RO 15–1788 ANTAGONIZES THE EFFECTS OF DIAZEPAM IN MAN WITHOUT AFFECTING ITS BIOAVAILABILITY

C. O'BOYLE, R. LAMBE, A. DARRAGH, W. TAFFE, I. BRICK AND M. KENNY

SUMMARY

In a double-blind, placebo-controlled three-way cross over study, the efficacy of Ro 15-1788 200 mg, a new benzodiazepine antagonist, in blocking the amnesic, cognitive, psychomotor and subjective effects of diazepam 20 mg, was investigated in a group of six healthy male volunteers. The amnesic effects of diazepam were markedly attenuated by the combined administration of Ro 15-1788. The psychomotor and subjective effects of diazepam by mouth were most pronounced 2.5 h after administration. Concurrent oral administration of Ro 15-1788 completely prevented these effects at 2.5 h. Plasma diazepam concentrations observed after administration of the combination of diazepam and the antagonist did not differ from those observed following diazepam alone.

One of the most useful properties of the benzodiazepines, as premedicants, is their ability to cause anterograde amnesia (Kanto, 1981). This property was discovered soon after the introduction of diazepam (Brandt and Oakes, 1965; Haslett and Dundee, 1968) and has subsequently been demonstrated by numerous authors (Clarke et al., 1970; Pandit and Dundee, 1970; Ghoneim, Mewaldt and Thatcher, 1975; Frumin, Herekar and Jarvik, 1976; McKay and Dundee, 1980). Clarke and colleagues (1970) have shown that diazepam i.v. caused dense anterograde amnesia for approximately 10 min after administration, and that this was not accompanied by a serious decrease in the level of consciousness. They concluded that impairment of memory was the result of an effect of the drug on the consolidation process, rather than a direct effect on the registration or retrieval of information. Further support for this theory was provided by the studies of Grove-White and Kelman (1971), Gregg, Ryan and Levin (1974), Ghoneim and Mewaldt (1975) and McKay and Dundee (1980).

The degree and duration of amnesia following the administration of diazepam is dependent on both dose and route of administration, being more pronounced, for example, following i.v. rather than i.m. administration (Pandit, Dundee and Keilty, 1971). Intravenous diazepam 10 or 20 mg consistently caused rapid onset, short duration amnesia (Clarke et al., 1970; Gregg, Ryan and Levin, 1974; Ghoneim, Mewaldt and Thatcher, 1975). The findings following oral administration are less consistent. A number of authors have been unable to demonstrate amnesia following diazepam by mouth (Harry and Richards, 1972; Wilson and Ellis, 1973), although it has been reported by Baird and Hailey (1972) and more recently by McKay and Dundee (1980).

Besides its amnesic properties, diazepam alters numerous other aspects of human performance such as reflex speed, attention and vigilance, decision making and motor co-ordination (McNair, 1973; Kleinknecht and Donaldson, 1975). These diverse actions must be taken into account, especially when the drug is used in outpatients.

There is now reliable evidence that the benzodiazepines produce their numerous effects on the central nervous system primarily by facilitating synaptic transmission which is mediated by the inhibitory neurotransmitter γ-amino butyric acid (GABA) (Haefely et al., 1975; Costa and Guidotti, 1979). Benzodiazepine receptors (Mohler and Okada, 1977, 1978; Squires and Braestrup, 1977) are thought to be associated with the postsynaptic GABA receptor complex in such a way that the enhancing effect of the benzodiazepines on GABAergic transmission and, consequently, their pharmacological activity is initiated by interaction between the benzodiazepines and their receptor sites (Guidotti, Toffano and Costa, 1978). The recent discovery of Ro 15–1788 (ethyl-8-fluoro-5, 6-dihydro-5-methyl-6-oxo-4H-imidazo-[1, 5-a] [1, 4]
The benzodiazepine-3-carboxylate) (Hunkeler et al., 1981; Mohler et al., 1981), a potent benzodiazepine antagonist, provides a unique opportunity for studying the relationship between benzodiazepine receptors and the pharmacological activity of these agents in man. Ro 15—1788 has already been shown to block the behavioural, neurological and electrophysiological effects of several benzodiazepines in animals (Hunkeler et al., 1981; Pole et al., 1981). Recently, the central effects of the potent benzodiazepine 3-methylclonazepam have been effectively antagonized in man following both oral and i.v. administration of Ro 15—1788 (Darragh et al., 1981a, b). Ro 15—1788 is well tolerated in man when administered alone as a single oral dose of up to 600 mg, and is devoid of any demonstrable pharmacological activity (unpublished data).

