Anxiolytic activity of chloral hydrate and hydroxyzine

M. Gladney, DMD, MS R.T. Stanley, DDS S.E. Hendricks, PhD

Abstract

The combination of chloral hydrate and hydroxyzine is given frequently to anxious pediatric dental patients. In order to observe and quantify the anxiolytic effects of these drugs given alone and in combination, highly explorative male C57/black mice were tested using the light/dark test box after injecting subhypnotic doses for increased transitions between the light and dark side of the test box. Fifty-one mice were subjected individually to a 10-min test in the box for dose responses following the i.p. administration of 32-, 64-, and 132-mg/kg doses of chloral hydrate; 1-, 4-, 7-, and 10-mg/kg doses of hydroxyzine; or a combination of each of these doses of hydroxyzine and chloral hydrate. The automated test box recorded the number of times a mouse crossed between the two chambers. Doses of chloral hydrate 132 mg/kg and hydroxyzine 1 mg/kg resulted in significantly increased transitions. None of the combinations studied produced significantly increased transitions when compared with the effective doses identified for each individual drug. The paradigm did not support the hypothesis that the anxiolytic effects of chloral hydrate and hydroxyzine are additive or synergistic. (Pediatr Dent 16:183–89, 1994)

Introduction and literature review

Antianxiety drugs are referred to by many terms[1] including "anxiolytic," which refers to drugs that have more specific anxiety reduction properties than CNS depression properties. Anxiolytics allow a patient to maintain near-normal motor function while sedatives (or sedative doses) severely impede motor and cognitive function.

Dentists have long sought a single, safe, orally administered drug that would reliably reduce anxiety in children and adults when administered prior to dental treatment. No single drug has all the effects desired by many dental practitioners, therefore there is considerable use of combinations of orally administered sedative agents.[2–5] Some combinations were initially used on an empirical basis. Few basic animal studies were done on these combinations prior to their use in dentistry. One notable animal study was done by Pruhs,[6] who investigated the effects of adding nitrous oxide to chloral hydrate. Pruhs' study, like this one, attempted to provide a basic understanding of some narrow part of the activity of a popular combination used in pediatric dentistry. There are a few animal studies of the sedative and antianxiety effects of chloral hydrate and hydroxyzine as single agents. Stuphel[7] studied the effect of hydroxyzine on aggressiveness of mice and Lenegre[8] used mice to find that amnesia induction was not a property of subhypnotic doses of hydroxyzine. Pollard[9] reviewed studies of pigeons and rats that tested the effects of many drugs, including chloral hydrate, on punished responses.

Most of the antianxiety studies of the currently popular dental combinations like chloral hydrate and hydroxyzine were done approximately 20 years ago and used a more aversive test than the one utilized in this study. Many of the modern benzodiazepine-type anxiolytic agents were tested prior to clinical use in the light/dark test box utilized in this study.[10] No readily available reports evaluate the antianxiety effects of hydroxyzine hydrochloride and chloral hydrate in a modern mouse anxiety paradigm. Many physiologic and behavioral clinical studies have appeared in the pediatric dental literature, but clinical use and research have not clearly established the anxiolytic effectiveness of the combination.

Justifiably or not, anxiety reduction is often alluded to in clinical studies, texts, lectures, and case reports on the use of combinations. There appears to be a collective opinion among pediatric dentists who have studied anxiolytic agents that an effective agent for uncooperative dental patients would have a primary effect against anxiety.[11]

Chloral hydrate

The efficacy of chloral hydrate as an anxiolytic agent has been questioned frequently. The pharmacological and medical literature frequently cites only limited anxiolytic effectiveness in old clinical reports.[9]

Chloral hydrate has been used by 25 to 40% of American and Canadian pediatric dentists surveyed between 1973 and 1987 to calm fearful or uncooperative pediatric dental patients.[2, 4, 5, 12, 13]

