Recovery and Skills Related to Driving After Intravenous Sedation: Dose-Response Relationship with Diazepam

K. Korttila and M. Linnoila

Summary
Skills related to driving, the ability to discriminate the fusion of flickering light, and hand and foot proprioception, were measured double-blind in 34 healthy volunteers before and after three doses of i.v. diazepam. The effects of diazepam were most harmful to co-ordination. With 0.15 mg/kg, 0.30 mg/kg and 0.45 mg/kg of diazepam the impairment of co-ordinative skills was statistically significant (P<0.05) up to 2, 6 and 8 hr respectively. No impairment of performance on any test was measurable at 6 hr after 0.15 mg/kg or at 10 hr after 0.30 or 0.45 mg/kg of diazepam. There were large interindividual variations in serum concentrations of diazepam within each dose level. The increases in serum concentrations of diazepam after the intake of food support the concept of an enterohepatic cycle for diazepam. It was concluded that patients should not drive or operate machinery for at least 6 hr after 0.15 mg/kg of i.v. diazepam and at least 10 hr after 0.30 mg/kg and 0.45 mg/kg.

Diazepam is generally used as an intravenous sedative drug for outpatient anaesthesia. Although rapid recovery after diazepam, measured by a paper and pencil test, has been reported (Driscoll et al., 1972), it is a common belief that recovery after i.v. diazepam is delayed (Baird and Flowerdew, 1970; Baird and Hailey, 1972; Fox, Wynards and Bhamharni, 1968). Advice against driving for 24 hr after i.v. diazepam has been given (Dixon and Thornton, 1973; O'Neil et al., 1970).

Since reports about delayed recovery and the recommendation not to drive after diazepam are mostly based on subjective assessments by patients or anaesthetists, we conducted the present investigation in order to provide objective data by measuring skills related to driving after three different doses of diazepam. The doses of diazepam were based on those found in the literature (Baird and Flowerdew, 1970; Brown and Dundee, 1968; Dalen et al., 1969; Dixon et al., 1973; Dundee and Haslett, 1970; Fox, Wynands and Bhamharni, 1968; Rao et al., 1973), and performance in the test used bears an approximate relationship to driving ability (Eklund, 1970; Hakkinen, 1958).

Material and Methods

Subjects.
We studied 34 healthy volunteer students divided into three groups which were broadly comparable with regard to age, weight, height, educational level and district of residence (table I). There were two females in each group. Allocation was made at random, and the study was carried out using a double-blind technique. None of the subjects had taken drugs for at least 1 month before the experiment and most of them had taken alcohol only occasionally. Informed consent was obtained for the procedure.

Sedation.
Diazepam (Valium, Roche, Basel) in quantities of 0.15, 0.30 or 0.45 mg/kg was injected into the left cubital vein at a rate of 5 mg/min. No premedication was used.

Trial design.
The subjects practised for 1 hr on every test apparatus on the evening before the actual test. Immediately after this period they were tested once in order to measure preinjection values. The drugs were given on the following morning, and the tests were repeated 4, 6, 8 and 10 hr after injection with 0.30 and 0.45 mg/kg of diazepam and 2, 4, 6 and 8 hr after injection with 0.15 mg/kg of diazepam. 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.

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TABLE I. Characteristics of the test groups and the injected drug doses. The values are means ± SD.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of volunteers</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 mg/kg</td>
<td>12</td>
<td>24±1.6</td>
<td>69±5.4</td>
<td>176±5.7</td>
</tr>
<tr>
<td>0.30 mg/kg</td>
<td>11</td>
<td>22±5.1</td>
<td>68±12.1</td>
<td>179±9.1</td>
</tr>
<tr>
<td>0.45 mg/kg</td>
<td>11</td>
<td>21±2.3</td>
<td>67±8.3</td>
<td>176±6.8</td>
</tr>
</tbody>
</table>

Food and drink were not allowed for 8 hr before the injection and for 2 hr after 0.15 mg/kg and 0.30 mg/kg and for 4 hr after 0.45 mg/kg of diazepam. Coffee, tea, cola and tobacco were not allowed during the experiment.