The purpose of the study reported here was to determine whether Ro 15—1788 by mouth was an effective antagonist of the central effects of diazepam in man and, in particular, to investigate its efficacy in blocking the amnesic effects of diazepam. A further objective was to determine whether Ro 15—1788 modified the plasma concentration profile of diazepam when both substances were administered orally.

SUBJECTS AND METHODS

Six healthy male volunteers aged between 18 and 25 yr participated. An extensive physical examination, including 12-lead electrocardiogram and laboratory screen, was conducted before and after the study. All subjects gave written informed consent to participate in the study, the programme for which was subject to Institutional Review Board approval. Subjects were excluded if there was any abnormality on physical examination or laboratory findings, a history of any allergic condition (including drug hypersensitivity), a history of drug abuse, or intake of any medication within 2 weeks before enrolment in the study, or a score of more than 13 or less than 3 on the neuroticism scale of the Eysenck Personality Inventory (Eysenck and Eysenck, 1964). Smoking, alcohol and caffeine-containing substances were forbidden for the duration of each study period.

Each subject received three separate treatments: (a) diazepam 20 mg; (b) diazepam 20 mg + Ro 15—1788 200 mg and (c) placebo. Each treatment was administered once only as a single oral dose after an overnight fast. Treatments were administered under double-blind conditions, with the order of administration randomized by means of two 3 x 3 latin square designs. In order to control for possible carry-over effects, a 14-day washout period was allowed between successive doses. Subjects were trained on the psychometric test battery on two separate occasions before the start of the study in order to minimize learning effects. On the night before each treatment day, subjects reported to the Institute at 19.00 h and remained under observation for 48 h after each dose.

Memory test

The memory test used in this study was similar to that developed by Clarke and colleagues (1970). The subject was asked to try to remember six sets of three words which were read aloud as six triplets, the three words in each triplet having phonetic similarity. His learning was then tested by prompting him with the first word of each triplet and asking for the other two words which were linked with it. The subject was corrected at once if he got any wrong and the procedure was carried out four times. The number of response words correct after the first hearing provided a measure of immediate recall, while the number correct summed over the four trials and the number correct three times in a row in these four trials provided measures of learning. Further training was given until at least four items were correct three times. The second part of the test was administered 30 min later. The subject was asked to recall as many of the 18 words as possible without regard to order or grouping (free recall). Next, he was prompted with the first word of each triplet and was asked to respond with the correct words as in the original learning condition (prompt recall). The learning part of the test was administered 1 h after the administration of the drug(s) and the retention part of the test 30 min later.

Psychomotor tests

In addition to the triple associate learning test the following psychomotor tests were administered at 2.5, 6, 26.5, and 50.5 h after each dose administration:

(a) Critical Flicker Fusion (CFF);
(b) Simple Reaction Time (SRT);
(c) Perceptual Speed Test (PST);
(d) Digit Symbol Substitution Test (DSST);
(e) Digit Copying Test (DCT);
(f) Subjective Rating of Mood.

This test battery is described in greater detail else-
where (Darragh et al., 1981b). DSST and PST provide measures of cognitive function, SRT and DCT are tests of psychomotor speed and integration while CFF provides a neural measure of cortical arousal. The subjective mood instrument consists of a series of 16 visual analogue scales which assess such dimensions as alertness, anxiety and contentedness (Bond and Lader, 1974).

