STUDIES OF DRUGS GIVEN BEFORE ANAESTHESIA
XIV: TWO BENZODIAZEPINE DERIVATIVES—CHLORDIAZEPOXIDE AND DIAZEPAM

BY
W. H. K. HASLETT AND J. W. DUNDEE

SUMMARY
Two benzodiazepine tranquillizers, chlordiazepoxide (50 and 100 mg) and diazepam (10 and 20 mg) were studied under standard conditions in females, as single-dose premedicants before a standard operation. The findings were compared with those obtained using saline and with previously reported data using opiates and phenothiazine derivatives. The claims that these drugs are capable of allaying pre-operative apprehension were fully substantiated and chlordiazepoxide 100 mg achieved this with very little soporific effect. The action of these drugs was as good as that of most opiates and side effects were much fewer. The eventual place for them may be for use as a "pre-preanaesthetic-medication" given by mouth on the day before operation.

Opiates have been the drugs of choice for sedative premedication in adults in this country for many years, although a few anaesthetists show a preference for the phenothiazine derivatives. Barbitalates, which are favoured in America (Eckenhoff and Helrich, 1958), have achieved little popularity in adults and are not commercially available in solution for parenteral injection. The classical approach, of a single pre-operative injection, has been challenged by Brandt, Lui and Briggs (1962) and by Inglis and Barrow (1965) who suggested the oral use of a benzodiazepine (chlordiazepoxide) for at least one day before operation. Another similar drug (diazepam) has been used with encouraging results either as a conventional form of premedication (Tornetta, 1965; Thuries and Poncet, 1964), before neuroleptanaesthesia (Du Cailar et al., 1964) or by mouth for one or more days before and on the morning of operation (Bruha, 1964; Dowell, 1966).

All workers claim that both preparations are particularly valuable in allaying apprehension. However, a number of other drugs were often given concurrently, the conditions of study varied greatly and different criteria were used in assessing results. Thus it was not possible, from published reports, to be certain that these benzodiazepine derivatives had any real advantages over opiates, when they were used under strictly comparable circumstances. This paper reports a study in which 50 and 100 mg chlordiazepoxide (Librium) and 10 and 20 mg diazepam (Valium) were given as sole premedication to a standard patient population undergoing a standard operative procedure in constant surroundings. The findings are compared with those obtained when an inert substance (saline) was given and with the findings in directly comparable reported studies with opiates and phenothiazine derivatives.

BENZODIAZEPINE DERIVATIVES
The formulae of four benzodiazepine derivatives in current clinical use are shown in figure 1. Apart from nitrazepam (Mogadon) which is recommended as a hypnotic, the other preparations are used as tranquillizers.
Chlordiazepoxide is a colourless crystalline substance highly soluble in water but unstable in solution. It is made up freshly for intramuscular injection by adding 2 ml of a special solvent to 100 mg powder. Diazepam is insoluble in water and is commercially available in ampoules containing 10 mg in 2 ml, made up with an organic solvent. Both drugs must be protected from light.

Randall (1960) found that chlordiazepoxide has sedative and muscle relaxant effects in mice, depressive effects on spontaneous movement in normal rats and calming effects in rats made irritable by brain lesions. Randall and associates (1961) showed that whilst diazepam has an action qualitatively similar to that of chlordiazepoxide, it is five times as potent as a tranquillizer and muscle relaxant. Their tranquillizing effects are thought to be due to an action on the amygdala, being that part of the limbic system which is the relay area for the expression of the emotions. Muscle relaxation is due to a central effect rather than a curare-like action at the periphery (Rushworth, 1965). An analgesic action has not been demonstrated for either drug (Haslett, 1967) and clinical doses of diazepam have no demonstrable anti-emetie effect in man (Jorgensen, 1964; McLeod, 1966), although opinions differ as to the action of chlordiazepoxide in this respect (Lamphier et al., 1962; Corey, Deaver and Haupt, 1962). In contrast with the phenothiazine derivatives, oculogyric crises have not been reported after large doses of these tranquillizers.

Clinical doses of both the benzodiazepine derivatives have negligible effects on the cardiovascular system (Coppolino and Wallace, 1961; Tornetta, 1963, 1965; Brown and Dundee, 1968), while neither significantly depresses the response to endogenous carbon dioxide (Sadove, Balagot and McGrath, 1965; Steen et al., 1966).

The 100-mg dose of chlordiazepoxide used in the present study is higher than that given by other workers except Tornetta (1963) and was given in view of the apparent ineffectiveness of 50 mg. The injectable form of diazepam has been used in premedication in doses as high as 30 mg (Thuries and Poncet, 1964), but the 10–20 mg studied here have been more widely employed.