Clinical observations and subjective assessments.
Clinical recovery was measured by recording the time until a negative Romberg's sign appeared. The depth of sedation was assessed by recording the degree of drooping of the upper eyelid. If ptosis occurred to the extent of covering half 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 after the injection.

At every test period each subject was asked to report if he (or she) felt tired, drowsy, had vertigo or an unsteady gait. He was asked also whether or not he thought he could drive as safely as usual and whether the feeling of sedation had been pleasant.

Test equipment.
Reactive skills. A choice reaction test was used to record cumulative reaction times and the number of mistakes when reacting to different light and sound stimuli.

Co-ordinative skills. Two co-ordination tests were used to measure the number of mistakes and the mistake percentage when the subjects were required to keep a black ball inside an illuminated track by turning a steering wheel. Driving time was recorded in co-ordination test II, which was driven at a free speed (Linnoila and Mattila, 1972a).

Attention. Divided attention was measured by means of an attention test, the variables recorded being the total number of responses and the number of correct responses on dials situated in the central and peripheral field of vision (Linnoila, 1973a).

Previously, we have described in detail the tests for reaction, co-ordination and attention (Korttila and Linnoila, 1974).

Critical flicker fusion frequency. 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 a light 90 cm away stopped flickering.

Proprioception. In order to measure proprioception of the hand, before the experiment, the subjects were taught to turn an accelerator grip of a motorcycle 30 degrees. Proprioception of the foot was measured when the subjects pressed an acceleration pedal of a car 5 cm. This activity was also taught to the subjects before the trial. In the test situation the subjects were asked to do the same tasks as during the training period, but without visual control, and the deviation was recorded in degrees or centimetres, respectively.

Drug concentrations in serum.
Venous blood samples were drawn from the right cubital vein after each test period. Sera were stored at $-22^\circ$C until serum diazepam and N-desmethyldiazepam concentrations were assayed by electron-capture gas liquid chromatography according to the method of Zingales (1973). The recovery for diazepam was 98% and that for N-desmethyldiazepam 100%.

Additivity of the results and within-cell variances were checked, and thereafter the two-way analysis of variance and Student's $t$ test were used for statistical treatment of the data.

RESULTS
Clinical observations and subjective assessments.
The incidence of positive Verril's sign and amnesia for pinching the abdomen was high with 0.30 and 0.45 mg/kg of diazepam (fig. 1). The time until the negative Romberg's sign appeared was significantly ($P<0.001$) shorter after 0.15 mg/kg than after 0.30 or 0.45 mg/kg of diazepam and the time with 0.30 and 0.45 mg/kg was the same (table II).

Pain in the arm during the injection was quite common (18–45%) with each dose of diazepam. At 4 hr vertigo or an unsteady gait were reported by 9% and 36% of the volunteers injected with 0.30 and 0.45 mg/kg respectively. At 6 hr the respective figure was only 18% of the volunteers injected with 0.45 mg/kg of diazepam (table II). After the greatest dose of diazepam, tiredness and
RECOVERY AND DRIVING SKILLS AFTER I.V. DIAZEPAM

FIG. 1. The percentage of volunteers developing positive Verrill's sign and of those not remembering the pinching of the abdomen after an i.v. injection of three doses of diazepam.

TABLE II. Clinical observations and some of the subjective assessments of the volunteers.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Diazepam (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of volunteers reporting pain in arm</td>
<td>0.15  0.30  0.45</td>
</tr>
<tr>
<td>during the injection (%)</td>
<td>25    45   18</td>
</tr>
<tr>
<td>Percentage of volunteers regarding the sedation</td>
<td>0.15  0.30  0.45</td>
</tr>
<tr>
<td>as pleasant (%)</td>
<td>50    55   64</td>
</tr>
<tr>
<td>Percentage of volunteers reporting vertigo or</td>
<td>0.15  0.30  0.45</td>
</tr>
<tr>
<td>an unsteady gait (%)</td>
<td>9     36   18</td>
</tr>
<tr>
<td>at 4 hr</td>
<td></td>
</tr>
<tr>
<td>at 6 hr</td>
<td></td>
</tr>
<tr>
<td>Time until the appearance of negative Romberg's</td>
<td>16±2.3* 36±8.9 36±8.3</td>
</tr>
<tr>
<td>sign (min)</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001: 0.30 v. 0.45 mg/kg.

drowsiness were common (fig. 2), and similarly the volunteer's opinion of his driving ability as poor persisted up to 4 hr after the injection (fig. 3).

