Plasma concentrations of flumazenil following intranasal administration in children

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Purpose: A pharmacokinetic study in children to determine plasma flumazenil concentrations after the intranasal administration of $40 \mu\text{g}\cdot\text{kg}^{-1}$.

Methods: Following institutional approval and informed written consent, 11 ASA physical status I-II patients, aged two to six years, undergoing general anesthesia for dental surgery were recruited. After induction, $40 \mu\text{g}\cdot\text{kg}^{-1}$ flumazenil Anexate®, Roche, $0.1 \text{ mg}\cdot\text{mL}^{-1}$ ($0.4 \text{ mL}\cdot\text{kg}^{-1}$) were administered via a syringe as drops, prior to nasal intubation. Venous plasma samples were drawn prior to administration of flumazenil ($t=0$), and then at 2, 4, 6, 8, 10, 15, 20, 30, 40, 60, and 120 min thereafter. The plasma samples were immediately processed by the on-site laboratory and then stored at -70°C , before batch analysis via high performance liquid chromatography assay. Pharmacokinetic data calculations were performed using WinNonLin software (Scientific Consulting Inc.).

Results: Eleven patients were studied, but data for one patient were discarded due to insufficient sampling. The median age was 4.3 yr (range 3 to 6), with a median weight of 18.9 kg (range 14.9 to 22.2). There were seven boys and three girls. Mean C_{max} was $67.8 \text{ ng}\cdot\text{mL}^{-1}$ (SD 41.9), with T_{max} at two minutes. The calculated half-life was 122 min (SD 99).

Conclusion: The mean plasma concentrations of flumazenil attained were similar to those reported after intravenous administration, and may be sufficient to antagonize the side-effects of benzodiazepines. This route of administration may be useful when the intravenous route is not readily available.

Objectif : Déterminer, par une étude pharmacocinétique chez des enfants, la concentration plasmatique de flumazénil après l'administration intranasale de $40 \mu\text{g}\cdot\text{kg}^{-1}$.

Méthode : Après avoir obtenu les autorisations écrites de l'institution et des parents, on a recruté 11 patients, d'état physique ASA I-II, âgés de deux à six ans, qui devaient subir une intervention dentaire sous anesthésie générale. À la suite de l'induction, $40 \mu\text{g}\cdot\text{kg}^{-1}$ de flumazénil (Anexate®, Roche, $0.1 \text{ mg}\cdot\text{mL}^{-1}$ ($0.4 \text{ mL}\cdot\text{kg}^{-1}$)) ont été administrés en gouttelettes au moyen d'une seringue avant l'intubation nasale. Des échantillons plasmatiques veineux ont été pris avant l'administration de flumazénil ($t = 0$), et ensuite à 2, 4, 6, 8, 10, 15, 20, 30, 40, 60, et 120 min. Les échantillons plasmatiques ont été immédiatement traités au laboratoire sur place et conservés à -70°C , avant l'analyse du tout par chromatographie à haute performance. Les calculs pharmacocinétiques ont été réalisés avec le logiciel WinNonLin (Scientific Consulting Inc.).

Résultats : Les données d'un seul patient sur 11 ont été refusées pour échantillons insuffisants. L'âge moyen des enfants, dont sept garçons et trois filles, était de 4,3 ans (limites de 3 à 6), et le poids moyen était de 18,9 kg (limites de 14,9 à 22,2). La C_{max} moyenne était de $67,8 \text{ ng}\cdot\text{mL}^{-1}$ (écart type de 41,9), et un T_{max} à deux minutes. La demi-vie était de 122 min (écart type de 99).

Conclusion : Les concentrations plasmatiques moyennes de flumazénil obtenues ont été similaires à celles qui suivent l'administration intraveineuse et peuvent être suffisantes pour contrer les effets secondaires des benzodiazépines. L'administration par voie nasale peut se révéler utile lorsque la voie intraveineuse n'est pas facilement accessible.

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BENZODIAZEPINE (BZD) sedation, especially midazolam, is commonly used to improve patient acceptance of surgical, diagnostic or emergency room procedures,^{1,2} and can be administered via the oral, rectal or intranasal route.² Oral BZD sedation is often used in pediatric patients, particularly toddlers, without concurrent intravenous access and, if adverse reactions such as excessive sedation, agitation and restlessness occur, antagonism may be required.³ However, flumazenil, a competitive BZD antagonist that reverses the central nervous system effects of all BZD,⁴ is only available as a parenteral preparation, and in those patients without intravenous access that require BZD antagonism, an alternative emergency route of flumazenil administration may be useful. Intranasally administered flumazenil may be such an alternative route, but has not been studied in children.

