A Comparison of 3 Routes of Flumazenil Administration to Reverse Benzodiazepine-induced Desaturation in an Animal Model

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Abstract

Purpose: The purpose of this study was to examine intralingual (IL) and submucosal (SM) delivery of flumazenil as viable alternatives to immediate intravenous (IV) administration for reversing benzodiazepine sedation in an animal model.

Methods: A dog animal model was chosen based upon comparable body weight to children (12-17 kg) and the ease of oral access in this species. Research design was a nonrandomized matched pair study. This type of "before-and-after study" allowed the dogs to receive 3 different routes of flumazenil administration (IV, IL, and SM) following an initial dose of midazolam (0.5 mg/kg IV). Blood samples were obtained (at 0, 2, 4, 8, 15, and 30 minutes) for high performance liquid chromatography (HPLC) analysis of flumazenil and midazolam, and oxygen saturation values were recorded.

Results: Both IL and SM delivery of flumazenil were determined to be viable alternatives to immediate IV administration for reversing benzodiazepine-induced oxygen saturation (SaO_2) desaturation. For flumazenil to be able to reverse the SaO_2 desaturation, the plasma levels must be greater than 5 ng/ml, which was exceeded by IL and SM drug delivery.

Conclusion: In a benzodiazepine-induced desaturation, the submucosal and intralingual routes are viable alternatives to intravenous administration of flumazenil in an animal model (Pediatr Dent 2006;28:357-362).

KEYWORDS: CONSCIOUS SEDATION, ORAL SEDATION, REVERSAL AGENTS, BENZODIAZEPINES, CHILDREN, DENTISTRY, ANIMAL MODEL

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Intravenous (IV) benzodiazepines such as diazepam (Valium) and midazolam (Versed) have been employed for more than 10 years:

1. as components of general anesthesia; and, where appropriate
2. for the purpose of conscious sedation for:
   a. endoscopy;
   b. urology;
   c. cardiology; and
   d. dental surgery.

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These drugs act through the enhancement of the binding of gamma-amino butyric acid (GABA) to specific receptors located in the central nervous system. In so doing, they produce a myriad of effects, such as: (1) muscle relaxation; (2) amnesia; (3) anticonvulsant action; and (4) anxiolysis.

Versed is a short-acting benzodiazepine that, unlike diazepam, is formulated as a water-soluble salt, thereby facilitating IV, intramuscular (IM), and oral administration with minimal local irritation.[1,2] Versed undergoes spontaneous chemical rearrangement at physiologic pH, yielding a highly lipophilic but short-lived product.[1] Although oral bioavailability is only 50%, Versed possesses a rapid onset of pharmacologic action with peak serum concentration being achieved in less than 1 hour. In dentistry, Versed is commonly administered orally (0.3-0.75 mg/kg, 20-30 minutes prior to initiation of treatment) or intranasally (0.2-0.4 mg/kg) for control of patient anxiety and for in-office sedation. In some countries like Sweden, it is common to administer such sedative medications rectally. The sedative effect of rectal administration is not significantly greater than that of oral Versed.[3]

Typical endpoints for benzodiazepine-induced conscious sedation (ptosis, dysarthria, and drowsiness) are very close to a hypnotic state in which the patient is unresponsive to verbal command.[2,4] More recently, anxiolysis, amnesia, and patient cooperation have been used as measures of drug effectiveness.[5] Historically, benzodiazepines are known for their overall safety. It is widely accepted that Versed may not be advisable for patients with asthma, due to the potential for drug-induced histamine release. The drug has, nevertheless, been shown to be effective and safe for use with these patients.[6]

One advantage of the use of benzodiazepines over other drugs to induce sedation is the availability of a specific and potent antagonist, flumazenil (Romazicon, Anexate, and Lanexate). Flumazenil has a very high specificity for the central nervous system benzodiazepine receptors, where displacement of the agonist results in recovery of cognitive function. [7] In doses of 1 mg or less, flumazenil produces recovery of cognitive function in a matter of seconds (ie, one circulation time from arm to brain). Presently, the antagonist is indicated for the partial or complete reversal of the sedative effects of benzodiazepines in:

1. cases where general anesthesia has been induced and/or maintained with benzodiazepines for diagnostic and therapeutic procedures; and
2. for patients with benzodiazepine intoxication resulting from iatrogenic overdose.[9-11]

Flumazenil is also employed to mitigate sedation induced by benzodiazepines. Utilizing titration of the reversal agent permits controlled depth of sedation such that the patient remains arousable upon command.[10]

An uncommon but potentially dangerous side effect of Versed is iatrogenic O_2 desaturation, which is reversible with the use of flumazenil. The present availability of flumazenil for intravenous use only represents both an inconvenience and a feasibility problem for the oral health professional. These professionals routinely employ an orally or intranasally administered benzodiazepine for in-office sedation, but in the emergency situation are not as accustomed to finding intravascular access.[9] Health professionals such as dentists have used benzodiazepines for decades for in-office sedation and continue to use them regularly today. Consequently, a more practical, yet just as effective route of flumazenil administration for the rare emergency situations is clearly desirable. Flumazenil is effective for the reversal of Versed-induced deep sedation in children when administered by alternative routes of administration (eg, rectally).[12,13] In the context of dentistry, however, both the oral mucosa and tongue are easily accessible and may represent the most viable routes for drug administration. This is because the dentist is skilled and accustomed to routinely making intraoral injections (eg, local anesthetic agents).

Mucosal tissue and intralingual tissue are highly vascularized, and these routes should provide immediate access of drug to the circulation. For example, clinical studies with the synthetic opioid meperidine have shown that the concentration-time curves for the drug are superimposed following submucosal or intravenous administration of an identical drug dose (1.8 mg/kg).[13] Studies have shown that intralingual administration of the narcotic antagonist naloxene in dogs reverses respiratory depression and results in increased mean minute ventilation.[14]

In a previous study completed by the current investigators, submucosal injections (with negative aspiration) were made into the mucobuccal fold in the area between the third and fourth premolars of dogs. This study showed that there was no significant difference in plasma drug concentrations achieved by intravenous or submucosal drug administration at 4 minutes.[15] These earlier studies represent a precedent for the present study comparing intralingual (IL) injections to SM and IV administration of flumazenil.

Currently, flumazenil is marketed only as an IV drug. In dentistry, the capacity for submucosal and intralingual administration of flumazenil in rare emergency situations would greatly facilitate the use of this benzodiazepine antagonist to reverse the effects of sedative drugs such as Versed. Data are lacking to demonstrate the ability of this route of administration to rapidly produce pharmacologically effective plasma drug concentrations and to correlate concentration levels of flumazenil with physiological signs of O_2 desaturations.

The purpose of this study was to examine IL and SM delivery of flumazenil as viable alternatives to immediate IV administration for reversing benzodiazepine sedation in an animal model.

Methods

Model description

The dog was chosen as an animal model based upon comparable body weight to children (12-17 kg) and the ease of oral access in this species. All experiments with dogs were conducted under protocols approved by the review process of the Animal Care and Use Committee (ACUC) of the University of Tennessee Health Science Center, Memphis, Tenn. At no time were the animals subjected to painful procedures, except where this was unavoidable in the adequate conduct of the study design. Overall supervision of the animal experiments was the responsibility of the University's Department of Comparative Medicine.

Research design

The research design was a nonrandomized. matched-pair study. This type of "before-and-after study" allowed the dogs to receive the 3 different treatments. In this type of study, the distribution of known and unknown variables is carried along with each dog as it receives one therapy and then the next. This allows for each dog to serve as its own control.

Animal studies

Ten anesthetized (isoflurane 0.6% and medical air) male dogs (12-17 kg; overnight fasted) each received a bolus IV dose of Versed (0.5 mg/kg) so that $Sa0_2$ desaturation was achieved. For the purposes of these studies, this was defined

as a 10% decline in $Sa0_2$ saturation (measured with pulse oximeter). Each dog had induction of $Sa0_2$ desaturation without receiving flumazenil, allowing each dog to serve as its own control. Immediately before (0 time) and at various times (2, 4, 8, 15, and 30 minutes following drug injection) blood samples (5 mL) were obtained from an indwelling cephalic vein catheter (20 G, 1.25 in). Catheter patency was maintained, as appropriate, by back flushing with heparinized saline. Blood was transferred into sterile vacutainers, which were immediately placed on ice.

