SKILLS RELATED TO DRIVING AFTER INTRAVENOUS DIAZEPAM, FLUNITRAZEPAM OR DROPERIDOL

K. KORTTILA AND M. LINNOILA

SUMMARY

Skills related to driving and the ability to discriminate the fusion of flickering light were measured double-blind in 62 healthy volunteer students before and 4, 6, 8 and 10 hours after intravenous injection of diazepam (0.3 mg/kg), flunitrazepam (0.03 mg/kg) or droperidol (5 mg), alone or in combination with pethidine (1 mg/kg) or fentanyl (0.2 mg). The dose of diazepam and flunitrazepam was halved in those subjects given pethidine but the dose of droperidol was the same with and without fentanyl. Impairment by droperidol in almost all tests remained up to 10 hours after injection. Droperidol proved more deleterious than the benzodiazepines. Flunitrazepam impaired flicker fusion discrimination and co-ordination for up to 10 hours. Diazepam impaired flicker fusion discrimination and co-ordination for up to 6 hours. The doses of narcotic analgesics used here did not enhance the effect of other drugs on performance in the tests used. It is concluded that patients should not drive or operate machinery for 10 hours after i.v. injection of diazepam and 24 hours after flunitrazepam and droperidol.

Diazepam is commonly used as an intravenous sedative in dentistry and minor outpatient surgery. Even though a rapid recovery, measured by a paper-and-pencil test, after diazepam has been reported (Driscoll et al., 1972; Newman et al., 1970), more recent studies suggest a delayed recovery (Baird and Flowerdew, 1970; Baird and Hailey, 1972, 1973; Fox, Wynands and Bhambhami, 1968).

Flunitrazepam is a new benzodiazepine which is chemically similar to diazepam. It is like diazepam in that it is sparingly soluble in water and is available in ampoules containing 1 mg of the drug to be dissolved in propylene glycol before the injection. Initial studies by DeCastro (1972), Stovner, Endresen and Österud (1973) and Ungerer and Erasmus (1973) have suggested that this new fluorinated benzodiazepine may be similar to diazepam as an induction agent. Doses of 2.5-10 mg of droperidol have also been used with success for outpatient anaesthesia both i.v. (Kempf, 1971; Smith and Hollis, 1966) and i.m. (Brockmüller and Niederfellman, 1972). The latter found that recovery from droperidol occurs within 6 hours but other workers suggest that its effect lasts much longer (Brown, 1969; Morrison, 1969).

Since the reports about delayed recovery after diazepam are mostly based on subjective assessments the present investigation was conducted in order to provide objective data by measuring skills related to driving after diazepam, flunitrazepam or droperidol, alone or in combination with a narcotic analgesic.

The performance in the tests used bears a close relationship to driving ability (Eklund, 1970; Häkkina, 1958). The doses of flunitrazepam and droperidol were based on those used in these studies, and the dose of diazepam was based on the reports of Dixon et al. (1973), Keilty and Blackwood (1969) and O'Neil et al. (1970).

MATERIAL AND METHODS

The subjects were 62 healthy student volunteers. They were divided into six groups which were broadly comparable with respect to age, weight, height, educational level and district of residence (table I). There were two females in each group. None of the subjects had taken any drugs for at least one month before the experiment though most of them took alcohol occasionally. Allocation was made at random and the study was carried out using a double-blind technique. Informed consent was obtained for the procedure.

The drugs administered (table I) were injected into the left cubital vein. Diazepam (Valium,
Table I. Characteristics of the test groups and injected drug doses. Two females in each group. The doses of the drugs refer to the base. The values are means±SD.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Code</th>
<th>Number of volunteers</th>
<th>Age (yr) ± SD</th>
<th>Weight (kg) ± SD</th>
<th>Height (cm) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam 0.3 mg/kg + saline</td>
<td>D</td>
<td>11</td>
<td>21 ± 1.4</td>
<td>69 ± 7.1</td>
<td>178 ± 6.8</td>
</tr>
<tr>
<td>Diazepam 0.15 mg/kg + pethidine 1 mg/kg</td>
<td>D-P</td>
<td>10</td>
<td>22 ± 5.1</td>
<td>68 ± 12.1</td>
<td>179 ± 9.1</td>
</tr>
<tr>
<td>Flunitrazepam 0.03 mg/kg + saline</td>
<td>F</td>
<td>10</td>
<td>22 ± 2.5</td>
<td>70 ± 12.6</td>
<td>179 ± 11.7</td>
</tr>
<tr>
<td>Flunitrazepam 0.015 mg/kg + pethidine 1 mg/kg</td>
<td>F-P</td>
<td>11</td>
<td>22 ± 2.5</td>
<td>68 ± 7.7</td>
<td>176 ± 7.2</td>
</tr>
<tr>
<td>Droperidol 5 mg + saline</td>
<td>DHB</td>
<td>10</td>
<td>23 ± 2.8</td>
<td>71 ± 8.2</td>
<td>176 ± 5.9</td>
</tr>
<tr>
<td>Droperidol 5 mg + fentanyl 0.2 mg</td>
<td>DHB-Fe</td>
<td>10</td>
<td>22 ± 3.0</td>
<td>73 ± 9.9</td>
<td>176 ± 8.6</td>
</tr>
</tbody>
</table>

