AMERICAN ACADEMY OF PEDIATRICS

Use of Chloral Hydrate For Sedation in Children

Committee on Drugs and Committee on Environmental Health

Publicity about the possible carcinogenicity of chloral hydrate along with the suggestion that alternative sedatives should be used in children has generated concern among physicians, dentists, and their patients.[1,2] Replacement of chloral hydrate with other sedatives would represent a major change in practice because it is one of the drugs most widely employed to sedate young children undergoing dental and medical procedures and imaging studies. This statement will assist the practitioner in making an informed decision regarding the use of chloral hydrate by summarizing (1) information pertaining to the potential for carcinogenesis associated with use of chloral hydrate, (2) the risk/benefit considerations of available sedatives, and (3) risks associated with prolonged sedation with chloral hydrate.

EVIDENCE FOR CARCINOGENESIS OF CHLORAL HYDRATE

Some of the concern regarding potential carcinogenicity of chloral hydrate is based on the assumption that chloral hydrate is a reactive metabolite of trichloroethylene, an industrial solvent, and is responsible for the carcinogenicity of trichloroethylene.[1,2] However, the validity of this assumption is open to question. Although chloral hydrate is a metabolite of trichloroethylene, there is evidence that the carcinogenicity of trichloroethylene is due to a reactive intermediate epoxide metabolite rather than chloral hydrate.[3] As is the case for most chemical carcinogens, trichloroethylene is carcinogenic in some laboratory animal species but not in others.[4] Multiple epidemiologic studies in humans have failed to document an increase in cancer incidence associated with trichloroethylene exposure,[5–10] although the ability of these studies to detect small increases in risk of cancer is limited.

There are no studies pertaining to chloral hydrate-associated carcinogenicity in humans. The evidence that chloral hydrate is carcinogenic comes from two studies in male B6C3F1 mice. Rijhsinghani and colleagues reported hepatic adenomas or carcinomas in 6 of 8 mice 48 to 92 weeks after they received a single 10 mg/kg dose of chloral hydrate orally as weanlings, whereas 2 of 19 control mice developed tumors.[11] In another study conducted by the Environmental Protection Agency,[12] 24 juvenile mice received 166 mg/kg chloral hydrate daily for 2 years. The incidence of hepatic tumors in the treated mice was 71%, whereas the rate in controls was 15%. Of the chloral hydrate-treated animals, 75% also had other hepatocellular pathologic changes including cytoplasmic alteration, hepatocellular necrosis, hepatocellular hyperplasia, chronic inflammation, and cytomegaly.

Chloral hydrate damages chromosomes in selected mammalian test systems under certain experimental conditions. At high in vitro concentrations, chloral hydrate produced nondisjunction in mouse spermatocytes and Chinese hamster cells resulting in aneuploidy.[13–15] In one study, orally administered chloral hydrate increased single-strand breaks in hepatic DNA of male B6C3F1 mice and Sprague-Dawley rats.[16] However, these observations have not been corroborated by others, and a recent study showed that chloral hydrate does not produce DNA strand breaks in the liver tissue of mice or rats, in primary cultures of rat or mouse hepatocytes, or in a cultured lymphoblastoid cell line.[17] Aneuploidy[18] and sister-chromatid exchanges[19] were observed in human lymphocytes exposed for 24 hours in vitro to concentrations of chloral hydrate ranging from 211 to 1000 mg/L.

Because toxicity data in humans are difficult to obtain and frequently are limited, laboratory studies are usually the basis for the regulation of environmental chemicals, food additives, and chemicals encountered in the work place. In general, chemicals found to be carcinogenic in animals are regulated very strictly or, in some cases, banned. Laboratory studies also provide a basis for evaluating the risk to humans from therapeutic agents, and such testing is required for new drugs. However, drugs, in contrast to environmental residue chemicals, offer some benefit, and there are many situations in which the benefit to the patient outweighs any potential risk. Therefore, therapeutically useful drugs that cause cancer in animals are sometimes used in the treatment of patients when the benefit from the drug outweighs the potential risk.

USE OF CHLORAL HYDRATE COMPARED WITH OTHER SEDATIVE/HYPNOTIC DRUGS

Sedative/hypnotic agents allow important diagnostic and therapeutic procedures to be performed safely and successfully in children. For decades chloral hydrate has been widely used for short-term sedation of children.[20–22] The acute toxicity of chloral hydrate when used in recommended single doses

for sedation is low. The lethal to therapeutic dose ratio is much higher than with the barbiturates.[23] However, acute overdoses may cause cardiorespiratory depression.[23] On rare occasions, excessive or repetitive doses have been associated with cardiac arrhythmias.[24–26]

Alternatives to chloral hydrate for short-term sedation of children include the barbiturates, phenothiazines, and benzodiazepines. Although the opiates produce sedation, they usually are reserved for situations in which some degree of analgesia in addition to sedation is desired and are not considered comparable to the nonanalgesic sedative/hypnotics.

