Chloral hydrate and its effects on multiple physiological parameters in young children: a dose-response study
Stephen Wilson, DMD, MA, PhD

Abstract
This study evaluated the dose-response effect of chloral hydrate (CH) used alone on several physiological parameters in 26 healthy children 21 to 42 months old. Selection criteria for the children in this institutionally approved study included: a) uncooperative behavior during an initial examination; b) a minimum of four sextants with caries involvement; c) healthy, ASA I; d) parental informed consent; e) a noncompromised airway (e.g., minimal tonsillar enlargement) and f) no known allergies. A repeated measures, Latin-square design was used in evaluating either a placebo and three dosages of CH (25, 50, 70 mg/kg) over four visits for each of eight patients or the same three dosages over three visits for each of the remaining patients. The physiological parameters included: heart and respiratory rate, systolic and diastolic blood pressure, peripheral oxygen saturation, and expired carbon dioxide. For statistical purposes, physiological parameters were analyzed during specific phases which included: baseline, topical and local anesthesia administration, at initiation of cavity preparation; and at the end of the appointment. A repeated measures ANOVA and descriptive statistics were used to analyze the data. The results indicated that the diastolic blood pressure and expired carbon dioxide were affected significantly by CH dosage (P < 0.02 and 0.005, respectively). The findings should be tempered in light of patient behavior during the visits. Dental procedures also had an influence on cardiovascular parameters. The significance of these findings related to patient safety and behavior in these very young children is discussed. (Pediatr Dent 14:171-77, 1992)

Introduction
Since the 1950s, most articles on sedation of children for dental treatment have focused on the behavioral changes mediated by pharmacologic agents. Occasionally, vital signs were mentioned, but rarely were they affected significantly.1, 2

The advent of modular and automated physiological monitors, along with other factors3 has stimulated interest in the physiologic parameters of children receiving sedative agents during dental treatment.4-14

Some of the first dental studies directly evaluating changes (using specialized monitors) of physiological systems of children as a function of sedative agents appeared as abstracts in 1984.15, 16 Subsequently, at least 16 articles reporting the quantitative physiological data on a total of 386 patients have appeared in the literature.4-14, 17-21 In those studies, nine different drugs, alone or in combinations, have been used.

Reported changes in physiological parameters have been associated, for the most part, with specific procedures (e.g., local anesthesia injection) that are painful or anxiety-provoking to the children, rather than with the direct effects of the agents.6 However, summary statistics rarely are reported. Furthermore, there have been few attempts to relate and report behavioral responses and/or pharmacologic influence on changes in physiologic function, although information exists supporting such associations.10, 13

A possible explanation for this hiatus in information is that the physiologic systems being monitored are not overly sensitive to mild behavioral (e.g., low-intensity crying) or pharmacologic influence at moderate doses. For example, pulse oximetry measures the degree of oxyhemoglobin saturation which may not be expected to significantly change unless profound alteration in respiratory function occurs (e.g., highly intense sobbing/crying and airway compromise).

The effect of chloral hydrate (CH) alone in a dose-response design on multiple physiological systems during dental treatment has not been reported. The purpose of this study was to determine the responsiveness of appropriate physiologic systems to three doses of CH and dentally related stimuli in a repeated measures design. The following physiological parameters were investigated: heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressure (SYS and DIA), expired carbon dioxide (CO2), and oxygen saturation (O2).

Methodology
Twenty-six healthy but uncooperative children participated in this double blind, repeated measures dose-response study using CH. All parents gave informed consent for their children to participate in this institutionally approved study. Children participating were required to: be healthy; have a minimum of four of six sextants of teeth that needed restoration or extractions; have uncompromised airways (i.e., no enlarged tonsils); and have no known allergies.
Each child was scheduled for either three or four appointments. For the child who required three appointments, CH was administered in one of three doses (25, 50, 70 mg/kg) at each appointment. The rest of the children received CH and a placebo with the dose (25, 50, 70 mg/kg) of CH and placebo sequentially varying across appointments. (Note: The placebo visit was dropped after the ninth patient entered the study, because we observed obvious distress in these very young children due to the dental appointment imposed. This decision was made after it became clear to the author that to continue would have been questionable, if not wrong morally and ethically.)