Test performances.
Reactive skills. The cumulative reaction times increased significantly (P<0.05) up to 2 hr after 0.15 mg/kg and up to 4 hr after 0.45 mg/kg of diazepam (fig. 4). At 4 hr the reaction times after 0.45 mg/kg were significantly (P<0.05) longer than after 0.15 mg/kg of diazepam. The number of mistakes did not significantly increase over the preinjection values. The results at 4 hr were, how-

FIG. 2. The percentage of volunteers reporting tiredness or drowsiness after an i.v. injection of 0.15 mg/kg (○○), 0.30 mg/kg (●●) and 0.45 mg/kg (■■) of diazepam.

FIG. 3. The volunteers' opinion of their driving ability. The percentage of volunteers reporting normal driving ability as a function of time after an i.v. injection of 0.15 mg/kg (○○), 0.30 mg/kg (●●) and 0.45 mg/kg (■■) of diazepam.

FIG. 4. The change in cumulative reaction times in the choice reaction test after an i.v. injection of 0.15 mg/kg (○○), 0.30 mg/kg (●●) and 0.45 mg/kg (■■) of diazepam. *P<0.05 as compared with the values before injection.
ever, significantly ($P<0.05$) worse after 0.45 mg/kg than after 0.15 mg/kg of diazepam.

**Co-ordinative skills.** Every dose of diazepam significantly modified the number of mistakes as compared with the preinjection results of co-ordination test I. The number of mistakes in this test was significantly ($P<0.05$) increased up to 2, 6 and 8 hr after 0.15, 0.30 and 0.45 mg/kg of diazepam respectively (fig. 5). The performance did not return to the preinjection status until 6 hr after 0.15 mg/kg and until 10 hr after 0.30 mg/kg and 0.45 mg/kg of diazepam. The performance after 0.45 mg/kg of diazepam at 6 hr was significantly ($P<0.05$) worse than after 0.15 mg/kg and at 8 hr significantly ($P<0.05$) worse than after both of the smaller doses. The mistake percentage in co-ordination test I and all the parameters measured in co-ordination test II did not change significantly.

**Attention.** The measurements in the attention test did not change significantly as compared with the preinjection values. However, the total number of correct responses on the peripheral dials was significantly ($P<0.05$) smaller at 4 and 6 hr after 0.45 mg/kg than after 0.15 mg/kg of diazepam.

**Critical flicker fusion frequency.** Critical flicker fusion frequency decreased significantly up to 4 and 6 hr after 0.45 mg/kg and 0.30 mg/kg of diazepam respectively as compared with the preinjection values. The ability to discriminate a flickering light after 0.30 mg/kg of diazepam was similar to that after 0.45 mg/kg and significantly worse at 4, 6 and 8 hr than after 0.15 mg/kg of diazepam (fig. 6).

**Drug concentrations in serum.**

The highest mean concentrations of diazepam were measured at 4 hr after 0.15 and 0.30 mg/kg of diazepam and at 6 hr after 0.45 mg/kg of diazepam. The highest concentrations were the first measurements after the volunteers had eaten, and after these peaks the concentrations of diazepam decreased as a function of time but were still high at 8 and 10 hr (table III). The concentrations of the main metabolite of diazepam, N-desmethyl-diazepam, increased with each dose steadily throughout the experiment. With each dose of diazepam there were variations between individuals of up to 80% in serum concentrations of diazepam and up to 150% in serum concentrations of N-desmethyldiazepam.

