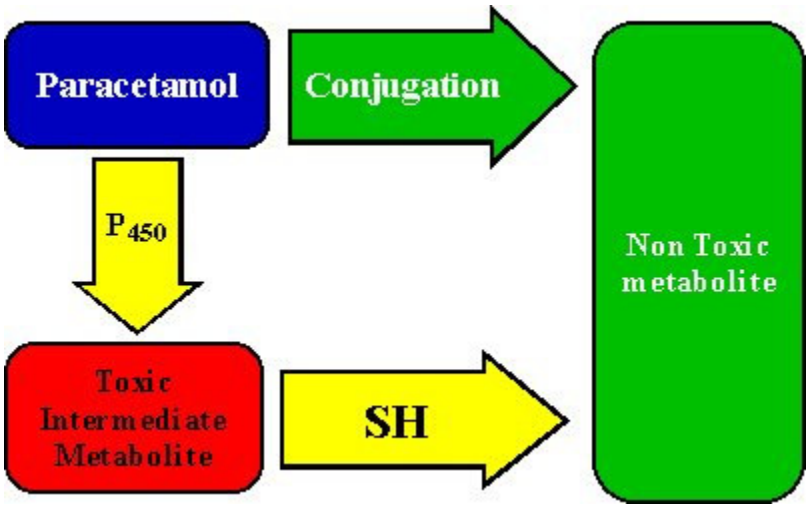
Paracetamol (known as acetaminophen in the US and Canada) is found in multiple combined analgesic preparations and the strengths vary considerably. There are two modified release products now available with different kinetics in therapeutic use.

MECHANISM OF TOXIC EFFECTS

Paracetamol can produce multiorgan failure via the production of an intermediate toxic metabolite. Minor oxidative pathways (P450 enzymes, mainly CYP2E1) produce the intermediate toxic metabolite N-acetyl-p-benzoquinonimine that requires glutathione for further metabolism to non-toxic metabolites. After glutathione supplies are exhausted, the toxic metabolite binds to sulphydryl- containing proteins in the liver cell and causes lipid peroxidation disrupting the cell membrane. These events eventually lead to cell death. Any organ that has P450 enzymes can suffer toxicity (i.e. liver, kidneys, heart, and pancreas).

VARIABILITY IN RISK FOR TOXICITY

There are a number of variables, which potentially influence the risk of toxicity. These are best appreciated by understanding the toxicokinetics of paracetamol.



Theoretically, toxicity is more likely if the P450 enzymes are induced by chronic alcohol ingestion, anticonvulsants, or barbiturates.

Inhibition of P450 enzymes at the time of the overdose may reduce the production of toxic metabolites. This occurs with acute alcohol ingestion (4-6 drinks) and may occur with coingestion or chronic medication with drugs that inhibit these enzymes (e.g. cimetidine).

Patients who are depleted of glutathione are also at theoretically increased risk of toxicity. This may occur in a number of situations, such as chronic ingestion of paracetamol, malnutrition, and eating disorders.

Patients who have increased sulphation enzymes (people on the oral contraceptive and children) will have lower bioavailability and faster clearance of paracetamol.

KINETICS IN OVERDOSE

Absorption

Paracetamol is rapidly absorbed and peak concentrations occur within 1-2 hours for standard tablet or capsules and even quicker (< 0.5 h) in liquid preparations. There are two sustained release preparations and absorption from them continues for up to 12 hours. This may be even longer in overdose due to the formation of pharmacobezoars (this makes the use of the nomogram impossible with sustained release preparations).

Distribution

After absorption, paracetamol distributes rapidly with a volume of distribution of 0.9 L/kg. Absorption and distribution are completed by 4 hours post overdose with standard release preparations and within 2 hours in liquid preparations.

Metabolism - Elimination

Paracetamol is metabolised by a number of pathways. The majority of metabolism in therapeutic use is by glucuronidation and sulphation. There is a significant first pass

metabolism of about 20%. This is predominantly due to sulphation in the gut wall. The half-life of paracetamol in therapeutic use is 1.5 to 3 hours. The clearance of paracetamol becomes saturated in overdose and the half-life may become prolonged to greater than 4 hours. A prolonged half-life indicates saturation of the conjugation pathways and that an increasing proportion of paracetamol is being metabolised by P450 enzymes.

