CLINICAL STUDIES OF INDUCTION AGENTS

XXV: DIAZEPAM

BY

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SUMMARY

Diazepam has been studied as an intravenous induction agent in intermittent and single doses. There is a delay of about 1 minute in onset of the soporific effect, and a great individual variation in response to the drug. Even with doses up to 0.8 mg/kg it was not possible to guarantee induction of anaesthesia. There was a remarkable absence of cardiovascular or other side effects, even from very large doses, and amnesia was also an outstanding feature. The eventual place of diazepam in anaesthesia will not be as a competitor with established induction agents.

For many years barbiturates have had almost unchallenged supremacy in the field of intravenous anaesthesia, apart from some interest in a steroid (hydroxydione) and a phenoxyacetic amine (propanidid). More recently continental workers (Camplan and Espagno, 1964; Stovner and Endresen, 1966) have suggested that diazepam (Valium) might be useful in this field.

Although the most popular use of diazepam in the field of anaesthesia is as a premedicant (Marrubini and Tretola, 1965; Cormier et al., 1966) it has been given intravenously with success to produce basal narcosis in volunteers (Touchard, 1965) and for cardioversion (Nutter and Masmum, 1965; Kernohan, 1966) as well as for induction of anaesthesia (McClish, 1966). Bruce (1966) described its use during anaesthesia, commenting favourably on the associated postoperative analgesia.

However, it was not always clear whether the above workers intended to use diazepam to produce basal narcosis or anaesthesia as with conventional induction agents. This study was carried out to investigate the latter use.

A pilot study in about twenty patients confirmed the findings of others, that there is a delay of 30–60 seconds in the onset of the soporific action of recommended doses of diazepam. Accordingly the investigation was divided into two parts: intermittent injection to try to establish an approximate anaesthetic dosage range and to study the toxic effects of large doses, and a single induction dose study at two dose levels.

INTERMITTENT INJECTION

This was carried out in twenty fit adult subjects in the immediate pre-operative period before the onset of surgery or the administration of any other

Diazepam (7-chloro-1-methyl-5-phenyl-3H-1, 4-benzodiazepin-2(1H)-one), a benzodiazepine tranquillizer (fig. 1), is chemically similar to chlordiazepoxide (Librium), being a colourless crystalline compound insoluble in water. The commercially available solution is slightly yellowish in colour, more viscid than aqueous solutions and supplied in ampoules containing 5 mg/ml; the approximate pH is 6.8 at 20°C.
agents. Irrespective of body weight, an initial dose of 15 mg was followed by 5 mg at either 2- or 3-minute time intervals to a total of 35-60 mg. In the majority of cases the drug was diluted to 2 mg/ml with water. Half the patients in each series were premedicated with pethidine 75 mg and atropine 0.6 mg, while the remainder received atropine alone. A continuous electrocardiogram tracing was taken and arterial blood pressure was monitored by auscultation at 1-minute intervals, at which time the depth of sleep was assessed according to an appropriate numerical scale (table I). Algesimetry readings were made on a few patients premedicated with atropine, using the tibial pressure technique of Dundee and Moore (1960).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slight drowsiness.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate drowsiness.</td>
</tr>
<tr>
<td>3</td>
<td>Extremely drowsy but easily roused.</td>
</tr>
<tr>
<td>4</td>
<td>Sleep.</td>
</tr>
</tbody>
</table>

There was great individual variation in the response to diazepam, which is illustrated in figure 2. Pethidine appeared to increase its efficacy but, even with this premedication, in some patients a total of 40 mg did not produce sleep. With atropine only the effect of the initial 15 mg was often just maintained by 5-mg doses given at 3-minute intervals. The onset of drowsiness and sleep was very smooth in all patients and restlessness, coughing, hiccough, extraneous muscle movements or obvious respiratory depression were not seen. Even the most apprehensive patients became calm after the initial dose, although there was some tendency to increased talkativeness before the onset of sleep. The subsequent transfer to volatile and gaseous anaesthesia (nitrous oxide-oxygen, halothane or trichloroethylene) was always smooth and uneventful. Such agents were always needed for even minor surgical procedures.

![Fig. 2](image1.png)

Serial histograms showing depth of sleep with intermittent doses of diazepam. Each block represents an individual case.

Open columns Atropine premedication.
Stippled columns Pethidine premedication.

![Fig. 3](image2.png)

Typical blood pressure and pulse rate records during intermittent injections of diazepam. Depth of sleep recorded as in table I.

