COMPARATIVE PHARMACOLOGY OF THE KETAMINE ISOMERS
Studies in Volunteers

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Preliminary clinical studies with the ketamine isomers suggested that there were quantitative and qualitative differences between the enantiomers in their effects on the central nervous system (White et al., 1980). We reported differences between the optical isomers of ketamine in terms of their anaesthetic potency, intraoperative effects, postoperative analgesia and side-effects in surgical patients. Based on this earlier study, the more potent S(+)-isomer appeared to offer significant clinical advantages over R(-)-ketamine.

Since racemic mixtures (of stereoisomers) do not necessarily behave as compounds containing equal proportions of the individual isomers (Haley and Gidley, 1970), further studies were needed to assess the potential advantages of S(+)-ketamine compared with the currently available racemate (Ketalar, Ketaject). The present investigation was designed to evaluate the pharmacokinetic characteristics and pharmacodynamic effects of the optical isomers (vs. racemic ketamine) in volunteers receiving the drugs in a controlled, cross-over fashion. The comparative effects of these drugs on the central nervous system (CNS) were assessed using clinical signs, the electroencephalogram (EEG), and a battery of psychometric tests. Finally, relationships between the serum concentrations of the three drugs and recovery times were used to assess their relative potencies.

SUBJECTS AND METHODS

Five healthy, male volunteers (age 36 ± 3 yr, weight 75 ± 3 kg (mean ± SD)) received racemic ketamine or one of the two F.D.A. Investigative New Drugs No. 14107, S(+)-ketamine, or R(-)-ketamine, by infusion i.v. at 7–14 day intervals using a cross-over experimental programme. Each

SUMMARY

The clinical and electroencephalographic (EEG) effects of the individual ketamine isomers were compared with the racemic mixture in five volunteers who received each drug on a separate occasion. Racemic ketamine 275 ± 25 mg, S(+)-ketamine 140 ± 21 mg or R(-)-ketamine 429 ± 37 mg produced an anaesthetic state lasting 6 ± 2 min (mean ± SD). However, the EEG evaluation of the R(-)-isomer revealed less overall slowing, and an absence of the large slow wave complexes produced by the S(+) isomer and the racemic mixture. The pharmacokinetic profiles for the individual isomers of ketamine did not differ significantly from the racemic mixture. Even though the apparent anaesthetic state produced in these healthy volunteers did not differ qualitatively between the three drug groups, recovery times (assessed using a standardized battery of psychometric tests) were consistently shorter following the individual isomers compared with the racemic mixture. The serum ketamine concentrations associated with regaining consciousness and orientation were consistent with an S(+):R(-) isomer potency ratio of 4:1. In terms of their ability to impair psychomotor function, the S(+):R(-) potency ratio varied from 3:1 to 5:1. After comparable degrees of CNS depression, we conclude that the more potent S(+) isomer of ketamine was associated with a more rapid recovery of psychomotor skills than the currently used racemic mixture.
volunteer received all three drugs on separate occasions. Two volunteers received $S(+)$ ketamine, followed by racemic ketamine, and then the $R(-)$ isomer. The remaining three volunteers received $R(-)$ ketamine, followed by racemic ketamine, and finally, the $S(+)$ isomer. The study was approved by the local Committee on Human Research, and informed consent was obtained from each subject.

Resolution of the two enantiomers followed a procedure involving recrystallization of the (+) or (-) tartaric acid salts (Meliska, Greenberg and Trevor, 1980). On treatment of (-) ketamine-free base with hydrochloric acid, the $S(+)$ ketamine hydrochloride salt was formed with m.p. 258–261 °C and $[\alpha]_{D}^{25} = +93.6^\circ$ (c = 2.0, water). On treatment of free base (+) ketamine with acid, $R(-)$ ketamine hydrochloride was formed with m.p. 256–258 °C and $[\alpha]_{D}^{25} = -93.5^\circ$ (c = 2.0, water). These separation procedures resulted in resolution exceeding 90% for each isomer. The two isomers were administered as the hydrochloride salt and all designations of sign of optical rotation refer to the respective salt forms.