Hydroxyzine hydrochloride

Hydroxyzine has an excellent safety record and has been widely used by dentists for many years.[1–14] Pediatricians have also used hydroxyzine to sedate mildly anxious children for less threatening medical procedures and for anxiety states such as those associated with school refusal.[15] The anxiolytic activity of hydroxyzine, like chloral hydrate, has been questioned

frequently. The medical literature on hydroxyzine consists mostly of old clinical reports that cite limited effectiveness as an anxiolytic.[9] Hydroxyzine's popularity as an anxiolytic has been described as "surprising in view of studies that suggest that it is not an effective antianxiety agent unless it is given in doses that produced marked sedation."[16]

Although little is written about the pharmacologic effects of the combination of chloral hydrate and hydroxyzine, the dental literature contains many studies and clinical reports on the use of the combination. Several studies involve the popular combination of chloral hydrate and the antihistamine promethazine, which could be expected to possess activity similar to those associated with the combination of chloral hydrate and hydroxyzine.[17,18] The available clinical studies involving the combination of chloral hydrate and hydroxyzine and the individual drugs alone, though numerous, present conflicting findings. The clinical studies conducted by Epstein[19] and Kopel[20] did not produce evidence of hydroxyzine efficacy in reducing dental apprehension. Linnenburg and Lang's studies claimed that hydroxyzine has value as premedication for anxious dental patients.[21, 22] Shapira rated hydroxyzine as "successful" in a majority of pediatric dental patients studied when he evaluated the effects of combining nitrous oxide and hydroxyzine. Shapira[23] found that a combination of the two agents made the sedation more "successful." Smith[24] found chloral hydrate to be no more effective than a placebo in a double-blind study of handicapped pediatric dental patients. Houpt[17] rated as successful 72% of the sedations of an experimental group of children receiving chloral hydrate. Badalaty,[25] in a study that compared chloral hydrate and diazepam, rated 46.6% of a group of chloral hydrate sedations to be excellent or good, which was not significantly different from that of diazepam.

The dental literature rarely makes any specific reference to the early use of combinations of oral anxiolytic/sedatives agents used in dentistry. Several popular dental texts recommend and describe using the combination of chloral hydrate and hydroxyzine, although numerous clinical studies describe conflicting and varying degrees of efficacy of these drugs alone or in combination.[14, 26]

Despite a lack of consistent, unchallenged clinical research, chloral hydrate alone or in combination with another agent is the most frequently used oral premedication for difficult patients.[2,3] The literature is replete with studies indicating success rates ranging from less than 30% to more than 85% when the combination is used to calm anxious dental patients. These studies evaluate the combination of chloral hydrate at varying doses, patient ages, pretreatment behaviors, mental capacities, environmental settings and concomitant use of other agents. The lack of consistency of variables and the use of inconsistent and sometimes subjective behavior evaluation criteria makes it difficult for practitioners to gain a good understanding of the indications, dosing, and realistic expectations of achievable results when using the combination of chloral hydrate and hydroxyzine.

Animal studies

In contrast to the many widely varying and difficult to control clinical studies, few studies have examined the efficacy of the combination of chloral hydrate and hydroxyzine in the more controllable animal population. The widely varying clinical conclusions and study criteria demonstrate a need to retreat and seek to answer basic questions: Can the anxiolytic effects of chloral hydrate or hydroxyzine be demonstrated in a modern, simple animal model? Does the addition of weakly anxiolytic hydroxyzine produce a synergistic or additive effect on the weakly anxiolytic properties of chloral hydrate?

The pharmacologic effects in which pediatric dentists are most interested are anxiety reduction, arousable sleep induction, and physiologic tolerance. Physiologic tolerance measurement in children has been adequately defined for oral sedatives including chloral hydrate and hydroxyzine by clinical studies and reports.[12, 27–33] Objectivity and control of variables are well established in such studies. Anxiety reduction and therapeutic efficacy, on the other hand, are difficult to measure and have been associated with contamination and with investigator and rater bias. Poorly controlled clinical studies have often proclaimed impressive efficacy, while controlled clinical studies have yielded inconsistent findings.[34]

