Seizure protection by intrapulmonary delivery of midazolam in mice

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1. Introduction

The lung provides a high capacity portal of entry that could be used to rapidly deliver anticonvulsant substances to the brain to treat seizures. In the present study, we demonstrate that midazolam, a water-soluble anticonvulsant benzodiazepine, confers potent seizure protection when administered via the intrapulmonary route. High dose (100 mg/kg) intraperitoneal midazolam induced loss-of-righting reflex in mice. Lower doses of midazolam (100–1000 µg/kg) when administered intraperitoneally did not induce loss-of-righting reflex but protected animals against pentylenetetrazol (PTZ)-induced seizures. Intrapulmonary administration of midazolam via a tracheal cannula protected against intraperitoneal PTZ seizures at lower doses. The minimal intraperitoneal and intravenous doses of midazolam required to elevate the threshold for seizure signs induced by intravenous PTZ were 500 and 100 µg/kg, respectively, whereas the minimal intrapulmonary midazolam dose was 12.5 µg/kg. Intratracheal midazolam caused a large increase in intravenous PTZ threshold 5 min after administration but the effect declined rapidly over 60 min and no antiseizure activity was evident at 120 min. The minimal intraperitoneal doses of midazolam required to elevate the threshold for seizure signs induced by intravenous picrotoxin and kainic acid were 100 and 2000 µg/kg, respectively; the corresponding values for intratracheal midazolam were 25 and 100 µg/kg, respectively. We conclude that midazolam is a highly effective anticonvulsant when administered by the intrapulmonary route. Midazolam is substantially more potent when delivered into the lung than when administered intraperitoneally or intravenously. Inhalation could be an alternative to other routes of administration for the delivery of midazolam to rapidly abort acute seizures.

The entire blood supply passes through the lungs and a portion of the blood exiting the lungs is directly carried to the brain via the carotid circulation, bypassing the liver. Drug metabolizing enzymes have low abundance in the lung allowing greater bioavailability for drugs that are subject to first-pass hepatic metabolism. Pulmonary drug delivery therefore provides an opportunity to deliver therapeutic substances to the brain for the treatment of central nervous system disorders. Delivery via the lung is particularly attractive in situations where a rapid onset of action is required. Inhaled preparations of drugs intended to act on the brain include inhalation anesthetics and a recently approved treatment for acute agitation (Keating, 2013); products are in clinical development for migraine (Aurora et al., 2009) and Parkinson’s disease (Grosset et al., 2013).

One promising application of pulmonary drug delivery is in epilepsy therapy. An inhaler system could be used to prevent the spread of epileptic activity during the aura phase of a seizure or to abort status epilepticus. Recently we reported that intrapulmonary propofol hemisuccinate, a propofol prodrug, provides rapid seizure protection in animal models (Dhir et al., 2010). In the present study, we characterized midazolam for this application. Midazolam is a water-soluble benzodiazepine with powerful anticonvulsant activity in animal seizure models (Pieri et al., 1981;
2. Materials and methods

2.1. Animals

Male NIH Swiss mice (22–30 g) were kept in a vivarium under controlled environmental conditions (temperature, 22–25 °C; relative humidity, 40–50%) with an artificial 12-h light/dark cycle. Wood chips were used in all cages. Experiments were performed during the light phase of the light/dark cycle after a minimum of 30 min period of acclimation to the experimental room. The animal facilities were fully accredited by the Association for Assessment and Accreditation of Laboratory Care and Use Committee of the University of California, Davis in strict compliance with the Guide for the Care and Use of Laboratory Animals of the National Research Council (National Academy Press, Washington, D.C.).

2.2. Midazolam and chemoconvulsant solutions

Midazolam aqueous solution (1 mg/ml midazolam, 0.8% sodium chloride, 0.01% disodium edetate, 1% benzyl alcohol; pH 3.0–3.6) was obtained from APP Pharmaceuticals, Inc. Vehicle solution was made with disodium edetate and benzyl alcohol (pH 3.0–3.6). The solution volume for intraperitoneal midazolam was 10 ml/kg and for intratracheal midazolam was 0.25 ml/kg. Vehicle solution was used as a diluent for the commercial midazolam solution. Pentylenetetrazol (PTZ), picrotoxin, and kainic acid (all from Sigma–Aldrich, St. Louis, MO) were dissolved in 0.9% saline.