A standard battery of psychomotor tests was administered on the evening before each study. The battery of tests included the time distortion index (Yesavage, Freeman and Bourgeois, 1978), Trieger test (Newman, Trieger and Miller, 1969), five separate visual analogue scales (Bond and Lader, 1974), and symbol–digit test (Lezak, 1967). The time distortion index relates to the subject's ability to estimate 30 s (the actual elapsed time was recorded). Trieger tests were scored in terms of the number of dots missed (maximum 40) and the total distance from the missed dots to the nearest line (maximum 200 mm). Each individual visual analogue scale was scored from 0 (almost asleep, tired, clumsy, fuzzy or drowsy) to 100 mm (wide awake, energetic, well-coordinated, clear-headed or alert). The symbol–digit test (matching a series of symbols and numbers) was scored in terms of the number of correct responses and number of attempted matches. The symbol–digit matching key was changed before each test. Temporal changes in the psychometric tests were evaluated using repeated measures of analysis of variance and the average time required to return to the predrug baseline (± 10%) was reported. Continuous variables were analysed using Statistical Analysis System (SAS) (SAS Institute, Inc., SAS Circle, P.O. Box 8000, Cary, North Carolina 27511) one-way analysis of variance and Duncan's multiple range test ($P < 0.05$). Categorical variables were evaluated with Chi-square analysis ($P < 0.05$).

A clinical assessment was performed at 1-min intervals during and immediately after the drug infusion and included: (1) responsiveness to verbal commands, (2) the presence or absence of the eyelid reflex, and (3) the degree of spontaneous motor activity, facial grimacing and vocalizations on a scale from 0 (none) to 3 (severe). After termination of the infusion, the times to regaining the eyelid reflex, responsiveness to simple commands (e.g., "open your eyes", "squeeze my hand"), and orientation to person, place and time were recorded. The duration of anaesthesia (min) was defined as the duration of loss of the eyelid reflex. The battery of psychomotor tests was repeated when the subject was fully-oriented and, subsequently, at 15-min intervals until the test scores returned to the predrug baseline values (± 10%). Amnesia was assessed at the time the subject was judged to be fully oriented (George and Dundee, 1977). A follow-up questionnaire was completed within 24 h of each study to assess the relative incidences of side-effects (e.g., dreaming, dizziness).

The total doses of racemic ketamine, $S(+)$ ketamine, and $R(-)$ ketamine were 275 ± 25 mg, 140 ± 21 mg, and 429 ± 37 mg, respectively (mean ± SD).
assayed for total ketamine and its principal metabolite (norketamine) using a modified version of the gas chromatographic procedure of Chang and Glazko (1972) as described previously (White, Johnston and Pudwill, 1975). Serum concentration v. time data for each volunteer were fitted to an open two-compartment model using extended least squares nonlinear regression analysis (L. Sheiner, unpublished report). Pharmacokinetic parameters were derived using standard formulae (Gibaldi and Perrier, 1975).

RESULTS
All three drugs produced an anaesthetic state (absence of eyelid reflex) 3 ± 1 min after starting the infusion and lasting 6 ± 2 min (mean ± SD). However, the individual ketamine isomers produced differing effects on the EEG. When S(+) ketamine or the racemic mixture were infused to produce a state of clinical anaesthesia, a progressive decrease in EEG amplitude and frequency occurred, followed by intermittent high amplitude polymorphic delta activity (figs 1 and 2). In contrast, R(−) ketamine was unable to suppress the EEG activity to the same extent even though larger doses of the (−) isomer were infused (fig. 2). Both isomers and the racemate were infused until plateau effects were observed with respect to changes in the EEG (maximal slowing).

The magnitude and duration of spontaneous motor (or myoclonic) activity, facial grimacing or vocalization during the infusions did not differ between the three treatment groups. In addition, haemodynamic changes during the infusions did not differ significantly between the three groups (fig. 3). Maximal increases (above baseline values) in mean arterial pressure and heart rate were 42–59% and 56–84%, respectively. There were no correlations between changes in arterial pressure or heart rate and the concentrations of ketamine or norketamine.

Pharmacokinetic parameters indicated a high clearance and a moderately large volume of distribution for racemic ketamine and its individual isomers (table I). Although there were no significant pharmacokinetic differences between the three drugs, the coefficient of variation for distribution phase kinetic parameters (initial volume of distribution, distribution half-life) ranged from 38% to 78%. In contrast, the coefficients of variation for elimination phase variables were less than 30%. Serum concentrations of ketamine after termination of the racemic ketamine, S(+) ketamine, or R(−) ketamine infusions are summarized in figure 4. The serum concentrations associated with regaining consciousness and orientation are summarized in table II. The ratios of these serum concentrations were consistent with a S(+):R(−) isomer potency ratio of 4:1. Recovery times were decreased following the individual isomers compared with the racemic mixture (table II). Results of the psychometric testing were also consistent with a more rapid recovery after the individual isomers, irrespective of the sequence of drug administration (table III). In terms of their ability to impair psychomotor functioning, the S(+):R(−)
Fig. 3. Percentage changes from predrug baseline values in mean arterial pressure (Δ MAP) and heart rate (Δ HR) during the infusion of racemic ketamine (••••), S(+) (••—••) or R(−) ketamine (▲—▲). Arrows indicate time of awakening, for example, opened eyes (1); ability to follow simple command, for example, squeezed hand (2); orientation to person, place and time (3); and return to predrug scores for Trieger (4) and symbol-digit (5) tests.