Following centrifugation, the resulting serum was transferred to labeled vials and immediately frozen (-70^{0}C) pending analysis. These sample collection times were based upon published pharmacokinetic data indicating a short plasma half-life and rapid decline in detectable blood levels of flumazenil.[7] In addition, the time for each dog to return to within 2 standard deviations of baseline SaO_2 values was also recorded at 1-minute intervals using a pulse oximeter. For example, for an animal with a baseline SaO_2 of 90%, it would be the time to reach an SaO_2 of 88% following a 10% desaturation. The decision to use 2 standard deviations was chosen to simulate and be clinically relevant to a human patient population.

One week following the aforementioned procedures, each dog again had its SaO_2 desaturated using experimental conditions identical to those previously described. Two minutes after delivery of IV Versed, each dog received IV flumazenil (Romazicon, 0.01 mg/kg). Blood samples were obtained and processed in a manner identical to that described for dogs given Versed only. In addition, the time for each dog to return to SaO_2 baseline values was also recorded.

In subsequent weeks, the dogs received flumazenil (0.2 mg/2 ml) submucosally (in the mucobuccal fold area between the third and fourth premolar) and intralingually (at the midline in the dorsal posterior one third of tongue at a depth of 1 cm). Blood samples were obtained as previously mentioned. The flumazenil dosages of 0.01mg/kg for 12 to 17 kg animals resulted in volumes of approximately 1.8 ml, equal to volumes of a dental local anesthetic cartridge. To rule out the change in O_2 saturation being caused by a painful stimulus, one dog also received an injection of a comparable volume of saline in the tongue and $SaO_2$was monitored, as aforementioned.

Following each treatment regimen, animals were returned to their pens with routine access to food and water. Approximately 48 hours and 7 days following IL drug injection, color photographs were taken of the flumazenil injection sites and corresponding contralateral (control) mucosal areas. Also, the IL injection site was biopsied using a 1.0 mm by 3.0 mm punch 1 week after injection, according to the same anatomic landmarks as injection. The material was placed in labeled containers of 10% buffered neutral formalin for subsequent histological examination. Tissue samples of the contralateral IL site were collected in the same manner as controls. The time schedule for the animal study's data collection was 4 weeks. Following each treatment arm, there was a 1-week washout period before a rechallenge using a different route of drug delivery. At the study's completion, the dogs were released to the University's Department of Comparative Medicine for disposal at their discretion.

Analytical studies

Quantification of flumazenil in plasma was made using a reversed-phase high performance liquid chromatography (HPLC) assay that was previously described.[7] Briefly, duplicate aliquots (0.5 mL) of thawed plasma samples were subjected to solid-phase extraction (Oasis MCX 30 mg extraction cartridges, Waters Associates, Melford, Mass) and eluted with methanolic NH_3OH (5%). For each sample, the organic phase was evaporated under vacuum at 37^{0}C. Dried samples were either reconstituted immediately or frozen for subsequent analysis.

Samples were reconstituted in a mobile phase (80 µL) and were placed in sealed disposable glass inserts (250 µL) in an injector tray for refrigerated (4^{0}C) automated HPLC analysis. This was conducted using Nova-Pak C_{18} reversed-phase column (4µm; 10 cm x 5mm, Waters Associates, Milford, Mass) using a mobile phase gradient HPLC-grade acetonitrile in sodium phosphate buffer (0.04 M, pH 7.2 containing 0.1% triethylamine) at 1.5 mL/minute. Detection of flumazenil was made by Waters Associates model no. 2487 dual wavelength UV detector set at 243 nm. Calibration curves were constructed according to standard techniques using blank human serum spiked with known concentrations of flumazenil and processed in an identical manner. Quantification was made by interpolation of unknown peak ratio (vs internal standard) values into the standard curves and values reported as the mean duplicate analyses.