There are a number of animal paradigms that can be specifically designed to test the anxiolytic versus sedative actions of drugs. In the strictest sense, anxiolytic activity occurs without producing sedation. Because anxiety reduction is mentioned in many dental articles about conscious sedation, it warrants study. Drugs that affect anxiety are often subjected to preclinical evaluation in rodents utilizing the light/dark transition box, the elevated plus maze and other paradigms.[10, 35–40]

Specific studies involving the combination of chloral hydrate and hydroxyzine were not done before clinical use of the combination became popular. Because human behavior is subject to a host of environmental, psychological, social, and metabolic variables that affect a child's cooperation level, this study makes no attempt to make conclusions other than those concerning the synergism, additive effects, or lack of effectiveness of the component drugs when they are used alone or combined, insofar as they can be demonstrated in a scientifically verified mouse antianxiety paradigm.[10]

The primary purpose of the experiment was to determine if chloral hydrate alone, hydroxyzine alone, or combinations of two drugs could be tested for anxiolytic activity in the light/dark test box. The secondary pur-

pose of the experiment was to determine if additive anxiolytic activity could be demonstrated when the two drugs were combined.

Methods and materials

Fifty-one male C57/Black mice, 6–8 weeks old, weighing from 21–25 g, (Jackson Laboratory, Bar Harbor, ME) were housed in the animal care unit of the National Institute of Dental Research in four groups of ten and one group of 11. The mice were randomly selected for the first of up to four tests using different treatment regimens resulting in a total of 195 10-min tests in the light/dark test box. Subsequent treatments selectively excluded repeating the test with the same drug regimen on any mouse.

The research described in this article was reviewed and approved by University of Nebraska Institutional Animal Care and Use Committee and the National Institute of Dental Research Animal Care and Use Committee.

Anxiety reduction in mice was measured by quantifying the exploratory behavior of mice isolated and placed in an aversive lighted environment of the light/dark test box after administration of:

1. Chloral hydrate (Geneva Pharmaceuticals—Bloomfield, CO) alone.
2. Hydroxyzine hydrochloride (Warner Chilcott Labs—Morris Plains, NJ) alone.
3. Combinations of subsedative doses of chloral hydrate and hydroxyzine hydrochloride.
4. USP Saline for Injection (Abbott Laboratories) used for both placebo and diluent. Placebo treatments were given throughout the experiment and formed the baseline value to compare increases or decreases in transitions.

A constant temperature of 21°C and a controlled lighting schedule of 0600 to 01800 hrs in the housing unit were maintained. The mice were fed ad lib with standard laboratory chow. Between 0700 and 1400 hours, a group of mice were brought to an animal procedure room. The mice were given a minimum of 1 hr to acclimate to the test room before receiving an intraperitoneal injection of the test drugs or placebo. A 0.5-cc, 28-gauge ultrafine needle, insulin syringe was used to inject the small volumes of medication needed. The intraperitoneal route was selected to facilitate more accurate dosing. Identification marks were placed on the tails of the mice immediately after injection. The injected mouse was then returned to the housing cage. After 30 min the mouse was removed from the housing cage and placed in the center of the lighted part of the light/dark test box. The number of times the animal would cross between the lit and darkened side of the test box in a 10-min period was recorded.

