Effect of Submucosal Midazolam on Behavior and Physiologic Response When Combined With Oral Chloral Hydrate and Nitrous Oxide Sedation

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Abstract

Purpose: This study was designed to examine the efficacy and safety of submucosal (SM) midazolam and oral chloral hydrate (CH) when used for pediatric conscious sedation in a clinical dental environment.

Methods: Twenty children ages 32 to 63 months participated in this institutionally approved study. Selection criteria included good health (ASA I), 2 to 5 years of age, uncooperative behavior, and the need for multiple restorative visits. In a double-blind crossover design, patients were randomly assigned to receive either oral CH (50mg/kg) and SM midazolam (0.2 mg/kg), or oral CH (50 mg/kg) and SM saline placebo on their first sedation visit. On the second sedation visit, the patient received the opposite drug regimen than the first visit. Nitrous oxide (50%) was used during each sedation visit. Behavior response was rated as quiet (Q), crying (C), movement (M), or struggling (S) every 2.5 minutes through 40 minutes of operative procedures. Sedations were monitored using a capnograph, pulse oximeter, an automated blood pressure cuff, and precordial stethoscope. Respiratory rate (RR), heart rate (HR), and blood pressure (BP) were evaluated for each procedure. Data was analyzed using ANOVA and multinomial repeated-measures logistic regression.

Results: Analysis showed a significant difference in behavior during sedation across drug regimen (chi-square=55.6, df=3, $P<.0001$). Patients given SM midazolam in addition to oral CH showed increased Q rating and decreased C, M, and S ratings. RR, BP, and HR for both groups remained within the normal values for 2- to 5-year-olds.

Conclusions: SM midazolam improved the quality of sedation without compromising safety. Quiet behavior was increased and struggling behavior was decreased. In addition, mean HR, RR, and BP analysis did not deviate from the norm for this age group. (*Pediatr Dent.* 2004;26:37-43)

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Pediatric dentists are continually looking for better ways to sedate patients safely and effectively. Oral chloral hydrate (CH) is a sedative hypnotic causing central nervous system (CNS) and respiratory depression that is used extensively in pediatric dentistry for conscious sedation. A 1983 survey of diplomates to the American Board of Pediatric Dentistry revealed that CH was used in 62% of all sedations, either alone or in combination with other drugs.[1] A 1985 survey of 1,105 American Academy of Pediatric Dentistry (AAPD) members listed the most frequent drug regimen as oral CH and hydroxyzine and N_2O.[2] In a 1992 follow up study, CH with hydroxyzine and N_2O was shown to be the most commonly used drug combination taught in residency programs.[3] There have been many studies to investigate CH's effect on children's behavior in the dental setting. Nathan et al conducted a literature review of

different drug combinations with CH as well as variable dosages. Success rates ranged from 18% to 90%. Most of the low success rates were seen when following the manufacturer's recommended dose (MRD) of 50 mg/kg. These dosage recommendations for sedative-hypnotics are calculated to provide sedation for cooperative individuals and are, therefore, best viewed as a minimum baseline standard dosage.[4] Additional factors such as physical activity level, emotional status, degree of cooperation, stomach contents, and time of day can contribute to the need to surpass baseline dosages.[5] Recently, there has been concern raised over using higher dosages, and the trend is to stay within the MRD.

While some dentists have tried adding more CH, others have turned to different sedative agents such as midazolam, a short-acting benzodiazepine. Midazolam has anxiolytic, sedative hypnotic, anticonvulsant, muscle-relaxant, and anterograde amnestic effects.[6-7] Midazolam's safety and efficacy has been examined in both the medical and dental literature.[8-20]