The sequential changes in the EEG produced by racemic ketamine and the S(+) isomer were similar to the EEG pattern reported previously by Domino.

**DISCUSSION**

The sequential changes in the EEG produced by racemic ketamine and the S(+) isomer were similar to the EEG pattern reported previously by Domino.

**Table I.** Pharmacokinetic parameters following administration of racemic ketamine or one of its individual isomers (mean values ± SD)

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Distribution half-life (min)</th>
<th>Elimination half-life (min)</th>
<th>Clearance (ml kg⁻¹ min⁻¹)</th>
<th>Vc (litre kg⁻¹)</th>
<th>Vd area (litre kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racemic ketamine</td>
<td>12.6 ± 8.6</td>
<td>132 ± 32</td>
<td>16.1 ± 4.6</td>
<td>1.0 ± 0.4</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>S(+) ketamine</td>
<td>22.8 ± 14.7</td>
<td>158 ± 45</td>
<td>21.3 ± 1.6</td>
<td>1.6 ± 0.7</td>
<td>4.7 ± 1.1</td>
</tr>
<tr>
<td>R(−) ketamine</td>
<td>11.8 ± 9.2</td>
<td>155 ± 42</td>
<td>17.4 ± 2.5</td>
<td>0.9 ± 0.7</td>
<td>3.9 ± 1.3</td>
</tr>
</tbody>
</table>

The incidence of dreaming did not differ between the drug groups. In general, the dreams were described as pleasant illusionary-type experiences. Amnesia was not associated with either the racemic mixture or the individual isomers. Incidences of postanaesthetic side-effects (dizziness 47%, floating sensation 67%, diplopia 60%) did not differ between the three groups.
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TABLE II. Time to awakening and orientation (min) and the associated serum concentrations of ketamine (\(\mu g \text{ ml}^{-1}\)) following infusion of racemic ketamine or one of its individual isomers (mean values ± SD). *Value significantly different from racemic: \(P < 0.05\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Racemic ketamine</th>
<th>(S(+)) ketamine</th>
<th>(R(-)) ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(min)</td>
<td>((\mu g \text{ ml}^{-1}))</td>
<td>((\mu g \text{ ml}^{-1}))</td>
</tr>
<tr>
<td>Opened eyes</td>
<td>11 ± 3</td>
<td>2.6 ± 0.7</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Squeezed hand</td>
<td>22 ± 8</td>
<td>1.6 ± 0.5</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>Oriented to person</td>
<td>33 ± 11</td>
<td>1.2 ± 0.3</td>
<td>14 ± 2*</td>
</tr>
<tr>
<td>Oriented to person, place and time</td>
<td>45 ± 10</td>
<td>1.0 ± 0.1</td>
<td>21 ± 2*</td>
</tr>
</tbody>
</table>

Chodoff and Corssen (1965). However, the present volunteer study has demonstrated qualitative morphological differences in the EEG patterns produced by the individual ketamine enantiomers (fig. 2). Although dose-response data regarding the ketamine isomers are not available, analyses of the individual EEG tracings using the median frequency demonstrated that a "plateau" effect (maximal slowing) had been reached with each isomer as well as with the racemic mixture (Schüttler, Stanski, White and Trevor; in preparation). Furthermore, there was a correlation between changes in the median frequency and the serum concentrations of ketamine.

The \(R(-)\) isomer was unable to achieve the degree of EEG slowing recorded during the infusions of the \(S(+)\) isomer or the racemic mixture. This observation is consistent with the reduced hypnotic and analgesic potency of the \(R(-)\) isomer (v. \(S(+)\) isomer) reported in our previous study (White et al., 1980). If the serum concentrations of ketamine associated with specific clinical endpoints (e.g. awakening, orientation) are compared, \(S(+)\) ketamine would appear to be approximately four times more potent than the \(R(-)\) isomer (tables II and III, fig. 4).

In our earlier clinical study, a significantly higher percentage of patients receiving \(R(-)\) ketamine required supplementary anaesthetic drugs to complete the surgical procedure, compared with those receiving the \(S(+)\) isomer of ketamine. The inability of \(R(-)\) ketamine to produce an adequate depth of anaesthesia in the presence of surgical stimulation might explain the higher incidence of intraoperative complications such as movement and tachycardia, and greater need for adjunctive drugs. Furthermore, we would postulate that these clinical differences may be related in part to the differing analgesic potencies of the individual isomers (Ryder, Way and Trevor, 1978). If the \(S(+)\) isomer is a more effective analgesic, this might also contribute to the lower incidence of emergence delirium observed in the early postoperative period in the prior clinical study. We would speculate that pain increases anxiety as well as the incidences of postanaesthetic emergence phenomena.