Roche), flunitrazepam (Ro 5-4200, Roche) and droperidol (Orion, Helsinki) were injected first and pethidine hydrochloride (Star, Tampere) or fentanyl citrate (Fentanyl, Orion, Helsinki) immediately after. No premedication was used. The volumes of the drug solutions injected per unit of time were similar. The doses of the benzodiazepines were halved in those subjects given pethidine but the dose of droperidol was the same with saline and fentanyl.

Trial design.

On the evening before the experiment the subjects were allowed to practise for 1 hour on each piece of test apparatus. Immediately after this period the subjects were tested once to find the preinjection values. The drugs were given next morning and the tests were repeated at 4, 6, 8 and 10 hours after the injection. All the subjects were informed about the tests by the same person, in the same way. The groups spent their spare time between the tests together. Food and drink was not allowed for 8 hours before the injection. Coffee, tea, cola or tobacco were not allowed during the experiment.

Clinical observations.

Clinical recovery was measured by recording the time until the appearance of a negative Romberg sign. The depth of sedation was assessed by recording the degree of drooping of the upper eyelid. If the ptosis occurred halfway across the pupil, Verril's sign was regarded as positive (O'Neil et al., 1970). Amnesia was determined by pinching the lower abdomen of the subjects.

Subjective assessments.

The subjects were asked after each test period whether or not they thought they could drive as safely as usual. They were also asked if they felt tired or drowsy or had vertigo or an unsteady gait.

Test equipment.

A commercially available choice reaction test ("Test d'attention diffuse", PPII, Ets Pierre Dufour, Paris) was used on every occasion. In this test the subject had to react to three different light stimuli by pushing either of two foot pedals, alone or both together. They had also to push a button in response to a low sound stimulus while a higher-pitched sound was given as a disturbance signal to which they were told not to react. The test consisted of 36 stimuli within 54 sec. A chronometer measured the cumulative reaction time with an accuracy of 1/100 sec, and the number of incorrect responses, termed "the number of mistakes" (Linnoila and Mattila, 1972a).

A commercially available co-ordination test ("Wiener Koordination gerät", J. C. Pöhlman, Munich) was used twice on each occasion: first at a fixed speed, and then at a speed adjusted to an optimum chosen by the subject himself. These two techniques are called co-ordination tests I and II respectively, in the text. There was a narrow illuminated track moving on the screen, and the subject had to keep a black ball on the track by turning a steering wheel. Co-ordination test I lasted for 30 sec, and co-ordination test II for 30-80 sec depending on the subject. The number of mistakes (the number of deviations from the track) was recorded. The cumulative length of the deviations from the track was calculated as a percentage of the total track length, and is called the mistake%. The driving time was recorded in co-ordination test II (Linnoila and Mattila, 1972a).

The attention test, lasting for 10 min, was of the
clock test type (Häkkinen, 1958). The apparatus consisted of four dials, two of which were situated beside each other in the middle of the field of vision of the subjects. Two other dials were placed symmetrically at the periphery of the field of vision, so that the angle required to see all the dials was 110 degrees. Every time a pointer passed one of the marks in any dial the subject had to react by pushing the corresponding button. The numbers of responses and the numbers of correct responses (responses from correct buttons during the time limit of 1.0 sec in the middle and 1.3 sec in the periphery) were recorded (Linnoila, 1973).

Critical flicker fusion frequency was measured at every test period (Haffner et al., 1972; Grove-White and Kelman, 1971). Each subject was instructed to announce when the light at 90 cm distance stopped flickering.