The minor pathways involving P450 enzymes account only for about 5-10% of paracetamol metabolism in therapeutic use. These lead to production of a toxic metabolite, N-acetyl-p-benzoquinonimine (NAPQI). This conjugates with glutathione and is excreted as a non-toxic conjugate in the urine. As glutathione is depleted, this reactive metabolite binds covalently to hepatic macromolecules and leads to cell death.

CLINICAL EFFECTS

Hepatic effects

Hepatotoxicity is the major clinical effect. A rise in the transaminases (ALT, AST) occurs within 24 hours and will usually peak 3-4 days later. AST and/or ALT greater than 1,000 U/L has been classified as hepatotoxicity by numerous authors, however clinical effects do not correlate closely with this definition.

Patients may complain of anorexia, nausea, vomiting, and hepatic tenderness.

They may develop any of the following complications

- hypoglycaemia
- hepatic encephalopathy
- jaundice
- coagulopathy

See also prognostic indicators in hepatotoxicity.

Renal effects

Acute renal failure with acute tubular necrosis is usually reversible and occurs in only a small proportion of patients with hepatotoxicity. It appears to correlate with a history of chronic alcohol use. It may, on rare occasions, occur in individuals with little hepatotoxicity.

INVESTIGATIONS

All adults should have a PLASMA PARACETAMOL CONCENTRATION at 4 hours post overdose or as soon as possible if presentation is after 4 hours, irrespective of reported ingested dose. Children 1-5 years of age do not need a paracetamol concentration drawn unless the ingested dose is > 225 mg/kg. In that case, draw the concentration at 2 hours (for elixir preparations) or 4 hours (for tablet preparations) and plot on the nomogram.

The following investigations should be done in all patients at risk of hepatotoxicity despite treatment:

- Full blood count (baseline)
- Coagulation studies
- Electrolytes, calcium, creatinine
- Blood glucose monitoring
- Liver enzymes

Blood concentrations

Conversion factor

- mg/L x 0.00662 = mmol/L
- mmol/L x 151 = mg/L

Plasma paracetamol should be estimated urgently in any patient who has paracetamol poisoning or presents unconscious with a drug overdose. The purpose of this is to determine the potential severity of the poisoning using the nomogram.

Coagulation studies

Coagulation studies should be done at least daily in patients who have a transaminase rise. These are the best prognostic indicators for paracetamol-induced liver failure. A very poor prognosis is indicated by

- a prothrombin time > 100 seconds (INR > 8) at any time
- a rising prothrombin time between days 3 and 4
- a prothrombin time in seconds which is greater than the number of hours post overdose (after 24 hours)
- Grade III or IV hepatic encephalopathy
- serum creatinine > 300 micromol/L
- elevated lactate at 4 or 12 hours

For more detail see hepatotoxicity below.

Due to the importance of the prothrombin time as a prognostic indicator, fresh frozen plasma should not be given unless there is active bleeding. Vitamin K may be given although it will not usually correct the prothrombin time.

The prothrombin time or INR may be elevated (up to an INR of 2.5 - 3.0) in up to 50% of paracetamol poisoned patients without any evidence of hepatotoxicity. This rise in INR is time, dose, and concentration dependent and is due to inhibition of the activation of coagulation factors. It occurs earlier than the rise associated with hepatotoxicity and should not be confused with the prognostic rises discussed above (Whyte et al, 2000).

Biochemistry

Patients with hepatotoxicity will require daily measurement of electrolytes and creatinine. This is to detect renal failure, acidosis and electrolyte abnormalities due to hepatic failure.

Blood glucose

Patients who develop hepatotoxicity require regular measurement of their blood glucose, particularly in those patients who are unable to eat. Patients may become hypo- or hyperglycaemic. However, hyperglycaemia should not be corrected unless it is very high.

Liver enzymes

An early rise (at 24 hours) in transaminases (ALT, AST) is an indicator of potentially serious hepatotoxicity. Almost all patients who will go on to develop hepatotoxicity (ALT or AST > 1,000 IU) will have abnormal transaminases at 24 hours. Peak enzymes in patients who recover usually occur between 2 and 4 days post overdose. The prothrombin time is the best prognostic indicator.

