

Expert information

**from the GV-SOLAS Committee for
Anaesthesia in collaboration with Working
Group 4 in the TVT**

Information on the use of chloral hydrate in experiments with rodents and rabbits

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Chloral hydrate

General information

Other names: trichloroacetaldehyde monohydrate

2,2,2-Trichloroacetaldehyde hydrate

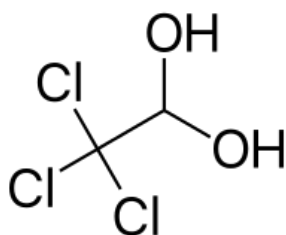
2,2,2-Trichloroethane-1,1-diol

Chemical formula: $C_2H_3Cl_3O_2$

Colourless translucent crystals

Risk: toxic or very toxic

Active substance class: Hypnotics / sedatives



General information and structural formula from https://en.wikipedia.org/wiki/Chloral_hydrate and <http://www.pharmawiki.ch/wiki/index.php?wiki=Chloralhydrat>.

The following details have been summarized on the basis of the literature (see literature list below). The experiences of the authors and personal reports have been taken into account in the statement.

Historical background and use in human medicine and veterinary medicine

First synthesized by Justus Liebig in 1832 it was used as a medicine in the late 19th century. After its introduction as a hypnotic by Oskar Liebreich in 1869, it found widespread use as a soporific agent in human medicine.

Chloral hydrate was used in animals mainly for anaesthesia, especially for induction of anaesthesia in horses and bovines. In 1875, for example, Humbert reported its use in horses and in 1872 Ore reported its use for anaesthesia in dogs and in tetanus patients.

A mixture of chloral hydrate, pentobarbital and magnesium sulphate had been used earlier in rats; however, the corresponding product Equithesin has not been commercially available for decades and nor has Chloropent, a product with a similar composition.

Today, chloral hydrate is little used in human medicine. In Germany it is approved as a prescription-only soporific and sedative agent for rectal administration in humans under the name Chloralhydrat-Rectiole®. For the treatment of sleep disorders in humans, Chloraldurat® soft gelatin capsules (250 mg, 500 mg) and Nervifene® solution are commercially available for oral administration in some countries.

Chloral hydrate is not currently approved as a veterinary agent. It was used in veterinary medicine as a pre-anaesthetic administered to horses i.v. in combination with other

substances. It has been replaced by modern and more effective methods of anaesthesia and is hardly used at all now (Frey & Löscher 2009).

Previous use in laboratory animals

In laboratory animals, chloral hydrate is used for anaesthesia in certain experiments if the effects and side effects of more modern substances interfere with the objective with the experiment.

In laboratory animals, chloral hydrate is administered by both the i.v. and the i.p. route. Paravenous injection leads to tissue necrosis. Intraperitoneal (i.p.) injection leads to local tissue reactions in the abdomen (such as serositis, steatitis and fibrosis) and ileus, the extent of the lesions being dependent on the concentration of the injection solution (Vachon et al. 2000, <http://vetmed.duhs.duke.edu/GuidelinesforChloralHydrate.html>, and others).

High doses of chloral hydrate can exert a hepatotoxic effect with repeated i.p. injections (Yu et al. 2015).

Practical use: Preparation, storage, properties of injection solution, route of administration

- Dry substance
 - Colourless, translucent crystals, evaporates on exposure to air, water and lipid-soluble
 - Bitter taste
 - Caustic: irritation of skin, subcutis and mucous membranes
- Concentrations of injection solution: 7-12%
- Reduction in the liver to trichloroacetic acid and trichloroethanol (active component, acts on GABA receptor)
- Renal elimination
- Slow crossing of blood-brain barrier results in delayed onset of action

In humans, chloral hydrate is currently administered by the oral or rectal route.

In animals, chloral hydrate is predominantly administered i.v., whereby dose titration is also practised until an effect is achieved (e.g. horse). Oral administration can evidently lead to vomiting especially in carnivores and omnivores (Branson 2001).

In small laboratory animals, chloral hydrate has also been administered intraperitoneally (i.p.).

Characterization of the anaesthetic: properties and side effects of anaesthesia

Cerebral depression with loss of reflexes

Hypnosis for some hours

Weak analgesic properties

Cardiovascular depression:

Sub-anaesthetic/hypnotic dosing: effect similar to that of natural sleep

Anaesthetic dosing: similar to barbiturates (pentobarbital), dose-dependent fall in blood pressure and cardiac output, "potentiates" vagal activity (questionable synergism with α_2 agonists)

Depression of respiratory centre:

Sub-anaesthetic/hypnotic dosing: effect similar to that of natural sleep

Anaesthetic dosing: similar to barbiturates (pentobarbital), dose-dependent decrease in minute volume and increase in PaCO₂.

Summary

Chloral hydrate is a hypnotic (soporific agent) without any (or if anything with a weak) analgesic effect.

Since there are no ready-made medical grade formulations available, the injection solutions have to be prepared in the laboratory "chemical grade", which poses an increased risk in the use of the substance. Aside from the potential risk to staff, errors or carelessness in the preparation of the injection solution (e.g. concerning the concentration, solvent, contamination, etc.) can lead to uncertainties with regard to the anaesthesia and morbidity.

The therapeutic index is very narrow. In other words, the dose required to achieve deep anaesthesia is relatively close to the lethal dose. As a single anaesthetic, it is only suitable when hypnosis and immobilization of medium duration are sought and other methods are ruled out by the nature of the experiment.

For surgical and other painful procedures, it must be combined with an analgesic substance, especially if the experiment entails recovery from the anaesthesia.

Major criticisms concerning the use of chloral hydrate are the tissue necrosis to be expected if it is not administered by strictly intravenous (i.v.) injection and also ileus and local inflammatory reactions following intraperitoneal (i.p.) injection. These complications are presumably due to the irritant effect of chloral hydrate on tissues. Since chloral hydrate is approved as a soporific and sedative agent for oral or rectal administration in humans, it is likely that these complications are primarily associated with the route of administration. In laboratory animals, therefore, chloral hydrate should only be administered intravenously. In this case, it must be guaranteed that the methodological requirements for safe intravenous administration (mastery of the administration technique and, where applicable, a venous line/catheter etc.) are met.

In principle, chloral hydrate should only be used in experiments in which other, more modern and safer substances are ruled out or in which it is concluded, after careful consideration, that all alternatives are less suitable.

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