Histology studies

Tissue specimens were submitted to the Oral and Maxillofacial Pathology Lab of the University of Tennessee Health Science Center in coded containers to enable unbiased interpretation. For each animal, the lab prepared microscopic slides of 5-µm tissue thickness and stained them with hematoxylin and eosin. Ten blinded raters examined unmarked photographs (preinjection and 48 hours postinjection) of the injection sites and reported whether clinical changes were present. The lab reported any tissue changes noted on each slide including, but not limited to, polymorphonuclear cells, macrophages, plasma cells, monocytes, and B and T lymphocytes.

Statistical analysis

A descriptive analysis of blood serum levels was used to examine the levels of flumazenil postdesaturation with Versed. A 1-way analysis of variance was used to look for differences in routes of administration and serum levels of flumazenil over the 30-minute study period. Paired *t* tests

Table 1. Mean±SD Serum Concentrations of Flumazenil According to Route of Administration in the Animal Model over the Study Time Period (n=5)

Time (min)	Intravenous	Intralingual	Submucosal
2	16.3±4.0	14.6±11.5	6.0±4.0
4	14.9±7.0	16.8±6.9	7.8±6.1
8	7.1±2.6	16.3±15.6	12.6±9.9
15	8.0±5.4	4.6±5.3	18.1±18
30	2.9±2.6	4.1±5.0	9.8±12.4

Table 2. The Mean±SD Oxygen Desaturation Recovery Time in Minutes for an Animal to Return to Within 2 SD of the Baseline Oxygen Saturation Level

Control	Intravenous (IV)	Intralingual (IL)	Submucosal
3.9±12.32	1.7±4.9*	3.3±11.8	2.3±1.2

*P<.01 IV administration vs IL, by 1-tailed t test; all other comparisons had no significant differences.

(Versed+IV f, Versed+IL f, Versed+SM f) were conducted to examine time of desaturation reversal compared to the control (Versed alone) as well as paired contrasts (*t* tests) for each flumazenil method of delivery (IV+IL, IL+SM, SM+IL). A descriptive analysis was used to report the observation of histological tissue changes. A McNamara test was used to analyze the biopsy reports for a significant change in pathology.[16]

Results

The mean serum flumazenil levels following IV, SM, and IL drug delivery can be seen in Table 1. Plasma levels of Versed at the time of flumazenil injection were approximately 750 ng/ml. As expected, peak serum levels of IV drug administration were seen in the first serum sample (16.3 ng/ml at 2 minutes), with concentrations declining thereafter. In the same manner, both IL and SM drug levels peaked in the 8-minute (18.4 ng/ml) and 4-minute (8 ng/ml) serum samples, respectively. Thereafter, the decline in drug level was comparable to that seen in IV for both SM and IL. In this animal model, at 2 minutes the flumazenil levels were greater than 5 ng/ml, which is sufficient to reverse benzodiazepine sedation in all 3 treatment groups (IV, IL, and SM). This serum level of 5 ng/ml is clinically important because it is the serum level needed to reverse benzodiazepine sedations. [8] The were no significant differences in the route of administration (IV, SM, or IL) and resulting serum levels over the 30-minute time period measured (*P*>.92).

Overall, physiological reversal of a SaO_2 desaturation was seen with all methods of flumazenil delivery, including the control, as noted in Figure 1. The SaO_2 desaturation reversal was determined to be when the SaO_2 saturation returned to within 2 standard deviations of the average baseline O_2 levels. There was not a significant difference in time to recovery (desaturation reversal) between the control (Versed) and all 3 of the flumazenil treatment groups (IL, SM, and IV). As shown in Table 2, control dogs that were given Versed alone took 3.9 minutes to reverse SaO_2 desaturation, which was not significantly different from IV, IL, or SM administration. Even though correlations between concentration levels of flumazenil with physiological signs of O_2 desaturations were not found between the Versed/control and the 3 delivery routes, certain delivery routes showed significantly faster recovery than others. Of the delivery methods, IV reversed SaO_2 desaturation within 1.7 minutes, which was significantly quicker (*P*<.01) than either SM or IL, which reversed SaO_2 desaturation within 2.3 minutes and 3.3 minutes respectively.