2.3. Intratracheal drug delivery

Midazolam was administered by the intratracheal route as described previously (Dhir et al., 2010). In brief, mice were briefly anesthetized with 4% isoflurane. The animals were immediately placed on a surgical board angled at 60°. The animal’s mouth was kept open by hanging the upper incisors on a hook to facilitate detection of the epiglottis. Under illumination from an operating light, the pharynx was visualized after displacement of the tongue with a spatula. A syringe fitted with a blunt 24-gauge needle (25 mm in length) was gently inserted into the soft palate to enter the trachea past the vocal cords. When the tracheal cartridge ring is felt, the needle is considered properly placed within the tracheal lumen. The needle was gently removed and mouse was held vertically with head up for 2 min to facilitate the downward movement of liquid in the lungs. The mouse was allowed to recover fully from the anesthesia as assessed by normal spontaneous exploratory behavior.

Midazolam is used clinically either intravenously or intramuscularly for terminating status epilepticus (Galvin and Jelinek, 1987; Hayashi et al., 2007; Shorvon and Ferlisi, 2011; Silbergleit et al., 2012). Intranasal or buccal (oromucosal) midazolam is gaining acceptance in emergency treatment of prolonged or serial seizures (Bhattacharyya et al., 2006; Gilat et al., 2003; Wermeling et al., 2009; Nakken and Lossius, 2011; Gornack-Jones, 2012; Anderson and Saneto, 2012). Intrapulmonary administration could provide more rapid delivery to the ultimate target in the brain than intranasal or oromucosal administration. Midazolam is uniquely suited for this application because it is the only clinically available anticonvulsant benzodiazepine that exists in a water soluble form, thus allowing formulation in aqueous solution without lipidoid excipients, such as propylene glycol which is used in the parenteral preparations of other benzodiazepines (Reves et al., 1985). At pH <5, midazolam is diprotonated and converts to an open ring structure (Orive et al., 1989). Commercial preparations of other benzodiazepines are nonirritating and could potentially be suitable for intrapulmonary administration. In the present study we demonstrate that intrapulmonary delivery of such a midazolam solution confers protection against seizures induced by various chemoconvulsants and that it is more potent via this route than with intraperitoneal and even intravenous administration.

2.4. PTZ seizure test

A dose of midazolam was administered either intraperitoneally or intratracheally and 10 or 7 min later PTZ was administered intraperitoneally at a dose of 80 mg/kg, which, in the absence of pretreatment with an active agent, causes clonic convulsions in >97% of mice (Dhir et al., 2006). Animals were observed for a period of 30 min following injection. The time of onset of myoclonic jerks, clonus and tonic extension, and the incidence of lethality was recorded.

2.5. PTZ and picrotoxin intravenous seizure threshold tests

The thresholds for various behavioral seizure stages induced by the GABA receptor antagonists PTZ and picrotoxin were determined by infusing the convulsant drugs via a 27 gauge, 3/4 inch “butterfly” needle inserted into the lateral tail vein. The needle was secured to the tail by a narrow piece of adhesive tape and the animal was permitted to move freely inside an inverted 2 L glass beaker with free aeration from the top. A dose of midazolam was administered either intraperitoneally or intratracheally and 10 min later (or at the time interval indicated in the time course experiment) PTZ (10 mg/ml; Akula et al., 2008) or picrotoxin (1 mg/ml; Chan et al., 2006) was infused at a constant rate of 0.5 ml/min using a Becton Dickinson (1 ml) syringe mounted on an infusion pump (Model ‘11’ plus syringe pump; Harvard Apparatus, Holliston, MA). In some experiments, flumazenil (5 mg/kg; Tocris Bioscience, Bristol, UK) was administered intraperitoneally immediately before intratracheal midazolam. The syringe was connected to the needle by polyethylene tubing. The infusion was stopped at 3 min or at the onset of tonic extension, whichever occurred first. The thresholds to the following endpoints were determined: (i) the first myoclonic jerk; (ii) the onset of generalized clonus with loss-of-righting reflex; and (iii) the onset of tonic extension. Latencies were measured from the start of convulsant infusion to the onset of all these three events. The threshold value (mg/kg) for each endpoint was determined according to the following formula: (infusion duration [sec] + infusion rate [ml/min] × convulsant drug concentration [mg/ml] = 1000/[60 [sec] × weight of mouse [g]]).

2.6. Kainic acid seizure threshold test in mice

Seizure thresholds with intravenous infusion of the excitatory amino acid agonist kainic acid (7.5 mg/ml) were determined according to the same protocol as described for the GABA receptor antagonists. Animals treated with kainic acid exhibit wild running followed by clonus and tonic extension. The infusion rate was 0.15 ml/min (Kaminski et al., 2005).

