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Oral Transmucosal Etomidate in Volunteers

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Background: **The oral transmucosal route of delivery is now used for many drugs, including fentanyl and midazolam. Etomidate's pharmacokinetic profile and physiochemical properties suggest it may be suitable for transmucosal delivery. Transmucosal delivery might extend etomidate's use to sedation and anxiolysis. This is the first study in humans to examine the oral transmucosal administration of a novel etomidate dosage form.**

Methods: **Ten healthy adult volunteers consumed 12.5-mg, 25-mg, 50-mg, and 100-mg doses of oral transmucosal etomidate (OTET) on four different study days. Serum etomidate concentrations, sedation, respiratory and cardiovascular variables, taste, and side effects were determined.**

Results: **Five minutes after OTET administration, etomidate was detected in the venous blood. Mean peak concentrations occurred 20–30 min later and ranged from 61–174 ng/ml, related to the dose administered. Drowsiness and light sleep occurred in a dose-related manner 10–20 min after administration and lasted for 30–60 min. No episodes of Sp_{O_2} <90%, hypotension, or emesis occurred at any dose throughout the study. Nausea was rare. Two volunteers exhibited a brief episode of involuntary tremor after the 100-mg dose. The bitter taste of OTET was judged increasingly unpleasant with escalating doses.**

Conclusions: **Oral transmucosal etomidate produces dose-related increases in sedation and clinically significant serum concentrations with minimal side effects. The time course of these effects suggests that OTET might be useful when brief mild to moderate sedation with rapid recovery is desirable. Further development of this novel dosage form is warranted. (Key words: Dose proportionality; etomidate; hypnotics; transmucosal drug delivery.)**

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IN the past decade, the oral transmucosal route of drug administration has been shown to be an effective means of administering many anesthetic drugs.[1,2] A drug administered through the oral mucosa is absorbed directly into the blood stream, bypassing hepatic metabolism, and thereby achieving higher blood concentrations more rapidly than when the same drug is administered by mouth and swallowed.

Etomidate, a rapidly acting sedative hypnotic agent, is available only in injectable form (Amidate; Abbott Laboratories, North Chicago, IL) for intravenous administration. Etomidate's pharmacokinetic profile, potency, and physiochemical properties (stability, pKa, lipid solubility, low molecular weight) make it suitable for oral transmucosal delivery. In dogs, Zhang *et al.*[3] found that peak blood concentrations (that would be expected to produce central nervous system depression in humans) occurred just 10 min after etomidate administration through the oral mucosa. This method of etomidate administration has not been investigated in humans.

We developed a solid dosage form of etomidate for oral transmucosal administration in humans. When the drug matrix dissolves in the mouth, etomidate is absorbed through the oral mucosa to produce sedation. We believe oral transmucosal delivery may extend etomidate's use to sedation and anxiolysis. This is the first study to characterize the time course of plasma

concentrations and clinical effects after oral transmucosal etomidate (OTET) in humans.

Materials and Methods

Approval was obtained from the Human Institutional Review Board of the University of Utah Medical Center, and informed written consent was obtained from 10 healthy adult male volunteers. Participants were nonsmokers who were 18–39 yr old and deviated no more than 15% from ideal body weight (56–90 kg). They had no history of drug or ethanol abuse and were not taking any sedative-hypnotic or opioid medications.

The OTET dosage units used in this study were manufactured by Anesta Corporation (Salt Lake City, UT) and consisted of crystalline dextro-etomidate (Abbott Laboratories) incorporated into a compressed powder matrix mounted on a handle. The dosage units were unflavored; identical in size, shape, and color; and supplied in four dosage strengths (12.5 mg, 25 mg, 50 mg, and 100 mg).

All volunteers received each of the four doses of OTET on four different days. First, the lower two doses (12.5 mg and 25 mg) were administered in a crossover design with random, double-blinded assignment. Then the higher two doses (50 mg and 100 mg) were administered similarly, with crossover and random double-blind assignment. Administration of the two lower doses was completed first for safety considerations, because this was the first exposure in humans of this dosage form. A minimum of 3 days separated each treatment.

Before starting the study, each volunteer gave a medical history and underwent physical examination and routine blood and urine testing (including a urine test for illicit substances). At the screening visit, the volunteer consumed a placebo, identically shaped, OTET unit so that a uniform consumption time (15 min) could be learned. The volunteers fasted overnight before each study session. At the start of each session, a peripheral 18-gauge catheter was inserted into a hand or forearm vein for blood sampling. Monitors included a noninvasive blood pressure cuff and a pulse oximeter. The participants consumed OTET by placing it in their cheek and sucking the unit. They were instructed to pace themselves to consume the OTET unit in 15 min.