**Plasma diazepam concentrations**

Blood for diazepam assay was taken before administration and 1, 2, 3, 4, 6, 8, 12, 24, and 48 h after administration of diazepam and the diazepam—Ro 15-1788 combination. Plasma diazepam concentration was measured by radioimmunoassay as described by Dixon and Crews (1978). Comparative bioavailability of diazepam following the two treatments was assessed by comparing the areas under the plasma concentration—time curves (AUC) using a $t$ test for paired data. The AUC from $t = 0$ to $t = 48$ h, were determined by the trapezoidal rule.

### RESULTS

#### Learning and memory

Mean scores, standard errors and significance levels for analysis of variance (ANOVA) pairwise contrasts for the triple associate learning test comparing diazepam and diazepam—Ro 15—1788 respectively with placebo, are shown in table I. Diazepam had no effect on the measure of immediate recall, but did significantly impair learning capacity. Total correct responses for the four trials (learning sum) and the total number of items reaching criterion in the first four trials (learning treble) were significantly lower following diazepam ($P < 0.05$ and $P < 0.01$ respectively). The effects of diazepam on learning are further illustrated in figure 1 which shows the mean learning curves for the three treatments. A 6 (subjects) $\times$ 2 (treatments) $\times$ 4 (trials) analysis of variance, comparing diazepam scores with placebo scores, revealed significant main effects for treatments ($P < 0.05$) and learning trials ($P < 0.01$). The interaction, however, was not significant, indicating that the effect of diazepam was not specific to any particular trial. Results from the second part of the test, in which memory was evaluated, indicated that prompt recall was significantly impaired by diazepam ($P < 0.05$), but free recall was not affected. This finding is in agreement with previous research and is considered to reflect the effect of diazepam on learning rather than a direct effect on the retrieval process itself (Clarke et al., 1970).

The significant impairment in learning capacity seen following diazepam was prevented when

### Table I. Mean scores (± SEM) for triple associate learning following the three treatment conditions. *$P < 0.05$; **$P < 0.01$ for pairwise ANOVA contrasts with placebo.

<table>
<thead>
<tr>
<th>Memory process</th>
<th>Placebo</th>
<th>Diazepam</th>
<th>Diazepam + Ro 15-1788</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Recall</td>
<td>3.83 ± 0.99</td>
<td>2.66 ± 0.97</td>
<td>2.66 ± 0.87</td>
</tr>
<tr>
<td>Learning Sum</td>
<td>26.80 ± 3.70</td>
<td>17.30 ± 4.20</td>
<td>21.00 ± 5.50</td>
</tr>
<tr>
<td>Learning Treble</td>
<td>1.83 ± 0.60</td>
<td>0.50 ± 0.50</td>
<td>1.50 ± 0.60</td>
</tr>
<tr>
<td>Free Recall</td>
<td>9.83 ± 0.80</td>
<td>7.10 ± 1.50</td>
<td>8.00 ± 1.30</td>
</tr>
<tr>
<td>Prompt Recall</td>
<td>9.33 ± 1.00</td>
<td>5.50 ± 1.30</td>
<td>6.33 ± 1.40</td>
</tr>
</tbody>
</table>