Table. Results of all treatments

	H0 mg/kg	*H1 mg/kg*	*H4 mg/kg*	*H7 mg/kg*	*H10 mg/kg*
C0 mg/kg	C0+H0 (Sal) N = 25 Tr = 55.04 SD = 7.07 SE = 1.41	•C0+H1 N = 8 Tr = 69 SD = 9.74 SE = 3.44	C0+H4 N = 8 Tr = 57.75 SD = 11.65 SE = 4.12	C0+H7 N = 8 Tr = 50.75 SD = 11.23 SE = 3.97	C0+H10 N = 8 Tr = 46.63 SD = 6.93 SE = 2.45
C32 mg/kg	C32+H0 N = 8 Tr = 61 SD = 6.87 SE = 2.43	C32+H1 N = 8 Tr = 64.75 SD = 7.40 SE = 2.62	†C32+H4 N = 8 Tr = 40.1 SD = 9.80 SE = 3.47	†C32+H7 N = 8 Tr = 41.14 SD = 12.33 SE = 4.36	†C32+H10 N = 8 Tr = 27.5 SD = 17.19 SE = 6.08
C64 mg/kg	C64+H0 N = 8 Tr = 54.25 SD = 14.46 SE = 5.11	C64+H1 N = 8 Tr = 49.88 SD = 12.21 SE = 4.32	C64+H4 N = 8 Tr = 57.25 SD = 13.70 SE = 4.84	C64+H7 N = 8 Tr = 50.88 SD = 16.60 SE = 5.87	C64+H10 N = 8 Tr = 43 SD = 27.75 SE = 9.81
C132 mg/kg	•C132+H0 N = 10 Tr = 74.8 SD = 14.66 SE = 4.64	C132+H1 N = 8 Tr = 52.25 SD = 11.13 SE = 3.94	C132+H4 N = 8 Tr = 50.25 SD = 18.27 SE = 6.46	†C132+H7 N = 8 Tr = 37.00 SD = 15.1 SE = 5.37	†C132+H10 N = 8 Tr = 33.25 SD = 24.89 SE = 8.80
	Doses used for dose responses only. Not used in combinations.		›	C0+H0.5 N = 8 Tr = 53.00 SD = 12.75 SE = 4.51	†C200+H0 N = 8 Tr = 28.13 SD = 20.22 SE = 7.15

Abbreviations: Saline (Sal) Chloral hydrate(C), Hydroxyzine (H), Transitions (Tr), Standard deviation (SD), Standard error (SE).

• Doses that significantly increased transitions. † Doses that significantly decreased transitions.

Testing apparatus

The light/dark test box consists of a polypropylene cage (44x21x21 cm) divided into a large uncovered transparent compartment and a painted and covered dark compartment half the size of the larger compartment. The dimensions were selected because mice prefer dark,

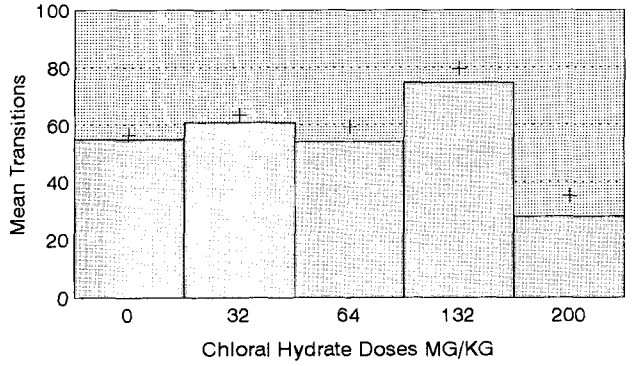

Fig 1. Chloral hydrate dose response.

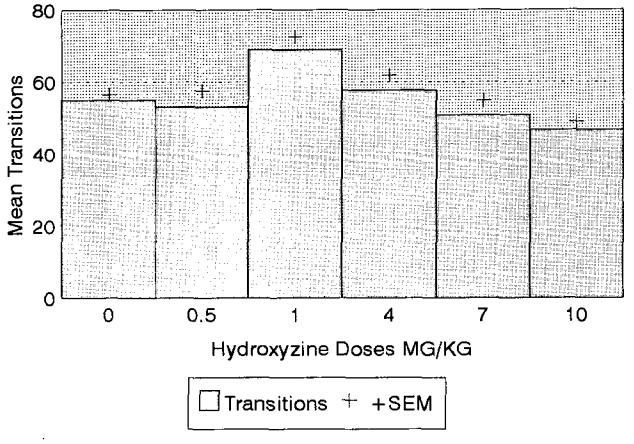

Fig 2. Hydroxyzine dose response.

small areas to larger, brightly lit areas when in an unfamiliar environment. The two compartments were separated by a Plexiglass (Plakolite Inc., Columbus, OH) partition with a 13x5-cm-high passageway. The number of transitions between the light and dark side and time spent on the dark side (seconds) were electronically measured by programming a set of photoelectric cells to sequentially exclude head pokes and count only full body transitions. The electronic circuitry included a timer that was set at the beginning of the experiment to stop counting light/dark transitions and time spent on the dark side automatically after 10 min.