Arterial blood pressure, heart rate, respiratory rate, and sedation were measured at baseline (immediately before drug administration), every 5 min through 60 min, and then 75, 90, and 240 min after initiation of consumption. Pulse oximetry was continuously monitored and any episodes of oxyhemoglobin saturation $<90\%$ were recorded. Sedation was assessed by the investigator according to the following scale: 4, asleep (eyes closed) and unresponsive to verbal stimulation (calling out the participant's name in a normal tone of voice); 3, asleep (eyes closed) but responsive to verbal stimulation; 2, drowsy, eyes open; and 1, awake. The same investigator (R.J.) made all sedation assessments throughout the study. The volunteers assessed taste 2.5 and 15 min after initiating consumption by filling out a nine-point visual analog scale (1, unbearable to 9, pleasant). Finally, the investigator examined the oral mucosa at baseline, 120, and 240 min.

Blood samples (8 ml) were obtained from the venous catheter at baseline (immediately before administration) and 5, 10, 12.5, 15, 17.5, 20, 25, 30, 45, 60, and 90 min after initiation of consumption. All samples were injected into Vacutainer tubes (Becton Dickinson, Rutherford, NJ) and allowed to clot. After centrifugation, the serum was placed into polypropylene tubes using pipettes and frozen at $-20°C$ until etomidate was assayed using a validated method consisting of liquid–liquid extraction of the drug from serum followed by high-performance liquid chromatographic analysis with ultraviolet detection.[4,5] Validation tests in which known quantities of etomidate were added to control human serum showed the method to have a run-to-run accuracy of $\pm 10\%$ of the spiked concentration over the range of 25–400 ng/ml. The total run-to-run variability (coefficient of variation) for serum controls ranged from 4.3% at 400 ng/ml to 21.7% at 25 ng/ml.

The maximum etomidate concentration (C_{max}) and the time to reach this concentration (T_{max}) were obtained from direct observation of the serum concentration *versus* time curves. No attempt was made to determine terminal elimination half-life because serum concentrations were determined for only 90 min after administration. Area under the concentration–time curve (AUC) from 0–90 min was calculated using the linear trapezoidal method.[6] Normalized C_{max} and AUC were calculated by $C_{max} \cdot (12.5 \cdot dose^{-1})$ and $AUC \cdot (12.5 \cdot dose^{-1})$.

Statistical Analysis

Values of C_{max}, AUC, T_{max}, normalized C_{max}, and normalized AUC were compared for statistical significance by analysis of variance of log transformed data with terms for subject and dose, followed by pairwise comparisons among doses. Probability values < 0.05 were

