Interaction Between Sedative Precediments and Ketamine in Man and in Isolated Perfused Rat Livers

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Premedication with diazepam, hydroxyzine, or secobarbital significantly increased ketamine-induced sleep time (137 ± 3.5 min, 135 ± 9.2 min, 128 ± 4.7 min) over that of unpremedicated controls (98.5 ± 4.4 min) in man. The corresponding mean plasma half-lives (t½) of ketamine were longer in patients premedicated with diazepam or secobarbital (57.5 ± 4.9 min, 46 ± 3.2 min) than in controls (36 ± 1.5 min). Ketamine t½ in the perfusate of isolated, perfused rat livers was prolonged from 30 to 50 per cent by addition of diazepam, secobarbital, or hydroxyzine. The data suggest that these commonly used premedicants decrease the rate of ketamine metabolism. (Key words: Anesthetics, intravenous, ketamine; Premedication; Pharmacology, drug interactions; Biotransformation, drug, ketamine.)

VARIOUS SEDATIVE DRUGS have been advocated as preanesthetic medication to decrease the incidence and severity of emergence hallucinations occasionally seen following ketamine anesthesia.1,2 It has been our clinical observation, however, that when a sedative drug is used prior to ketamine, the postanesthetic recovery time is prolonged. This observation stimulated the present investigation.

Materials and Methods

ANALYTICAL METHODS

Plasma ketamine levels were measured using a modification of a gas–liquid chromatographic method described by Chang and Glazko.3 Pheniramine maleate1 was used as an internal standard. It extracted well from aqueous solutions by the method used and gave a sharp peak that did not interfere with peaks from ketamine or ketamine metabolites. Plasma (2 ml) was added to a reaction vessel containing chloroform (10 ml), NaOH 1N (0.2 ml) and pheniramine maleate (8 μg). The mixture was shaken for 15 minutes on an Eberbach shaker, then centrifuged for 15 minutes at 1,500 rpm. A portion of the chloroform layer (9 ml) was transferred to a second 32-ml reaction vessel containing 6 ml HCl, 0.1 N. This was shaken for 15 minutes, then centrifuged as before. The HCl (5 ml) was transferred to a third reaction vessel containing 10 ml n-hexane, and made strongly alkaline by the addition of NaOH, 10 N, 0.1 ml. This mixture was shaken for 15 minutes, centrifuged, and 9 ml of hexane transferred to an evaporating tube. The hexane was evaporated to dryness on a Buchler rotary evaporator. Chloroform (25 μl) was added, the mixture was agitated briefly on a Vortex mixer, and 1 to 2 μl of the solution placed on a Barber Coleman gas–liquid chromatograph. A 6-foot glass U-tube of 4 mm internal diameter was packed with ECNSS-M, 1 per cent, on Gas-chrome P (80/100 mesh).§ The column temperature was maintained at 185 C, and the flash evaporator at 210 C. The carrier gas was argon, and the inlet pressure was maintained at 30 pounds/square inch.

A standard curve was constructed for each day's determinations by adding known concentrations of ketamine HCl4 to blank plasma, and treating as described above. The ratio of

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† Obtained from Schering Research Division.
‡ Applied Science Laboratories, Inc. P.O. Box 410, State College, Pennsylvania.
§ Ketamine HCl powder obtained from Parke-Davis Co., dissolved in 0.9 per cent NaCl prior to addition to plasma.
were given intramuscularly 30 minutes prior to induction of anesthesia.

Anesthesia was induced by intramuscular injection of ketamine hydrochloride (10 mg/kg). Duration of sleep was measured as the time from administration of the ketamine until the patient responded to his or her name by opening of the eyes and directing vision to the voice source. Beginning 20 minutes after induction, serial 4-ml samples of venous blood were taken at 20-minute intervals until the patient responded as mentioned. The plasma was separated by centrifugation, and the plasma ketamine levels were measured by gas-liquid chromatography as already described.