- Stippled bar Nitrous oxide/oxygen.
- H Halothane 1 per cent.
- X X Limits of surgery.

This technique is not suitable for the intravenous induction of anaesthesia but may have a place in production of basal narcosis. It did, however, show the complete lack of the obvious cardiovascular effects of large doses of diazepam. No irregularities were detected by the electrocardiogram and hypotension or tachycardia did not occur in any of the twenty patients. Figure 3 shows a typical blood pressure response following injection of a total of 50 mg. It should be noted that even this dose did not obtund the stimulant effect of subsequent surgery on blood pressure.
Only a moderate degree of analgesia was found during intermittent diazepam, figure 4 illustrating a typical result. However, there was no evidence of antanalgesia with any dose.

**FIG. 4**
Typical algometer readings and depth of sleep following intermittent doses of diazepam. Algesimetry readings refer to pressure applied to anterior surface of tibia when pain became intolerable.

On questioning later, all patients were quite pleased with the induction of anaesthesia; few remembered anything following the initial injection and there were no unpleasant subjective side effects.

**SINGLE INJECTION**
The above study showed the feasibility of using single doses of 35 and 50 mg. Each was given to twenty patients scheduled for minor gynaecological procedures and followed by nitrous oxide-oxygen, with trichloroethylene as required. Premedication was as in the previous series. Observations were similar to those recorded in previous investigations of intravenous anaesthetics (Dundee, Moore and Nicholl, 1962).

In this study diazepam was given undiluted into large forearm veins and through these no other drugs were injected. A tourniquet was not applied to the arm so as to make the findings, with respect to venous sequelae, comparable to those of Hewitt and colleagues (1966). In addition to the usual 6-hour follow up for emetic sequelae, patients were visited again on the second postoperative day and venous sequelae (thrombosis/phlebitis) looked for. Serum bilirubin, cholinesterase and transaminase levels were estimated before, and 24 hours after anaesthesia in twenty-three patients (fourteen receiving 35 mg, nine receiving 50 mg), as tests of liver function.

The important findings are shown in table II, which also includes a comparison with data obtained under similar circumstances using thio-pentone or methohexitone (Dundee, 1963). Even with these large doses of diazepam, sleep was not invariably induced although subsequent anaesthesia was smooth. Induction complications (irrespective of whether sleep was induced or not) were much fewer than in the corresponding barbiturate series. However, in comparison with these,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diazepam</th>
<th>Thio-pentone</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 mg</td>
<td>50 mg</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>Number of cases</td>
<td>20</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>Sleep not induced in 1 minute</td>
<td>40</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Induction complications:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory phenomena</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory upset</td>
<td>0</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Recovery:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsafe 2 minutes after end of anaesthesia</td>
<td>50</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Sequele:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emetic—first 6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Dizziness persisting for 24 hours post-op</td>
<td>15</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>
recovery from sleep was very prolonged. The persistence of dizziness for 24 hours in 30 per cent of patients was a complication never found with barbiturates.

Three patients with each dose complained of pain during injection of the undiluted drug, a figure identical with that found with the diluted preparation. Three of those who were given 35 mg developed localized venous thrombosis while this complication was found in six who had 50 mg.

The results of the liver function study are summarized in table III, from which it can be seen that hepatic dysfunction was not demonstrated.

**COMBINED DATA**

To clarify the dosage scheme required for induction of anaesthesia with diazepam, a dose response curve has been constructed from all the above results (fig. 5).

This shows that induction of anaesthesia may result from administration of a dose of 0.2 mg/kg in patients premedicated with an opiate, and from a dose of 0.45 mg/kg following premedication with atropine alone, but a minimum dose of 0.8 mg/kg is required to be reasonably certain of inducing anaesthesia irrespective of the premedication given.

Postoperative visits to the patients revealed a noteworthy feature of the use of diazepam. It was found that in all groups consistently complete amnesia occurred from the time of injection, regardless of the depth of sleep achieved by the initial dose. Even when there was an apparent failure of a given dose to induce anaesthesia, patients had no memory of the application of the facepiece.

**DISCUSSION**

In order to obtain maximum flexibility of dosage, it is expected that an intravenous anaesthetic will induce sleep in one arm-brain circulation time. There is a greater risk of overdosage with a drug which has a delayed onset of action, and minute-to-minute control of the depth of anaesthesia is difficult with such a preparation. This limits the use of diazepam to the single injection of a predetermined dose for induction of sleep. Despite its lack of toxicity it would not appear to be the ideal drug for use in patients with a full stomach or in obstetric anaesthesia.