Oral midazolam has a 15-minute onset and potential 2- to 6-hour duration, while intramuscular (IM) midazolam has an onset within 15 minutes and shorter 15- to 80-minute duration.[21] The submucosal (SM) route is considered an enteral method of administration similar to the IM route. The pharmacokinetics of midazolam is also similar when administered either SM or IM.[22] The administration of enteral midazolam requires the same diligence with airway support as do oral conscious sedations. Competency in airway management and readily accessible equipment capable of delivering positive pressure ventilation are necessary. In dentistry, the successful use of SM midazolam for sedation has been mainly anecdotal. In 1990, Alfonzo-Echeverri et al examined the absorption and elimination of midazolam by SM and IM routes.[22]

More recently, a 5-year pilot study by Griffen showed promising results with the administration of submucosal midazolam for 122 patients who presented for dental surgery or general dentistry.[23] Another study looked into the possibility of submucosal midazolam as an alternative to intravenous sedation.[24] In a dental setting, midazolam is ideal for those patients who have minimal to moderate dental needs and appear nonbelligerent but uncooperative.[25]

CH combined with midazolam has many potentially positive interactions that warrant investigation. Midazolam can be given as a SM injection into the mucobuccal fold after the child has been presedated with CH (50mg/kg). This would decrease the risk of oversedating some children if a higher baseline dose was used. If the child exhibits behavior indicating an underdosage, for example, somnolence during the latent period but fully aroused and unmanageable when stimulated, an increased level of sedation can be accomplished with SM midazolam. Precedence exists for SM injections with meperidine,[26] but serious adverse reactions can occur with narcotic sedation of children.[27] Narcotic agonists possess potent CNS and respiratory depressant properties as well as the tendency to induce nausea and vomiting, especially in ambulatory patients.[28] Opioids such as meperidine also increase plasma levels of local anesthetics such as lidocaine, thereby increasing the risk of lidocaine toxicity.[29] Sedative doses of midazolam, however, minimally depress respiration or cardiovascular function,[6,20] and no such increase in plasma levels of local anesthetic is seen. Midazolam also has a shorter duration of action than meperidine, and it has amnestic properties not found in CH.[30] Another advantage of midazolam is the existence of a reversal agent, flumazenil, further increasing the safety of the sedation.

The package insert for midazolam states "concomitant use of barbiturates, alcohol, or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect." It is possible the pharmacological interaction of midazolam and CH could cause increased respiratory depression. A CH metabolite (trichloroethanol) is an alcohol analog.

The purpose of this study was to examine the efficacy and safety of SM midazolam and CH as a method for sedating young, uncooperative children needing dental treatment.

Methods

In this institutionally approved study, 20 patients were selected from new patients examined at the Virginia Commonwealth University/Medical College of Virginia Pediatric Dental Clinic. The procedures, possible discomforts, or risks, as well as possible benefits were explained fully to the human subjects involved, and their informed consent (via parent or legal guardian) was obtained prior to participation. Inclusion criteria obtained at the initial examination included healthy ASA-I patients 2 to 5 years of age, uncooperative behavior, and need for at least 2 conscious sedation visits for completion of treatment. Patients having prior dental extractions or restorative procedures were not used in this study. It has been shown that a child's presedation temperament can have an effect on sedation success.[26] This study used Venham's behavior and anxiety rating scale[31] to screen patients and eliminate the compliant and potentially compliant child (categories 1-3), as well as the very difficult child (category 6). Only patients that exhibited behavior in categories 4 (reluctant) and 5 (interference) were selected for the study.

A randomized, double-blind, crossover design was used in this study. The sedation protocol followed the AAPD guidelines for conscious and deep sedation.[32] The MRD of CH (50 mg/kg, not to exceed 1,000 mg) was used during each patient visit. N_2O/O_2 was administered at a ratio of 50% N_2O and 50% O_2.[33] Each treatment session was recorded on videotape and viewed at a later time to analyze and record behavioral patterns.