2.7. Horizontal screen test for motor impairment

Motor impairment was evaluated using a modification of the horizontal screen test (Coughenour et al., 1977) that determines an animal’s ability to support its own body weight by grasping an inverted grid for 1 min. Unless intoxicated, mice do not fall from the grid.

2.8. Loss-of-righting reflex test

Loss-of-righting reflex, an indication of profound sedation/anesthesia, was assessed as described previously (Dhir et al., 2010). In brief, a dose of midazolam was administered intraperitoneally and the animal was returned to its cage. When arrest of spontaneous ambulation occurred, the animal was placed on a filter paper stage and gently turned onto its back every 10 s to assess the time of onset and recovery of loss-of-righting reflex. Animals unable to right themselves (return to normal posture) were scored as positive.

2.9. Data analysis

Results are expressed as mean ± S.E.M.; the significance of the difference in the responses of treatment groups with respect to control is based on one-way analysis of variance (ANOVA) followed by specific post-hoc comparisons using Tukey’s test. Differences were considered statistically significant when the probability of error was less than 0.05 (P < 0.05). Control values in the threshold tests were the mean threshold values for vehicle-treated groups.

3. Results

3.1. Comparison of intraperitoneal and intratracheal midazolam on PTZ-induced seizures

Intraperitoneal PTZ (80 mg/kg) induced clonic seizures, tonic seizures and mortality in all vehicle pretreated animals (Table 1).
When administered 10 min prior to PTZ, intraperitoneal midazolam (100–1000 μg/kg) conferred seizure protection in a dose-dependent fashion. At 100 μg/kg there was partial protection against tonic seizures and the mortality that invariably accompanies tonic seizures. With higher doses there was complete protection against tonic seizures and mortality and dose-dependent protection against clonic seizures and myoclonic jerks. However, even at the highest dose tested (1000 μg/kg) only 50 percent of animals were protected from myoclonic jerks.

Intratracheal midazolam (12.5–200 μg/kg) also conferred seizure protection when administered with pretreatment times of 10 and 7 min, however the effective doses were substantially lower (Table 1). The lowest dose producing significant protection against tonic seizures and mortality was 25 μg/kg. Higher doses produced increasing seizure protection in a dose-dependent fashion. Complete protection against all seizure signs was obtained at 200 μg/kg in the experiment with the 10 min pretreatment time and 100 μg/kg with the 7 min pretreatment time.

### 3.2. Comparison of intraperitoneal, intravenous and intratracheal midazolam in the PTZ threshold test

Intravenous infusion of PTZ (10 mg/ml at 0.5 ml/min) induced a progressive sequence of seizure signs consisting of myoclonic jerks, clonus and tonic extension followed by death. Pretreatment (10 min) with midazolam by the intraperitoneal route at doses of 500, 1000, 2500 and 5000 μg/kg but not 100 μg/kg caused a significant elevation in the thresholds for all seizure signs with respect to the values in vehicle-treated animals (Fig. 1A). Pretreatment (10 min) with midazolam by the intravenous route also effectively raised the threshold for all seizure signs at doses of 100 and 200 μg/kg but not 25 and 50 μg/kg (Fig. 1B). In contrast, pretreatment (10 min) with midazolam by the intratracheal route was effective at lower doses of 25, 50 and 100 μg/kg (Fig. 1C). Intratracheal administration of midazolam at 12.5 μg/kg raised the threshold for clonic seizures but the effect on myoclonic jerks and tonic extension did not reach statistical significance.

### Table 1

<table>
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<th>Midazolam dose (μg/kg)</th>
<th>Percentage showing myoclonic jerks</th>
<th>Percentage showing clonus</th>
<th>Percentage showing tonic extension</th>
<th>Percentage mortality</th>
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Vehicle or midazolam was administered by the specified route followed by PTZ at a dose of 80 mg/kg, i.p. The solution volume for intraperitoneal midazolam was 10 ml/kg and for intratracheal midazolam was 0.25 ml/kg. Values indicate percent of animals exhibiting indicated seizure sign or mortality. Each group consisted of 6 animals. *P < 0.05 as compared to vehicle treated control group (ANOVA followed by Tukey’s test).