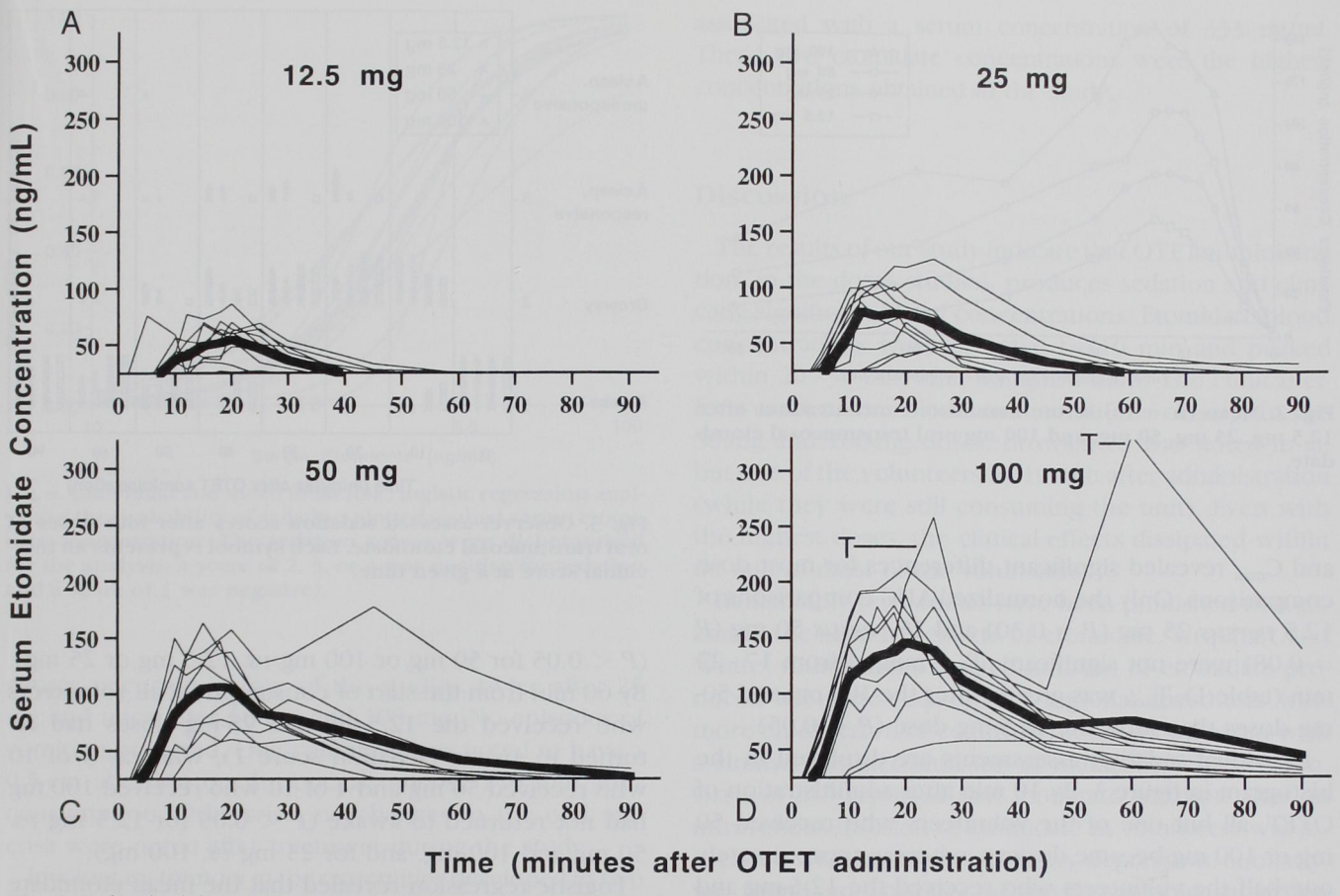

Fig. 1. Individual (n = 10) and mean (*bold line*) serum etomidate concentrations after 12.5 mg (*A*), 25 mg (*B*), 50 mg (*C*), and 100 mg (*D*) oral transmucosal etomidate. The T's represent volunteers who experienced tremors and the time when the tremors occurred.

considered significant. Values for continuous variables are presented as mean ± SD.

A Mantel-Haenszel dose-response test was used to compare sedation scores between doses at each time point. The time when the volunteers were at least drowsy during a study was analyzed with a two-way (volunteer and dose) analysis of variance, followed by pairwise comparison of doses. Finally, the Wilcoxon signed-rank test was used to compare doses for taste at each time point.

Logistic regression analysis was used to relate the etomidate serum concentration to probability of sedation. The sedation scores were dichotomized so that a sedation score of 1 (awake) was no response, whereas sedation scores of 2 (drowsy), 3 (asleep, responsive), and 4 (asleep, unresponsive) were considered a positive response. Using this method, each volunteer's individual curve was fit from data taken from all four doses. Then an overall mean value was determined. SAS version 6.11 software (SAS Institute Inc., Cary, NC) run on a Windows-based personal computer was used for all statistical calculations.

Results

Figure 1 shows the individual and mean serum etomidate concentrations for each dose, 12.5, 25, 50, and 100 mg. The mean values are shown compared in figure 2. Mean C_{max} and AUC increased with increasing doses of etomidate (table 1). Pairwise comparisons showed significant differences in C_{max} and AUC between all doses. However, C_{max} and AUC did not increase proportionately with increasing dose (table 1). That is, as the dose was doubled, C_{max} and AUC did not also double. Pairwise comparisons between dose-normalized AUC

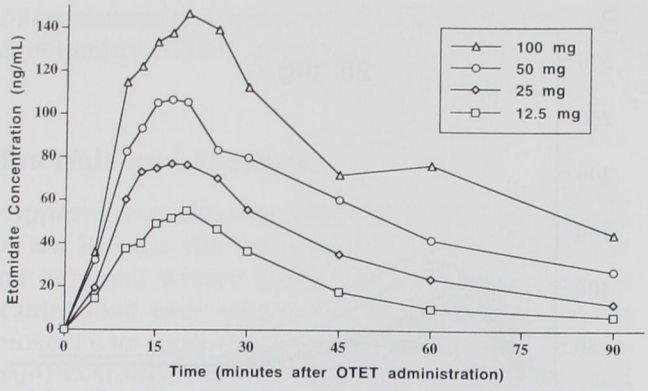

Fig. 2. Mean (n = 10) serum etomidate concentrations after 12.5 mg, 25 mg, 50 mg, and 100 mg oral transmucosal etomidate.

