

Data Sheet

Paraldehyde

Paraldehyde Injection Solution 100%

Presentation

Paraldehyde Injection BP is a sterile liquid containing paraldehyde BP with hydroquinone 100 micrograms/mL as an antioxidant. It is a colourless or pale yellow transparent liquid, with a strong odour and disagreeable burning taste.

Uses

Actions

Paraldehyde has sedative and hypnotic actions. It is believed to depress many levels of the central nervous system (CNS), including the ascending reticular activating system to cause an imbalance between inhibitory and facilitatory mechanisms. Doses of 4 to 10 mL administered intramuscularly (IM) have produced sleep within 5 to 15 minutes which lasted about 8 hours in patients with normal liver function. In sub-hypnotic doses, paraldehyde has anticonvulsant actions, although the dose margin between the anticonvulsant and hypnotic effects is small. At sub-anaesthetic doses, it is not an analgesic and may produce excitement or delirium in the presence of pain.

Pharmacokinetics

Paraldehyde is rapidly absorbed from intramuscular injection sites. Maximum serum levels, which may range from 34 to 150 micrograms/mL are reached within 20 to 60 minutes of intramuscular injection of 0.25 mL/kg. The drug diffuses into the cerebrospinal fluid (CSF) and also crosses the placental barrier. Maximum paraldehyde concentrations have been reached in the CSF, 30 to 60 minutes after intramuscular administration of the drug. Although tissue distribution of paraldehyde has not been extensively studied, it is known that the concentration of the drug in CSF is approximately 25 to 30% lower than that in the blood. It appears that about 80 to 90% of the dose is metabolised in the liver to acetaldehyde, which is oxidised by aldehyde dehydrogenase to acetic acid, then further metabolised to carbon dioxide and water. A significant proportion of the drug is excreted unchanged through the lungs (giving a characteristic odour to the breath) and only small amounts are excreted unchanged in the urine. The biological half-life of paraldehyde is approximately 3.5 to 9.5 hours with an average of 7.5 hours in patients with normal liver function.

Indications

Paraldehyde has been used as a sedative and hypnotic in a variety of clinical situations, although it has been largely replaced by safer and/or more effective agents. It may also be used in the treatment of convulsive episodes arising from tetanus, status epilepticus and poisoning by convulsive drugs, when other agents are inappropriate or ineffective. Paraldehyde may be effective in reducing the anxiety associated with withdrawal from drugs such as narcotics or barbiturates, as well as in the management of acute agitation or delirium tremens due to alcohol withdrawal. Paraldehyde is only recommended for use in these conditions when other treatments are ineffective or deemed inappropriate.

Dosage and Administration

Paraldehyde may be administered intramuscularly undiluted by deep injection into the buttocks taking care to avoid the vicinity of the nerve trunks. Not more than 5 mL should be administered per injection site. The usual doses are as follows:

Indication	Adult Dose	Children's Dose
Hypnotic	10 mL IM	0.3mL/kg/daily IM
Sedative	5 mL IM	0.15mL/kg/daily IM
Convulsions (e.g.Tetanus)	5 to 10mL IM	Not recommended
Convulsions poisons	from 5 to 10mL IM	Not recommended
Status epilepticus	5 to 10mL IM	0.1 to 0.15mL/kg/dose IM every 4 to 8 hours
Alcohol withdrawal	5mL IM every 4 to 6 hours for 24 hours, then every 6 hours. Maximum of 30mL IM on first day and 20 mL/day IM thereafter.	

Contraindications

Paraldehyde is contraindicated in patients hypersensitive to the drug.

Paraldehyde is contraindicated in patients with severe hepatic insufficiency.

Paraldehyde should not be used for obstetric anaesthesia, as the drug diffuses across the placenta and has been known to cause respiratory depression in neonates.

Paraldehyde Injection is contraindicated in patients with bronchopulmonary disease, as unmetabolised paraldehyde (11 to 28%) is excreted via exhalation.

Warnings and Precautions

Use only freshly opened ampoules. Paraldehyde must not be used if the container has been opened as it decomposes on storage. The administration of partly decomposed paraldehyde is dangerous as it may cause metabolic acidosis. Deaths from corrosive poisoning have been reported following the use of decomposed paraldehyde. It must not be used if it has a brownish colour or a sharp penetrating odour of acetic acid.

Due to the solvent action of paraldehyde, plastic syringes must not be used. Contact between paraldehyde and rubber should be avoided.

Avoid contact with the skin, eyes and clothing.

Prolonged use of paraldehyde may lead to dependence of the barbiturate-alcohol type, especially in alcoholics. Prolonged use may also produce tolerance and physical and/or psychological dependence on the drug. Sudden withdrawal of paraldehyde from physically

dependent persons may cause delirium tremens and hallucinations. In dependent persons, the drug should be withdrawn slowly.

Toxic hepatitis, nephrosis, and metabolic acidosis have been reported following prolonged use of paraldehyde (see **Adverse Reactions**).

Paraldehyde should not be administered subcutaneously because it is irritating to tissues.

Avoid intramuscular injection near nerve trunks as this may cause severe and permanent nerve damage (see **Adverse Reactions**).

Intravenous administration is extremely hazardous since it may cause pulmonary oedema and haemorrhage, hypotension and cardiac dilatation, and circulatory collapse. Thrombophlebitis is also associated with intravenous administration. Paraldehyde should be used cautiously, if at all, in patients with cardiovascular disease, asthma or other bronchopulmonary disease.

Impaired hepatic function may result in unpredictable rates of paraldehyde metabolism and so it should be administered with caution to patients with hepatic dysfunction. Close observation should be employed to detect signs of paraldehyde toxicity. Paraldehyde is contraindicated in severe hepatic insufficiency.