In order to administer midazolam intratracheally, animals were briefly anesthetized with isoflurane during placement of the tracheal cannula. Isoflurane was not administered prior to intravenous or intraperitoneal midazolam injection. Therefore, it is conceivable that residual isoflurane could account for the increased potency of midazolam in the intratracheal experiments. To investigate this possibility, we determined the effect of...
intraperitoneal midazolam on PTZ threshold in mice that were lightly anesthetized with isoflurane. Groups of 6 mice were treated with 4% isoflurane followed by vehicle or midazolam at doses of 25 and 50 μg/kg. The PTZ thresholds (in mg/kg) for myoclonic jerks, clonus, and tonic extension, respectively, were 52.84 ± 2.73, 57.05 ± 2.64, 89.59 ± 10.93 in the vehicle group; 48.57 ± 1.69, 53.60 ± 2.54, 77.00 ± 4.49 in the 25 μg/kg midazolam group; and 48.35 ± 1.12, 53.55 ± 1.91, 78.73 ± 5.03 in the 50 μg/kg midazolam group. Comparison with values obtained in the absence of isoflurane or after recovery from isoflurane (see caption to Fig. 1) indicate that isoflurane anesthesia elevates PTZ seizure thresholds. However, low intraperitoneal doses of midazolam failed to elevate PTZ thresholds in the presence of isoflurane. Thus, residual isoflurane is unlikely to account for the high potency of intratracheal midazolam.

3.3. Time course of action in intratracheal midazolam in the PTZ threshold test

We next sought to assess the time course of action of midazolam administered by the intratracheal route. As shown in Fig. 2, 100 μg/kg intratracheal midazolam caused an elevation in threshold for tonic extension at 5, 10, 20, 40, 60 and 120 min with respect to the corresponding threshold values in vehicle pretreated animals. There was also an elevation in threshold for myoclonic jerks and clonus at the same time points (not shown). The effect was no longer evident at 120 min. It was not practical to assess pretreatment times shorter than 5 min due to the residual effect of isoflurane on seizure thresholds discussed above. Indeed, the small decline in mean threshold values after intratracheal vehicle administration is likely due to anesthesia effects.

3.4. Effects of flumazenil on the response to intratracheal midazolam

To assess whether the action of intratracheal midazolam is mediated by an action on the benzodiazepine site of GABAA receptors, we utilized the benzodiazepine receptor antagonist flumazenil (Haefely, 1988). By itself flumazenil did not alter the PTZ threshold (Fig. 3). Intratracheal midazolam, at doses of 100 μg/kg and 200 μg/kg, but not intratracheal vehicle caused significant elevations in the threshold for all seizure signs with respect to the values in intratracheal vehicle treated (intraperitoneal vehicle or flumazenil pretreated) animals. However, when animals were pretreated intraperitoneally with flumazenil immediately before intratracheal midazolam, the threshold elevations were eliminated.

3.5. Comparison of intraperitoneal and intratracheal midazolam in the picrotoxin seizure threshold test

Intravenous infusion of picrotoxin (1 mg/ml) produced the same sequence of seizure signs as observed with PTZ. As shown in Fig. 4A, pretreatment (10 min) with midazolam (100–1000 μg/kg) by the intraperitoneal route caused a dose-dependent increase in the threshold all seizure signs, which reached statistical significance at the 250 μg/kg dose except for the effect on clonic seizures which was significant at 100 μg/kg. In contrast, as shown in Fig. 4B, pretreatment (10 min) with midazolam at a dose of 50 μg/kg by the intratracheal route caused a significant increase in all seizure signs and a dose of 25 μg/kg significantly elevated the threshold for clonus and tonic extension but not myoclonic jerks.

3.6. Effects of intratracheal midazolam in the kainic acid seizure threshold test

Intravenous infusion of the excitatory amino acid agonist kainic acid (7.5 mg/ml) induced a similar sequence of seizure signs as did the GABAA receptor antagonists PTZ and picrotoxin. Pretreatment (10 min) with midazolam by the intraperitoneal route at dose of 2000 μg/kg but not 1000 μg/kg caused a significant elevation in the thresholds for clonus and tonic extensor phases induced by kainic acid (Fig. 5A). In contrast, pretreatment (10 min) with midazolam by the intratracheal route was effective at a dose of 100 μg/kg (Fig. 5B).