Drug concentrations in serum.

Venous blood samples were drawn from the right cubital vein after each test period. Sera were stored at −22°C until serum diazepam and N-desmethyl-diazepam levels were assayed by electron capture gas liquid chromatography according to DeSilva and Puglisi (1970). The recovery for diazepam was 97-98% and that for N-desmethyldiazepam was 100%. Serum flunitrazepam, N-desmethylflunitrazepam and 7-aminoflunitrazepam concentrations were measured spectrofluorimetrically on a thin-layer chromatography plate according to Haefelfinger (1974).

The results of Romberg's test were analysed statistically using the Student t-test. Other results were analysed with the two-way analysis of variance, which was found to be a proper statistical method by additivity tests.

RESULTS

Clinical observations and side effects.

Figure 1 shows the number of subjects who developed positive Verril's sign and who did not remember the pinching of the abdomen. There was a high incidence of both of these with the two benzodiazepines either given alone or with an opiate but a much lower incidence in the subjects who were given droperidol. The time until the negative Romberg sign appeared was significantly longer after flunitrazepam as compared with the other treatments (table II).

One volunteer in the droperidol group and one in the droperidol-fentanyl group developed an oculogyric crisis at 4 and 8 hours but 60 mg of orphenadine given intravenously abolished these extrapyramidal side effects. In addition, three of the volunteers who received droperidol in this experiment showed minor extrapyramidal symptoms but these did not require treatment.

Subjective assessments.

Forty-five per cent of the volunteers in the diazepam group and 60% in the diazepam-pethidine group reported pain in the arm during the injection. There was a high incidence of tiredness

<table>
<thead>
<tr>
<th>Treatment</th>
<th>D</th>
<th>D-P</th>
<th>F</th>
<th>F-P</th>
<th>DHB</th>
<th>DHB-Fe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>36±8.9</td>
<td>42±26.8</td>
<td>90±29.3*</td>
<td>55±20.2</td>
<td>25±5.0</td>
<td>25±9.1</td>
</tr>
</tbody>
</table>

*P<0.01 in comparison with diazepam group.
or drowsiness after droperidol and droperidol with fentanyl (fig. 2). Vertigo or unsteady gait was common up to 6 hours after flunitrazepam, but at 8 and 10 hours there were no adverse reactions and no patient reported vertigo or unsteady gait (fig. 3). The subjects assessed their driving ability as poor, especially after droperidol (fig. 4).

Test performances.

Skills measured, when compared with the pre-injection values, were impaired in at least one test of the test battery after each drug. The impairment was most marked after droperidol and droperidol with fentanyl.

Reactive skills.

The results were similar if the drugs were injected alone or with analgesic. The changes in cumulative reaction times after the three drugs with analgesics are shown in figure 5. None of the treatments caused statistically significant changes in cumulative reaction times as compared with the preinjection values. However, droperidol and droperidol with fentanyl significantly prolonged the reaction times at 4 hours as compared with diazepam and diazepam with pethidine (P<0.05).

Co-ordinative skills.

Every treatment modified significantly the parameters measured in the preinjection co-ordination tests. The numbers of mistakes in co-ordination test I were significantly increased up to 10 hours after droperidol and flunitrazepam (P<0.05). The numbers of mistakes after diazepam returned to normal at 8 hours (fig. 6). The results were not modified by the analgesics. The mistake% changed in parallel with the numbers of mistakes after each treatment. In co-ordination test II droperidol and droperidol with fentanyl increased the numbers of mistakes and the mistake% significantly (P<0.05) more than the benzodiazepines at any test time. The driving times remained unaltered after every treatment.

Attention.

The total numbers of correct responses in the peripheral dials were significantly smaller (P<0.01) after droperidol than after flunitrazepam which actually increased the numbers of correct responses.
between 6 and 10 hours (fig. 7). The results after the combination with an analgesic were similar to those after the drugs alone. In the central dials the numbers of responses increased in each group, the increase being significantly smaller after droperidol and droperidol with fentanyl than after the benzodiazepines (P<0.01).

The critical flicker fusion frequency after any treatment was significantly decreased for up to 6 hours (P<0.05 to P<0.01) and impairment was still significant at 10 hours (P<0.05) in those patients given droperidol (fig. 8).