Results

The table summarizes all treatment results. Note that the doses of 0.5 mg/kg of hydroxyzine and 200 mg/kg of chloral hydrate were used to define anxiolytic dose response endpoints, and hence were not used in the combinations. None of the combinations produced an increase in mean baseline transitions significantly greater than that produced by chloral hydrate alone at a dose of 132 mg/kg.

Analysis of single-drug treatments

Analysis of variance applied to mean transitions for mice receiving chloral hydrate alone (32, 64, 132, or 200 mg/kg) or saline revealed a significant overall effect for drug treatment ($F = 17.29$, $P < 0.0001$). Mean transitions for each dose of chloral hydrate are presented in Fig 1. Dunnett's t-test (alpha = 0.05, confidence = 0.95) revealed that a 132-mg/kg dose of chloral hydrate resulted in significantly increased transitions compared to saline. A 200-mg/kg dose of chloral hydrate resulted in significantly decreased transitions compared with the saline.

Similarly, ANOVA applied to mean transitions for mice receiving hydroxyzine alone (0.5, 1, 4, 7, or 10 mg/kg) or saline revealed a significant overall effect for drug treatment ($F = 7.45$, $P < 0.0001$). Mean values for each dose of hydroxyzine are presented in Fig 2. Dunnett's t-test (alpha = 0.05, confidence = 0.95) revealed that only a 1-mg/kg dose of hydroxyzine resulted in significantly increased transitions compared with saline. No doses of hydroxyzine alone caused significantly decreased mean transitions.

Analysis of chloral hydrate/hydroxyzine drug treatments

ANOVA applied to mean transitions for mice receiving 32 mg/kg of chloral hydrate combined with either 1, 4, 7, or 10 mg/kg of hydroxyzine or saline revealed significant overall effect for drug treatment ($F = 18.52$, $P < 0.0001$). Mean values for each dose are presented in Fig 3. Dunnett's t-test (alpha = 0.05, confidence = 0.95) revealed that doses of 4, 7, and 10 mg/kg of hydroxyzine added to 32 mg/kg of chloral hydrate resulted in significantly decreased transitions compared with saline.

ANOVA applied to mean transitions for mice receiving 64 mg/kg of chloral hydrate alone, chloral hydrate 64 mg/kg combined with either 1, 4, 7, or 10 mg/kg of hydroxyzine, or saline revealed no significant overall effect for drug treatment ($F = 1.36$, $P > 0.2602$). Mean values for each dose are presented in Fig 4.

ANOVA applied to mean transitions for mice receiving 132 mg/kg of chloral hydrate alone, chloral

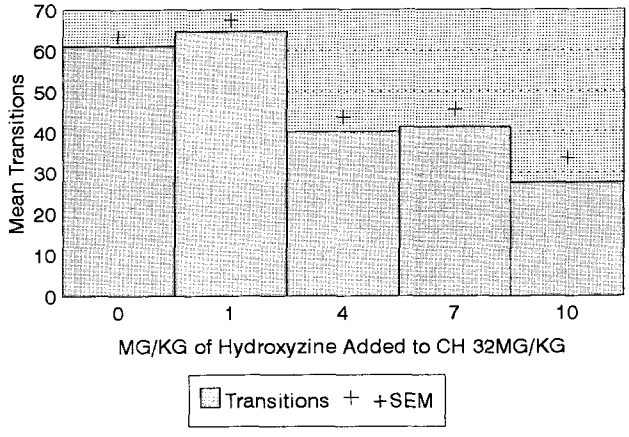

Fig 3. Chloral hydrate 32 mg/kg + hydroxyzine.

