

paracetamol overdose
[created by Paul Young 02/10/07]

definition most common cause of poisoning in western countries

- rapidly absorbed from GI tract in therapeutic doses with peak plasma levels in 30-60 minutes
- bioavailability ranges from 68-90%
- time to peak plasma concentration may be delayed by presence of coingestants that delay gastric emptying
- vol of distribution is 1L/kg and plasma protein binding is less than 50%
- metabolism occurs in the liver via glucuronidation, sulphation & via metabolism to NAPQI which is conjugated to glutathione. Following overdose glucuronidation and sulphation pathways are rapidly saturated resulting in increased metabolism to NAPQI which begins to accumulate once glutathione is depleted >70% & produces hepatocellular death
- production of toxic metabolites is enhanced by barbiturates, carbamazepine, oral contraceptives, chronic alcohol ingestion & starvation; acute ethanol ingestion may inhibit microsomal metabolism and in theory may confer a hepatoprotective effect

aetiology

- groups at risk for paracetamol poisoning:
1. underlying hepatic impairment
 - viral hepatitis
 - alcoholic liver disease
 2. microsomal enzyme induction
 - phenobarbitone
 - carbamazepine
 - phenytoin
 - rifampicin
 - oral contraceptives
 - chronic alcohol ingestion
 - starvation
 3. acute glutathione depletion states
 - acute illness with decreased nutrient intake
 - anorexia / bulimia / malnutrition
 - chronic alcoholism
 - HIV

symptoms & signs (for untreated cases)

- stage 1 (0-24hrs)**
 - asymptomatic or GI upset only
- stage 2 (24-48hrs)**
 - resolution of nausea & vomiting
 - right UQ pain and tenderness
 - progressive elevation of aminotransaminases, bilirubin & prothrombin time
- stage 3 (48-96hrs)**
 - signs / symptoms of progressive hepatic failure including jaundice, coagulopathy or encephalopathy
- stage 4**
 - death from hepatic failure OR
 - normalisation of LFTs & complete resolution of hepatic architecture by 3 months

investigation

- paracetamol levels
- compare levels to the Rumack-Matthews nomogram
 - nomogram has no role in chronic toxicity where liver failure has been reported with use of as little as 4g/day in patients with acute illness
 - serum paracetamol level above probable toxicity line is associated with a 60% chance of hepatotoxicity if untreated
 - risk increases to 87% for a line beginning at 2000umol/L at 4hrs
- peak transaminotransferases are observed at around 72hrs
- patients with a prothrombin time of greater than 180 secs or a rising prothrombin time on day 4 post-ingestion are at risk of developing fulminant liver failure with a less than 8% chance of survival without transplant

renal failure may develop in patients with severe paracetamol toxicity

treatment

1. consider activated charcoal
 - three studies show lower plasma paracetamol levels when activated charcoal is given in acute overdose (see best bets)
 - will impair absorption of antidote if it is given orally
 - it should probably be given to all patients who present within 4 hrs
 2. give specific antidote if indicated based on 4 hour levels
 - iv parvolex is treatment of choice but oral therapy can be given if iv access is not possible
 - there is no evidence to support giving antidote prior to knowing four hour levels but good evidence to show that delaying therapy for more than 10 hours leads to increased hepatotoxicity; empirical therapy is indicated if levels with not be available before 10 hours post ingestion and significant overdose has been consumed (>150mg/kg)
 - give parvolex if level is over 'probable hepatotoxicity' range or possible hepatotoxicity range in patients who are at risk
 - patients who present >24hrs after ingestion may benefit from antidotal therapy; the nomogram is not useful. Therapy should be commenced empirically and continued if there are clinical or laboratory signs of toxicity
 3. treat nausea and vomiting
- NB: pregnant patients should be treated the same as non-pregnant (paracetamol & N-acetylcysteine both cross the placenta. Toxicity is caused and treatment is effective)

disposition

- medical or gastro admission
- ICU admission or liver transplant unit admission may be required in particular circumstances
- psych referral will be required