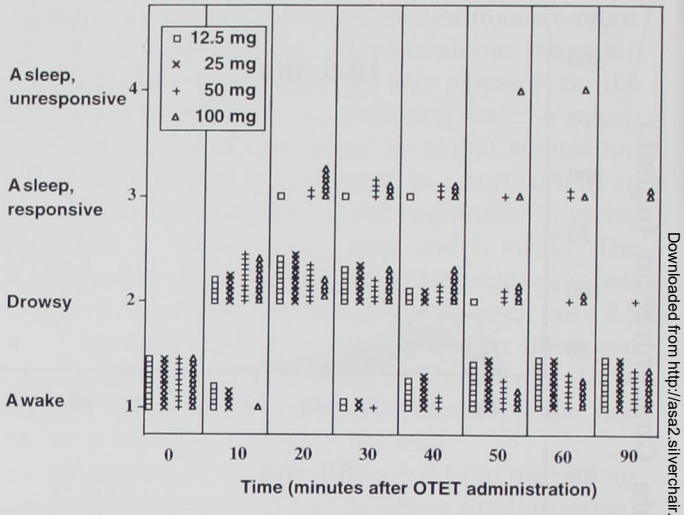

Fig. 3. Observer-assessed sedation scores after four doses of oral transmucosal etomidate. Each symbol represents an individual score at a given time.

and C_{max} revealed significant differences for most dose comparisons. Only the normalized AUC comparisons of 12.5 *versus* 25 mg ($P = 0.30$) and 25 *versus* 50 mg ($P = 0.08$) were not significant. T_{max} ranged from 17–27 min (table 1). T_{max} was greater after the 100-mg and 50-mg doses than after the 12.5-mg dose ($P < 0.05$).

Individual sedation assessments are displayed in the histogram in figure 3. By 10 min after administration of OTET, all but one of the volunteers who received 50 mg or 100 mg became drowsy, whereas approximately one half the volunteers who received the 12.5-mg and 25-mg doses became drowsy. By 20 min, sedation scores of 3 (asleep, responsive) were noted in 6 of 10 volunteers who received 100 mg, whereas this level of sedation was rare in the other three groups ($P < 0.05$ for 100 mg *versus* 12.5 mg, 25 mg, and 50 mg). Only one volunteer (who received the 100-mg dose) became unresponsive to gentle stimulation (sedation score: 4). The total time (mean ± SD) that volunteers were sedated (sedation scores: 2, 3, or 4) during an individual study was 22 ± 11, 23 ± 7, 41 ± 22, and 48 ± 20 min for 12.5-mg, 25-mg, 50-mg, and 100 mg doses, respectively ($P < 0.05$ for 50 mg or 100 mg *vs.* 12.5 mg or 25 mg). By 60 min from the start of consumption, all volunteers who received the 12.5-mg and 25-mg doses had returned to awake (sedation score 1), whereas 3 of 10 who received 50 mg and 4 of 10 who received 100 mg had not returned to awake ($P < 0.05$ for 12.5 mg *vs.* 50 mg and 100 mg, and for 25 mg *vs.* 100 mg).

Logistic regression revealed that the mean etomidate concentration for a 50% likelihood of sedation scores 2, 3, or 4 was 40 ± 7 ng/ml (fig. 4). The mean slope of the probability response (γ) was 4.4 ± 1.9.

No clinically significant changes in heart rate, systolic and diastolic blood pressure, and respiratory rate occurred with any dose during the study. In addition, there were no occurrences of oxyhemoglobin saturation <90%.

The taste of the OTET units was judged increasingly more "unpleasant" with increasing doses both 2.5 and 15 min after consumption (table 2). Mild, self-limiting

Table 1. Pharmacokinetic Parameters after Oral Transmucosal Etomidate Administration in Volunteers

	12.5 mg	25 mg	50 mg	100 mg
C_{max} ($ng \cdot ml^{-1}$)	61 ± 19	87 ± 26	119 ± 38	174 ± 79
C_{max} (dose normalized)	61 ± 19	44 ± 13	30 ± 10	22 ± 10
AUC ($ng \cdot ml^{-1} \cdot min$)	2,003 ± 791	3,263 ± 1,175	5,085 ± 2,066	7,415 ± 3,581
AUC (dose normalized)	2,003 ± 791	1,631 ± 587	1,271 ± 516	927 ± 448
T_{max} (min)	17 ± 6	20 ± 6	26 ± 12	27 ± 13

Values are mean ± SD.