Use as a hypnotic or sedative should be short term only. Patients should be warned that the hypnotic effect occurs very rapidly. Paraldehyde causes drowsiness. Hence, patients receiving paraldehyde should not drive a motor vehicle or operate machinery.

Use in pregnancy

Category D. Paraldehyde readily diffuses across the placenta and has been known to cause respiratory depression in neonates (see **Contraindications**). Therefore the use of Paraldehyde Injection BP in pregnancy is contraindicated. Pregnancy should be excluded before commencing therapy.

Use in lactation

It is not known whether paraldehyde crosses into breast milk although problems in humans have not been documented. Nevertheless because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to paraldehyde in breastfed infants, a decision should be made either to discontinue breastfeeding or the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines

Paraldehyde causes drowsiness and patients should not be allowed to drive or operate machinery.

Adverse Effects

Intramuscular administration of paraldehyde is extremely painful and has produced sterile skin abscesses, sloughing of skin, fat necrosis, and muscular irritation. Severe and permanent nerve damage has occurred when paraldehyde was injected intramuscularly too close to nerve trunks; care must be taken when administered by the intramuscular route.

Intravenous administration of paraldehyde is not recommended as it has caused pulmonary oedema, pulmonary haemorrhage, dilatation of the right side of the heart, circulatory collapse, thrombophlebitis, respiratory distress and cyanosis.

Paraldehyde may cause skin rashes. Other side effects, such as dizziness, muscle cramps, trembling and unusual sweating have been reported.

Toxic hepatitis and nephrosis have been reported following prolonged use of paraldehyde. Metabolic acidosis has also occurred following overdosage of Paraldehyde Injection and has been associated with nausea, muscular tremor, severe epigastric cramps, mental confusion, agitation, pseudoketosis, hyperacetaldehydemia. Prolonged use may also produce tolerance and physical and/or psychological dependence on the drug.

Interactions

Concomitant administration of paraldehyde with other CNS depressants such as barbiturates or alcohol should be avoided due to possible potentiation of CNS depression.

Animal studies indicate that disulfiram slows the metabolism of paraldehyde via inhibition of acetaldehyde dehydrogenase resulting in an increase in blood concentrations of paraldehyde and acetaldehyde. Therefore concomitant administration of paraldehyde and disulfiram should be avoided.

Overdosage

Paraldehyde overdosage results in short and troubled, rapid breathing. Other characteristics include cloudy urine, decreased urination, a slow heartbeat and general weakness. This may lead to coma, severe hypotension, respiratory depression, pulmonary oedema and cardiac failure. Paraldehyde-induced coma may last for several hours because it is slowly metabolised. Paraldehyde overdosage is distinguished from other CNS depressants by the odour of the drug on the breath. Metabolic acidosis with increased anion gap may also occur. Renal function may be impaired and may result in azotaemia, oliguria and albuminuria. Nephrosis, fatty changes in the kidneys or liver and/or toxic hepatitis may also occur.

Fatalities are uncommon, but when they occur they are usually caused by respiratory failure. A few fatalities have been attributed to pulmonary oedema and right-sided heart failure or metabolic acidosis.

Treatment

Treatment should be supportive and symptomatic and should include re-establishment of adequate respiratory exchange by maintenance of an adequate airway, control of respiration and oxygen administration.

Metabolic acidosis may be corrected by intravenous (IV) administration of sodium bicarbonate or sodium lactate.

Body temperature should be maintained and circulation supported, with intravenous fluids or vasopressors, if necessary.

Pharmaceutical Precautions

Store below 25°C. Protect from light. Use promptly after opening. Do not use if solution has a brownish colour or a sharp penetrating odour of acetic acid. Paraldehyde solidifies to form a crystalline mass at temperatures around 12°C. Warm gently if crystallised.

Incompatibilities

Due to its solvent action, paraldehyde is incompatible with many plastics and rubber. The use of plastic syringes for storage or administration of paraldehyde and contact with rubber

should therefore be avoided. Needles with plastic hubs may be used with Paraldehyde Injection BP. The use of polypropylene syringes with rubber-tipped plastic plungers, or glass syringes with natural rubber-tipped plastic plungers is acceptable only for the immediate administration or measurement of paraldehyde doses. It is recommended that all-glass syringes should be used for the injection of paraldehyde.

Medicine Classification

Prescription Medicine

Package Quantities

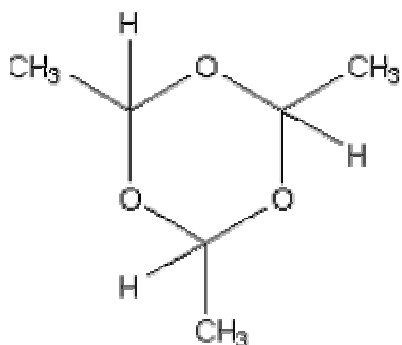
Paraldehyde Injection BP is available in 5mL vials in packs of 5.

Further Information

Paraldehyde is soluble 1 in 10 of water, but is only soluble 1 in 17 in boiling water. It is miscible with alcohol, chloroform, ether and volatile oils. Paraldehyde solidifies to form a crystalline mass at low temperatures, but can be liquefied by warming.

The chemical name of paraldehyde is 2,4,6-trimethyl-1,3,5-trioxane. Paraldehyde is a cyclic trimer of acetaldehyde. The molecular formula of paraldehyde is $(C_2H_4O)_3$. Its molecular weight is 132.2 and its CAS registry number is 123-63-7.

The chemical structure of paraldehyde is shown below:



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