None of the raters reported any signs of clinical changes or inflammation in the photographs of the IL and SM injection and control sites in the tongue. No clinical signs of tissue changes were seen on postinjection photos at both 24 hours and 7 days. Regarding histological examination, no differences in inflammation levels were noted in the controls or at the injection site. A McNamara test revealed no significant differences in the comparison of histological examination between the control tissue samples and those samples of the intralingual injection site.[16]

Discussion

This study examined IL and SM delivery of flumazenil as viable alternatives to immediate IV administration for reversing benzodiazepine sedation in an animal model. Although the serum flumazenil level from the IV administration was higher in all samples, the other 2 delivery routes also achieved serum concentrations of flumazenil exceeding 5 ng/mL, and there were no significant differences between the administration routes. The serum level of 5 ng/ml is clinically important because it is the level needed

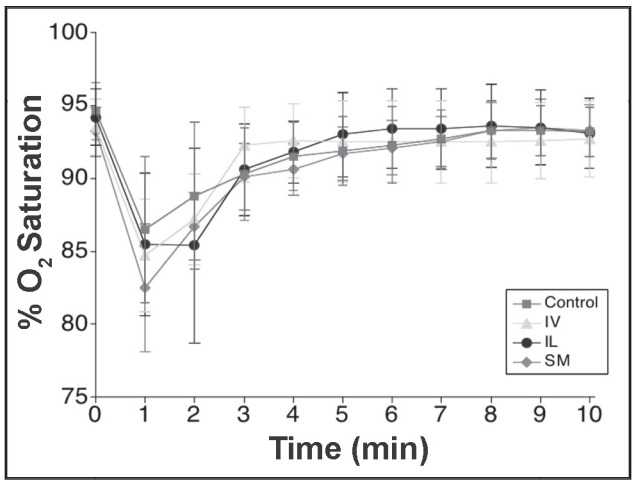

Figure 1. Oxygen saturation levels (mean±SD) in animals (n=10) following intravenous Versed (control) at time=0 and flumazenil administration at time=1 route of administration: IV, IL, or SM.

to reverse benzodiazepine sedations.[8] In this animal model, at 2 minutes all administration routes resulted in levels of flumazenil greater than 5 ng/ml and sufficient to reverse benzodiazepine sedation.

Regarding physiologic effects, all 3 delivery routes reversed Versed-induced SaO_2 desaturation within a maximum of 3.3 minutes, the longest being the IL route. The SM and IV routes reversed SaO_2 desaturation quicker than IL in 2.3 minutes and 1.7 minutes, respectively. Though not statistically significant, all 3 routes were quicker than no reversal agent, which took 3.9 minutes for reversal. Even though the SM route reversed O_2 desaturation faster than the IL, the absolute drug levels were higher for the IL route. This study limitation may be attributed to the small number of dogs used in the study, and the results were not consistent enough to see minor differences in efficacy over such a short time scale and monitoring only at minute intervals. An additional study limitation may have been the animal population itself, with the dogs having developed over their lifetimes conditioned responses to drugs and building up tolerance to the benzodiazepine used in this study.

Other studies are warranted to determine if a smaller volume of drug administered with the recommended or lower concentration into either the tongue or submucosal area would achieve viable flumazenil redosing. Because drug volume is a limiting factor for the amount of drug that can be delivered via SM or IL, a reformulated drug could allow for less volume of flumazenil with an increased concentration. Future studies should evaluate redosing in the SM or IL area witha reformulated and more concentrated drug that would avoid exceeding the maximum of 3 mL in those areas. Concerning the potential toxicity of flumazenil, no clinical signs of tissue changes were seen on postinjection photos at both 24 hours and 7 days. Regarding histological examination, no differences in inflammation levels were noted in either the controls or at the injection site. The one dog given a bolus of saline IL produced no changes in the O_2 saturation. This may rule out the potential of a painful stimulus causing the saturation changes that were seen. Thus, it can be assumed that SM and IL routes of drug delivery at the concentration and formulation used are viable alternatives to the IV route.

