RELATIVE BIOAVAILABILITY OF MIDAZOLAM FOLLOWING SUBLINGUAL VERSUS ORAL ADMINISTRATION IN HEALTHY VOLUNTEERS

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The extent of bioavailability of midazolam following sublingual and oral administration were evaluated. Three healthy volunteers received a single 15-mg dose of midazolam maleate by sublingual and oral routes on two occasions in a crossover design. Concentrations of midazolam in plasma during 4 h after each dose were measured by gas-liquid chromatography with an electron-capture detector.

The mean $\text{AUC}_{0-4}$ value following sublingual administration was significantly greater than that following oral administration ($14889 \text{ vs } 3594 \text{ ng} \cdot \text{min/ml, } p < 0.05$). The peak plasma concentration after sublingual dose was also significantly higher than that after oral administration ($p < 0.05$). The mean $\text{AUC}_{0-4}$ value of midazolam after sublingual administration was increased four times compared with that after oral administration, possibly due to avoidance of first-pass effect. Thus, the clinical effects of midazolam may likewise be enhanced by sublingual administration of midazolam.

KEYWORDS—midazolam; sublingual administration; bioavailability; first-pass effect

INTRODUCTION

Midazolam is a new water-soluble, ultrashort-acting benzodiazepine with an elimination half-life of two hours. 1-4) Its therapeutic use has been extended to premedication prior to surgery and the induction of anesthesia. Midazolam is rapidly absorbed after oral administration, but first-pass hepatic metabolism of midazolam significantly reduces its bioavailability after oral administration. About 50% of midazolam was reported to be eliminated by the liver after oral administration. 5-6)

Previous studies of the benzodiazepines such as lorazepam, 7) flunitrazepam, 8) triazolam, 9) and lormetazepam 10) demonstrated that their

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bioavailability was greater via the sublingual route than it was via the oral route. The present study is designed to evaluate the pharmacokinetic properties of sublingual midazolam.

MATERIALS AND METHODS

Experimental Design—Three healthy volunteers, whose biological data are given in Table I, participated in this study. None of the subjects received any medication within 4 weeks prior to the study and no drug other than midazolam was given during the study. The ethical aspects of the present study were guided by the Declaration of Helsinki, since an institutional review board has not been established in our institution. An informed consent was obtained from each subject. The study was a single-dose, two-way, randomized crossover design. The two trials were separated by at least one week. A tablet, 13 mm in diameter, containing 15 mg each of midazolam maleate was prepared in our laboratory by mixing the drug and crystalline cellulose and compressing the mixture with a press at 50 kg for 10 s. The drug in the tablet dissolved rapidly in the 1st fluid of the disintegration test, JP XI.

On each occasion, the subjects received 15 mg each of midazolam maleate in tablet orally with 200 ml of water or sublingually. Subjects were fasted for at least 11 h before and 4 h after drug administration. In sublingual administration, the tablet was placed under their tongues and they abstained from swallowing saliva for 15 min although the drug in the tablet dissolved in a few minutes. They also abstained from gargling during the study.

Venous blood samples were withdrawn before and at predetermined time intervals up to 4 h after administration. The blood samples were centrifuged and plasma was separated and stored at -20 °C pending analysis.

Concentrations of midazolam in plasma were determined by gas-liquid chromatography with a \( ^{63} \text{Ni} \) electron capture detector (GC-R1A, Shimadzu Manufacturing Co., Kyoto). A mixture of 1 ml of plasma, 2 ml of saturated trisodium phosphate solution and 50 ng of diazepam as an internal standard material, was extracted with 6 ml of benzene. Following centrifugation, the organic layer was evaporated to dryness under reduced pressure. The residue was redissolved with 50 \( \mu \)l of methanol. One \( \mu \)l aliquot of the sample was injected into an injection port of a GC system. A column of Megabore DB-17, 0.53 mm\( \times \)15 m (J&W Scientific, California, USA) was used. \( \text{N}_2 \) gas was used as a carrier gas. The operating temperatures of GC were set as follows: injection port, 260°C; column,
255°C; and detector, 255°C. A standard curve was linear up to 100 ng/ml and the limit for quantitation was 1 ng/ml. A standard curve was obtained for each set of samples.

Pharmacokinetic and Statistical Evaluation—The slope of the terminal log-linear phase of the plasma concentration profile of midazolam was determined by linear regression analysis and the apparent elimination half-life was calculated. An AUC value up to the last detectable concentration was determined by the trapezoidal rule. The effect of the route was compared by a paired t test.

RESULTS AND DISCUSSION

The mean AUC0-4 value following sublingual administration was significantly larger than that following oral dose (14889 vs. 3594 ng·min/ml, p<0.05, Fig. 1 and Table II). The sublingual administration of midazolam produced significantly higher plasma levels than those after oral administration (p < 0.05). The plasma concentrations of midazolam following sublingual administration increased rapidly.

![Fig. 1. Plasma Midazolam Concentration Profiles after Oral (○) and Sublingual (●) Administration of 15 mg of Midazolam Maleate in Three Volunteers. Mean ± SEM, n = 3.](image)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Oral AUC0-4, ng·min/ml</th>
<th>Sublingual AUC0-4, ng·min/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. I.</td>
<td>1326</td>
<td>15266</td>
</tr>
<tr>
<td>J. F.</td>
<td>5242</td>
<td>10925</td>
</tr>
<tr>
<td>S. N.</td>
<td>4216</td>
<td>18475</td>
</tr>
</tbody>
</table>

Mean ± SEM 3594 ± 1172 14889 ± 2188

p < 0.005
and remained at higher levels for 2 h and then slowly decreased (t1/2 = 5.5±3.1, mean ± SEM, h), while those following oral administration were also increased rapidly, but subsequently decreased rapidly (t1/2 = 2.3±0.42, mean ± SEM, h). The long elimination half-life after sublingual administration may be explained by continuous absorption of midazolam by the sublingual route because subjects abstained from gargling during the study. The mean AUC0-4 value of midazolam administered sublingually was found to be 4 times greater than that given orally (p < 0.05). These results may be due to the avoidance of first-pass hepatic extraction of midazolam 5,6) as a result of the direct systemic absorption of midazolam following sublingual administration.

REFERENCES


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