DETERMINATION OF SEVERITY

In the initial assessment of the potential risk of the poisoning there are 3 areas that may be considered. The usefulness each is dependent on the nature of the presentation:

- Dose ingested
- Paracetamol concentration (see nomogram)
- Clinical assessment of risk (in late presentations only)

Ingested dose

The ingested dose is useful in risk assessment in the following clinical scenarios

- In the absence of a paracetamol concentration
- When the time of ingestion is not known
- In controlled release preparations
- When patients have taken multiple doses within a 24 hour period

A conservative estimate of a dose with the potential for hepatotoxicity if untreated in an adult is greater than 150 mg/kg body weight. The safety margin at this dose is considerable and the minimum risk dose may be closer to 200 mg/kg.

Recent data supports a minimum risk dose for children 1-5 years of age of 225 mg/kg. A dose less than 150 mg/kg in an adult is very unlikely to produce hepatotoxicity, although the reported dose ingested is often inaccurate. In addition, many other factors such as vomiting, first pass metabolism, coingested drugs, and age may influence the paracetamol concentration achieved after a given dose.

To give some safety margin for inaccuracies in dose estimation, we treat any adult who has taken more than 150 mg/kg in a 24 hour period with the exception of patients who define themselves as low risk by paracetamol concentration.

Paracetamol concentration

Paracetamol concentrations taken between 4 and 12-15 hours after an acute single ingestion correlate with clinical severity when plotted on the Rumack/Matthew nomogram.

