BACD British Academy of Childhood Disability

BPNA British Paediatric Neurology Association

Association for Paediatric Palliative Medicine

NPPG Neonatal & Paediatric Pharmacists Group

Position statement

Off label use of Chloral Hydrate in the Management of Intrusive Movement and Motor Disorders in Children and Young People

Introduction

In October 2021, the MHRA *Drug Safety Update* described a new restriction to use of chloral hydrate and cloral betaine due to the potential for carcinogenic effects, based on animal data. Licensed use is now limited to short-term (maximum 2 weeks) treatment of severe insomnia, only in patients with a suspected or confirmed neurodevelopmental disorder and when the insomnia affects normal daily life.

Chloral hydrate is however also used for other, off-label indications. This position statement outlines considerations for off-label use of chloral hydrate to manage distressing symptoms in patients with movement and motor disorder when all other therapies have failed. It also provides recommendations for appropriate discontinuation of chloral hydrate where it is being used to treat insomnia in the absence of movement and motor disorders. Off-label use for other indications, e.g. sedation in paediatric intensive care and procedural sedation is outside the scope of this document.

Take Home Summary

Use of chloral hydrate for insomnia

- In line with the MHRA position, chloral hydrate use for insomnia should be limited to patients with a suspected or confirmed neurodevelopmental disorder, with a maximum duration of 2 weeks.
- Where a patient is currently receiving regular, long-term chloral hydrate for the management of insomnia:
  - They should be reviewed by a relevant specialist and a plan made for discontinuation of the drug. Due to risks associated with sudden cessation of chloral hydrate, this will usually require a gradual, controlled discontinuation. Do not stop abruptly if patients have been taking the drug regularly for over 2 weeks.
  - Alternative pharmacological or non-pharmacological treatments may be required. Consider referring to a local sleep service where appropriate and available.

Use of chloral hydrate in children and young people with movement disorders

- It may be appropriate to use chloral hydrate off-label to manage distressing symptoms in patients with movement and motor disorder when all other therapies have failed OR rapid stabilisation of symptoms is required. This may include:
  - Acute, time-limited regular use to manage symptom exacerbations: this must be under very close, specialist supervision
  - Longer term (duration over 1 month), regular (daily or more frequently) use in children and young people with severe intrusive movement and motor disorders preventing the initiation and maintenance of sleep, after assessment by a consultant with expertise in paediatric neurology.
  - Longer term "when required" use, or repeated short courses for break through symptoms as part of a symptom management plan. Such plans should specify a maximum number of doses per month or continuous days of treatment over which the patient should be reassessed by the relevant specialist team.
- When using chloral hydrate for movement disorders, use the lowest effective dose, at the lowest frequency and for the shortest period possible. The need for ongoing use should be regularly assessed and documented.
- Where use of chloral hydrate is considered appropriate:
  - Informed consent to use chloral hydrate must be obtained and documented.
  - Use must be under the supervision of a named consultant with appropriate experience and competency in paediatric neurology, neurodisability, and/or palliative care who must regularly review the patient, being alert to signs of inappropriate use and aiming to deescalate wherever possible.
  - A written emergency escalation plan which includes the contact details for the supervising clinical team should be provided to the family and other healthcare professionals. Such plans should specify a maximum number of doses per month or continuous days of treatment above which the patient should be reassessed by the relevant specialist team.
- Hospitals and primary care providers must work together to identify and plan for timely review of all patients currently receiving chloral hydrate. Development of local guidelines to describe the governance arrangements for any ongoing use should be considered.
- Where a chloral hydrate liquid is required, the standardised concentration of 500mg in 5mL should be used.

Supporting Information

Chloral hydrate

Chloral hydrate and its prodrug cloral betaine are enterally administered sedative agents, and have been widely used in paediatric practice for many years. After absorption chloral hydrate is rapidly converted to its active metabolite trichloroethanol[1], the exact mechanism of action of which is unclear, though agonism at GABA receptors is likely[2].

Adverse effects of chloral hydrate include apnoea, desaturation, vomiting and prolonged sedation; these features are more likely to be seen in patients under 6 months of age[3]. Disorientation, paradoxical excitement, delirium, gastritis, depressed cardiac contractility and arrhythmia have also been reported[3,4]. Features of toxicity include prolonged CNS depression, tachycardia, hypotension, supraventricular and ventricular dysrhythmias and torsade de pointes[5]. Corrosive effects in the gastrointestinal tract may lead to gastric necrosis and perforation[5].

Chloral hydrate has been used for a range of indications including night time sedation; management of dystonia and other movement disorders; sedation in critical care; and sedation for painless procedures [6-9]. Use for night time and procedural sedation has declined in the USA, and the drug is now not readily available in America[8,10]. Reasons cited for the decline include a narrow therapeutic index, no known antidote, prolonged sedation or clinical re-sedation and fatalities associated with chloral hydrate sedation[10]. In 2009, following a national review of safety and efficacy, the MHRA limited the licensed indication for chloral products to "*severe insomnia that is interfering with normal daily life and where other therapies have failed, as an adjunct to nonpharmacological therapies*" [11].

In October 2021, after a subsequent review of published evidence, the MHRA issued a Drug Safety Alert further restricting the licensed indication to the "*short term treatment (maximum 2 weeks) of severe insomnia only when the child or adolescent has a suspected or definite neurodevelopmental disorder and when the insomnia is interfering with normal daily life*" [12]. No new safety concerns had been identified. However, in view of known carcinogenic effects in animal models and a lack of long-term studies in humans, the risk of harm associated with extended use could not be excluded.

Management of movement disorders

Dystonia in children can be particularly challenging, interfering with normal movements, mobility and the delivery of daily care, as well as causing problems with feeding and communication[13]. Dystonia can have a significant adverse effect on quality of life, and is associated with disturbed sleep[14].

Use of chloral hydrate for management of dystonia and other movement disorders is off label. None of the chloral products in the UK are licensed for these indications. Whilst use in these conditions is not widespread, chloral remains a valuable tool in their management[6,7]. Although chloral hydrate is not considered a first-line treatment for movement disorders, it can be valuable for the acute management of established status dystonicus and in preventing progression from worsening dystonia to a full dystonic crisis.

There are a number of circumstances where there may be a role for chloral hydrate in children and young people with intrusive/distressing symptoms of a movement or motor disorder:

- When severe exacerbations of symptoms occur (e.g. status dystonicus) time-limited use of regular chloral hydrate may be necessary to achieve acute symptom improvement. Use in these circumstances must be closely supervised, ideally in an inpatient setting, and should not ordinarily last for more than a few days. Clinicians must carefully monitor for symptoms of respiratory depression (particularly in children and young people receiving other sedative medications), the risk of developing tolerance and dependency, gastric irritation and the adverse effects that higher doses of chloral hydrate can have on cognition and psychological wellbeing. The lowest effective dose of chloral hydrate should be used, with the longest time interval possible between doses. Use in these circumstances should be seen as temporising, providing symptom control whilst more definitive interventions are applied (e.g. escalation of background anti-dystonic medication).
- Longer term, to facilitate sleep to support pain, distress and/or agitation management strategies when other therapeutic options have been exhausted.
- Longer term use for break through dystonia symptoms as part of a formalised symptom management plan.

Prolonged use must always be with explicit and documented consent from parents/carers, having informed them of the potential risks as outlined above.

References

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Disclaimer

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Key changes from Version 2 (published December 2021):

- Expansion of supporting information on situations where use of chloral hydrate in use of dystonia may be appropriate.

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