In addition, there is no standard intravenous pediatric flumazenil dose reported. The therapeutic clinical dose in adults is $20 \mu\text{g}\cdot\text{kg}^{-1}$, with a maximum intravenous bolus dose of 0.2 mg .^{5,6} In another study, the mean dose required to antagonize midazolam-induced anesthesia in children was $24 \mu\text{g}\cdot\text{kg}^{-1}$ (SD 19).⁷ The suggested neonatal dose is also $20 \mu\text{g}\cdot\text{kg}^{-1}$.⁸ Based on these studies, the intravenous therapeutic dose in children was assumed to be $20 \mu\text{g}\cdot\text{kg}^{-1}$. Since intranasally administered midazolam has a bioavailability between 32-57%,^{1,9} and flumazenil is structurally related to midazolam (Figure 1), a bioavailability of 50% was assumed for intranasally administered flumazenil. Consequently, in order to determine the plasma concentrations of flumazenil after intranasal administration in pediatric patients, a dose of $40 \mu\text{g}\cdot\text{kg}^{-1}$ ($0.4 \text{ mL}\cdot\text{kg}^{-1}$) was selected.

Methods

Following institutional approval and informed written consent, 11 ASA physical status I-II pediatric patients, aged two to six years, undergoing general anesthesia for outpatient dental surgery were recruited. Exclusion criteria included rhinopharyngitis, current BZD therapy, BZD allergies, and hepatorenal disorders. After a standard intravenous induction of $5 \text{ mg}\cdot\text{kg}^{-1}$ propofol, $3 \mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and $0.2 \text{ mg}\cdot\text{kg}^{-1}$ mivacurium, $40 \mu\text{g}\cdot\text{kg}^{-1}$, $0.1 \text{ mg}\cdot\text{mL}^{-1}$ flumazenil (Anexate®, Roche, ($0.4 \text{ mL}\cdot\text{kg}^{-1}$)) was administered via a syringe as drops, prior to nasal intubation. The first four patients received the total flumazenil dose via one nostril, while in the other patients it was divided equally between each nostril. Anesthesia was maintained with halothane, 0.5-2%, in nitrous oxide and oxygen. Venous plasma samples were drawn, via an indwelling Jelco® (Johnson and Johnson) catheter, before administration of

Fig 1: Flumazenil and Midazolam Structures

FIGURE 1

flumazenil ($t=0$), and then at 2, 4, 6, 8, 10, 15, 20, 30, 40, 60, and 120 min thereafter. Prior to venous sampling, 2 ml dead space fluid was withdrawn from the Jelco® and discarded, and immediately thereafter the catheter was flushed with 3 ml normal saline to maintain patency. All samples were drawn in the operating room. The plasma samples were immediately processed by the on-site laboratory and then stored at -70°C , before batch analysis via high performance liquid chromatography (HPLC) assay.

The plasma flumazenil concentrations were determined by a HPLC assay published previously,¹⁰ and was linear at concentrations ranging from 2 to $200 \text{ ng}\cdot\text{mL}^{-1}$. Inter- and intra-day coefficients of variation for accuracy and precision of the flumazenil assay, as measured using quality control samples (2 to $100 \text{ ng}\cdot\text{mL}^{-1}$), were $<4\%$.

Pharmacokinetic parameters were calculated from the plasma concentration-time data using a non-compartmental model with extravascular input (WinNonLin, Scientific Consulting Inc. Apex, North Carolina).

FIGURE 2

Results

Eleven patients were studied, but data for one patient were discarded as the intravenous cannula clotted, resulting in insufficient sampling. The median age was 4.3 yr (range 3 to 6), with a median weight of 18.9 kg (range 14.9 to 22.2). There were seven boys and three girls.

Pharmacokinetic analysis of the data from all ten patients yielded a mean C_{max} was $67.8 \text{ ng}\cdot\text{mL}^{-1}$ (SD 41.9), at a T_{max} of two minutes. Plasma flumazenil concentrations of each patient, as well as the sample mean, are displayed in Figure 2. The calculated pharmacokinetic data included a clearance of $200.6 \text{ mL}\cdot\text{min}^{-1}$ (SD 85.7), volume of distribution of 29.9 L (SD 20.4), and half-life of 122 min (SD 99). Data from the final six patients were reanalyzed as a subgroup distinct from the whole study group because the flumazenil dose was divided equally between the two nostrils in these patients. This subgroup analysis yielded a mean C_{max} of $93.99 \text{ ng}\cdot\text{mL}^{-1}$ (SD 22.4; T_{max} at two minutes), and a mean calculated plasma half-life of 75 min (SD 65.7).

Discussion

Benzodiazepine sedation of pediatric patients for procedures is occurring with increasing frequency in hospitals and outpatient settings, including dental practices.^{1,11} However, these patients do not usually have intravenous access established until the procedure is being performed and, although the preferred BZD, midazolam, has a low incidence of side-effects, there have been reports of apnea, hypotension, hypoxia and cardiac arrest.¹² Furthermore, the incidence of

paradoxical reactions is unknown, but ranges from less than 1% of all patients receiving midazolam,¹¹ to 40% of children receiving rectal midazolam in doses from $0.35 \text{ mg}\cdot\text{kg}^{-1}$ to $0.45 \text{ mg}\cdot\text{kg}^{-1}$.¹³ These reactions were described as agitated excitement, restlessness, irritation, lack of co-operation, disorientation or confusion, emotional crying, and visual disturbances.¹³ Those patients that require urgent antagonism of BZD side-effects or of paradoxical reactions, will need rapid intravenous placement. This may be difficult in children, especially in a setting where non-anesthetists may not have the optimal skills or equipment available. An alternate emergency route of flumazenil administration may thus be useful in these situations.