The sequence of drug-placebo visits was determined randomly in a Latin-Square design for each patient. This investigator was the sole operator in this study, and the children were instructed to be NPO from midnight before the morning of each appointment. All appointments began at 7 AM and usually were completed within 2 hr. The placebo was Tang, which also was used to flavor the drugs.

Usually, one week separated each visit for every child in this study. The following procedure occurred at each appointment: the medical history was reviewed for changes, then the child was weighed and taken with the parent to the dental operatory. Attempts were made to obtain baseline information for SYS and DIA (Dinamap, Model 1846-SX, Critikon, Inc., Tampa, FL), RR, HR and O₂ (Nellcor pulse oximeter and printer, Model N-100 and N-9000, respectively, Nellcor, Inc. Hayward, CA), and CO₂ concentration (Datex CO₂ Monitor, Model 223, Helsinki, Finland, manufactured for Puritan-Bennett Corp., Wilmington, MA). During the restorative phase, the appropriately sized (pediatric) inflatable blood pressure cuff always was placed on the right arm. The oxygen saturation electrode was affixed to the first toe adjacent to the right large toe and a small inverted thimble-like port was placed into the right naris for detection of expired CO₂.

The child then was administered either the placebo or CH and taken with the parent to a waiting area. The child remained with the parent in the waiting area for 45 min and was monitored periodically by dental personnel. Then the child was separated from the parent and returned to the dental operatory, where all of the monitors were reattached and the child restrained in a Papoose Board, Olympic Medical Group, Seattle, WA. The operator administered topical and local anesthesia (usually not exceeding 1 carpule of Xylocaine 2% with epinephrine 1:100,000) and in most instances, placed a rubber dam. The teeth either were restored or extracted. After the operative phase was completed, the monitors were detached and the child was returned to the parents. Once the children were stable and oriented, they were released with appropriate postoperative instructions.

Data for each physiologic parameter were collected either continuously or every 5 min, depending on the monitor and its function. For statistical purposes, special recording times were identified and included baseline, topical and local anesthesia administration, initiation of tooth preparation with a high-speed handpiece, and the end of the operative procedures. All readings were obtained directly from the monitors.

Descriptive statistics were used to characterize the sample of children. A repeated measures factorial ANOVA was used to analyze each physiologic parameter across dental procedures as a function of drug dose. An a priori level of statistical significance was set at 0.05.

**Results**

Thirteen females and 13 males whose mean age was 30.8 ± 4.5 months (range 21–42 months) with a mean weight of 13.50 ± 1.6 kg (range 10.5–17 kg) participated in the study. Not every patient completed the planned sequence of visits, since some parents failed to return for scheduled appointments. The data set is based on the following breakdown of patients completing visits: four visits (8); three visits (11); two visits (4); and one visit (3).

Those measures associated with respiratory function (RR and CO₂) were missing most frequently because of patient crying and struggling patterns. Under those conditions, irregular RR are meaningless and expired air shunting through the oral cavity occurs.

There was no significant difference noted among physiologic systems as a function of visits, which suggested no visit-order effect.

**Drug Dose Effect**

Evaluation of the physiologic data during the specified procedures (see above) with a repeated measures ANOVA indicated that CH dose produced significant differences only on the physiological parameters of DIA and CO₂ (Table 1, next page). All other parameters did not show significant drug effects. A summary of descriptive statistics for each parameter is shown in Table 2 (page 174).