Vital signs were monitored using an electrocardiograph (ECG), automated noninvasive blood pressure cuff, and a pulse oximeter. A capnograph with side stream carbon

dioxide (CO_2) sampling and precordial stethoscope were additionally utilized to assess the airway patency. Vital signs were observed continuously and recorded every 5 minutes during the operative procedure. Respiration rate (RR), mean heart rate (HR), and systolic/diastolic blood pressure (BP) were collected for evaluating potential respiratory or cardiac depression. RR was provided by the ECG leads and/or capnograph. Respiratory rates occurring when the child was crying and struggling were not reliably recorded due to movement and/or dislodgment of the nasal hood. These values were therefore removed from the collected data set.

Patients were randomly assigned to receive CH and the midazolam at the first visit and CH and the placebo (equal volume of sterile saline) at the second visit, or receive CH and the placebo at the first visit and CH and the midazolam at the second visit. The second visit was scheduled within 4 weeks of the initial visit. A single operator performed treatment on all subjects. Sedation protocol was the same for all visits. A 50 mg/kg dose of oral CH was given with cherry syrup. If the patient was noncompliant, the medicine was administered slowly into the buccal vestibule with a disposable syringe. After 45 minutes, the child returned to the dental operatory where N_2O (50%) was started via a nasal hood, monitors were affixed, and videotaping commenced. The patient was secured on a Papoose Board (Olympic Medical Corp, Seattle, Wash), and the parent returned to the waiting room. Topical and local anesthetic were delivered, and midazolam (0.2 mg/kg) or the placebo was administered submucosally into the area above the maxillary buccal vestibule on the side opposite the local anesthetic. Treatment was not performed in the quadrant where the SM injection was administered. Behavior assessment was recorded when dental treatment was initiated.

The 0.2 mg/kg dosage was used based upon the United States Pharmacopeial Dispensing Information (USPDI) recommendations for children (0.1- 0.5 mg/kg) and literature precedence for using 0.2 mg/kg IM dosage.[16,34] A reversal agent, flumazenil (0.01 mg/kg, IV dose), was available if needed. A rubber dam was placed, and the dental start time was recorded with the initiation of dental treatment. If, on the first visit, the child became disruptive at any point after 40 minutes from the dental start time, all treatment was ended as soon as safely possible to limit undue bias during the second visit. The parent or legal guardian on arrival for the second appointment was questioned as to whether or not the child had complained of pain in the area of the previous maxillary vestibular injection of midazolam/placebo. A 4-week follow-up phone evaluation of all second sedations was performed to ascertain any pain associated with the vestibular injection.

Rating of behavior

A single pediatric dentist, blinded to the sedation regimen used, reviewed the videotape of each sedation. A simple method of behavior analysis was used, rating the behavior as (1) Q=quiet, no movement; (2) C=crying, no struggling; (3) M=movement, no crying; or (4) S=crying and struggling. The time the SM injection was administered was recorded, and a point in time evaluation was made at the initiation of dental treatment and every 2.5 minutes thereafter. This simple method of behavior evaluation has been statistically correlated to more sophisticated, tedious, and expensive methods such as The Ohio State University Behavior Rating Scale.[33]

Statistical analysis

Each patient was used as his or her own control due to the crossover study design. For analyses of HR, RR, and BP, a repeated-measures ANOVA was used. In addition to subject-number, the analysis variables were drug condition (CH-placebo, CH-midazolam) and visit number (first sedation, second sedation). Observations from dental start time through 40 minutes were used in the analysis. The percentage of total behavior observations as Q, C, M, and S were used as the response variable and were analyzed using a multinomial repeated-measures logistic regression. This logistic regression model had identical analysis variables (subjects, drug condition, visit number), and modeled the probability of a subject being in each of the behavior states as a function of the drug condition and visit number.[35]

Results

The population sample of 20 patients included 10 females and 10 males whose age ranged from 32 to 63 months (mean=48±9). The patients' weight ranged from 13 to 23 kg (mean=17±3). Random assignment resulted in 7 patients who received CH/midazolam first and 13 patients who received CH/placebo first.