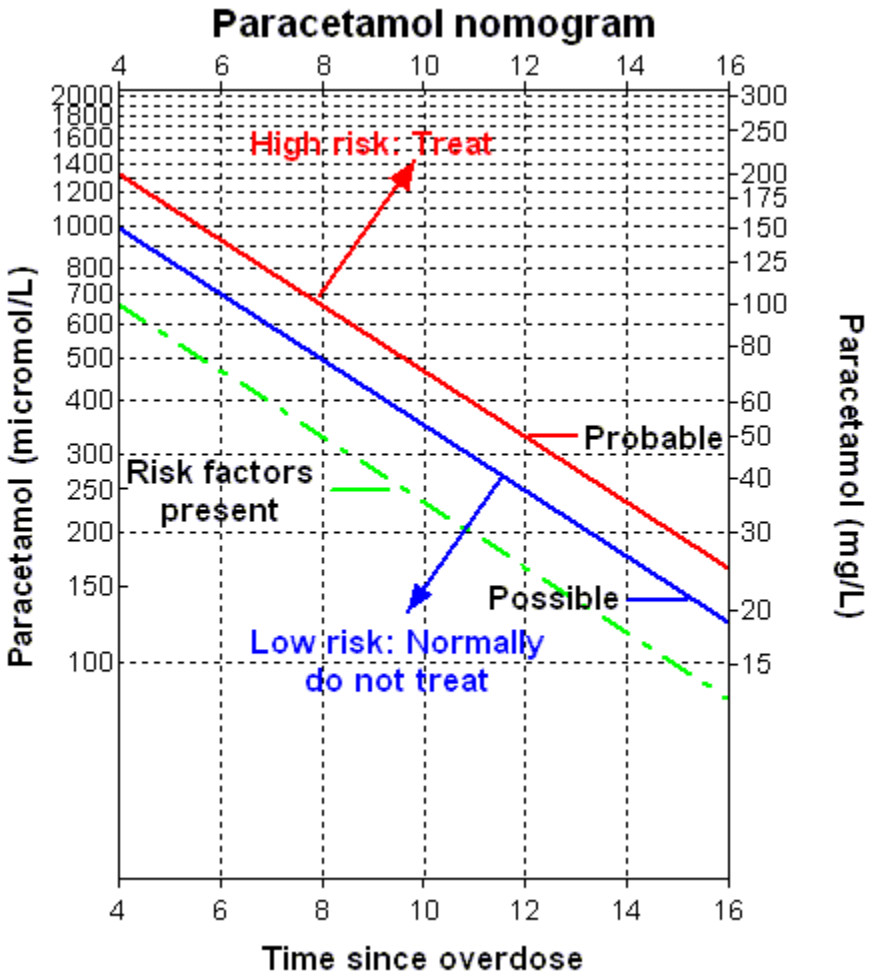
Conversion factor

- mg/L x 6.62 = micromol/L
- micromol/L x 0.151 = mg/L

Nomogram ▲

Table for SI units

Table for mass units



Uncertain time of ingestion ▲

Patients with uncertain time of ingestion can be treated

- on the basis of their ingested dose (treat anyone with a total daily dose > 150 mg/kg)
- by using a best and worst case analysis
- by determining the paracetamol half life

The following are examples of latter two techniques.

Worst case analysis

For example, a paracetamol concentration of 910 micromol/L is likely to require treatment if more than 4 hours might have elapsed.

Determination of paracetamol half-life

- a half-life greater than 4 hours indicates a high risk of hepatotoxicity

Methods

Take 2 concentrations about 2 hours apart (e.g. first concentration: 700 micromol/L, concentration 2 hours later: 580 micromol/L)

You can then either

1. Plot them anywhere on the nomogram (see example). If the slope of the line joining these concentrations is flatter than the treatment line then the half-life is > 4 hours and the patient requires treatment.

2. Calculate half-life using this formula:

Half life = ln 2 * [T2-T1]/[ln C(T1) - ln C(T2)]

[T2-T1] is the time between samples. ln C(T1) & ln C(T2) are the natural logs of the concentrations)

e.g. Half life = ln2 * 2 hours/(ln 700 - ln 580) =0.693 * 2/(6.551 - 6.363) hours = 7.35 hours

3. If the samples are exactly 2 hours apart and the half-life is greater than 4 hours, then the second sample will be greater than 70% of the first sample

e.g. 580 is greater than 490 (70% of 700) therefore half life is greater than 4 hours

Clinical assessment of risk

Patients who have a delayed presentation (>15 hours) or who have already developed hepatitis need to be assessed using different criteria as the nomogram has not been validated for this group of patients. Initial treatment should be based on dose ingested and the presence of symptoms or signs of hepatotoxicity. Liver function tests and a paracetamol concentration should be measured.

If at 24 hours after the overdose, the patient is asymptomatic, liver function tests are normal and plasma paracetamol concentration is undetectable, they will not develop significant toxicity. The presence of abnormal transaminases or a measurable

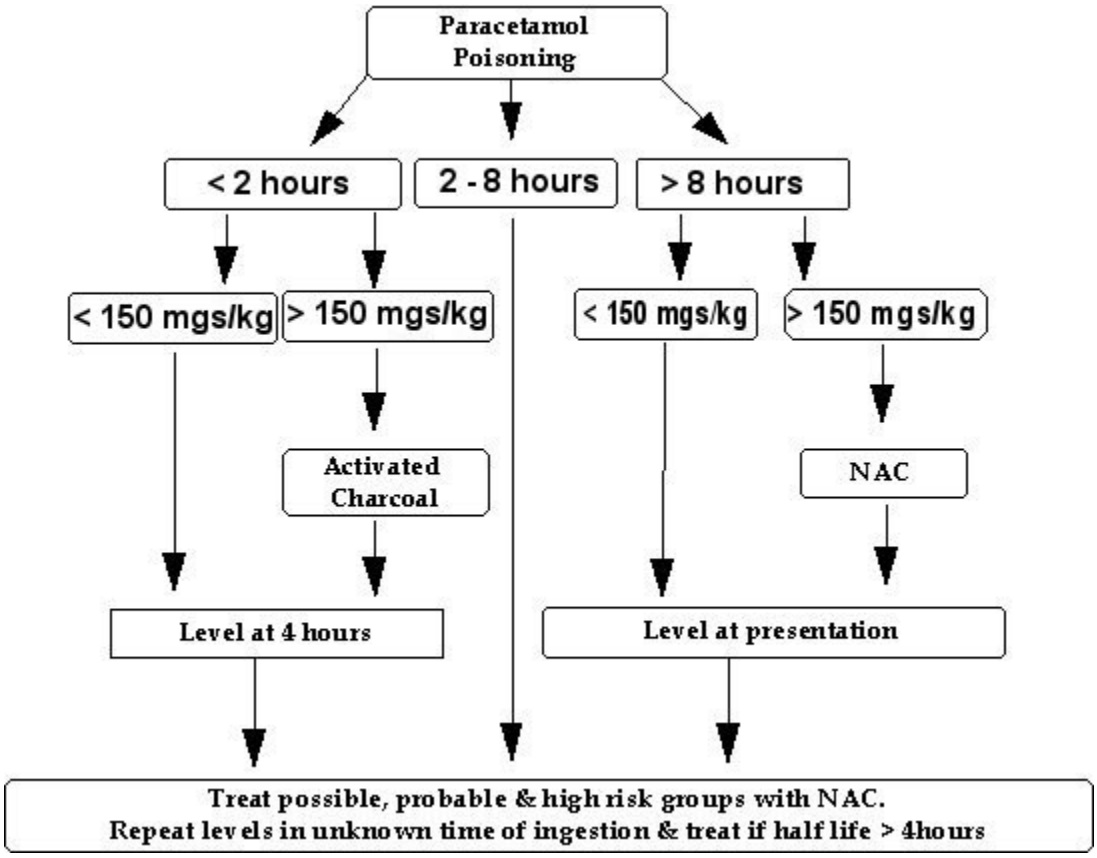
concentration of paracetamol indicates there is still a potential risk of significant hepatotoxicity.