This study aimed to establish whether $40 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$ flumazenil administered intranasally would result in plasma concentrations that are sufficient to antagonize adverse BZD reactions. However, therapeutic plasma flumazenil concentrations have not been accurately determined. Klotz *et al.*⁴ concluded that plasma concentrations of 10 to $20 \text{ ng}\cdot\text{mL}^{-1}$ may effectively reverse BZD induced CNS depression. In another study, the mean plasma concentration of flumazenil required to reverse midazolam, as measured by the ability of the patient to identify him- or herself verbally after midazolam anesthesia, was $29.9 \text{ ng}\cdot\text{mL}^{-1}$.¹⁴ Even though these studies reported mean plasma flumazenil concentrations, as opposed to individual patient responses, it is evident that attaining a plasma concentration of 10 - $30 \text{ ng}\cdot\text{mL}^{-1}$ may result in clinical reversal of BZD side-effects. In our study, the mean C_{max} was $67.8 \text{ ng}\cdot\text{mL}^{-1}$, and was measured at two minutes after administration. Therefore, based on the reported therapeutic range of 10 - $30 \text{ ng}\cdot\text{mL}^{-1}$,^{4,14} the administration of intranasal flumazenil is likely to clinically antagonize the BZD side-effects.

Using the intravenous formulation of flumazenil intranasally results in the administration of large volumes of solution. A toddler, aged two to three years, weighing approximately 15 kg, will receive 6 mL of solution. This may result in some oromucosal and gastric absorption, in addition to the proposed nasal mucosal absorption. In this study, three of the first four patients failed to achieve high plasma flumazenil concentrations. This may reflect individual patient pharmacokinetic variability, but may also be due to the technique of administration. The first four patients received the entire dose of flumazenil in one nostril and, given the large volumes, it is conceivable that some, if not most, of the flumazenil was absorbed via the gastrointestinal tract. This would result in first pass hepatic metabolism with reduced bioavailability, as reported by Klotz *et al.*,⁴ where oral flumazenil has a bioavail-

ability of only 16%. Indeed, the pharmacokinetic analysis of the final six patients yielded a peak plasma concentration that was 50% greater than that of the whole study group. This is consistent with more complete absorption and reduced first pass hepatic metabolism as the flumazenil was absorbed via the nasal mucosa in these six patients. Consequently, to ensure reliable absorption of intranasal flumazenil, the dose should be divided equally between the two nostrils.

Intranasal flumazenil administration may theoretically produce laryngospasm or aspiration in semiconscious patients, especially considering the large volumes of solution being administered. Although this study was performed on supine anesthetized patients that had received neuromuscular paralysis, there was no evidence of aspiration at the time of intubation. However, when administering intranasal flumazenil, positioning the patient in the Trendelenburg or in the recovery position, may minimize this risk of aspiration. In addition, the selected dose of 40 $\mu\text{g}\cdot\text{kg}^{-1}$ flumazenil in this study resulted in a mean plasma concentration that exceeded previously reported mean concentrations. A smaller dose, for example 20 $\mu\text{g}\cdot\text{kg}^{-1}$, will result in less volume administered, and may further reduce the risk of aspiration, while still resulting in therapeutic plasma concentrations. However, this dose should be divided equally between the two nostrils to maximize the nasal mucosal surface area exposed to the drug.

After flumazenil administration in anesthesia, the most common side effect is nausea (10.8%).¹⁵ Other effects include tears, tremors, dizziness and anxiety (all in <1% of patients).¹⁵ Furthermore, flumazenil has a half-life of 0.7 to 1.3 hr,⁴ which is less than the half-life of midazolam of 1.5 to 3.5 hr.¹⁶ Consequently, resedation may occur once the flumazenil is metabolized. In our study, mean plasma concentrations of flumazenil was maintained above the therapeutic levels of 10–30 $\text{ng}\cdot\text{mL}^{-1}$ for at least 20 min. This should provide sufficient time to establish secure intravenous access and adequate patient monitoring to detect possible resedation.

Conclusion

Intranasally administered flumazenil, in doses of 40 $\mu\text{g}\cdot\text{kg}^{-1}$, result in mean plasma concentrations similar to those obtained after intravenous administration, and may be sufficient to antagonize BZD induced side-effects. This route of administration may be useful to reverse adverse effects resulting from oral midazolam administration in situations when intravenous access is not readily available. However, further studies to evaluate the clinical effects of intranasal flumazenil administration in non-anesthetized patients are required.

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