There were no serious complications or adverse outcomes with either drug regimen. There were 2 desaturation incidents (pulse oximetry levels at 85 and 88) that were quickly resolved with head repositioning and mouth suctioning. Both occurred during sedations with CH alone. One patient vomited during the CH-alone regimen, after which the mouth was suctioned and the procedure continued with no desaturation event or adverse outcome. Patients were discharged in accordance with AAPD guidelines. Recovery times ranged from 10 to 55 minutes. Postoperative evaluations indicated no prolonged pain at the injection site for all patients.

Behavior was evaluated every 2.5 minutes beginning with the start of the dental procedure through 40 minutes for a total of 17 observations. One patient receiving the midazolam became unmanageable and treatment was terminated, resulting in a 100% struggling (S) behavior rating. One sedation visit finished before 40 minutes, and therefore had only 15 observations. Observations in each category (Q, C, M, S) were converted to percentage of the total observations, and the results are presented in Table 1.

Logistical regression showed the probability of each of the behavior categories occurrence was dependent upon the

Table 1. Mean Percent Behaviors of Total Observations

	Behavior			
	Quiet (Q)	Crying (C)	Movement (M)	Struggling (S)
CH alone	62	5	6	27
CH/ midazolam	84	2	4	10

drug used (chi-square=55.6, df=3, *P*<.0001) and was not dependent on visit number (chi-square=2.87, df=3, *P*=.4127). Therefore, the overall decrease in negative behavior and increase of quiet behavior was not due to chance or any effect created by the order of sedation visits and can be directly attributed to the SM midazolam.

The duration of time from the SM injection to the dental start time was a mean 7.0 minutes for the CH/ midazolam group and 7.8 minutes for the CH/placebo group. ANOVA showed no difference in the duration of time from the SM injection to the dental start time across drug groups (F [1,18]<1, *P*=.3640) or visit number (F [1,18]=1.34, *P*=.2627). ANOVA also showed no difference in the duration of time from administration of CH to the dental start time across drug groups (F [1,18]<1, *P*=.8310) or between visit 1 or visit 2 (F [1,18]<1, *P*=.7806). This data indicates the difference in behavior seen was not due to differences in wait time or delays after the midazolam/ placebo was administered.

Results for HR, RR, and BP are presented in Table 2. ANOVA showed a significant difference in HR and RR across drug groups, (F [1,18]=84.28, *P*<.0001) and (F [1,18]=9.92, *P*=.0019), respectively. HR and RR were both elevated for the patients receiving midazolam. HR was determined by ANOVA to be statistically different across visit number (F [1,18]=7.88, *P*=.0054), while RR was not (F [1,18]<1, *P*=.7479).

Discussion

The number of subjects in this study was small, but allowing each subject to be their own control and the multiple number of behavior ratings obtained for each visit created statistical power for the ANOVA analysis. The results show that adding SM midazolam significantly increased quiet behavior and decreased struggling behavior. Struggling behavior considerably disrupted delivery of treatment, while crying and movement seemed to be coping mechanisms that still allowed effective delivery of dental treatment. Quiet behavior for CH alone was displayed at 62% of the ratings. This value is much higher than in Nathan's 1987 study of CH at 50 mg/kg, which reported a success rate of 25%.[36] This difference is most likely due to patient selection.

Table 2. Mean Heart Rate (HR) ± SD*, Respiration Rate (RR), and Systolic/Diastolic Blood Pressure (BP)

	HR	RR	BP sys	BP dias
CH alone				
Visit 1	112 (17)	26 (6)	107 (18)	57 (14)
Visit 2	115 (34)	24 (5)	105 (16)	56 (13)
CH/ midazolam				
Visit 1	119 (22)	24 (4)	102 (10)	50 (10)
Visit 2	122 (20)	29 (8)	108 (14)	56 (11)

*Standard deviation.