**Fig. 1.** Triple associate learning test: mean learning curves following placebo (P), diazepam (D) and the diazepam—Ro 15—1788 combination (C). *Significant ($P < 0.05$) impairment compared with placebo.
TABLE II. Mean values and standard errors (SEM) for the five performance measures at each post-dose observation period. *P < 0.05; **P < 0.01: Significant impairment when compared with placebo scores (pairwise ANOVA contrasts)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment</th>
<th>2.5</th>
<th>SEM</th>
<th>6.0</th>
<th>SEM</th>
<th>26.5</th>
<th>SEM</th>
<th>50.5</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCT (Scores correct /60 s)</td>
<td>Placebo</td>
<td>113.5</td>
<td>6.8</td>
<td>117.0</td>
<td>6.8</td>
<td>119.0</td>
<td>5.2</td>
<td>121.0</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>101.7</td>
<td>7.6</td>
<td>106.0</td>
<td>8.2</td>
<td>111.5</td>
<td>6.8</td>
<td>116.8</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Diazepam + Ro 15-1788</td>
<td>115.8</td>
<td>5.0</td>
<td>111.5</td>
<td>6.0</td>
<td>112.0*</td>
<td>4.7</td>
<td>116.7</td>
<td>3.7</td>
</tr>
<tr>
<td>DSST (Scores correct /90 s)</td>
<td>Placebo</td>
<td>62.8</td>
<td>3.4</td>
<td>64.3</td>
<td>2.5</td>
<td>65.3</td>
<td>3.6</td>
<td>68.0</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>54.6*</td>
<td>3.0</td>
<td>54.8*</td>
<td>5.0</td>
<td>62.0</td>
<td>3.0</td>
<td>67.8</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Diazepam + Ro 15-1788</td>
<td>57.5</td>
<td>4.5</td>
<td>54.5**</td>
<td>3.2</td>
<td>58.5</td>
<td>3.5</td>
<td>66.6</td>
<td>2.8</td>
</tr>
<tr>
<td>PST (Scores correct /45 s)</td>
<td>Placebo</td>
<td>15.6</td>
<td>1.7</td>
<td>14.7</td>
<td>1.0</td>
<td>13.6</td>
<td>1.5</td>
<td>13.2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>11.2**</td>
<td>1.1</td>
<td>11.5*</td>
<td>0.9</td>
<td>10.9</td>
<td>1.4</td>
<td>14.0</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Diazepam + Ro 15-1788</td>
<td>13.3</td>
<td>1.4</td>
<td>11.4*</td>
<td>1.3</td>
<td>12.7</td>
<td>1.3</td>
<td>13.6</td>
<td>1.6</td>
</tr>
<tr>
<td>SRT (ms)</td>
<td>Placebo</td>
<td>241</td>
<td>10</td>
<td>272</td>
<td>10</td>
<td>257</td>
<td>12</td>
<td>251</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>256</td>
<td>14</td>
<td>278</td>
<td>19</td>
<td>242</td>
<td>12</td>
<td>257</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Diazepam + Ro 15-1788</td>
<td>255</td>
<td>15</td>
<td>280</td>
<td>15</td>
<td>254</td>
<td>10</td>
<td>251</td>
<td>7</td>
</tr>
<tr>
<td>CFF (cycles s⁻¹)</td>
<td>Placebo</td>
<td>35.3</td>
<td>1.5</td>
<td>35.8</td>
<td>1.4</td>
<td>35.0</td>
<td>1.6</td>
<td>36.4</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>30.2*</td>
<td>1.4</td>
<td>33.6*</td>
<td>1.6</td>
<td>33.5</td>
<td>1.2</td>
<td>35.0</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Diazepam + Ro 15-1788</td>
<td>33.7</td>
<td>1.6</td>
<td>34.0</td>
<td>0.8</td>
<td>35.2</td>
<td>1.4</td>
<td>36.5</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Ro 15-1788 was concurrently administered. No significant differences were observed when scores following the combined drugs were compared with those following placebo (table I). Figure 1 shows that, although the learning curve following the combination was lower than that seen after placebo, the difference was not significant. Results from the second part of the test (free and prompt recall) also reflect the lack of impairment following diazepam in combination with Ro 15-1788.

TABLE III. Directional mood shifts and significance following administration of diazepam alone, or diazepam + Ro 15-1788, when compared with placebo. n.s. = No significant mood shifts (pairwise ANOVA contrasts)

<table>
<thead>
<tr>
<th>Placebo compared with</th>
<th>Mood</th>
<th>2.5</th>
<th>P</th>
<th>6</th>
<th>P</th>
<th>26.5</th>
<th>P</th>
<th>50.5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Drowsy</td>
<td>&lt;0.01</td>
<td>Muzzy</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Feeble</td>
<td>&lt;0.05</td>
<td>Clumy</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muzzy</td>
<td>&lt;0.05</td>
<td>Mentally slow</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Clumy</td>
<td>&lt;0.05</td>
<td>Dreamy</td>
<td>&lt;0.05</td>
<td></td>
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<tr>
<td></td>
<td>Lethargic</td>
<td>&lt;0.05</td>
<td>Incompetent</td>
<td>&lt;0.05</td>
<td></td>
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<tr>
<td></td>
<td>Mentally slow</td>
<td>&lt;0.05</td>
<td>Withdrawn</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>Dreamy</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>Incompetent</td>
<td>&lt;0.05</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Withdrawn</td>
<td>&lt;0.05</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>n.s.</td>
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<td>n.s.</td>
<td></td>
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<tr>
<td>Diazepam + Ro 15-1788</td>
<td>Lethargic</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>Mentally slow</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>Relaxed</td>
<td>&lt;0.05</td>
<td></td>
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</tbody>
</table>
Psychomotor tests