3.7. Horizontal screen and loss-of-righting reflex tests

Intratracheal midazolam did not produce signs of motor toxicity or loss-of-righting reflex at any of the doses tested. Specifically, in the time course experiment of Fig. 2, mice receiving 100 μg/kg intratracheal midazolam were assessed for motor toxicity with the inverted horizontal screen and the loss-of-righting reflex tests immediately before PTZ infusion. At no time point did any of the mice exhibit motor impairment or loss-of-righting reflex.
intraperitoneal midazolam at doses up to 5 mg/kg did not cause loss-of-righting reflex. Midazolam did induce loss-of-righting reflex at a very high dose of 100 mg/kg. At this dose, loss-of-righting reflex occurred at 8.3 ± 0.7 min and the righting reflex was regained at 72.0 ± 7.2 min, for a total sleep time of 63.7 min.

4. Discussion

In this study, we confirm the anticonvulsant activity of midazolam in several mouse chemoconvulsant models. Moreover, we demonstrate that the drug has high potency when administered as an aqueous solution into the lung. Midazolam did induce loss-of-righting reflex at a very high dose of 100 mg/kg. At this dose, loss-of-righting reflex occurred at 8.3 ± 0.7 min and the righting reflex was regained at 72.0 ± 7.2 min, for a total sleep time of 63.7 min.

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In this study, we confirm the anticonvulsant activity of midazolam in several mouse chemoconvulsant models. Moreover, we demonstrate that the drug has high potency when administered as an aqueous solution into the lung. The potency of intrapulmonary midazolam is greater than with intraperitoneal administration and, remarkably, also greater than with intravenous administration. Midazolam is unique among clinically available 1,4-benzodiazepine GABA<sub>α</sub> receptor positive modulators in that it is readily soluble in water at acidic pH (<5). It becomes highly lipophilic at physiological pH (7.4), with an octanol–water partition coefficient as much as 6–8-fold that of diazepam and lorazepam (Jones et al., 1988). These characteristics are ideal for intrapulmonary delivery where an aqueous solution is delivered into the deep lung. Upon contact with the physiological pH environment of the alveoli, midazolam would convert to the lipophilic form facilitating diffusion across the alveolar membrane into the pulmonary capillary circulation and ultimately into the brain.

The present series of experiments demonstrate for the first time the high anticonvulsant activity of intrapulmonary midazolam. It has previously been shown that midazolam is protective against seizures induced by PTZ (Pieri et al., 1981; Pieri, 1983; Raines et al., 1990) and other chemoconvulsants, including picrotoxin and kainic acid (Czontkowska et al., 2001; Turski et al., 1990). This was confirmed in the present study. In the PTZ model, intraperitoneal midazolam conferred seizure protection at doses of 500–1000 mg/kg whereas the minimally effective intravenous dose was 100 mg/kg, values similar to those reported previously (Pieri et al., 1981). In contrast, seizure protection was obtained with intratracheal midazolam at doses as low as 12.5–25 mg/kg. Midazolam is therefore at least 20 times more potent when administered into the lung than when administered intraperitoneally and at least 4 times more potent than when administered intravenously. An elevation in seizure threshold was obtained with intrapulmonary midazolam within 5 min of administration in the intravenous PTZ seizure threshold test and the effect on seizure threshold persisted for lorazepam (Arendt et al., 1987). These characteristics are ideal for intrapulmonary delivery where an aqueous solution is delivered into the deep lung. Upon contact with the physiological pH environment of the alveoli, midazolam would convert to the lipophilic form facilitating diffusion across the alveolar membrane into the pulmonary capillary circulation and ultimately into the brain.