Almost all patients who develop hepatotoxicity will have abnormal transaminases (ALT or AST >= 2 x normal) by 24 hours.

Peak hepatotoxicity in patients who recover usually occurs between 2-4 days post overdose. The prothrombin time is the best prognostic indicator in those with established hepatotoxicity.

TREATMENT

Treatment algorithm for adults



In children 1-5 years of age exposed to paracetamol elixir, concentrations should only be measured if the ingested dose is > 225 mg/Kg. Blood can be taken as early 2 hours after exposure in this circumstance.

GI Decontamination

Oral activated charcoal should be given to all adults and older children ingesting more than 150 mg/kg of paracetamol standard release tablet or capsule preparations presenting within 2 hours. For children 1-5 years of age, the at risk dose is > 225 mg/kg. If an elixir preparation is taken, absorption is so rapid GI decontamination is not indicated.

Gastric lavage is not indicated.

Repeated doses of activated charcoal are not useful.

Whole bowel lavage should be considered in slow-release paracetamol ingestions.

N-acetylcysteine

N-acetylcysteine is a glutathione precursor and is a source of sulphydryl groups that allows the intermediate toxic metabolite to be conjugated to non-toxic metabolites. It also may have secondary benefits as an antioxidant (preventing lipid peroxidation) and as a free radical scavenger.

Treatment offers complete protection from toxicity if it is started within 8 hours of ingestion.

Treatment between 8-24 hours lowers mortality but offers incomplete protection from hepatotoxicity.

Dose

Intravenous therapy

Dosage protocol for intravenous N-acetylcysteine (Parvolex)

Adults

1. 150 mg/kg in 200 mL of 5% Dextrose over 15-60 minutes then
2. 50 mg/kg in 500 mL of 5% Dextrose over 4 hours then
3. 50 mg/kg in 500 mL of 5% Dextrose over 8 hours then
4. 50 mg/kg in 500 mL of 5% Dextrose over 8 hours.

The total dose over 20-21 hours is 300 mg/kg.

The treatment may be continued for longer than 20 hours in late presentations and patients with evidence of liver damage by continuing the infusion rate at 50 mg/kg in 500 mL of 5% Dextrose over 8 hours (see late presentations).

Children > 20 kg

1. 150 mg/kg in 100 mL of 5% Dextrose over 15-60 minutes then
2. 50 mg/kg in 250 mL of 5% Dextrose over 4 hours then
3. 50 mg/kg in 250 mL of 5% Dextrose over 8 hours then
4. 50 mg/kg in 250mL of 5% Dextrose over 8 hours.

The total dose over 20-21 hours is 300 mg/kg.