Chloral hydrate is not the only sedative that is a carcinogen in experimental animals. Some of the benzodiazepine and barbiturate sedatives also have been shown to be carcinogenic in animal studies.[27–29] In addition, the barbiturates have been associated with a possible increased incidence in malignant tumors in humans.[30]

Each of the sedative/hypnotics has advantages and disadvantages that should be considered when selecting one for inducing short-term sedation. Administration of any sedative entails some degree of risk and requires proper monitoring of the patient to minimize that risk.[31] Drugs from each of the classes of sedatives may be administered safely and effectively by physicians and dentists who are experienced in their use and who exercise proper monitoring procedures. Currently, sufficient data are not available in infants and children to establish any of the available sedatives as superior with respect to either efficacy or safety. Furthermore, available information regarding long-term theoretical risk of carcinogenicity does not provide a basis at this time for sufficient concern to warrant selection of an alternative sedative to chloral hydrate. Therefore, physicians and dentists should select a sedative based on the type and degree of sedation required and their knowledge and experience with the respective sedatives. A sudden switch by physicians and dentists from a sedative with which they are familiar to one with which they have less experience and for which there are not sufficient safety and pharmacologic studies in children may pose a greater immediate risk to children than a theoretical risk of carcinogenesis from a single sedative dose of chloral hydrate. In this case, the brief episodic nature of the exposure to chloral hydrate and the lack of clearly superior alternatives argue for its continued use when, in the judgment of the physician or dentist, it is indicated.

REPETITIVE DOSING WITH CHLORAL HYDRATE

It is common practice in many hospitals to administer chloral hydrate in repetitive doses to maintain prolonged sedation in infants and children during mechanical ventilation.[32,33] However, there is reason to be concerned about this practice. Chloral hydrate is metabolized to trichloroethanol and trichloroacetic acid, both of which are pharmacologically active and may contribute to the acute toxicity of chloral hydrate. The half-life of trichloroethanol ranges from 9 to 40 hours, depending on age and maturity of the patient.[34] The half-life of trichloroacetic acid is even longer; in one study its concentration did not decline in infants for 6 days after a single 50 mg/kg dose of chloral hydrate.[34] The long half-lives of these metabolites lead to their accumulation during repetitive dosing with chloral hydrate.[32,34] Although the accumulation of active metabolites is of concern, published documentation of clinical toxicity is limited. There is evidence that chloral hydrate and/or trichloroethanol may increase the risk of both direct and indirect hyperbilirubinemia in newborns.[32,35] Furthermore, trichloroacetic acid is highly protein-bound[36] and theoretically could compete with bilirubin for albumin binding sites. It also has been suggested that high concentrations of trichloroacetic acid may contribute to metabolic acidosis.[37] Toxicity characterized by respiratory depression and hypotonia associated with a trichloroethanol plasma concentration seven times that associated with sedation in adults was reported in an infant receiving multiple doses of chloral hydrate while on mechanical ventilation.[38] The infant recovered 7 days after discontinuation of chloral hydrate administration.

CONCLUSIONS AND RECOMMENDATIONS

1. Chloral hydrate is an effective sedative with a low incidence of acute toxicity when administered orally in the recommended dosage for short-term sedation. There is a great deal of experience with chloral hydrate and most practitioners are familiar with its use.
2. Repetitive dosing of chloral hydrate is of concern because of accumulation of the metabolites, trichloroethanol and trichloroacetic acid, which may produce excessive central nervous system depression, predispose newborns to conjugated and nonconjugated hyperbilirubinemia, decrease albumin binding of bilirubin, and contribute to metabolic acidosis.
3. Although available information regarding theoretical long-term risk of carcinogenicity is of concern, it does not provide a basis for sufficient concern to warrant selection of an alternative sedative rather than chloral hydrate.
4. Sufficient data are not available for children to establish any of the available sedatives as superior with respect to either efficacy or safety. A sudden switch by physicians and dentists from a sedative with which they are familiar to one with which they have less experience and for which there are not sufficient safety and pharmacologic studies in children may pose a greater immediate risk to children than a theoretical risk of carcinogenesis from short-term sedation with chloral hydrate.
5. Additional well-designed studies in infants and children need to be conducted to provide the information necessary for the safest and most efficacious use of sedatives in pediatric patients.

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