**DISCUSSION**

**Doses of diazepam.**

The doses were based on those previously reported in the literature. A 0.15 mg/kg dose of diazepam should be sufficient for cardiac catheterizations (Dalen et al., 1969) and for some dental procedures (Dixon et al., 1973); 0.30 mg/kg should be sufficient for dentistry and minor surgery (Dixon et al., 1973; Keilty and Blackwood, 1969); and 0.45 mg/kg has been used in outpatient anaesthesia for endoscopy (Rao et al., 1973), and in the induction of anaesthesia (Brown and Dundee, 1968; Fox, Wynards and Bhambhami, 1968).
Table III. Serum concentrations of diazepam and N-desmethyldiazepam after i.v. administration of 0.15 mg/kg, 0.30 mg/kg and 0.45 mg/kg of diazepam. The values are means±SD of the volunteers. Asterisks denote first measurement after the volunteers had eaten food.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Drug measured</th>
<th>Drug concentration in serum (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 hr</td>
</tr>
<tr>
<td>Diazepam</td>
<td>diazepam</td>
<td>165±33</td>
</tr>
<tr>
<td>0.15 mg/kg</td>
<td>N-desmethyldiazepam</td>
<td>16±2</td>
</tr>
<tr>
<td>0.30 mg/kg</td>
<td>diazepam</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>N-desmethyldiazepam</td>
<td>—</td>
</tr>
<tr>
<td>0.45 mg/kg</td>
<td>diazepam</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>N-desmethyldiazepam</td>
<td>—</td>
</tr>
</tbody>
</table>

**Trial design.**

Testing was omitted at 2 hr after the injection with doses 0.30 and 0.45 mg/kg because, according to previous reports, patients may be able to drive, at the earliest, only 4 hr after i.v. sedation with diazepam. For obvious reasons it was not desirable to repeat the anaesthesia, and since diazepam may induce its own metabolism (Kanto et al., 1974), the study was not done in a cross-over fashion. Likewise a placebo group was omitted in order to maintain the double-blind design. Despite training on the apparatus many subjects showed improved performances on co-ordination and attention tests at 8 and 10 hr as compared with pre-injection values.

**Tests used.**

The tests have been discussed previously and found to be suitable for the investigation of drug effects on psychomotor skills (Linnoila and Mattila, 1972a; Linnoila, 1973a; Korttila and Linnoila, 1974). The results of the choice reaction, co-ordination, and attention tests have been demonstrated to correlate with real traffic behaviour (Ekland, 1970; Hukkanen, 1958).

If the value of the tests for measuring dose-response relationship with recovery after i.v. diazepam is considered, the attention test and the proprioception tests seemed to be under the sensitivity range of the effects of the diazepam doses used, the co-ordination and choice reaction tests were at the highest sensitivity range, and the flicker fusion test seemed to be over the sensitivity range when measuring the effects of diazepam.

**Effects of diazepam.**

**Amnesia.** Dundee and Pandit (1972) managed to produce anterograde amnesia for 50% and 90% of their patients with diazepam 5 and 10 mg i.v. respectively. In this study 0.30 and 0.45 mg/kg of diazepam were sufficient to produce amnesia for 90% of the subjects, but the smaller dose of 0.15 mg/kg caused amnesia in only 25%. However, all of the subjects injected with 0.15 mg/kg and most of the subjects injected with 0.30 mg/kg and 0.45 mg/kg of diazepam realized during the sedation that they were being pinched on the abdomen and reacted to it by moving their legs or hands. Injection time in this study was similar to that of Dundee and Pandit (1972), but the pinching in this study after 0.15 mg/kg of diazepam might have been performed slightly before the peak effect of amnesia (2-3 min) found by Dundee and Pandit, or it is easier to remember the pinching of the abdomen than it is to remember different pictures as used by Dundee and Pandit. Our finding that the duration of amnesia with the two greater doses was 15-20 min is in agreement with previous reports of Clarke and colleagues (1970) and Dundee and Pandit (1972). A diazepam dose of 0.15 mg/kg injected with pethidine (1 mg/kg) produced amnesia for 90% of the volunteers in another study (Korttila and Linnoila, 1974), and that result is greater than the 25% observed with 0.15 mg/kg of diazepam alone in this study.