### METHODS

These have been described in detail elsewhere (Dundee, Moore and Nicholl, 1962a, b) and only the relevant data will be summarized here. The drugs under study were given by intramuscular injection as routine premedication at least 90 minutes before induction of anaesthesia to fit women of the reproductive age group, from the same hospital unit, who were scheduled for minor gynaecological operations. They were not told that they were participating in a clinical trial. Except in the case of chlordiazepoxide, which had to be mixed freshly with the solvent provided, a double blind technique was employed throughout (using specially prepared ampoules containing 20 mg diazepam in 2 ml) and this study was run concurrently with similar continuing investigations of opiates, opiate antagonists, anti-emetics and other related drugs.

Half of each series of patients were visited 20, 40, 60 and 90 minutes after drug administration while the remainder were seen once at 90 minutes. During these visits the sedative and toxic effects of the drugs were assessed according to predetermined criteria. Their overall desired side effects were scored on a linear scale. The efficacy scores ranged from 5 (ideal premedication) to 1 (ineffective) while toxic scores ranged from 1 (no side effects) to 5 (very severe). Both the distribution and average scores are presented.

A standard form of anaesthesia consisted of methohexitone-nitrous-oxide-oxygen and the incidence of various complications during anaesthesia was noted, as well as the incidence of emetic effects during the first 6 postoperative hours (Dundee, Nicholl and Moore, 1962).

### RESULTS

The important pre-operative findings are summarized in table I, which also shows that all series were broadly comparable with respect to average ages and weights of the patients.

It is interesting to note that saline produced the expected placebo effect whereby 20–30 per cent of patients had a notable (good and fair) degree of drowsiness. Approximately two-thirds of the patients did not appear to be apprehensive when given an inert preparation.

The effects of chlordiazepoxide 50 mg were not significantly different from those of the placebo.
in any respect apart from the persistence of pain at injection site. Chlordiazepoxide 100 mg caused a highly significant (P<0.0005) reduction in apprehension as compared with saline though this was accompanied by only a moderate increase in the frequency and intensity of drowsiness.

In contrast, both doses of diazepam caused a notable degree of drowsiness in two-thirds of the patients and was much more soporific than chlordiazepoxide 100 mg. Although diazepam caused a significant reduction in apprehension as compared with saline (P<0.025), this effect was not as marked with the 10-mg dose as with 100 mg of chlordiazepoxide but was very obvious with the 20-mg dose of diazepam. Over all, chlordiazepoxide 100 mg appeared to be better in relieving apprehension and, in so doing, little drowsiness was produced.

Apart from persistent pain at the site of injection, neither drug showed a greater toxicity than did saline. Figure 2 suggests that the action of chlordiazepoxide, as judged by the onset of the soporific effect, came on more quickly than did that of diazepam.

Neither drug had an adverse effect on the course of anaesthesia (table II), nor was followed by a higher incidence of nausea and vomiting than the placebo.

In addition to the findings shown in these tables, the use of diazepam was occasionally followed by some logorrhoea, but this was short-lasting and never troublesome. Amnesia was a common finding after diazepam 20 mg, but its exact incidence and degree is not known because it was not sought for specifically until near the completion of the study. No comparable data are

### Table I
Comparison of the pre-operative effects (percentage incidence) of diazepam 10 mg and 20 mg, chlordiazepoxide 50 mg and 100 mg, with a placebo (saline) as observed 60-90 minutes after intramuscular injection in female patients.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Saline</th>
<th>Chlordiazepoxide</th>
<th>Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Average age</td>
<td>200</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td>Average weight (kg)</td>
<td></td>
<td>50</td>
<td>31</td>
</tr>
</tbody>
</table>

### Table II
Percentage incidence of induction complications, satisfactory inductions, and emetic sequelae.

<table>
<thead>
<tr>
<th></th>
<th>Exhitory phenomena</th>
<th>Respiratory upset</th>
<th>Satisfactory induction</th>
<th>Emetic sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>45</td>
<td>33</td>
<td>91</td>
<td>20</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>38</td>
<td>38</td>
<td>84</td>
<td>20</td>
</tr>
<tr>
<td>100 mg</td>
<td>38</td>
<td>39</td>
<td>93</td>
<td>16</td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>32</td>
<td>33</td>
<td>97</td>
<td>18</td>
</tr>
<tr>
<td>20 mg</td>
<td>41</td>
<td>45</td>
<td>96</td>
<td>13</td>
</tr>
</tbody>
</table>
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Fig. 2
Incidence of patients showing good and fair sedation expressed as a percentage of those showing this effect at 90 minutes.