In Nathan's study, patient selection was intentionally skewed toward the very difficult young patient. In an attempt to be as clinically applicable as possible, this current study excluded the very difficult young patient (Venham category 6), with the assumption that, in most pediatric practices, the very difficult young patients are treated under general anesthesia. This study also included 3 patients who were over 20 kg, which is typical of this study's pediatric patient population in the 2- to 5-year age group. In accordance with the MRD, these patients were given only 1,000 mg of CH. This had no influence on the results, however, as all 3 were rated 100% quiet behavior (Q) during both sedation visits. One noncompliant patient required the administration of oral CH via syringe for both visits. Both sedations had a majority of recordings rated as struggling.

The study by Alfonzo-Echeverri et al discouraged the use of the SM route for administration of midazolam due to prolonged pain at injection site as well as no absorption advantage over the IM route.[22] Neither this study nor Griffen's pilot study involving 122 patients found any incidence of prolonged pain at the injection site.[23] It may be significant that this research design called for midazolam to be given in the opposite quadrant as the local anesthetic with a vasoconstrictor.

Any time 2 or more drugs are combined, it is important to be aware of any unforeseen synergistic pharmacological effect that may cause respiratory and/or cardiovascular depression. Therefore, monitoring is important. According to the AAPD's guidelines for conscious and deep sedation,[32] the addition of BP monitoring is recommended and CO_2 monitoring is desirable for conscious sedation level 3 and above. Because this was a new drug regimen with no previous citations in the medical or dental literature, it was decided to include these monitors in the event a level 3 or higher sedation occurred. Additionally, a purpose of the study was to determine the physiologic response to this drug regimen, therefore additional monitoring was warranted. The level of sedation achieved with this study can be described as alternating between conscious sedation levels 2 and 3. Expired CO_2 was analyzed only qualitatively to help evaluate airway

patency. Quantitative CO_2 values are not consistently obtained via side stream sampling as compared to those obtained when an endotracheal tube and closed system are utilized; therefore, values for CO_2 were not recorded for statistical analysis.

Vital signs fell within the normal ranges for children 2 to 5 years of age,[37] thus indicating no adverse physiologic responses to this drug regimen. Statistical analysis of the data gathered in this study showed a significant increase in both HR and RR for the CH/midazolam group, but these values still fell within normal ranges. BP also fell within normal ranges for the CH/midazolam group.[37] One would have expected the HR to be higher for CH alone due to the increased struggling behavior and more frequently agitated state. Increased HR can be a side effect of midazolam.[21] RR was difficult to accurately measure if the child was in an agitated state, as body movement and crying behavior created many false readings from the capnograph and EKG leads. In an effort to reduce this error, all RR values occurring when the child was struggling (S) were eliminated from the data set.

When midazolam is used in any form, it is important to be aware of the possibility of paradoxical reactions. The package insert states a 2% occurrence, but as midazolam is increasingly used in a conscious sedation setting as opposed to a general anesthesia setting, this value may increase. Two of the 20 patients in this study showed a paradoxical type reaction occurring within 5 minutes of SM injection. The 10% occurrence of paradoxical reaction in this study was most likely due to the small sample size. It is important to note that this type of reaction is not just a child becoming agitated or struggling.

Litchfield reported an unusual reaction to IV diazepam and accurately summed up what occurs during these "paradoxical reactions." He described the patient as appearing "normal at the commencement of the procedure, but soon after exhibited strange and unusual body movements...all of which resembled the person possessed in the film, 'The Exorcist.'[38] Fraone et al reported paradoxical reactions manifesting approximately 20 to 40 minutes after oral midazolam had been administered and lasting as long as several hours.[8] Both patients in this study exhibited inconsolable agitation, crying, and struggling with the patient seemingly stuck in a nightmarish state. One patient settled down after 15 minutes and dental treatment was completed with no complications or interruptions. The other patient remained agitated and treatment was aborted. Interestingly, this second patient accounted for the majority of the struggling behavior reported for the CH/midazolam regimen in this study. The medical literature reports the use of flumazenil, 0.01mg/kg or a single 0.5 mg IV dose, to break these paradoxical reactions.[39-41] Further studies are needed to determine the incidence of paradoxical reactions and the action of flumazenil. The current study limited the use of flumazenil to medical emergencies. Any practitioner using midazolam should be aware of the possibility of paradoxical reactions as well as prepare the parent for that possibility. A possible concern among pediatric dentists utilizing flumazenil is the lack of practice or training in IV access. Interestingly, a study by Oliver et al, describes a potential acceptable administration of flumazenil submucosally.[42]

An area of future research should be evaluating recovery time. This study did not look closely at differences in recovery time, but the 3 longest recovery times observed were all with SM midazolam. Increased recovery time would be an important factor for any practitioner considering using SM midazolam.