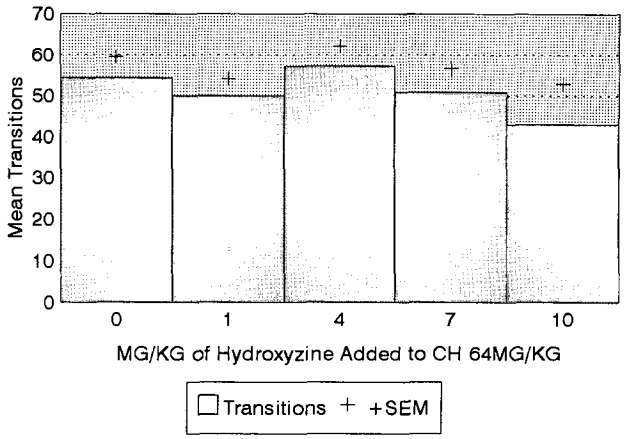

Fig 4. Chloral hydrate 64 mg/kg + hydroxyzine.

hydrate 132 mg/kg combined with either 1, 4, 7, or 10 mg/kg of hydroxyzine or saline revealed a significant overall effect for drug treatment ($F = 5.18$, $P < 0.0014$). Dunnett's t-test (alpha = 0.05, confidence = 0.95) revealed significantly decreased transitions when the mice received 132 mg/kg of chloral hydrate plus 7 or 10 mg/kg of hydroxyzine when compared with saline. Mean values for each dose are represented in Fig 5.

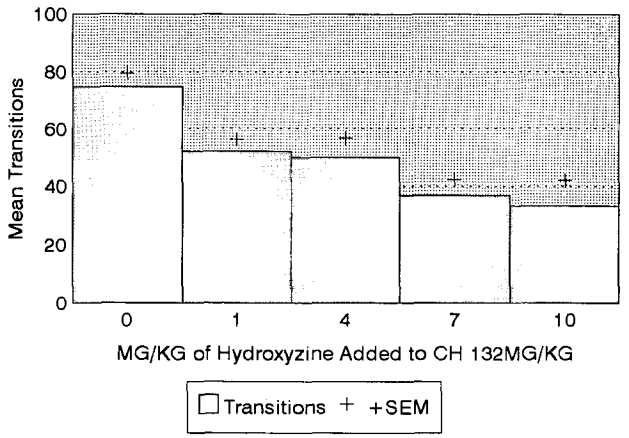

Fig 5. Chloral hydrate 132 mg/kg + hydroxyzine.

Discussion

Species specificity

The strains of mice most suitable for testing antianxiety agents in the light/dark test box are the C57/Black mice and the Swiss Webster (NIH—Bethesda, MD) mice.[41] Selecting the species and strain to be used in the light/dark test box was a critical factor in the design of this study. Although rats and mice are good choices for antianxiety tests, rats and some species of mice don't exhibit any consistent antianxiety effects of exploration that are measurable in this paradigm.[41–45] Male C57/Black mice tested in the light/dark test box have been shown to be particularly sensitive to anxiolytics. It has been postulated that this highly active and exploratory species as well as several other species with high baseline exploratory activity, may be particularly responsive to the test due to a genetically determined substrate for spontaneous exploratory behaviors.[41, 45]

Paradigm rationale

The fundamental premise of this paradigm and several other currently accepted methods for using mice to evaluate the effects of drugs on anxiety is that mice tend to explore new environments unless an aversive situation causes anxiety that limits this natural activity.[10, 42] If a mouse is removed from the population with that it is housed and placed in a new lighted environment an aversion is created that is loosely analogous to anxiety states which inhibit the mouse's natural instinct to explore a new environment. The aversive nature of light in an unknown environment causes the mouse to seek a smaller and darker area and inhibits the normal exploratory transitions between the light and dark side that the mouse would instinctively make in a uniformly darker unknown environment. A number of antianxiety agents — when given at an effective dose — mitigate the aversion and cause the mouse to travel between the dark and light sides of the test box significantly more than it would if given just a placebo.

Increased transitions in the testing apparatus compared with a control group are associated with anxiolytic activity; decreased transitions are associated with sedation. Dose response curves were generated for the doses of chloral hydrate, hydroxyzine, and the combinations used in the study. The subhypnotic doses of chloral hydrate that didn't cause a significant decrease in mean transitions were used in combination with selected doses of hydroxyzine to study the existence and magnitude of antianxiety response (increase in transitions) due to combining the two drugs.