**Systolic Blood Pressure**

No statistical difference among doses was seen for the SYS, but the SYS changed significantly as a function of dental procedure (F = 3.81, P < 0.005). The SYS increased from baseline during the period from administration of local anesthesia through the initiation of tooth preparation. Then, there was a tendency for SYS to decline slowly throughout the rest of the appointment period (Fig 1, next page).
Table 1. ANOVA F ratio and probability for dose, procedure, and interaction of the physiological parameters studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose</th>
<th>Procedure</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>1.18* (0.324)*</td>
<td>3.81 (0.005)</td>
<td>1.52 (0.118)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>3.52 (0.02)</td>
<td>3.33 (0.011)</td>
<td>1.67 (0.075)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.39 (0.253)</td>
<td>23.6 (0.001)</td>
<td>3.18 (0.001)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>1.43 (0.251)</td>
<td>1.26 (0.290)</td>
<td>0.63 (0.811)</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>1.39 (0.254)</td>
<td>0.60 (0.663)</td>
<td>0.74 (0.710)</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>4.84 (0.005)</td>
<td>0.90 (0.466)</td>
<td>2.81 (0.002)</td>
</tr>
</tbody>
</table>

* F ratio; * Probability.

Diastolic Blood Pressure

A statistically significant dose and procedural effect on the DIA were seen (F = 3.52, P < 0.02; F = 3.33, P < 0.01, respectively). In general, the trend was for the magnitude of DIA to be less as the dose of CH increased for any given procedure. A post hoc analysis indicated the significance to lie between the highest dose (70 mg/kg) and that of the placebo and 25 mg/kg dose. However, it should be noted that some procedures (e.g., injection) tended overall to increase the absolute magnitude of DIA for the placebo and low to medium dose visits, whereas the high dose visits were either not affected or slightly decreased compared to baseline readings (Fig 2). There was no difference in DIA between placebo nor any CH visits for baseline and end of visit recording phases.

Heart Rate

There was no dose effect on the HR; however, there was a significant change in HR as a function of dental procedures (F = 23.6, P < 0.001). The HR increased during topical and local anesthesia administration and remained elevated throughout most of the dental visit (Fig 3, page 175). The HR appeared to be most variable and responsive of all physiological parameters to operator-imposed procedures.

Respiratory Rate

The RR was not affected significantly by either drug dose nor dental procedure (Fig 4, page 175). Caution in the lack of an effect is advised, however; RR was the most difficult to measure because bouts of crying interfered with consistent data collection. In general, the highest dose of CH produced the most consistent and slowest RR, compared with the other doses.

Peripheral Oxygen Saturation

The O₂ was not influenced significantly by either drug dose or dental procedure and remained least variable of all recorded parameters (Fig 5, page 176). Momentary desaturations due to movement artifacts were observed occasionally.