**Subjective recovery.** The literature about subjective tiredness or drowsiness after i.v. diazepam is controversial. Baird and Hailey (1972) reported a recurrence of clinical sedation at 6 hr after injection in five volunteers who were given diazepam 20 mg and 60% of the volunteers who were given diazepam 0.36 mg/kg were tired at 24 hr after the injection. On the other hand, Brown and Dundee (1968) found that with a greater dose of diazepam (0.45 mg/kg) 30% felt dizzy at 24 hr after the injection. In this study the incidence of tiredness or drowsiness was about the same with the two smaller doses and only one subject (10%) injected
with 0.45 mg/kg of diazepam felt tired 10 hr or later after the injection. However, the performance of this subject on the tests at 10 hr was as good as before the injection.

Clinical recovery. Clinical recovery as assessed by Romberg's test, was 36 min with 0.30 and 0.45 mg/kg of diazepam in this study, while Baird and Hailey (1972) found 40% of their volunteers to have ataxia and a positive Romberg's test 1 hr after the injection of 20 mg of diazepam. Clinical tests of recovery have previously been reported to be unreliable in assessing patients' psychomotor skills (Linnoila and Mattila, 1972b).

Test performances. Grove-White and Kelman (1971) found the critical flicker fusion frequency after 0.05 mg/kg of diazepam to be depressed significantly 90 min after the i.v. injection, and Dixon and Thornton (1973) reported that 90 min after the injection the performance on their paper and pencil test was at the preinjection level for only 14% of the subjects given 0.12–0.32 mg/kg of diazepam i.v.

In this study the undesired effects of diazepam could be measured best by the choice reaction and co-ordination tests, the effects on flicker fusion were also significant, but attention and proprioception were not impaired. These findings agree with previous findings that benzodiazepines impair co-ordination especially (Korttila and Linnoila, 1974; Linnoila and Mattila, 1972a) and that the effects on attention are minimal or even positive when compared with the effects of a placebo (Linnoila and Mattila, 1972a). The harmful effects of 0.15 mg/kg of diazepam on test performances seemed to disappear after 6 hr.

When, in our previous study, 0.15 mg/kg of diazepam was given with pethidine (Korttila and Linnoila, 1974), the performance was still significantly impaired 6 hr after the injection, which suggests that pethidine delays recovery when given with the same dose of diazepam.

The effects of 0.45 mg/kg of diazepam did not last substantially longer than those after 0.30 mg/kg except in co-ordination test I, where performance was worse at 8 hr after 0.45 mg/kg than after diazepam 0.30 mg/kg. At 10 hr the results were similar with 0.30 and 0.45 mg/kg. One must remember that the results relate to young healthy volunteers and the effects of diazepam on ill and old persons may be more deleterious and more prolonged, as noticed previously when nitrazepam was given by mouth (Linnoila, 1973b).

Serum concentrations of diazepam.

With each dose of diazepam the serum concentrations of diazepam increased after taking food. This might be the result of the possible enterohepatic cycle of diazepam (Baird and Hailey, 1972; Korttila and Linnoila, 1974). Thus, although the increases were not statistically significant and the serum concentrations of diazepam did not correlate well with performance, fatty meals which can be expected to increase bile secretion should be avoided after sedation with diazepam.

Pethidine seems not to alter the metabolism of diazepam, since the serum concentrations of diazepam with 0.15 mg/kg in this study were similar to those when diazepam was injected with pethidine in our previous study (Korttila and Linnoila, 1974).