Dose selection

Initial hydroxyzine doses were selected based on prior experiments that evaluated anxiolytic activity in mice. Similarly, initial doses of chloral hydrate were selected based on prior studies[6, 46] using foot shock disinhibition of explorative mouse activity. Additional doses were included in the study to the extent that each mouse could be tested four times with at least one day of rest between each test. Blumstein[45] confirmed that a limited number of repeat trials with as little as one day of rest between them was not associated with drug tolerance, circadian variability, and test learning when the C57/Black mouse was tested in the light/dark test box.

Chloral hydrate doses of 132 mg/kg simulated anxiolytic activity in this study. Doses of 64–128 mg/kg of chloral hydrate in other classical tests simulated anxiolytic activity using different mouse paradigms.[6, 46]

Pruhs[6] investigated the effect of adding nitrous oxide inhalation to chloral hydrate administration in a mouse staircase test that associated an increased number of rears with anxiolytic activity. His study found that individually, both drugs produced antianxiety effects as simulated by the mouse staircase test and that coadministration of nitrous oxide with chloral hydrate produced an enhanced anxiolytic activity. Pruhs'[6] study produced results that paralleled those obtained in a clinical study conducted by Houpt,[47] which found that nitrous oxide augments the effects of chloral hydrate sedation.[32] This linked pharmacologic activity between humans and mice at least partially confirms the applicability of animal paradigms for the study of combinations used or contemplated for pediatric dental sedation. Our study sought to determine if coadministration of chloral hydrate and hydroxyzine would produce a similar additive or synergistic action. This was attempted despite the historically poor response of the hydroxyzine component to the other "classical" disinhibitory tests.[8]

The animal model studied indicates that there was no advantage in using a combination of chloral hydrate and hydroxyzine to increase anxiolytic activity without producing sedation. Admittedly, there may be an effective dose between those selected that may show additive anxiolytic activity. The limited range of that effective dose may not prove to be practical considering variable metabolisms in any species tested. No claim is made that there is or is not any anxiolytic activity concurrent with the obvious sedation produced by several treatments. The light/dark test box is not designed to quantify concurrent sedation when it occurs with anxiolytic activity.

It is apparent from the data and consistent with our previous knowledge that additive sedation activity does occur when the two CNS drugs are combined. The additive sedation observed was not spectacular because it was no different than the sedating dose of 200 mg/kg of chloral hydrate alone. Unless the 200-mg/kg dose causes physiologic compromise for the mouse, single-drug therapy is likely the more prudent sedative regimen. This finding is consistent with the current medical studies involving the use of high doses of chloral hydrate alone for the sedation of young children undergoing medical procedures.[48-50]

More animal studies may be needed to define the specific properties of the various combination agents that have been used clinically for many years without ever being preclinically evaluated. Such studies could lead to more narrowly focused antianxiety clinical studies than the present clinical studies. Dentists, psychologists, physicians, and pharmacologists need to clearly define the role of anxiety (if one exists) in the uncooperative pediatric dental patient. The knowledge gained by then merging exhaustive animal, narrowly focused clinical, and psychological investigations may give the clinician keys as to which specific regimen will consistently produce the desired results in specific patients.

Conclusions

The light/dark test paradigm demonstrates that at subhypnotic doses:

1. Chloral hydrate has anxiolytic activity.
2. Hydroxyzine has weaker anxiolytic activity than chloral hydrate.
3. The combinations of chloral hydrate and hydroxyzine tested did not demonstrate additive anxiolytic activity.

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Dr. Gladney is an active duty commissioned officer in the US Public Heath Service, currently assigned as Oklahoma City Area Pediatric Dentistry Consultant. Dr. Stanley is assistant professor, department of pediatric dentistry, University of Nebraska Medical Center, Omaha, Nebraska. Dr. Hendricks is associate professor, department of psychology, University of Nebraska, Omaha.

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