Normal therapeutic doses of thiopentone, methohexitone, or similar barbiturates or thio-barbiturates, and more especially propanidid, are followed by a rapid recovery with minimal residual effects in the postoperative period. This certainly does not apply to those doses of diazepam which are required in order to be fairly certain of inducing sleep. For this reason diazepam cannot be recommended for use in out-

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**Table III**

Liver function tests taken immediately before, and 24 hours after intravenous diazepam.

<table>
<thead>
<tr>
<th></th>
<th>Pre-operation</th>
<th>Post-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Serum bilirubin (mg/100 ml)</td>
<td>0.6</td>
<td>0.3–1.0</td>
</tr>
<tr>
<td>Serum pseudocholinesterase (units)</td>
<td>74.9</td>
<td>52–110</td>
</tr>
<tr>
<td>Transaminase:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s.g.o.t. (units)</td>
<td>19.2</td>
<td>11–26</td>
</tr>
<tr>
<td>s.g.p.t. (units)</td>
<td>16.6</td>
<td>7–54</td>
</tr>
</tbody>
</table>
patient procedures, and would seem to be of minimal value for minor in-patient procedures.

Although in this study sleep was not induced in every patient, it is noteworthy that none had any memory of events following the initial intravenous injection. This amnesic action should be explored further. It suggests that doses much smaller than those required to induce anaesthesia could be used. This might be valuable in poor-risk subjects in view of the noticeable lack of side effects, and it may have a particular place in cardiac patients (McClish, 1966) or in those with multiple trauma (Blondeau, 1965; Cushman, 1966) as well as in cardioversion (Nutter and Massumi, 1965; Kernohan, 1966). As suggested by others, it could be useful in neuroleptanaesthesia (Richter, 1966) or for supplementation of local anaesthetic techniques (Huguenard and Margelidon, 1964) where the amnesic effect would be particularly useful.

Hydroxydione (Viadril, Presuren) is the only other intravenous anaesthetic, with a delayed onset of action, which is in current clinical use. Compared with this drug the onset of the soporific action of diazepam is much quicker. It is more important that the continuing respiratory and cardiovascular depression, which often does not reach its maximum until 15–20 minutes after injection of hydroxydione, is not seen with diazepam. Like hydroxydione, diazepam has an irritant effect on veins, but in this case it is probably due to the solvent, rather than the active drug.

REFERENCES


ETUDES CLINIQUES D'AGENTS D'INDUCTION. XXV: DIAZEPAM

SOMMAIRE
Diazepam a été étudié comme agent intraveineux d'induction, en doses intermittentes et uniques. Il se manifeste un délai d'environ une minute jusqu'au début de l'effet soporifique, ainsi qu'une grande diversité individuelle des réactions au médicament. Même à des doses atteignant 0,8 mg/kg, il fut impossible de garantir l'induction de l'anesthésie. Il y eut une absence remarquable d'effets secondaires cardiovasculaires et autres, même à une posologie élevée, et l'amnésie constituait une caractéristique primordiale. Diazepam ne trouvera pas sa place en anesthésie, en concurrence aux agents d'induction reconnus.

KLINISCHE UNTERSUCHUNGEN VON MEDIKAMENTEN ZUR NARKOSEEINLEITUNG. XXV: DIAZEPAM

ZUSAMMENFASSUNG
Als Medikament zur Narkoseeinleitung wurde Diazepam untersucht, wobei es intravenöse intermittierend und in Einzelgaben verabreicht wurde. Die einschläfernde Wirkung trat mit einer Verzögerung von etwa einer Minute nach der Injektion ein. Dabei ergab sich bezüglich des Ansprechens auf das Mittel eine große individuelle Variationsbreite. Auch mit Gaben bis zu 0,8 mg/kg war es nicht möglich, die Einleitung der Narkose zu gewährleisten. Bemerkenswert war, daß kardiovaskuläre oder andere Nebenwirkungen sogar bei sehr hohen Dosen ausblieben. Ein herausragendes Merkmal war die Amnesie, der dem Diazepam bei der Narkose möglicherweise zukommende Platz soll nicht darin zu sehen sein, daß dieses Mittel als Konkurrenz für bereits vorhandene Medikamente zur Narkoseeinleitung auftritt.