Expired Carbon Dioxide

The CO₂ was influenced significantly by drug dose (F = 4.84, P < 0.005). The concentration for CO₂ was elevated slightly compared to baseline for the highest drug dose; however, this effect appeared to be related to a lack of shunting of expired air which otherwise occurred when the patient cried. At no time was the elevated CO₂ outside of normal physiological values (Fig 6, page 176).
Table 2. Mean values of measured physiological parameters as a function of dose across dental procedures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose</th>
<th>Base</th>
<th>Topical</th>
<th>Inject</th>
<th>Drill</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYS</td>
<td>P</td>
<td>96.5 ± 10.3</td>
<td>118.5 ± 37.4</td>
<td>114.5 ± 11.7</td>
<td>115.2 ± 18.4</td>
<td>103.1 ± 13.0</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>102.1 ± 11.6</td>
<td>110.1 ± 18.9</td>
<td>116.9 ± 23.7</td>
<td>115.7 ± 36.7</td>
<td>108.0 ± 16.4</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>104.0 ± 12.7</td>
<td>101.0 ± 21.1</td>
<td>112.6 ± 20.4</td>
<td>110.0 ± 27.7</td>
<td>105.8 ± 17.3</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>101.1 ± 10.3</td>
<td>93.6 ± 13.6</td>
<td>101.0 ± 16.1</td>
<td>107.4 ± 29.0</td>
<td>103.8 ± 15.8</td>
</tr>
<tr>
<td>DIA</td>
<td>P</td>
<td>61.1 ± 8.8</td>
<td>80.1 ± 20.2</td>
<td>75.6 ± 10.2</td>
<td>71.5 ± 9.6</td>
<td>64.0 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>63.7 ± 9.0</td>
<td>69.3 ± 15.0</td>
<td>73.4 ± 18.8</td>
<td>74.6 ± 24.1</td>
<td>66.1 ± 13.2</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>66.6 ± 14.1</td>
<td>62.5 ± 16.0</td>
<td>77.2 ± 25.0</td>
<td>68.8 ± 18.8</td>
<td>65.2 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>60.5 ± 7.7</td>
<td>52.1 ± 14.0</td>
<td>61.6 ± 15.2</td>
<td>64.7 ± 26.0</td>
<td>61.8 ± 10.6</td>
</tr>
<tr>
<td>HR</td>
<td>P</td>
<td>110.6 ± 14.5</td>
<td>145.3 ± 34.4</td>
<td>149.1 ± 26.2</td>
<td>139.6 ± 36.1</td>
<td>126.6 ± 15.3</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>113.6 ± 15.6</td>
<td>140.8 ± 28.4</td>
<td>147.7 ± 30.0</td>
<td>141.7 ± 28.9</td>
<td>132.8 ± 26.4</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>115.4 ± 16.2</td>
<td>130.1 ± 27.0</td>
<td>141.4 ± 22.7</td>
<td>142.9 ± 29.4</td>
<td>147.4 ± 31.1</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>109.5 ± 14.1</td>
<td>114.1 ± 23.9</td>
<td>128.7 ± 29.0</td>
<td>130.0 ± 25.6</td>
<td>140.1 ± 34.9</td>
</tr>
<tr>
<td>RR</td>
<td>P</td>
<td>24.3 ± 0.7</td>
<td>28.0 ± 5.6</td>
<td>29.4 ± 5.2</td>
<td>29.6 ± 5.7</td>
<td>28.1 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>26.6 ± 5.5</td>
<td>27.2 ± 3.9</td>
<td>27.1 ± 3.5</td>
<td>32.0 ± 15.6</td>
<td>26.5 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>26.8 ± 4.1</td>
<td>27.6 ± 5.5</td>
<td>27.8 ± 4.7</td>
<td>28.2 ± 5.1</td>
<td>28.1 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>26.5 ± 3.2</td>
<td>24.8 ± 3.5</td>
<td>26.4 ± 4.3</td>
<td>27.0 ± 7.0</td>
<td>28.0 ± 6.3</td>
</tr>
<tr>
<td>O₂</td>
<td>P</td>
<td>99.3 ± 1.1</td>
<td>98.8 ± 1.2</td>
<td>98.5 ± 1.2</td>
<td>98.5 ± 2.5</td>
<td>99.1 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>99.4 ± 0.9</td>
<td>99.2 ± 1.0</td>
<td>99.1 ± 0.9</td>
<td>99.3 ± 1.0</td>
<td>99.0 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>99.2 ± 0.7</td>
<td>98.7 ± 1.2</td>
<td>98.7 ± 1.5</td>
<td>98.9 ± 1.1</td>
<td>95.1 ± 18.3</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>99.0 ± 2.0</td>
<td>98.8 ± 1.4</td>
<td>99.0 ± 1.0</td>
<td>98.6 ± 1.5</td>
<td>98.7 ± 1.7</td>
</tr>
<tr>
<td>CO₂</td>
<td>P</td>
<td>27.5 ± 10.2</td>
<td>31.2 ± 6.9</td>
<td>30.5 ± 4.5</td>
<td>31.6 ± 3.8</td>
<td>33.2 ± 4.9</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>33.6 ± 3.2</td>
<td>30.0 ± 5.1</td>
<td>31.5 ± 5.1</td>
<td>30.9 ± 5.9</td>
<td>32.4 ± 5.7</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>33.4 ± 4.7</td>
<td>33.9 ± 3.5</td>
<td>31.9 ± 5.8</td>
<td>33.4 ± 5.3</td>
<td>32.5 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>33.0 ± 3.1</td>
<td>37.0 ± 3.5</td>
<td>36.0 ± 4.1</td>
<td>35.6 ± 4.1</td>
<td>35.8 ± 3.3</td>
</tr>
</tbody>
</table>