Limitations that existed with this study include a single dose concentration of midazolam, and use of the papoose board. The use of the papoose board may preclude an accurate evaluation of sedated behavior, as restraint falsely decreases ratings for body movement and falsely decreases ratings of quiet behavior. The use of the papoose board was elected to simulate a typical pediatric dental oral conscious sedation. The papoose board was utilized for both study groups.

CH at a dose of 50mg/kg is often ineffective, leaving children undersedated and possibly less able to cope with treatment than before.[4] When this occurs, an additional sedative can be given or treatment can be aborted. In the past, the pediatric dentist's options were to:

1. increase the dose of CH given initially—which left many patients oversedated;
2. add additional CH in the middle of the procedure—which is contrary to AAPD guidelines;
3. use an opiate such as meperidine—which is a potent respiratory and CNS depressant, has a long half-life, increases the risk of lidocaine toxicity, and increases the incidence of nausea and vomiting.[28-29]

SM midazolam could prove useful to the practitioner who is reluctant to exceed the MRD initially and does not wish to orally titrate additional medication. When necessary, SM midazolam can be safely and easily delivered at the time of local anesthesia. Peak serum levels will be obtained faster if the injection is not at the same site where epinephrine was administered. Some practitioners may want to use SM midazolam combined with oral CH as an initial regimen for all sedations. Further study in this area is needed to determine what dosage combination is most effective.

Conclusions

1. The addition of SM midazolam (0.2 mg/kg) to 50 mg/kg of oral chloral hydrate for pediatric conscious sedation resulted in significantly increased quiet behavior, and decreased struggling behavior for an overall better quality of sedation when compared to oral CH alone.
2. Mean HR, RR, and BP remained within the normal range for patients 2 to 5 years old that were administered oral CH with SM midazolam.
3. The level of sedation achieved in this study can be described as alternating between conscious sedation level 2 and 3. BP and CO_2 monitoring may be recommended or desirable, depending on the level of sedation achieved.

4. This SM route of administration allows a practitioner not to have to commit to midazolam's use preoperatively; instead it can be used as an option for sedations that require augmentation due to negative behavior.