**Drug levels in serum.**

Mean measured serum concentrations of diazepam were highest at 4 hours, decreasing thereafter to 70% of the 4-hour value at 10 hours. The concentrations of its main metabolite N-desmethyldiazepam increased steadily throughout the experiment (table III). The serum concentrations of both flunitrazepam and its metabolite 7-aminoflunitrazepam were highest at 4 hours decreasing but
TABLE III. Serum concentrations of diazepam and N-desmethyl diazepam, flunitrazepam and 7-amino flunitrazepam after intravenous administration of diazepam (0.3 and 0.15 mg/kg) and flunitrazepam (0.03 and 0.15 mg/kg), respectively. The values are means ±SD.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Measured drug</th>
<th>Drug levels in serum (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 hr</td>
</tr>
<tr>
<td>Diazepam 0.3 mg/kg</td>
<td>Diazepam</td>
<td>336 ± 82</td>
</tr>
<tr>
<td></td>
<td>N-desmethyl diazepam</td>
<td>27 ± 11</td>
</tr>
<tr>
<td>Dialepam 0.15 mg/kg</td>
<td>Diazepam</td>
<td>204 ± 34</td>
</tr>
<tr>
<td></td>
<td>N-desmethyl diazepam</td>
<td>15 ± 14</td>
</tr>
<tr>
<td>Flunitrazepam 0.03 mg/kg</td>
<td>Flunitrazepam</td>
<td>10.4 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>7-aminoflunitrazepam</td>
<td>10.4 ± 3.0</td>
</tr>
<tr>
<td>Flunitrazepam 0.015 mg/kg</td>
<td>Flunitrazepam</td>
<td>6.0 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>7-aminoflunitrazepam</td>
<td>6.0 ± 1.5</td>
</tr>
</tbody>
</table>

Fig. 8. The change in flicker fusion frequency. Points represent mean values. F=the value of F in the two-way analysis of variance.

still being high at 10 hours. Between 6 and 10 hours, N-desmethylflunitrazepam could be measured in only 4 volunteers. In 4 of 21 subjects the blood concentrations of diazepam increased at 6 hours after the injection. Similar increases were observed in 7 subjects who received flunitrazepam.

Seven subjects were retested with diazepam: 3 who showed an exceptional increase in serum diazepam concentration, and 4 others whose concentration declined after the first test. Blood samples were taken at 4, 5, 6, 7 and 8 hours after the injection of 0.3 mg/kg of diazepam. The serum alkaline phosphatase, glutaric-aspartic transaminase and creatinine concentrations in these subjects were normal. In table IV it can be seen that there were considerable differences of up to 25% in serum diazepam and up to 50% in serum N-desmethyl diazepam concentrations in the same individual receiving the same drug. One of the volunteers received diazepam three times, and each time the serum diazepam and N-desmethyl diazepam concentrations differed from each other.

DISCUSSION

The drugs.

The doses of diazepam and flunitrazepam are based on previously reported studies and should be sufficient for dental and minor surgery. The dose
of droperidol was also based on previous studies and has been used in outpatient practice. According to common practice, pethidine was used with the benzodiazepines (Metz and Halveg, 1974) and fentanyl with droperidol (Morrison, 1969). The drooping of the upper eyelid is used as a guideline for the intravenous dosage of diazepam (Dixon et al., 1973; O'Neil et al., 1970). From the present results this index did not seem to be suitable for adjusting the dose of droperidol (fig. 1).

**Trial design.**

Testing was not performed at 2 hours after injection because it is generally accepted that the shortest recovery period before attempting to drive after anaesthesia is 4 hours. The training period may not have been quite sufficient because most of the subjects showed improved performance at 8 and 10 hours as compared with the preinjection values.

**The tests.**

The results of the tests used have been shown to correlate with real traffic behaviour (Eklund, 1970; Håkkinen, 1958) and to be suitable for the investigation of drug effects on psychomotor skills (Linnoila, 1973; Linnoila and Mattila, 1972). The discrimination of flicker fusion frequency probably measures the effects of drugs on central nervous functions (Simonson and Brozek, 1952) and the test has proved especially sensitive to benzodiazepines (Haffner et al., 1972; Grove-White and Kelman, 1971). This very sensitivity of flicker fusion has been suggested as invalidating the test in assessment of recovery from anaesthesia (Grove-White and Kelman, 1971). In this study, however, depression of flicker fusion discrimination was in agreement with the results of the other tests used.