Discussion

Diastolic Blood Pressure and Expired Carbon Dioxide

The main findings of this study suggest that the dose of CH significantly affected the DIA and CO₂. Interpretation of these findings must be made in light of the children's behavior under the conditions of this study. The children were, on the average, less than three years old (recognized as a criterion for precooperative behavior). Their normal behavioral pattern in a strange environment may be expected to contain elements of crying, aggressive struggling, and lack of cooperation. Thus, these behaviors would be expected to affect recorded physiological parameters.

The observed patterns of increased DIA with lower CH doses and placebo confirmed expectations that the child was overly stimulated and responsive (i.e., either angry or frightened) to the dental environment and procedures. However, the normally expected physiological expression (i.e., increased blood pressure) to physical stimulation, in general, was suppressed by the highest dose of CH in these young children. This finding implies that the highest dose of CH mediated a moderate sedative effect compared to the other doses. In many instances, the child slept during portions of the restorative visit after receiving medium to high doses of CH. The slight suppression of DIA was congruent with the effects one might expect from normal sleep. Yet, the predictability of the depth of drug-mediated "sleep" (viz., unconsciousness with central nervous system depression) becomes an important clinical and scientific issue with significant implications for the monitoring and safety of the child.

Although changes in CO₂ as a function of drug dose were statistically significant, this effect must be interpreted with caution. The higher doses of CH caused many children to sleep and the entire CO₂ concentration was routed through the nostrils. This is compared to the awake or lightly sedated child who, because of crying, shunted a considerable amount of the expired air through the oral cavity (Fig 6). Any CO₂ passing
through the nose was diluted with deadspace resulting in reduced CO₂ concentration recorded from the nares. Consequently, the logical interpretation is that higher doses of CH resulted in increased (albeit normal) concentrations of CO₂ compared to lower doses because the child was shunting less expired air through the mouth. Therefore, it is plausible to suggest that CH, in the conditions of this study, had little direct effect on CO₂ retention.

Tissue obstruction (i.e., enlarged tonsils) has been reported to significantly alter respiratory function, resulting in increased CO₂ levels during sleep. Interestingly CH, in a hypnotic dose, has been reported to decrease genioglossus activity in animals. Thus, it is important to conduct a presedation evaluation of the airway patency and oropharyngeal tissues whenever CH is being considered as a sedative agent.

The capnograph is an excellent monitor for evaluating airway patency. Decreases in the CO₂ concentration should be caused by either patients shunting air through the oral cavity (i.e., crying) or by partial blockage of the airway. Such effects should be detectable immediately. Because of this capability, the capnograph is as appropriate in the preliminary defense against the development of secondary adverse patient conditions (i.e., hypoxia) as is the pulse oximeter, which theoretically should follow airway blockage by variable time frames. A recent report involving general anesthesia provides partial support for this concept.

Heart Rate

One may speculate that HR may have been affected significantly by CH dose if statistical analysis was conducted on a continuous versus procedural basis. The HR, especially in children, is most sensitive to stimuli and metabolic demands and was altered strongly by certain procedural effects. The HR consistently demonstrated the greatest variance of all parameters between and within patients. The wide variance decreases the probability that a statistically significant effect would be found. But the higher the CH dose, the less change in HR was observed as a function of dental procedures (Fig 3). Since HR is related to cardiac output which influences SYS, one might expect that SYS would follow a pattern similar to that of HR. This expectation was noted, in part, in this study and others.