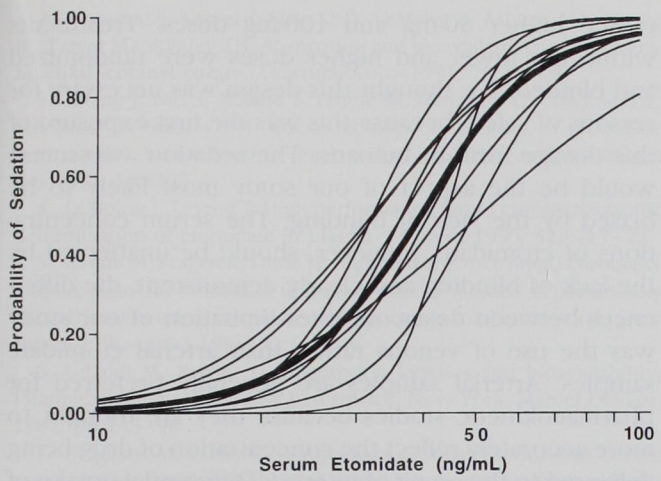

Fig. 4. Individual and mean (*bold line*) logistic regression analysis of the probability of sedation plotted against serum etomidate concentration. The sedation scores were dichotomized for the analysis; a score of 2, 3, or 4 was positive for sedation and a score of 1 was negative).

nausea occurred in four of the studies, twice after 25 mg and once after 50 mg and 100 mg. No episodes of vomiting occurred. One volunteer was noted to have a 0.5-cm abrasion on the buccal mucosa 240 min after consumption. Otherwise, no changes to the oral mucosa were noted after treatment during the study.

Involuntary tremors in the extremities developed in two volunteers after they received the highest OTET dose (100 mg). One remained conscious and slowly responded to simple commands although he could not stop shaking when asked. In this volunteer, the tremors started 19 min from administration, lasted 10 min, and was associated with a peak serum etomidate concentration of 259 ng/ml. The other volunteer became unresponsive at 50 min. Tremors started 60 min from administration while the volunteer was still unresponsive, lasted 6 min, and was associated with a serum concentration of 333 ng/ml. These two etomidate concentrations were the highest concentrations obtained in the study.

Table 2. Taste Assessment 2.5 and 15 min after Oral Transmucosal Etomidate Administration

Dose (mg)	2.5 min*	15 min†
12.5	4.0 ± 1.8	4.0 ± 1.7
25	3.6 ± 1.4	4.1 ± 1.6
50	3.0 ± 1.8	3.0 ± 1.6
100	2.0 ± 1.3	2.8 ± 1.9

Nine-point visual analog assessment scale: 1 (unbearable) through 9 (pleasant tasting).

* Pairwise significant difference, $P < 0.05$ 100 mg <12.5 mg, 25 mg.

† Pairwise significant difference, $P < 0.05$ 100 mg, 50 mg <12.5 mg, 25 mg.

Discussion

The results of our study indicate that OTET administration, in the doses studied, produces sedation and clinically significant blood concentrations. Etomidate blood concentrations were detected by 10 min and peaked within 20–30 min after administration. The clinical effects tracked the blood concentrations closely. In the 50-mg and 100-mg doses, drowsiness was noted in all but one of the volunteers by 10 min after administration (while they were still consuming the unit). Even with the highest doses, the clinical effects dissipated within 60 min in most of the volunteers.

Remarkably few studies have been published that examine the sedative effects of etomidate. Urquhart and White[7] found that a titrated infusion of etomidate produced adequate sedation for regional anesthesia with more rapid return of cognitive function compared with a similarly titrated infusion of midazolam. In addition, Glass *et al.*[8] reported that moderate sedation after an intravenous infusion of etomidate in volunteers was associated with minimal respiratory depression. Similarly, we found no episodes of oxyhemoglobin saturation <90% after OTET.