The values for ketamine concentration in plasma were plotted against time on semilogarithmic paper, and the best-fitting line derived by a least-squares regression method. From this line the half-life ($t_{1/2}$) of ketamine in plasma was derived. The $t_{1/2}$ served as the means of comparison of the rates of disappearance of ketamine from plasma in various patients. Student's t test was used to analyze the difference between the mean of the control $t_{1/2}$ values and that of each of the test groups.

**ISOLATED LIVER PERFUSION STUDIES**

Perfusion of isolated rat livers was performed by the method of Brauer, et al., using a modified apparatus of Miller et al. as described by Northrup and Parks. The perfusion medium consisted of a mixture of heparinized rat blood and 0.9 per cent sodium chloride (70:30). Following installation of the liver in the perfusion system, an equilibration time of 30 to 45 minutes was allowed. The color of the liver and the amount of bile output were noted as indications of adequate oxygenation and liver function. The rate of perfusion was then adjusted so that the outflow of perfusate from the liver was 1 ml/g liver/min. The total volume of perfusate used was 100 ml.

Ketamine hydrochloride, 4 mg, was instilled into the reservoir flask of the perfusion system (40 µg/ml perfusate). Serial 4-ml samples of the perfusate were taken

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**Clinical Studies**

Patients 2 to 9 years of age scheduled for short surgical procedures for which single intramuscular doses of ketamine were planned as the only anesthetic were studied. Each patient was assigned randomly to the control or a test group; each group consisted of four patients. Patients assigned to the control group received premedication atropine sulfate (0.02 mg/kg) only. Those assigned to test groups received the same amount of atropine sulfate plus secobarbital sodium (2 mg/kg), hydroxyzine hydrochloride (2 mg/kg), or diazepam (0.15 mg/kg). All drugs

**Secobarbital sodium used was supplied by Eli Lilly and Company, Inc. Hydroxyzine hydrochloride used was Vistaril, from Pfizer. Diazepam used was Valium, from Roche Laboratories. Ketamine hydrochloride was given as Ketalar HCl solution, from Parke-Davis and Company.**

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**Footnotes:**

1. **Ketamine HCl powder obtained from Parke-Davis, dissolved in 0.9 per cent NaCl as needed.**
at 5-minute intervals from the inflow tubing until four samples were drawn. After each sampling, 4 ml of fresh perfusate were replaced to maintain the perfusate volume at 100 ml.

Following the initial administration and sampling of ketamine, 20 minutes were allowed for biotransformation of the residual ketamine. Livers that served as controls were then given a second similar administration of ketamine and the sampling repeated as previously described. This procedure allowed an estimate of any effect of time on the ability of the system to biotransform ketamine. Livers in the experimental groups were treated similarly to control livers except that between the first and second administrations of ketamine, experimental livers were treated by the addition to the perfusate of one of the following: secobarbital sodium, 2 mg; hydroxyzine hydrochloride, 2 mg; or diazepam, 0.15 mg. The secobarbital sodium and hydroxyzine were dissolved in distilled water. Diazepam was dissolved in the commercial solvent provided with Valium, which contains propylene glycol 40 per cent, ethanol 10 per cent, buffers and preservatives.

Ketamine concentrations of the perfusate samples were estimated using the gas–liquid chromatographic method described. The values obtained were plotted on semilogarithmic paper, and the best-fitting line was calculated by a least-squares regression method. From the slope of this line, the $t_1$ of the disappearance of ketamine from the perfusion medium was plotted. This value served to compare the rates of disappearance of ketamine from the perfusate achieved by the various isolated livers. Student’s t test for paired data was used to compare the $t_1$ values of the first and second doses of ketamine administered to each preparation in each group.

**Results**

**Clinical Studies**

All three groups of patients who received a sedative premedicant slept significantly longer than the control group ($P < 0.05$) (fig. 1). Mean sleep times of the diazepam-, hydroxyzine-, and secobarbital-premedicated groups were $137 \pm 3.8$, $138 \pm 9.2$, and $128 \pm 4.7$ minutes, respectively; that of the control group was $98.5 \pm 4.4$ minutes. Among the three premedicated groups, sleep times did not differ significantly.