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LE RETABLISSEMENT ET LES ATTITUDES EN MATIERE DE CONDUITE APRES SEDATION INTRAVEINEUSE: LE RAPPORT DOSE/REACTION AVEC LE DIAZEPAM

RESUME
Les aptitudes liées à la conduite, la faculté de distinguer la fusion de la lumière qui clignote, et la proprioception des pieds et des mains, ont fait l’objet de mesures à double-cache chez 34 volontaires en bonne santé avant et après trois doses de diazepam par intraveineuse. Les effets du diazepam étaient extrêmement nuisibles à la coordination. Avec 0,15 mg/kg, 0,30 mg/kg et 0,45 mg/kg de diazepam, les facultés de coordination étaient affectées de manière significativement (P<0,05) pendant 2, 6 et 8 h respectivement. Aucune altération de la performance lors d’un essai quelconque n’était mesurable à 6 h après 0,15 mg/kg ou à 10 h après 0,30 ou 0,45 mg/kg de diazepam. On notait des variations importantes entre les individus quant à la concentration sérique de diazepam à chaque niveau de dosage. Les augmentations de la concentration sérique de diazepam après l’absorption d’aliments confirme le concept d’un cycle entéro-hépatique pour le diazepam. On peut conclure que les patients ne devraient pas conduire ni faire marcher de machines pendant au moins 6 h après l’injection intraveineuse de diazepam à 0,15 mg/kg et pendant au moins 10 h après des doses de 0,30 mg/kg et de 0,45 mg/kg.

ERHOLUNG UND FAHREREIGENSCHAFTEN NACH INTRAVENÖSER VERABREICHUNG VON BERUHIGUNGSMITTEL: DOSIS-REAKTION-VERHALTNIS BIEI DIAZEPAM

ZUSAMMENFASSUNG
Fahrereigenschaften, die Fähigkeit zur Wahrnehmung flackernder Lichter und körperlicher Reize von Hand und Fuß wurden mit einer Doppelblind-Methode bei 34 gesunden Personen vor und nach Verabreichung von 3 Dosen Diazepam intravenös gemessen. Die Drogeneinwirkungen waren besonders schädlich für die Koordination. Bei Dosen von 0,15, 0,30 und 0,45 mg/kg wurde die Beeinträchtigung der Koordinationsfähigkeit statistisch bedeutsam (P<0,05) bis zu 2, 6, bzw. 8 h. Kein Leistungsabsinken konnte festgestellt werden nach 6 h bei 0,15 mg/kg oder nach 10 h bei 0,30 oder 0,45 mg/kg Diazepam. Innerhalb jeder Dosis kam es zwischen-individuell zu großen Schwankungen der Serumkonzentrationen von Diazepam, und der Anstieg der Serumkonzentrationen nach Nahrungsaufnahme unterstützt das Konzept eines enterohepatischen Zykels für Diazepam. Patienten sollten daher wenigstens 6 h nach 0,15 mg/kg und wenigstens 10 h nach 0,30 und 0,45 mg/kg Diazepam kein Kraftfahrzeug lenken und keine Maschinen bedienen.

RECUERACION Y CONOCIMIENTOS PRACTICOS RELATADOS PARA APLICAR DESPUES SEDACION INTRAVENOSA: RELACION DOSIS-RESPUESTA CON DIAZEPAM

SUMARIO
Se midieron los conocimientos relativados para dirección, la habilidad para discriminar la fusión de luz oscilante y la propriocepción de mano y pie, con blindaje doble en 34 voluntarios sanos antes y después de tres dosis de diazepam i.v. Los efectos del diazepam fueron los más perjudiciales para la coordinación. Con 0,15, 0,30 y 0,45 mg/kg de diazepam se deterioró de los conocimientos prácticos coordinativos que estaban estadísticamente significativos (P=0,005) hasta 2, 6 y 8 hr como máximo respectivamente. No se encontró ningún deterioro de la ejecución de cualquier prueba 6 hr después de 0,15 mg/kg o 10 hr después de 0,30 o 0,45 mg/kg de diazepam. Existieron grandes variaciones interindividuales en las concentraciones de diazepam en el suero dentro de cada nivel de dosis. Los aumentos de las concentraciones de diazepam del suero después de ingerir alimentos sostienen el concepto de un ciclo entero-hepático para el diazepam. Se concluyó que los pacientes no debían de conducir o hacer funcionar máquinas por al menos 6 horas después de 0,15 mg/kg de diazepam i.v. y al menos 10 hr después de 0,30 y 0,45 mg/kg.