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highest doses we tested did not cause motor impairment although and lethality (Pieri et al., 1981). Intrapulmonary midazolam at the midazolam causes respiratory depression (Megarbane et al., 2005) at 100 mg/kg intraperitoneally (this study); at even greater doses, 430 P450 (CYP) isozyme 3A4 (Gorski et al., 1994; Guengerich, 1999) has 100% bioavailability when administered intravenously. Mid- azolam undergoes metabolism in the liver, primarily by cytochrome P450 (CYP) isozyme 3A4 (Gorski et al., 1994; Guengerich, 1999) although other isozymes including CYP3A5 may contribute (Huang et al., 2004). CYP3A4 and CYP3A5 have similar metabolic capability with respect to midazolam (Williams et al., 2002; Soars et al., 2006). CYP3A4 is present, albeit at much lower levels than in the liver, in the mucosa of the gastrointestinal tract, but it is absent or expressed at low levels in the lung including the alveolar epithelium (Anttila et al., 1997; Ding and Kaminsky, 2003; Nishimura et al., 2003). CYP3A5 may, however, be expressed in the lung (Aoki et al., 2010). The major hydroxylated metabolite of midazolam is 1- hydroxymidazolam (75%) and there are several minor metabolites including 4-hydroxymidazolam (3%) and 1-4-dihydroxymidazolam (1%) (Ameire et al., 1998). 1-2-Hydroxymidazolam is substantially less potent than midazolam as an anticonvulsant as assessed by the elevation of PZT seizure threshold in mice (Pieri et al., 1981). The reduced potency is likely due to a combination of factors. First, the affinity of 1-2-hydroxymidazolam for GABA_A receptors has been reported to be one-fifth that of the parent (Arendt et al., 1987; although see Pieri et al., 1981; where it was found to be equal to midazolam) and, second, the metabolite has lower lipophilicity, so that uptake into the brain is reduced (by 4-fold) (Arendt et al., 1987). The receptor affinity and brain uptake of 4-hydroxymidazolam (and likely 1,4-dihydroxymidazolam) are even lower. Therefore, it has been concluded that the metabolites are unlikely to contribute substantially to the biological activity of midazolam (Arendt et al., 1987). These considerations indicate that differences in the metabolism of midazolam when it is administered by the intrapulmonary route are unlikely to account for the enhanced potency. Rather, avoidance of liver metabolism is a more plausible explanation. Midazolam is extracted by the lung when delivered by the circulation although to a lesser extent than by the liver (Aoki et al., 2010). The extent to which midazolam is metabolized in the lung when administered via the airways is not known but could be even less. In any case, it is plausible that midazolam is less well extracted by the lung when administered by the intrapulmonary route than by the liver following intravenous delivery. Following entry into the pulmonary circulation and passage through the left heart, midazolam is carried directly to the brain via carotid circulation thus avoiding metabolism by the liver. By contrast, intraperitoneal and intrave- nous administration would subject the drug to hepatic metabolism prior to access to the brain. At the doses conferring seizure protection, midazolam did not cause general anesthesia (loss-of-righting reflex), which in the mouse requires 40 mg/kg intravenously (Kilpatrick et al., 2007) or 100 mg/kg intraperitoneally (this study); at even greater doses, midazolam causes respiratory depression (MegaRabe et al., 2005) and lethality (Pieri et al., 1981). Intrapulmonary midazolam at the highest doses we tested did not cause motor impairment although intravenous dosing even as low as 100 μg/kg can cause transitory motor impairment (Pieri et al., 1981). There is therefore a separa- tion between midazolam doses that are anticonvulsant and those inducing gross neurological side effects. However, midazolam may cause more subtle neurobehavioral effects at anticonvulsant doses, such as memory impairment (Sanday et al., 2012), which were not assessed in the present study. Benzodiazepines are frequently used in the acute treatment of epi-leptic seizures including status epilepticus. Midazolam is effi- cacious when administered by the intravenous, intramuscular, intranasal and buccal routes. Nasal and oromucosal delivery are convenient, noninvasive approaches that are well accepted by patients and caregivers. However, these portals provide a relatively small absorptive surface; drugs deposited at these sites are subject to flushing away by local secretions; and access is restricted by a mucus layer. In contrast, the lung provides a much larger absorptive surface; the alveoli serve as natural traps; and access to alveolar epithelium is normally not limited by a mucus barrier. In addition, the nasal epithelium and buccal mucosa are less vascularized than the lung and provide access to the venous circulation whereas the entire circulation flows through the lung and substances absorbed across the alveolar wall enter the arterial blood supply that directly feeds the brain. These considerations suggest that lower doses of midazolam may be required to stop seizures when administered into the lung than with intranasal or buccal delivery, and the antiseizure effects may occur more rapidly. In sum, midazolam has several characteristics that make it suitable for use in an inhaler system to abort epileptic attacks. The drug is highly potent when administered into the lung; low milligram doses or less are expected to be effective in humans. The onset of action is rapid providing an opportunity for faster termination of seizures than with any other delivery approach, including intramuscular and even intravenous, particularly when the time required to achieve venous access is taken into account. Midazolam is shorter acting than other clinically available benzodiazepines so that any untoward sedative action would be as brief as possible. Midazolam has a large therapeutic window, minimizing side effects and serious toxicity. Given its favorable properties, it is conceivable that midazolam could be self-administered with an inhaler device during a seizure aura (or following warning of an impending seizure by a seizure prediction device) to prevent the development of a full-blown seizure. Mid- azolam could also be administered by a caregiver via a face mask inhaler to abort status epilepticus or acute repetitive seizures (seizure clusters). In these applications, intrapulmonary dosing may be more acceptable than intramuscular injection, and more rapid and effective than intranasal or buccal administration.

References


