Product registration dossier

Paracetamol injection 300mg/2ml

ANHUI CHENGSHI PHARMACEUTICAL CO., LTD.

Module 1 :

ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

ANHUI CHENGSHI PHARMACEUTICAL CO., LTD.

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Paracetamol injection 300mg/2ml

2. Qualitative and quantitative composition

Each ampoule contains: Paracetamol 300mg.

3. Pharmaceutical form

Injection

A colorless or almost colorless slightly viscous clear liquid.

4. Clinical particulars

4.1 Therapeutic indications

Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties. It does not possess any anti-inflammatory activity. Paracetamol is often the analgesic or antipyretic of choice especially in patients in whom salicylates or other nonsteroidal anti-inflammatory drugs are contra-indicated.

4.2 Posology and method of administration

Intramuscular route (I.M.):

Adult : 300mg per 2ml every 4 to 6 hours for adult using.

Children: For children under 3 months, 5mg per kg bodyweight was recommended. For Children aged 3 months to 12 years: 30mg to 200mg every 4 to 6 hours could be chosen to age. If necessary, 4 times per 24 hours can be used.

Intravenous route(I.V.):

Dilute the injection as 1g Paracetamol in 100ml 5% Glucose IV solution for Intravenous infusion.

Adults :Paracetamol 1 g per administration, in one 100 mL vial, up to four times a day. The minimum interval between each administration must be 4 hours in patients without hepatic or

renal impairment. In patients with renal and/or hepatic impairment the minimum interval between doses must not be less than 6 hours.

The maximum daily dose from all sources of paracetamol must not exceed 4 g.

Neonates, infants and children weighing up to 33 kg (about 11 years old)

15 mg/kg of paracetamol per administration, i.e. 1.5 mL of solution per kg, up to four times a day.

The minimum interval between each administration must be 6 hours.

The maximum daily dose must not exceed 60 mg/kg.

Neonates (< 10 days): it is recommended to reduce the dosage by half, i.e. 7.5 mg/kg paracetamol per administration, without exceeding 4 administrations per day.

4.3 Contraindications

Paracetamol is contraindicated:

In patients with known hypersensitivity to acetaminophen or to any of the excipients in the formulation.

In patients with severe hepatic impairment or severe active liver disease.

4.4 Special warnings and precautions for use

Side-effects of paracetamol are rare and usually mild, though haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported.

Paracetamol should be given with care to patients with impaired kidney or liver function and also be given with care to patients taking other drugs that affect the liver.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which induce hepatic microsomal enzymes such as alcohol, barbiturates and other anticonvulsants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.

The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

Probenicid inhibits the glucuronidation of paracetamol which can affect the clearance of paracetamol. This should be considered when these medicines are administered concomitantly.

Paracetamol may affect the pharmacokinetics of chloramphenicol. This interaction should be considered when these medications are administered concomitantly, especially in malnourished patients.

Enzyme-inducing medicines, such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine, primidone) have been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approx. 60 %. Other substances with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of causing lowered concentrations of paracetamol. In addition, the risk of liver damage during treatment with maximum recommended doses of paracetamol will be higher in patients being treated with enzyme-inducing agents.

4.6 Pregnancy and lactation

Not applicable.

4.7 Undesirable effects

Side-effects of paracetamol are rare and usually mild, though haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported.

Paracetamol should be given with care to patients with impaired kidney or liver function and also be given with care to patients taking other drugs that affect the liver.

4.8 Overdose

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after administration and clinical symptoms generally culminate after 4 to 6 days. 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 clinically significant early symptoms, patients should be referred urgently to hospital for immediate medical attention. This is because early 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.

As concentrations soon after paracetamol ingestion are unreliable, plasma paracetamol concentration should be measured at 4 hours or later after the initial administration. Treatment with N-acetylcysteine may be used for up to 24 hours after administration of paracetamol; however, the maximum protective effect is only obtained up to 8 hours post-administration. The effectiveness of this antidote declines sharply after this 8 hour time period. If required, the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, then oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of those patients presenting with serious hepatic dysfunction 24 hours after paracetamol administration should be discussed with the National Poisons Information Centre (NPIS) or a liver unit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Paracetamol is classified as a mild analgesic. It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, paracetamol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients. Though paracetamol is used to treat inflammatory pain, it is not generally classified as an NSAID because it exhibits only weak anti-inflammatory activity.

In therapeutic doses paracetamol is a safe analgesic, but in overdosage it can cause severe hepatic necrosis. After IM/IV administration, its systemic bioavailability being dose-dependent and ranging from 70 to 90%.

5.2 Pharmacokinetic properties

Paracetamol is extensively metabolised (predominantly in the liver), the major metabolites being the sulphate and glucuronide conjugates. A minor fraction of drug is converted to a highly reactive alkylating metabolite which is inactivated with reduced glutathione and excreted in the urine as cysteine and mercapturic acid conjugates. Large doses of paracetamol (overdoses) cause acute hepatic necrosis as a result of depletion of glutathione and of binding of the excess reactive

metabolite to vital cell constituents. This damage can be prevented by the early administration of sulfhydryl compounds such as methionine and N-acetylcysteine.

In healthy subjects 85 to 95% of a therapeutic dose is excreted in the urine within 24 hours with about 4, 55, 30, 4 and 4% appearing as unchanged paracetamol and its glucuronide, sulphate, mercapturic acid and cysteine conjugates, respectively. The plasma half-life in such subjects ranges from 1.9 to 2.5 hours and the total body clearance from 4.5 to 5.5ml/kg/min. Age has little effect on the plasma half-life, which is shortened in patients taking anticonvulsants. The plasma half-life is usually normal in patients with mild chronic liver disease, but is prolonged in those with decompensated liver disease.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections.

Studies on local tolerance of Paracetamol 10 mg/ml Solution for Infusion in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

6. Pharmaceutical particulars

6.1 List of excipients

Polyethylene glycol 400

Benzyl alcohol

Lidocaine hydrochloride

Anhydrous sodium sulfite

Edetate disodium

Water for injection

6.2 Incompatibilities

None known

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30 ℃.

6.5 Nature and contents of container

Glass ampoule