The treatment may be continued for longer than 20 hours in late presentations and patients with evidence of liver damage by continuing the infusion rate at 50 mg/kg in 250

mL of 5% Dextrose over 8 hours (see late presentations).

Children < 20 kg

1. 150 mg/kg in 3 mL/kg of 5% Dextrose over 15-60 minutes then
2. 50 mg/kg in 7 mL/kg of 5% Dextrose over 4 hours then
3. 50 mg/kg in 7 mL/kg of 5% Dextrose over 8 hours then
4. 50 mg/kg in 7 mL/kg of 5% Dextrose over 8 hours.

The total dose over 20-21 hours is 300 mg/kg.

The treatment may be continued for longer than 20 hours in late presentations and patients with evidence of liver damage by continuing the infusion rate at 50 mg/kg in 7 mL/kg of 5% Dextrose over 8 hours (see late presentations).

Oral therapy

- 140 mg/kg as a 5 percent solution (diluted in soft drink, juice, or water) then
- 70 mg/kg per dose every four hours for 17 doses

The total dose over 72 hours is 1,330 mg/kg. In late presentations of patients with evidence of liver damage convert to intravenous therapy at the infusion rate at 50 mg/kg in 500 mL of 5% Dextrose over 8 hours (see established hepatotoxicity).

Complications

Nausea, vomiting and diarrhoea are common after oral therapy. Anaphylactoid reactions can occur with intravenous N-acetylcysteine in up to 20-25% of patients and rarely in oral therapy. They are due to drug induced histamine release, are dose related and not due to an allergic response. Asthmatics have an increased risk of reaction.

Management

Anaphylactoid reactions commonly occur with the initial loading dose in the first hour of treatment. The infusion should be ceased temporarily. An antihistamine and hydrocortisone should be given in severe cases although most reactions settle without specific treatment. Once the reaction has settled, recommence the infusion (if still indicated) at 25% of previous rate, increasing to the normal rate over the next hour.

Indications

The management is determined by the time from ingestion until a paracetamol concentration can be obtained but is modified in high-risk patients:

Less than 8 hours post overdose

If the patient has taken a POTENTIALLY TOXIC DOSE (> 150 mg/kg body weight in adults or > 225 mg/kg in children aged 1-5 years) and presents within two hours then activated charcoal should be given unless an elixir has been taken.

Blood is taken for a paracetamol concentration at 4 or more hours post ingestion (2 hours for children 1-5 years). If the paracetamol concentration is above the treatment line on the nomogram, N-acetylcysteine is commenced.

If the result of the paracetamol concentration will not be available within 8 hours of ingestion and the dose is above the risk level, commence N-acetylcysteine while awaiting the result.

Patients 8 - 15 hours post overdose

N-acetylcysteine is given to any patient who has ingested a dose greater than 150 mg/kg body weight in adults or > 225 mg/kg in children aged 1-5 years. A plasma paracetamol concentration is taken and treatment may be ceased if the concentration is below the treatment line on the nomogram.

Late presentation (after 15 hours)

Patients who have a delayed presentation (>15 hours) or who have already developed hepatitis require a longer than usual course of N-acetylcysteine treatment and close supportive care.

N-acetylcysteine is started if ingested dose is greater than 150 mg/kg in adults or > 225 mg/kg in children aged 1-5 years or their liver function tests are abnormal. The infusion should be continued as below if hepatotoxicity develops. The infusion should be ceased if the patient is asymptomatic, liver function tests are normal and plasma paracetamol concentration is undetectable.

Patients with established hepatotoxicity

These patients should all be commenced on N-acetylcysteine. If they have already received N-acetylcysteine, this should be continued at an infusion rate of 50 mg/kg per 8 hours until their prothrombin time and liver enzymes (ALT and AST) begin to plateau or fall.

High risk patients

Patients at high risk by virtue of being on enzyme inducing drugs, having chronic alcohol use or malnutrition should receive N-acetylcysteine at a lower threshold for treatment than other patients. There are no good data to guide recommendations but we suggest

- That a line that is parallel to but 50% below the standard treatment line is used for these patients
- Treatment should be given if more than 100 mg/kg has been ingested and concentrations are unavailable within 8 hours

Treatment decisions based on the half-life of paracetamol should not be used in this group.