The degree of impairment in psychomotor performance and the changes in subjective mood following each of the three treatments are outlined in tables II and III.

At 2.5 h diazepam significantly impaired DSST ($P < 0.05$), CFF ($P < 0.025$), DCT ($P < 0.05$) and PST ($P < 0.01$). Impairment in SRT at this time approached significance ($P < 0.10$). At the 6-h testing time, scores on the two measures with predominantly motor components were not significantly different from those following placebo. Impairment was still present, however, on the DSST ($P < 0.05$), and PST ($P < 0.01$) while CFF values were lower than corresponding placebo values ($P < 0.05$). No significant impairment was observed on any measures at 26.5 or 50.5 h.

When Ro 15-1788 was administered concurrently with diazepam, the impairment in performance observed after diazepam alone was completely prevented, 2.5 h after administration (table II). Six hours after the combined dose, however, significant impairment occurred on the two measures of cognitive function, DSST ($P < 0.01$) and PST ($P < 0.05$), while impairment on the DCT was seen at 26.5 h.

Data derived from the 16 bipolar mood scales are summarized in table III (only those shifts in mood found to be significant by analysis of variance comparisons are included). Following diazepam alone significant changes were seen on nine of the 16 mood scales at 2.5 h. All of the scales affected load onto the alertness factor (Bond and Lader, 1974) and reflect drug-induced sedation, inco-ordination, lethargy and mental slowness. Some of these effects persisted for 6 h but had returned to placebo values by 26.5 h. Following the diazepam–Ro 15–1788 combination there were no significant mood changes at 2.5 or 6 h, although at 26.5 h subjects reported feeling more lethargic, mentally slow and relaxed, indicating a mild degree of residual sedation at this time.

Plasma diazepam concentrations

Mean plasma diazepam concentrations for the six subjects, following either diazepam alone or the diazepam–Ro 15–1788 combination, are illustrated in figure 2. The two curves are very similar and statistical analysis confirmed that the mean AUC did not differ significantly for the two treatments.

**DISCUSSION**

The amnesic effects of diazepam observed in this study are in good agreement with the findings of Clarke and colleagues (1970) and the results provide further evidence that diazepam administered by the oral route causes significant anterograde amnesia (McKay and Dundee, 1980). Diazepam did not significantly affect immediate recall, but did impair

![Fig. 2. Mean plasma diazepam concentrations (±SEM) following administration of diazepam 20 mg (●) and diazepam 20 mg + Ro15-1788 200 mg (▲) to six subjects.](https://academic.oup.com/bja/article-abstract/55/4/349/295406)
learning ability and subsequent recall. These findings are consistent with the model suggested by Clarke and co-workers (1970) and elaborated by Ghoneim and Mewaldt (1975), in which the amnesic actions of diazepam were attributed to impairment in the consolidation process, rather than to a direct effect on storage or retrieval. Since these authors found that the recall of information learned before the administration of diazepam was unaffected, it seems likely that the impairment in recall observed in the present study reflected impairment in earlier learning capacity rather than an effect on the recall process itself.

Concomitant administration of Ro 15-1788 markedly attenuated the amnesic actions of diazepam. Although antagonism was not complete, scores following the combination were not significantly different from placebo on any of the indices of learning or memory. It seems likely that more complete antagonism would have resulted from the use of a larger dose of Ro 15-1788. Nevertheless, the results of the study implicate the benzodiazepine receptor in the amnesic action of diazepam and introduce the interesting possibility that an endogenous ligand, such as that suggested by Mohler and colleagues (1979), may be intimately involved in the memory process.