The perceived “noxiousness” or fear-provoking potential of dental procedures for children of this age group is undoubtedly high and for most parameters, the results not unexpected. This conjecture is supported by the fact that the greatest deviation from baseline readings for any of the physiologic parameters occurred during the injection of local anesthesia and/or tooth preparation. Similar findings have been noted previously.

The degree of deviation from baseline during injection or tooth preparation for most parameters was dampened increasingly by higher doses of CH. The drug’s ability to depress appropriate physiological responsiveness progressively increases as the dosage increases. Clinically, this emphasizes the importance of that gray area between conscious and deeper levels of sedation. In reality, significantly high doses of CH will be needed to overpower the influence of certain dental procedures effectively in these precooperative
children. But the high doses will, in many cases, place the child in an unconscious state. This compromise needs to be well conceived and weighed by the clinician. Sophisticated monitoring techniques, appropriate training of the operator, and constant vigilance during deep sedation become imperative.

The doses used in this study did not result in any significantly compromised situation; however, it was my clinical impression that some of the children were sedated deeply following a 70 mg/kg dose.

**Peripheral Oxygen Saturation**

Oxygen saturation was not affected significantly by CH under the conditions of this study. CH in combination with other agents has been reported to cause incidents of desaturation.\(^7,10\) Other medications also reputedly have caused desaturations.\(^7,9,21\) However, it is unclear in any of these studies whether the desaturations were caused by the drugs or by other factors that influence oximetry function. Pulse oximetry is very susceptible to movement artifact, especially in young children sedated for dental procedures.\(^13\) Desaturations during dental treatment in children without premedication\(^26\) and in association with a placebo\(^12\) have been reported.

Desaturations were noted in this study, but the overwhelming majority were associated with patient movement. It is impossible to designate those desaturations that were not associated with patient movement as true desaturations because no blood gas analysis was performed.

**Respiratory Rate**

Those measures associated with respiratory function (i.e., RR and CO\(_2\)) most frequently were unobtainable as a result of patient behavior during the indicated recording phases. Crying, sobbing, and occasionally brief apneic responses prevented an accurate count of RR during an observation period. Such behavior also resulted in shunting of CO\(_2\) from the nasal orifices which dramatically decreased or eliminated the capnograph's ability to record this parameter. HR and O\(_2\) derived from the pulse oximeter most often were unaffected in terms of missing data during the specified observation periods; this is probably a function of the monitor's operation.

**Conclusions**

In summary, CH when used alone resulted in significant changes in DIA and CO\(_2\). The DIA increased during delivery of dental care whenever placebo and low doses of CH were used; however, higher doses suppressed this normally increased DIA response. Likewise, CO\(_2\) was decreased due to crying and shunting of expired air through the mouth in placebo and low dose CH visits. High doses of CH suppressed patient responsiveness, but not to levels considered physiologically inappropriate.

As the dose of CH increased, cardiovascular parameters were suppressed statistically for certain dentally imposed procedures which are otherwise excitatory to very young children.

The oxygen saturation as a function of CH dose appears to be the least insensitive measure of change in patient status whenever movement artifact is eliminated. Patient movement was responsible for mild to moderate, but brief desaturation artifacts. DIA, CO\(_2\), and HR apparently are more sensitive in terms of
detecting change in patient status as a function of CH and dental procedures. These findings are interpreted as increasing degrees of sedation as the dose of CH increases, leading in some cases from consciousness to unconscious, but arousable states.

This study was supported by NIH Grant RO3 DE08277-01A1.

Dr. Wilson is associate professor and director of the postdoctoral program of pediatric dentistry and research, Department of Pediatric Dentistry, College of Dentistry and Columbus Children’s Hospital, The Ohio State University, Columbus, OH.