Staggered or multiple ingestions

Patients who present with a history of multiple ingestions of paracetamol occurring within a 24 hour period should be treated if the history of ingestion is greater than 150 mg/kg in adults (or > 225 mg/kg in children aged 1-5 years) in the 24 hour period. The nomogram must not be used for these patients as it may seriously underestimate risk.

Methionine

In cases where N-acetylcysteine is not available, methionine may be used as an oral antidote. It also appears effective if started within 8-10 hours of exposure but may have more side effects than N-acetylcysteine. It can only be given orally and produces, nausea and persistent vomiting in a patient often nauseated by paracetamol ingestion. The dose is 2.5 G initially followed by three more 2.5 G doses at 4 hour intervals to a total dose of 10 G.

Aggressive management (e.g. -setrons) may be necessary to ensure absorption of methionine in a vomiting patient. The effect of activated charcoal on methionine absorption is unclear but is potentially significant if administered within 1 hour of methionine.

There is no evidence to support methionine in late paracetamol poisoning but all other indications are as for N-acetylcysteine (above).

Treatment of specific complications

Hepatotoxicity

All patients should receive N-acetylcysteine.

The overall prognosis for most patients with paracetamol hepatotoxicity is good. Management requires good supportive care. See hepatic failure guidelines flow chart.

Liver transplantation criteria

Patients with liver damage who have signs of a poor prognosis should have consultation with or be referred to a specialist liver unit or a liver transplant unit. Patients who should be considered for liver transplantation are those fulfilling the O'Grady criteria with the modification of Bernal.

O'Grady criteria

- Arterial blood pH < 7.3 or H^+ > 50 mmol/L after resuscitation

or

- A prothrombin time greater than 100 seconds

and

- Serum creatinine > 300 mmol/L

in

- Patients with Grade III or Grade IV encephalopathy

Bernal modification

- Serum lactate > 3.0 mmol/L at 4 hours or > 3.5 mmol/L at 12 hours

Transport of patients with grade 3 or grade 4 encephalopathy is life threatening. Therefore, patients who appear to be continuing to worsen after 3 to 4 days should be transferred early if possible.

In addition, supportive care is directed at detecting and treating

Hypoglycaemia

Hypoglycaemia is due to hepatic failure. Some patients may have symptomatic hypoglycaemia despite a low - normal blood sugar.

- All patients with hepatotoxicity and CNS depression or seizures should receive an intravenous bolus of 50% glucose regardless of their blood sugar
- Finger prick glucose 4th hourly
- Constant carbohydrate intake, IV and oral

Hepatic encephalopathy

Treatment of hepatic encephalopathy includes specific interventions and regular assessment.

- A low protein/high carbohydrate diet
- Lactulose 15-30 mL QID
- Regular monitoring of severity
- Constructional apraxia (star chart)
- Handwriting chart
- Sleep/awake chart
- Hepatic flap

Prolonged prothrombin time

An early rise (in the first 15 hours) in the prothrombin time in the absence of a transaminase rise is a transitory direct effect of paracetamol and not of prognostic importance. In the absence of bleeding. Prothrombin times of less than 60 seconds do not require treatment. Patients with prothrombin times greater than 60-100 seconds should be referred to a specialist liver unit and considered for transplant.

Acute renal failure

This is due to acute tubular necrosis, although this may be compounded by hepatic failure. The treatment of renal failure in this setting is no different from acute tubular necrosis from any other cause. The prognosis of the renal function is good if the patient's

liver function improves.

LATE COMPLICATIONS, PROGNOSIS - FOLLOW UP

The prognosis for paracetamol poisonings who present to hospital is very good. Patients treated within 8 hours may be medically discharged as soon as treatment with N-acetylcysteine has ceased.

Patients who present greater than 8 hours after ingestion can be discharged if their transaminases are normal 24 hours following the ingestion.

Patients who develop hepatotoxicity have a mortality of less than 10% with good supportive care.

No long-term follow up is required after recovery but patients should probably be advised to avoid alcohol and other hepatic insults for a further month or two.

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