- ○○○ chlordiazepoxide 50 mg
- ●●● chlordiazepoxide 100 mg
- ○○○ diazepam 10 mg
- ●●● diazepam 20 mg

Fig. 3
Percentage incidence of efficacy (desired effects) and toxic scores, with average scores.

<table>
<thead>
<tr>
<th>Desired effects</th>
<th>Toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid areas</td>
<td>average score 2.62</td>
</tr>
<tr>
<td>Stippled areas</td>
<td>2.64</td>
</tr>
<tr>
<td>Open areas</td>
<td>3.60</td>
</tr>
<tr>
<td></td>
<td>3.79</td>
</tr>
<tr>
<td></td>
<td>3.61</td>
</tr>
<tr>
<td></td>
<td>3.81</td>
</tr>
<tr>
<td></td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td>3.88</td>
</tr>
<tr>
<td></td>
<td>3.57</td>
</tr>
<tr>
<td></td>
<td>3.32</td>
</tr>
<tr>
<td></td>
<td>3.84</td>
</tr>
</tbody>
</table>

Desired effects
- =good (scores 4 and 5)
- =fair (score 3)
- =poor (scores 1 and 2)

Toxic effects
- severe (scores 4 and 5)
- slight (scores 2 and 3)
- nil (score 1)
available for diazepam 10 mg or either dose of chlordiazepoxide, but had it occurred frequently it would probably have been detected during the routine postoperative visit.

**COMPARISON WITH OTHER DRUGS**

The efficacy and toxic scores are used as means of an overall assessment of the action of chlordiazepoxide and diazepam in figure 3, which gives data obtained in comparable series with morphine 10 and 15 mg (Clarke, Dundee and Love, 1965), papaveretum 20 mg (Loan, Dundee and Clarke, 1966), pethidine 100 mg (Dundee, Moore and Clarke, 1964), promethazine 50 mg and promazine 50 mg (Dundee et al., 1965).

Chlordiazepoxide 100 mg and both doses of diazepam appear to be as good for premedication as morphine, pethidine or promazine, although not quite as good as papaveretum, and slightly better than promethazine. When the toxic effects are compared, chlordiazepoxide and diazepam are clearly superior to the other preparations. In this respect several drugs were particularly bad, especially pethidine 100 mg (high incidence of vomiting), promazine 50 mg (cardiovascular effects) and promethazine 50 mg (restlessness). Carrying this comparison into the postoperative phase (fig. 4) the undesirable effect of the opiates with regard to vomiting, retching and nausea can be seen. Both chlordiazepoxide and diazepam were followed by fewer emetic sequelae than the phenothiazines.

**DISCUSSION**

There is little doubt that the claims made with respect to the ability of 100 mg chlordiazepoxide and 10–20 mg diazepam to reduce pre-operative

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**FIG. 4**

Percentage incidence of postoperative emetic sequelae (1st 6 hours) after various premedicants.

Solid areas = vomiting, including retching. Stippled areas = nausea.

(When vomiting and nausea both occurred, vomiting only was recorded.)
apprehension have been confirmed in the present investigation and apply even to a single dose given 90 minutes before induction of anaesthesia.

The findings of Brandt, Lui and Briggs (1962), that 50 mg of chlordiazepoxide can adequately relieve apprehension, are at variance with the current observations. These workers gave to each patient a 50-mg dose on the night before operation as well as 2 hours before induction of anaesthesia, so that a critical dose of chlordiazepoxide may be required before this effect becomes obvious. Although much smaller single doses are recommended when the drug is used in the treatment of psychosomatic disease and anxiety associated with organic illnesses, treatment has usually been continued for several days before the maximum effect was observed (Fishbein and Jones, 1961; Rosenstein and Silverblatt, 1961; Fromhagen, 1963) so that a dose effect is not excluded. However, Cromwell (1962) and Moore (1962) found that very small daily doses (10-20 mg) were adequate in relieving anxiety associated with gynaecological conditions, but the "stress" here may not have been as severe as in the immediate pre-operative period.

In strictly comparable series of patients, the incidence of anxiety following effective doses of the benzodiazepine tranquilizers was less than that observed after pethidine 100 mg (Dundee, Moore and Clarke, 1964), morphine 10 and 15 mg (Clarke, Dundee and Love, 1965), diamorphine 5 and 7.5 mg (Dundee, Loan and Clarke, 1966) or papaveretum 20 mg (Loan, Dundee and Clarke, 1966). They were also superior to several phenothiazine derivatives (Dundee et al., 1965) and non-phenothiazine anti-emetics (Dundee et al., 1966). Workers from Loma Linda found that both chlordiazepoxide 50 mg and diazepam 20 mg were superior to pentobarbitone 100 mg in relieving pre-operative anxiety, when given under strictly comparable conditions (Brandt, Lui and Briggs, 1962; Brandt and Oakes, 1965). Apart from the work of Marrubini and Tretola (1965), who reported that diazepam 10 mg was superior to hydroxyzine 200 mg as a premedicant, a finding which could be partly due to its hypnotic effect, neither drug has been compared in detail with other tranquilizers.