Common side effects reported with intravenous etomidate include myoclonus, involuntary muscle movements, and nausea and vomiting.[9] In our study there were only two episodes of tremor and two episodes of nausea, a significantly lower incidence than what has been reported. The probable reason for this difference is that the high incidence of side effects reported in the literature come from studies in which unconsciousness induced by etomidate was followed by a general anesthetic, whereas in our study sedation without loss of consciousness associated with lower blood concentrations occurred. We did not address adrenocortical suppression, reported in studies in which etomidate was given for anesthetic induction or sedation in the intensive care unit.[10,11]

Although it is impossible from our study to distinguish the route of etomidate absorption (buccal mucosal *vs.* gastrointestinal), the rapid appearance of etomidate in the blood suggests that at least some etomidate was absorbed through the buccal mucosa. Further, etomidate is highly permeable through the buccal mucosa in

dogs.[3] However, gastrointestinal absorption of etomidate is the likely explanation for the "second peak" of serum etomidate observed in a few of our participants (fig. 1).

With most drugs, doubling the dose will result in a twofold increase in C_{max} and AUC, quadrupling the dose results in a fourfold increase in C_{max} and AUC, and so forth. In fact, dose proportionality has been demonstrated with oral transmucosal fentanyl citrate, a similar dosage form to OTET but with fentanyl as the active drug.[12] However, although C_{max} and AUC increased with increasing doses of OTET, the increase was not linearly proportional to dose (table 1; fig. 2). Because etomidate's pharmacokinetic profile is linear after intravenous administration,[13] the most likely cause for this observation is decreasing dose normalized absorption with increasing dose. Different lozenge geometry does not explain this finding because the dosage forms at each dose were identical in shape and size. We can only speculate about the reason for the nonlinearity. One possibility for decreasing absorption with higher doses is that increasing doses are increasingly bitter and thus cause more saliva production. This in turn would lead to a greater proportion of the drug being swallowed rather than being absorbed through the oral mucosa. Swallowed drug would undergo gastrointestinal absorption and hepatic metabolism before appearing in the central circulation. Another possibility is that proportionately less etomidate was exposed to the mucosal surfaces with increasing doses because of the low solubility of etomidate in saliva.[3]

The doses of OTET that we studied produced mild to moderate sedation without loss of consciousness. Indeed, in only one case did etomidate blood concentrations exceed 300 ng/ml, the threshold for unconsciousness and lack of response to verbal command determined by Schuttler *et al.*[14] One volunteer, while not unconscious, was slow to respond to simple commands and exhibited involuntary tremors. Based on our data for C_{max} and assuming a log normal distribution, it would be expected that 9.5% of patients receiving 100 mg OTET would exceed 300 ng/ml, whereas it would be very unlikely (less than 0.2%) for a patient receiving 50 mg to exceed 300 ng/ml. Yet the desired effect of drowsiness was noted in all volunteers receiving 50 mg 10 to 20 min after administration. Thus 50 mg was the preferred OTET dose in terms of efficacy and safety.

One limitation of our study design was that it was not fully blinded and randomized. All volunteers completed the lower 12.5-mg and 25-mg doses before proceeding to the higher 50-mg and 100-mg doses. Treatments within the lower and higher doses were randomized and blinded. We thought this design was necessary for reasons of safety because this was the first exposure of this dosage form in humans. The sedation assessment would be the aspect of our study most likely to be biased by the lack of blinding. The serum concentrations of etomidate, however, should be unaffected by the lack of blinding and clearly demonstrate the differences between doses. Another limitation of our study was the use of venous rather than arterial etomidate samples. Arterial samples are generally preferred for pharmacokinetic studies because they are thought to more accurately reflect the concentration of drug being delivered to the organ of interest. Differential uptake of a drug as it passes through various tissues make venous samples less desirable. Arteriovenous differences in drug concentration are usually greatest when a drug is given as an intravenous bolus because arterial concentrations decline rapidly as venous concentrations may continue to increase during the first minutes of sampling. Because absorption of etomidate from OTET is relatively slow compared with an intravenous bolus, these differences should be limited. Furthermore, we did not believe it was appropriate to subject the volunteers to four arterial catheterizations in a relatively short period of time.

We did not try to modify the flavor of the OTET units studied. The bitter taste of OTET probably can be attributed to etomidate itself because increasing doses of etomidate were associated with worsening taste scores. Further development of this dosage form will require an adjustment to the formulation to improve the taste and mask the bitterness caused by etomidate.

This was the first study of OTET in humans. These early results suggest that oral transmucosal administration may be a viable means to deliver etomidate to produce mild to moderate sedation and anxiolysis before surgery or for brief procedures. Further study of this novel dosage form of etomidate is warranted.

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