The impairment seen on other tests of psychomotor performance following diazepam alone is consistent with that reported elsewhere (Kleinknecht and Donaldson, 1975; Wittenborn, 1979).

The effects of the drug were most marked when plasma diazepam concentrations were highest, with progressive recovery occurring during the elimination phase. Impairment on all measures was prevented at 2.5 h by concomitant administration of Ro 15-1788, although sedative effects became apparent at 6 h, indicating that the antagonistic effect was relatively short. It is possible that this finding reflects the short elimination half-life of Ro 15-1788 (unpublished data). These results are in good agreement with our previous observations (Darragh et al., 1981a, b) where Ro 15-1788 effectively blocked the central effects of the potent benzodiazepine 3-methylclobazepam in healthy volunteers for up to 2.5 h.

The ability of Ro 15-1788 to antagonize the central effects of diazepam does not seem to be mediated by interference with the bioavailability of the parent compound and is likely to reflect activity at the receptor level. The finding of some residual sedation 26.5 h after the diazepam-antagonist combination, which was not observed following diazepam alone, is surprising and the possibility that the antagonist may modify the plasma concentrations of active diazepam metabolites cannot be ruled out.

The discovery of such a benzodiazepine antagonist is analogous to that of the opiate antagonists and should have considerable scientific and therapeutic significance. Previous attempts to antagonize the central effects of diazepam using cholinesterase inhibitors (Di Liberti, O'Brien and Turner, 1975; Rupreht, 1980) or naloxone (Bell, 1975; Christensen and Huttel, 1979) have yielded inconclusive results, but have highlighted the potential usefulness of such an antidote in benzodiazepine overdose, or for abolishing the central effects of the benzodiazepine administered for surgical or diagnostic reasons, when rapid reversal of sedation may be required.

REFERENCES


LA RO 15-1788 ANTAGONISTE LES EFFETS DU DIAZEPAM CHEZ L'HOMME SANS MODIFIER SA BIODISPOSIBILITE

RESUME

Dans une etude en double aveugle, a triple recouplement, controlee par un placebo, l'efficacite de 200 mg de RO 15-1788, un nouvel antagoniste des benzodiazepines, pour bloquer les effets amnesiques, cognitifs, psychomoteurs et subjectifs de 20 mg de diazepam, a ete etudee dans un groupe de six volontaires en bonne sante, de sexe masculin. Les effets amnesiques du diazepam ont ete nettement attenues par l'administration simultanee de RO 15-1788. Les effets psychomoteurs et subjectifs du diazepam administrer per-os etaien a leur maximum 2,5 h apres l'administration. L'administration simultanee de RO 15-1788 per os prevenait completement la survenue de ces effets apres 2,5 h. Les concentrations plasmatiques de diazepam observes apres administration d'un mélange de diazepam et de l'antagoniste n'etaient pas differentes de celles observes apres administration de diazepam seul.

RO 15-1788 ANTAGONISIERT DIE EFFEKTEN VON DIAZEPAM BEIM MENSCHEN, OHNE SEINE BIOLOGISCHE WIRKSAMKEIT ZU BEEINTRACHTIGEN

ZUSAMMENFASSUNG


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En un estudio doble-ciego entrecruzado de tres sentidos controlado por placebo, se investigó la eficacia de 200 mg de Ro 15-1788, nuevo antagonizador benzodiazepínico, en el bloqueo de los efectos amnésicos, cognoscitivos, sicomotores y subjetivos de 20 mg de diazepam en un grupo de seis voluntarios masculinos sanos. La administración combinada del Ro 15-1788 attenuó notablemente los efectos amnésicos del diazepam. Los efectos sicomotores y subjetivos del diazepam oral fueron más marcados 2,5 h después de la administración. La administración oral concurrente de Ro 15-1788 impidió por completo dichos efectos a 2,5 h. Las concentraciones de diazepam en el plasma observadas después de la administración combinada de diazepam y del antagonizador no diferían de la observada después del diazepam solo.