ABPARA I.V

(Paracetamol)

For intravenous infusion

Rx only

COMPOSITION

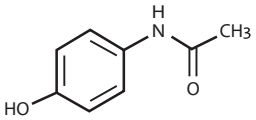
Each 100ml contains:

Paracetamol B.P. ……1.0g

Water for injection …….. q.s

DESCRIPTION

ABPARA is a sterile, non-pyrogenic solution of Paracetamol B.P in water for injection for intravenous injection. The solution contains no bacteriostatic or antimicrobial agent. Paracetamol is a p-aminophenol derivative with analgesic and antipyretic activities. Although the exact mechanism through which Paracetamol exerts its effects has yet to be fully determined, Paracetamol may inhibit the nitric oxide (NO) pathway mediated by a variety of neurotransmitter receptors, resulting in elevation of the pain threshold. The antipyretic activity may result from inhibition of prostaglandin synthesis and release in the central nervous system (CNS) and prostaglandin-mediated effects on the heat-regulating center in the anterior hypothalamus. Paracetamol, BP is a white crystalline solid freely soluble in alcohol and slightly soluble in cold water. It has the following chemical formula $C_8H_9NO_2$ structural formula



CLINICAL PHARMACOLOGY

Paracetamol is thought to act primarily in the central nervous system, increasing the pain threshold by inhibiting isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis but does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory affects. Studies have found that paracetamol indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why paracetamol is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that paracetamol selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works. The antipyretic properties of acetaminophen are likely due to direct effects on the heat-regulating centers of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation.

Paracetamol is readily 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 metabolized 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 over dosage and cause tissue damage.

INDICATIONS

For temporary relief of fever, minor aches, and minor to moderate pains.

ABPARA I.V solution provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

CONTRAINDICATIONS

ABPARA is contraindicated in

- acute hepatic Failure, Severe Renal Impairment and Shock.
- in cases of severe hepatocellular insufficiency
- in cases of hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients.

PRECAUTIONS

ABPARA should be given with care to patients with impaired kidney or liver function. It should also be given with care to patients with alcohol dependence.

Breast feeding. No adverse effects have been seen in breastfed infants whose mothers were receiving paracetamol, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding. The BNF also considers that the amount of paracetamol distributed into breast milk is too small to be harmful to a breast-fed infant. Pharmacokinetic studies in 12 nursing mothers given a single dose of paracetamol showed that peak paracetamol concentrations in breast milk of 10 to 15 micrograms/mL were achieved in 1 to 2 hours. Plasma concentrations were determined in 2 mothers; a breast milk/plasma ratio of about 1 was reported. Similar findings have been reported from other studies.

Hepatic impairment. A short review concluded that there was 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. The BNF warns that large doses should be avoided.

Pregnancy. Paracetamol is generally considered to be the analgesic of choice in pregnant patients. However, the frequent use of paracetamol (defined as most days or daily use) in late pregnancy may be associated with an increased risk of persistent wheezing in the infant which may persist into childhood.

Renal impairment. 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. It has been suggested that paracetamol itself may be regenerated from these metabolites. There is conflicting data on whether the conjugates of paracetamol accumulate in patients with renal impairment receiving multiple doses.

Exposure even temporarily to sunlight will discolor the paracetamol solution Do not administer unless solution is clear, colorless and container is undamaged. Discard unused portion.

DRUG INTERACTIONS

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Antibacterials. The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as rifampicin. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid, alone or with other drugs for tuberculosis.

Antiepileptics. The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, oprimidone.

Probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. Although urinary excretion of the sulfate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

ADVERSE REACTIONS

Paracetamol only rarely causes gastrointestinal problems or allergic skin reactions. Blood dyscrasia (e.g. thrombocytopenia), methaemoglobinemia, and hemolytic anemia are very rare. A minority of the subjects with so-called aspirin intolerance respond to paracetamol with bronchospasms. It is not safely established if paracetamol can cause a nephropathy, like drug combinations containing phenacetin. When metabolized in the liver, small amounts of an intensely active metabolite, which is normally immediately inactivated by glutathione, are produced. An overdose causes a glutathione deficiency; the reactive metabolite may then cause hepatocellular damage and necrosis leading to acute liver failure. Toxic effects have been observed in adults treated with doses of more than 10 g (20 tablets). However, if there is a pre-existing liver insufficiency, paracetamol can be hepatotoxic even in small amounts. Contact your doctor or nurse and stop treatment immediately if you experience any symptoms after an IV infusion of paracetamol.

Over dosage

Acute overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and toxic doses. Ingestion of as little as 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Patients should be considered at risk of severe liver damage if they have received more than 150 mg/kg of paracetamol or 12 g or more in total, whichever is the smaller. 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 supra-therapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity. Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at special risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia or AIDS. It has also been suggested that fasting may predispose to hepatotoxicity. Early signs of over dosage (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 and acetylcysteine 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.

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 over dosage include myocardial abnormalities and pancreatitis. The mechanism of toxicity in over dosage 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) 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 over dosage, 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 over dosage. Acetylcysteine may also be involved in the repair of damaged tissue.

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. Intravenous use has been associated with anaphylactic reactions but is the preferred route because of fears that oral absorption might be reduced by vomiting. However, the oral route is also used, and is clearly effective. The use of methionine by mouth is licensed in the UK, despite the same risks of impaired absorption due to vomiting. It is cheaper and easier to give than intravenous acetylcysteine and may be 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. 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, and studies of patients treated up to 36 hours suggest that benefit may be obtained up to and possibly beyond 24 hours. Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.

- An initial dose of 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given intravenously over 15 minutes. This is followed by an intravenous infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg 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. 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.
- Acetylcysteine may also be given orally 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.

Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamol over dosage.

However, it is not as effective if treatment is delayed 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 over 6 years 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 under 6 years should be given 1 g every 4 hours for 4 doses. It has also been given intravenously. The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used.

DOSAGE AND ADMINISTRATION

ABPARA is administered by intravenous infusion based on patient weight. Dosing recommendations are presented in the table below:

Patient Weight	Paracetamol dose (10 mg/mL) per administration	Minimum interval between each administration	Maximum daily dose #
> 50 kg	1 g (i.e. one 100 mL vial) Up to 4 times per day	4 hours *	≤ 4 g Must not exceed 4 g in 24 hours
> 33 kg and ≤ 50 kg	15 mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	4 hours *	≤ 60 mg/kg, without exceeding 3 g Must not exceed 3 g in 24 hours
> 10 kg and ≤ 33 kg	15 mg/kg (i.e. 1.5 mL solution per kg) Up to 4 times per day	6 hours	≤ 60 mg/kg, without exceeding 2 g Must not exceed 2 g in 24 hours
≤ 10 kg **	7.5 mg/kg (i.e. 0.75 mL solution per kg) The volume must not exceed 7.5 mL per dose Up to 4 times per day	6 hours	≤ 30 mg/kg Must not exceed 30 mg/kg in 24 h

* The minimum interval between each administration must be 4 hours in patients without hepatic or renal impairment. However, in patients with renal and/or hepatic impairment the minimum interval between doses must not be less than 6 hours.

The maximum daily dose takes into account all medicines containing paracetamol or propacetamol.

** No safety and efficacy data are available for premature neonates. There is limited data on the use of ABPARA in neonates and infants <6 months of age.

Presentation

Clear, colorless solution in sterile plastic bottle of 100ml

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Shelf life

The manufacturing and expiry dates are indicated on the packaging.

Storage

KEEP AWAY FROM DIRECT LIGHT, store below 30° C but do not freeze.

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