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References

1. Duncan WK, Pruhs RJ, Ashrafi MH Post AC. Chloral hydrate and other drugs used in sedating young children: Survey of American Academy of Pedodontics Diplomates. *Pediatr Dent.* 1983;5:252-256.
2. Houpt MI. Report of project USAP: The use of sedative agents in pediatric dentistry. *J Dent Child*. 1989;56:302-309.
3. Houpt MI. Report of project USAP: The use of sedative agents in pediatric dentistry. *Pediatr Dent*. 1993;15:36-40.
4. Nathan JE. Management of the refractory young child with chloral hydrate: Dosage selection. *J Dent Child*. 1987;54:22-29.
5. Musselman, RJ, McClure D. Pharmacotherapeutic approaches to behavior management. In: G Wright, ed. *Behavior Management in Dentistry for Children*. Philadelphia: WB Saunders Co; 1975:146-155.
6. Kupietzky A, Houpt MI. Midazolam: A review of its use for conscious sedation of children. *Pediatr Dent*. 1993;15:237-241.
7. Kupietzky A, Holan G, Shapira J. Intranasal midazolam better at effecting amnesia after sedation than oral hydroxyzine: A pilot study. *Pediatr Dent*. 1996;18:32-34.
8. Fraone G, Wilson S, Casamassimo PS, Weaver J, Pulido AM. The effect of orally administered midazolam on children of 3 age groups during restorative dental care. *Pediatr Dent*. 1999;21:235-242.
9. Silver T, Wilson C, Webb, M. Evaluation of two doses of oral midazolam as a conscious sedation for physically and neurologically compromised pediatric dental patients. *Pediatr Dent*. 1994;16:350-359.
10. Reeves ST, Weidenfeld KR, Wrobleski J, Hardin CL, Pinosky ML. A randomized double-blind trial of chloral hydrate/hydroxyzine versus midazolam/acetaminophen in the sedation of pediatric dental outpatients. *J Dent Child*. 1996;63:95-100.
11. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: A comparison of midazolam and ketamine. *J Anesth*. 1994;41:221-226.
12. Naqvi A. Oral midazolam in paediatric dentistry. *Middle East J Anesthesiol.* 1996;13:427-440.
13. Saarnivaara L, Lindgren L, Klemola UM. Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. *Br J Anaesth*. 1988;61:390-396.
14. McCluskey A, Meakin GH. Oral administration of midazolam as a premedicant for pediatric day-case anesthesia. *Anesth Analg*. 1994;49:782-785.
15. Connors K, Terndrup T. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. *Ann Emerg Med*. 1994;24:1074-1079.
16. Payne KA, Coetzee AR, Mattheyse FJ et al. Oral midazolam in pediatric premedication. *S Afr Med J*. 1991;79:372-375.
17. Karl HW, Keifer AT, Rosenberger JL, Larach MG, Ruffle JM. Comparison of the safety and efficacy of intransanal midazolam and sufentanil for preinduction of anesthesia in pediatric patients. *Anesthesiology*. 1992;76:209-215.
18. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. *J Anesth*. 1992;39:545-550.
19. Weldon BC, Watcha MF, White PF. Oral midazolam in children: Effect of time and adjunctive therapy. *Anesth Analg*. 1992; 75:51-55.
20. Jones RD, Visram AR, Kornberg JP et al. Premedication with oral midazolam in children–An assessment of psychomotor function, anxiolysis, sedation and pharmacokinetics. *Anaesth Intensive Care*. 1994;22:539-544.
21. Omoigui S. *The Anesthesia Drugs Handbook*. 2nd ed. St. Louis: Mosby; 1995:229-232.
22. Alfonzo-Echeverri E, Troutman KC, George W. Absorption and elimination of midazolam by submucosal and intramuscular routes. *Anesth Prog*. 1990;37:277-281.
23. Griffin JW. Submucosal Sedation 5-year pilot study [abstract]. *Anesth Prog*. 2000;47:88.
24. Takahashi S, Kurasawa Y, Furuya H. Sedative effect of midazolam injected with epinephrine containing lidocaine into oral tissues [abstract]. *Anesth Prog*. 2000;47:113-114.
25. Marshall WR, Weaver BD, McCutcheon P. A study of the effectiveness of oral midazolam as a dental preoperative sedative and hypnotic. *Spec Care Dent*. 1999;19:259-266.
26. Lochary ME, Wilson S, Griffen AL, Coury DL. Temperament as a predictor of behavior for conscious sedation in dentistry. *Pediatr Dent*. 1993;15:348-352.
27. Moore PA, Goodson MJ. Risk appraisal of narcotic sedation for children. *Anesth Prog*. 1985;32:129-139.
28. Malamed SF, Quinn CL, Hatch HG. Pediatric sedation with intramuscular and intravenous midazolam. *Anesth Prog*. 1989;36:155-168.
29. Goodson MJ, Moore PA. Life-threatening reactions after pedodontic sedation: An assessment of narcotic, local anesthetic, and antiemetic drug interactions. *J Am Dent Assoc*. 1983;107:239-245.
30. Garty M, Ben-Zvi Z, Hurwitz A. Opioid effects on lidocaine disposition and toxicity in mice. *J Pharmacol Exp Ther*. 1985;234:391-394.