Anaesthetic recovery following an i.v. infusion of either racemic ketamine or one of its optical isomers was assessed using clinical signs and a battery of psychomotor tests. These tests were consistent with a more rapid rate of recovery following either of the isomers compared with the currently used racemic mixture (tables II and III). One might speculate that the more rapid recovery following the \(R(-)\) isomer was a result of its more limited depressant effects on the CNS. Yet, how does one explain a slower recov-

TABLE III. Time required for psychomotor scores to return to predrug baseline score (min) and the associated serum ketamine concentrations (\(\mu g \text{ ml}^{-1}\)) following infusion of racemic ketamine or one of its individual isomers (mean values ± SD). *Value significantly different from racemic: \(P < 0.05\)

<table>
<thead>
<tr>
<th>Test</th>
<th>Racemic ketamine</th>
<th>(S(+)) ketamine</th>
<th>(R(-)) ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(min)</td>
<td>((\mu g \text{ ml}^{-1}))</td>
<td>((\mu g \text{ ml}^{-1}))</td>
</tr>
<tr>
<td>Analogue scales</td>
<td>161 ± 21</td>
<td>0.4 ± 0.1</td>
<td>150 ± 22</td>
</tr>
<tr>
<td>Trieger test</td>
<td>164 ± 17</td>
<td>0.4 ± 0.1</td>
<td>87 ± 13*</td>
</tr>
<tr>
<td>Symbol – digit</td>
<td>178 ± 19</td>
<td>0.4 ± 0.1</td>
<td>122 ± 29</td>
</tr>
<tr>
<td>Time distortion</td>
<td>118 ± 24</td>
<td>0.5 ± 0.2</td>
<td>74 ± 12*</td>
</tr>
</tbody>
</table>
ery following the racemic mixture compared with S(+) ketamine? The two most plausible explanations are, first, that a greater depth of anaesthesia was achieved with the racemic mixture (v. S(+) ketamine) or, second, that the presence of the less potent R(−) isomer in the racemic mixture exerted an inhibitory effect on the rate of recovery from S(+) ketamine. The fact that the EEG patterns achieved with the racemic mixture and the S(+) isomer were virtually identical would argue against the first explanation. However, it is possible that the EEG is simply not a good index of anaesthetic depth.

Regarding the second possibility, the pharmacokinetic profiles for the S(+) isomer and the racemic mixture appear to be similar (table I). However, the gas chromatographic method used to measure serum ketamine concentrations does not permit assessment of the actual concentrations of the individual isomers in the serum following administration of racemic ketamine. It is possible that the measured concentrations following racemic ketamine do not reflect a constant 50:50 distribution of the individual isomers. In fact, chiral interactions in which metabolism of one enantiomer of a drug is inhibited by its optical antipode have been reported for the isomers of the analgesic propoxyphene (Murphy et al., 1976) and the psychotomimetic amine 1-(2, 5-dimethoxy-4-methylphenyl)-2-aminopropane (McGraw, Callery and Castagnoli, 1977). Thus, inhibition of metabolism of the more potent enantiomer, S(+) ketamine, by the R(−) isomer could account for the prolongation of recovery observed following racemic ketamine.

When psychometric tests are administered repeatedly, a certain degree of improvement (so-called learning behaviour) would be expected; however, a plateau of performance is usually attained after two to four repetitions (Jenson and Rohwer, 1966). In our volunteers, the baseline scores before the initial drug exposure were not significantly different from those measured before the third infusion. Furthermore, since this learning phenomenon would be expected to occur irrespective of the drug administered, it could not explain the differing recovery rates for the two optical isomers (v. the racemic mixture). Alternatively, it might be suggested that the development of “acute” tolerance (Cumming, 1976), or tolerance which develops after only a single prior exposure to the drug (Meliska and Trevor, 1978) could explain the more rapid recovery times for the individual enantiomers of ketamine. However, the fact that the relative recovery times following racemic ketamine (or either one of its isomers) were similar irrespective of the sequence of drug administration, would argue against tolerance as an explanation of our findings.

In summary, R(−) ketamine was unable to produce the same degree of EEG slowing as S(+) ketamine and, therefore, one would predict that it would be more difficult to achieve an adequate depth of anaesthesia with the less potent R(−) isomer. The more potent S(+) isomer, on the other hand, was able to achieve the same degree of EEG slowing produced by racemic ketamine. Furthermore, after comparable degrees of CNS depression, a more rapid recovery of psychomotor skills was noted with the S(+) isomer than the racemic mixture. We conclude that the more potent S(+) isomer of ketamine would offer clinically useful advantages over the currently used racemic mixture.

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