**The effects of diazepam.**

Baird and Hailey (1972) have reported a recurrence of clinical sedation at 6 hours in 5 volunteers who were given 20 mg of diazepam intravenously. Seven of their 10 subjects still felt tired at 24 hours after the injection. Baird and Flowerdew (1970) had found that 60% of patients injected with 0.36 mg/kg of diazepam and 20% of those injected with 0.14 mg/kg of diazepam felt tired 24 hours after the treatment. Driscoll et al. (1972) and Newman et al. (1970) found a rapid recovery after diazepam as assessed with a paper-and-pencil test described by Trieger, Newman and Miller (1969). In this test skills are assessed by the ability to join points on a graph with smooth pen lines. Recovery is assumed when the score returns to or approaches the preoperative level. On the other hand, Dixon and Thornton (1973) found a delayed recovery by means of a similar paper-and-pencil test. The follow-up time in these experiments was 90 min only. In the present study only 10% of the volunteers injected with diazepam felt tired or drowsy 10 hours after the injection and flicker fusion discrimination and co-ordination were reduced only up to 6 hours after the injection.

Baird and Hailey (1972, 1973) found serum concentrations of diazepam had increased at 6 hours in their 5 volunteers, while in the present experiment the mean serum concentrations of diazepam generally decreased as a function of time, though there was an increase at 6 hours after the injection in 4 volunteers. The attention of these 4 subjects was worse at 8 hours than at 6 hours and worse than the attention of the other 17 at 8 hours. The differences were not statistically significant and at 10 hours the results were similar in both groups. Since the effect of diazepam on attention correlated with serum diazepam concentrations, it seems unlikely that exceptional serum concentrations of diazepam are the result of partial decomposition of some of the samples during storage. This difference in pharmacokinetics between different subjects is in accordance with the great individual variations in response to intravenous diazepam found by Brown and Dundee (1968).

When the injection of diazepam was repeated in 7 volunteers the serum diazepam concentrations were different from those obtained following the first injection. The increase in serum diazepam concentration occurred at different times after injection in the two experiments (table IV). Baird and Hailey (1972) and Kleijn et al. (1971) have suggested that the irregular decrease in serum diazepam concentration might be the result of an enterohepatic cycle of diazepam. The differences between different injections in the same subject in the present study may depend on occasional variations in this proposed enterohepatic circulation of diazepam.

These results indicate that where cross-over studies are undertaken a large number of subjects is required in order to diminish the effect of large within-subject variations on results. The differences in serum diazepam or N-desmethyl-diazepam concentrations did not correlate with the smoking
habits of the subjects. Generally the serum diazepam levels did not correlate well with the objective measurements of performance.

The effects of flunitrazepam.

To the best of our knowledge recovery after flunitrazepam has not been measured objectively, but DeCastro (1972) reported that its effects can last up to 10 hours in some patients. Our finding of tiredness and drowsiness up to 10 hours is in agreement with this and at this time there was also deterioration of co-ordinating skills. This impairment of skills is in agreement with the long period (90 ±29.3 min) until the appearance of negative Romberg's sign, and with the high incidence of vertigo and unsteady gait till 6 hours after flunitrazepam. This has not been reported previously, and the reason for it remains to be investigated.

The changes in serum flunitrazepam concentrations were similar to those after diazepam. The 7-aminomethyl metabolite was the main metabolite. Individual variations were similar to those after diazepam, suggesting that this drug might also have an enterohepatic cycle.

The effects of droperidol.

Brown (1969) and Morrison (1969) have both warned that the effects of droperidol can last for more than 24 hours, whereas Doenicke et al. (1966) suggested that the drug's effect might last for as long as 4 days. Our studies demonstrate a considerable impairment of action for 10 hours after droperidol and at this time the effect was significantly more marked than that of either of the two benzodiazepines (P<0.05 to P<0.001). For this reason and because of the extrapyramidal side effects observed, droperidol is probably not suitable for outpatient practice.

The combined effects of analgesics and psychotropic drugs.

Even though there are warnings in the literature about the deleterious effects of narcotic analgesics on psychomotor performance (Jaffe, 1970) there were no such effects detected in the present study. Moreover, fentanyl in combination with droperidol caused a feeling of improved performance at 6–10 hours after the injection. This may be a result of the euphoric effects of the narcotic analgesic (Jaffe, 1970), or it may be because the doses of the benzodiazepines in combination with pethidine were lower than those with saline.

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Hoffmann-La Roche & Co. Ltd, Basle, personal communications.