31. Ochs MW, Tucker MR, White RP. A comparison of amnesia in outpatients sedated with midazolam or diazepam alone or in combination with fentanyl during oral surgery. *J Am Dent Assoc*. 1986;113:894-897.
32. ten Berge M, Veerkamp J, Hoogstraten J: Dentists' behavior in response to child dental fear. *J Dent Child*. 1999;66:36-40.
33. American Academy of Pediatric Dentistry. Guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric dental patients. *Pediatr Dent.* 2002;24:80.
34. United States Pharmacopeial Drug Index, Vol. I. *Information for the Health Care Professional.* 23rd ed. Greenwood Village, Co: Micromedex; 2003:1898-1905.
35. McCann W, Wilson S, Larsen P, Stehle B. The effects of nitrous oxide on behavior and physiological parameters during conscious sedation with a moderate dose of chloral hydrate and hydroxyzine. *Pediatr Dent*. 1996;18:35-41.
36. Downs AT, Dembo J, Ferretti G, Lyons TD, Pelphery A. A comparative study of midazolam to meperidine/promethazine as an IM sedative technique for the pediatric dental patient. *J Dent Child*. 1997;64:197-200.
37. Hosmer DW, Lemeshow S. In: *Applied Logistic Regression*. 2nd ed. New York: Wiley; 2000.
38. Nathan JE, West MS. Comparison of chloral hydrate-hydroxyzine with and without meperidine for management of the difficult pediatric patient. *J Dent Child*. 1987;54:437-444.
39. American College of Emergency Physicians. In: GR Strange, ed. *The Pediatric Emergency Medicine Course.* 3rd ed. Dallas: American Academy of Pediatrics; 1998:5, 43.
40. Litchfield NB. Complications of entravenous diazepam—Adverse psychological reactions (an assesment of 16,000 cases). *Anesth Prog*. 1980;27:175-183.
41. Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy. *Clin Pediatr*. 1997;36:681-684.
42. Rodrigo CR. Flumazenil reverses paradoxical reaction with midazolam. *Anesth Prog*. 1991;38:65-68.
43. Fulton SA, Mullen KD. Completion of upper endoscopic procedures despite paradoxical reaction to midazolam: A role for flumazenil? *Am J Gastroenterol*. 2000;95:809-811.
44. Oliver FM, Sweatman TW, Unkel JH, Kahn MA, Randolph MN, Arheart KL, et al. Comparative pharmacokinetics of submucaosal vs. intravenous flumazenil (Romazicon) in an animal. *Pediatr Dent*. 2000;22:489-493.

Abstract of the Scientific Literature

Developmental Biology and Building a Tooth

This review article discusses the new developments regarding the mechanisms of tooth development at the gene level. It is anticipated that the new knowledge about molecules which drive tissue and organ development and cell differentiation will eventually lead to tissue regeneration as well as the possibilities of growing new organs such as teeth. Molecular geneticists have discovered that there are specific cell signals that control the advancement of tissue development. The most studied signals include 4 different families: (1) fibroblast growth factor; (2) bone morphogenic proteins; (3) hedgehog; and (4) Wnt. Research has further identified several specific genes involved in tooth development. For example, mutations in the gene encoding transcription factor RUNX2 has been linked to the development of cleidocranial dysplasia. Still other studies indicate that signaling centers, called "enamel knots," are responsible for guiding the patterning of tooth crowns such as the height and location of cusps. Finally, molecular geneticists have identified possible stem cells in the dental pulp of adult teeth. In conclusion, the path to tooth "regrowth" is still long and tortuous, however, the dreams of tooth regeneration may not be as farfetched as originally speculated.

Comments: This article presents a cursory look at the fascinating field of molecular genetics as it relates to tooth development. **BB**

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Thesloff I. Developmental biology and building a tooth. Quintessence Int. 2003;34:613-620.
25 references