The mean plasma half-lives of ketamine in patients who received diazepam, 0.15 mg/kg, or seobarbital, 2 mg/kg, as preanesthetic medication ($57.8 \pm 4.9$ and $46 \pm 3.2$ minutes, respectively) were each significantly longer than the mean value of $36 \pm 1.8$ minutes found in control patients ($P < 0.05$) (fig. 2). However, the mean $t_1$ for the patients premedicated with hydroxyzine, $40 \pm 6.1$ minutes, did not differ significantly from the control value. Of the four patients in the hydroxyzine-premedicated group, three showed increases in ketamine $t_1$ within a narrow range of values, 42–44 minutes. The fourth patient had received prolonged treatment with phenobarbital for cerebral palsy and showed a ketamine half-life of 32 minutes, which reduced the mean and increased the standard deviation for this group. Were this last patient excluded, the mean half-life of ketamine in plasma for the other three patients would have been $43 \pm 0.58$ minutes, a significant increase over control, $P < 0.05$.

Figure 3 shows the mean plasma levels of
ministration of ketamine demonstrated no significant difference in the half-time of disappearance of ketamine on the second as compared with the first administration. The other three groups, which were pretreated with diazepam, secobarbital, and hydroxyzine, respectively, before the second administration of ketamine, showed significantly longer half-times of disappearance of ketamine from the perfusate after the second administration compared with the first \((P < 0.05)\).

**Discussion**

Many drugs are oxidatively biotransformed by the hepatic microsomal system. Among them are ketamine\(^3\) and the preanesthetic medications examined in this study.\(^8\)–\(^10\) Unrelated drugs undergoing different types of oxidative biotransformation by the hepatic microsomal system may have to compete for the same oxygen transfer enzymes, a limited supply of NADPH, cytochrome P-450, or any other common requisite. In recent years, extensive studies of drug interactions have been done.\(^11\)–\(^13\) Many examples where two drugs biotransformed by the hepatic microsomal system may act as inhibitors one of the other are now known. The intensity and duration of drug action may thereby be increased. Rubin et al.\(^14\) found that the N-demethylation of ethylmorphine was inhibited by hexobarbital, chlorpromazine, phenylbutazone and acetanilide. All these drugs are known to be biotransformed by the hepatic microsomal mixed-function oxidases.

In our human studies, the mean half-life of ketamine in plasma of patients premedicated with diazepam or secobarbital was significantly longer than that in the control group (fig. 2). This suggests that both diazepam and secobarbital decrease the rate of ketamine

**TABLE 1.** Results of Liver Perfusion Studies Showing Ketamine \(t_1\) before and after Administration of a Sedative Premedicant

<table>
<thead>
<tr>
<th>Premedicant Drug Given before Second Ketamine Administration</th>
<th>Number of Rat Livers Perfused</th>
<th>Ketamine (t_1) (Min) after First Administration Mean ± SE</th>
<th>Ketamine (t_1) (Min) after Second Administration Mean ± SE</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I Control (no premedicant added)</td>
<td>3</td>
<td>6.5 ± 0.76</td>
<td>6.5 ± 0.80</td>
<td>N.S.</td>
</tr>
<tr>
<td>Group II Diazepam, 0.15 mg/100 ml</td>
<td>5</td>
<td>5.95 ± 0.63</td>
<td>8.2 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group III Secobarbital, 2 mg/100 ml</td>
<td>4</td>
<td>5.52 ± 0.66</td>
<td>7.25 ± 0.85</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group IV Hydroxyzine, 2 mg/100 ml</td>
<td>4</td>
<td>7.72 ± 1.82</td>
<td>11.8 ± 4.47</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* Statistical analysis by Student's t test for paired data.
metabolism by microsomal enzymes. One patient premedicated with hydroxyzine had a history of prolonged treatment with phenobarbital. Phenobarbital is known to produce induction of hepatic microsomal drug-metabolizing enzymes in both man and animals.\textsuperscript{15,16} In view of the above history, it was not surprising that this patient showed a shorter half-life of ketamine in plasma than did the other three patients premedicated with hydroxyzine. This observation supports the suggestion that ketamine disappears from plasma due to biotransformation in the liver. It also suggests that phenobarbital given over a long period will stimulate the metabolism of ketamine in man.