IL and/or SM drug delivery is a possible alternative for the pediatric dentist to IV flumazenil delivery to reverse benzodiazepine-induced SaO_2 desaturation. Given that the pediatric dentist is skilled and accustomed to routinely making intraoral injections, either of these routes would be a viable alternative. Re-emergence of sedation, albeit at a reduced intensity, could theoretically reoccur. This is unlikely, however, given the doses and routes of Versed administration commonly employed in pediatric dentistry. Because pediatric dentists rarely obtain IV access, an intraoral route of flumazenil delivery would allow flumazenil to be delivered immediately during an emergency situation. This would allow for a window of time to then gain IV access. One should not assume that SM or IL administration is preferred over IV flumazenil delivery to achieve minute-to-minute control over depth of sedation.

Procedural sedation and analgesia have been found to be safe and effective for use in an emergency department. In a study by Pitetti et al, complications occurred 18% of the time—most commonly hypoxia that could be easily treated. Sedation was successful 99% of the time. It was found that procedural sedation and analgesia can be safely and effectively administered by non-anesthesiologists in a pediatric emergency department.[17]

It is a universal agreement that dentists need to have emergency drugs readily available. These drugs should include: (1) oxygen; (2) epinephrine; (3) nitroglycerin; (4) injectable diphenhydramine or chlorpheniramine; (5) albuterol; and (6) aspirin. Other drugs should also be considered, such as: (1) glucagons; (2) atropine; (3) ephedrine; (4) hydrocortisone; (5) morphine or nitrous oxide; (6) naloxone; (7) Versed; (8) lorazepam; and (9) flumazenil.[18] These data will be useful in justifying the design of further clinical studies; such studies will be necessary for US Food and Drug Administration approval of this alternative route of drug administration. Studies in humans are the next step in confirming the safety and effectiveness of SM and IL flumazenil administration.

Conclusions

Based on this study's results, the following conclusions can be made:

1. In an animal model, SM and IL flumazenil injections may constitute a safe and effective alternative to IV flumazenil administration.
2. In an animal model, there were no differences in delivery route (IV, SM, or IL) to produce serum drug levels above the minimal 5 ng/ml required for clinical reversal of benzodiazepine-induced respiratory depression.
3. In dogs, IL flumazenil administration does not appear to be associated with soft tissue inflammation or toxicity.

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Abstract of the Scientific Literature

Relationship Between Periodontal Disease and Adverse Pregnancy Outcomes

There has been increasing evidence suggesting a relationship between periodontal disease and certain systemic diseases. The purpose of this prospective, longitudinal case study was to determine whether maternal periodontal status influences gestation time and birth weight. A total of 374 pregnant women were recruited, of which 96 subjects were selected who met strict inclusion criteria for this study. They were examined intraorally in their first, second, and third trimester to record plaque scores, clinically assessed gingival inflammation, and probing depth (>3 mm). Validity of bleeding and probing depth measurements was enhanced with interexaminer calibration. The weight of newborns was recorded, identifying low weight (<2,500 g), and gestational time, considering less than 37 weeks as preterm. The 96 women delivered 89 newborns: 16 were preterm and 7 of these were low birth weight infants. No statistically significant association was found between any periodontal parameters and gestational age. Therefore, no adequate evidence was found to indicate that poor periodontal status during pregnancy represents a risk factor for delivering premature babies. A statistically significant (P=.0038) relationship was observed between low birth weight and probing depth measurements, especially the percentage of sites with a depth greater than 3 mm, for which gestational age was controlled. This study suggests that periodontal disease is a significant risk factor for low birth weight, but not a risk factor for preterm delivery.

Comments: Perhaps the future role of pediatric dentists will include routine bacterial screening of mothers for Streptococcus mutans as well as periodontal markers. There is presently a generalized interest and new evidence suggesting oral disease may have a profound effect on various organ systems. The National Institute of Dental and Craniofacial Research is presently supporting $20 million in large, multicenter clinical trials known as obstetric and periodontal therapy and maternal oral therapy to reduce obstetric risk to provide sound evidence as to whether periodontal care can reduce incidence of adverse pregnancy outcomes. These results should be available in 1 year. **SU**

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33 references