Patients premedicated with diazepam had higher plasma ketamine levels on awakening than did either control patients or patients premedicated with hydroxyzine or secobarbital (fig. 3). The latter three groups had waking levels which did not differ from one another. It is unlikely that in this study the prolongation of sleep time resulted from the presence in the central nervous system of an additional depressant drug. The higher plasma ketamine level on awakening in the patients premedicated with diazepam cannot be explained on the basis of the data presented here. Although the plasma ketamine level on awakening was higher than that of the unpremedicated control patients, patients premedicated with diazepam nevertheless slept significantly longer than did controls and showed a longer half-life of ketamine in plasma. The evidence presented here indicates that the ketamine-induced prolongation of sleep time observed in premedicated patients is predominantly due to reductions in the rates of ketamine metabolism in these patients.

In our liver perfusion studies, stability of the preparation was demonstrated by the observation that two successive administrations of ketamine resulted in perfusate $t_1$ values for ketamine that did not differ from one another. Administration of diazepam, secobarbital, or hydroxyzine prior to the second ketamine administration resulted in a significant increase in the second ketamine $t_1$ compared with the first (table 1). This was an invariable observation in all the preparations. In the isolated, perfused liver system, ketamine could disappear from plasma only by biotransformation, by binding to liver, or by excretion into bile. Other workers have demonstrated that biliary excretion is unlikely.\textsuperscript{3} Binding to liver, while possible, would not be likely to result in a log-linear disappearance from plasma as noted here, and one would expect the hepatic tissue to become saturated, particularly when a second administration of ketamine was given. It is probable, then, that the disappearance of ketamine from perfusate in this system resulted from biotransformation by the liver. It is also probable that diazepam, secobarbital, and hydroxyzine interfere with this biotransformation, resulting in the longer $t_1$'s for ketamine following their administration. The mechanism of this inhibition cannot be determined from this study.

The log-linear disappearance of ketamine from plasma in man (examples of which are shown in fig. 4) is strongly suggestive of a single means of disposition. Since ketamine is not excreted unchanged in any significant amount in urine or feces,\textsuperscript{3} and the isolated

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig4}
\caption{Examples of plasma ketamine disappearance curves plotted from data from two patients. Patient A received premedication of atropine sulfate, 0.02 mg/kg, plus diazepam, 0.15 mg/kg (both im) 30 minutes prior to anesthetic induction. The $t_1$ was 64 minutes and sleep time 140 minutes. Patient B received only atropine sulfate, 0.02 mg/kg, im, 30 minutes prior to induction. The $t_1$ was 38 minutes and sleep time was 106 minutes. Both curves indicate an exponential disappearance of ketamine during the time of sampling.}
\end{figure}
liver perfusion studies presented here showed a rapid disappearance of ketamine from perfusate, it is a reasonable assumption that the disappearance of ketamine from plasma in man is predominantly due to biotransformation in the liver. Many drugs, including many of the barbiturates, will, upon repeated administration, stimulate the hepatic microsomal biotransformation of themselves and other drugs by enzyme induction. However, when two drugs are used simultaneously, there may be inhibition of the metabolism of one by the other. Inhibition of the metabolism of one drug by another takes place rapidly and can be demonstrated within a few minutes after the inhibitor is administered. On the other hand, the earliest evidence of induction of hepatic microsomal enzymes by drugs is seen about 12 hours after the administration of the drug, and usually requires a longer period. Since the premedicants were administered to our patients 30 minutes before ketamine, there was not sufficient time for enzyme induction to occur. However, there would be sufficient time for inhibition to take place. It appears that ketamine metabolism is retarded by the concurrent use of sedative premedicants that are also metabolized by the liver.

These studies suggest that sleep time following ketamine anesthesia is increased when patients are given one of the three common sedative premedicants used in this study and that this is caused by a reduction in the rate of hepatic metabolism of ketamine.

References