The value of the hypnotic action of diazepam, as compared with the relatively non-soporific chlordiazepoxide, depends on the circumstances in which the drugs are used, but it would appear to be a useful property in patients scheduled for major surgery. The 20-mg dose has no advantage over 10 mg in this respect. In fairly comparable series of patients Tornetta (1963, 1965) also reported that more drowsiness occurred after 7.5-mg and 10-mg doses of diazepam than following 50-100-mg doses of chlordiazepoxide. In no patient in the present series did diazepam 20 mg result in an excessive hypnotic action as reported by Du Cailar and associates (1964); these workers gave the drug to patients of various ages and degrees of physical fitness and the authors specifically remarked that it is not to be recommended in young and robust patients because of its inadequate effect.

In a well-planned comparison of pethidine 100 mg and diazepam 20 mg, concerned with several facets of the action of premedicants, Cormier and associates (1966) found little difference between the two drugs, although diazepam had the advantage of causing less nausea and vomiting, as was found in the present study.

A number of workers have used diazepam for induction of anaesthesia (Stovner and Endresen, 1966; Touchard, 1965; McClish, 1966) or before cardioversion (Nutter and Massumi, 1965; Kernohan, 1966) and under these conditions amnesia was commonly noted. It is regretted that the present data is not more complete in this respect, since Tornetta (1965) found that over half the patients given diazepam 7.5-10 mg could not recall events taking place immediately before induction of anaesthesia, as compared with about one-quarter of a similar group of patients given pentobarbitone 100 mg. Huguenard and Margeidon (1964) commented on the "total amnesia" when 20 mg was given intravenously, but the subsequent use of chlorprothixene (Taractan) and dextromoramide (Palfium) by these workers makes it impossible to attribute this effect solely to the diazepam.

The findings in figures 3 and 4 show that both tranquilizers are useful premedicants and diazepam 10 mg would appear to be particularly worthy of further study. It has been suggested that its relaxing properties could be utilized in the treatment of disorders associated with muscle spasm or in fractures (Frasso, 1963; Brumagne,
1964). Others have used it alone (Rogers et al., 1965) or with pethidine (Ticktin and Trujillo, 1965) before endoscopy carried out under local anaesthesia, when its muscle-relaxant effects are a useful additive to its tranquillizing action. The calming effect would appear to be particularly useful in dental surgery, when combined with local anaesthesia (Peabody, 1965). However, care should be taken in giving it to ambulant patients in whom "buckling" of the knees and weakness of the legs has been reported (Bruha, 1964). This complication should be remembered when patients have received the drug for a day or so before operation or have been given their premedication before being fully prepared for surgery.

The present investigation deals only with the drugs given to a specific patient population and the findings may not be strictly transferable to other circumstances. However, the evolution of an effective, yet notably non-toxic premedicant which causes a negligible degree of respiratory depression or emesis, offers a challenge to those engaged in obstetric anaesthesia. The reports of Lecant and Cavanagh (1964) and Berger and Neuwiler (1962) suggest that diazepam might be particularly useful in this field. Its use before local anaesthesia (Jaquenoud, 1965) is another sphere where it may be superior to opiates or other currently available drugs. There would also appear to be little risk in giving effective doses to shocked patients, using the intravenous route (Blondeau, 1965).

If the present findings with either chlordiazepoxide or diazepam can be confirmed in other groups of patients with different pathological conditions, then anaesthetists will certainly have useful additions to their present range of premedicants. Of more importance is the fact that this study shows the undoubted safety of relatively large doses of both drugs when given by intramuscular injection. This should encourage those who wish to explore the newly evolved "pre-premedication" approaches as means of making surgery and anaesthesia less frightening experiences for their patients.

With respect to the pre-operative use of these drugs it should be noted that a single effective injection of diazepam costs about thirteen times that of morphine or pethidine, with chlordiazepoxide being approximately twice as expensive again. In contrast, promethazine and promazine are only about four times as expensive as the opiates. It may be anticipated that more widespread use of the tranquillizers, with their obvious advantages to patients, might reduce these differences.

ACKNOWLEDGEMENTS
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REFERENCES


hypnogène. L'activité de ces médicaments fut aussi prononcé que celle de la plupart des opiacés, et les effets secondaires furent moins fréquents. Ils peuvent éventuellement trouver une application comme "médication avant pré-anesthésie", administrés par voie orale le jour avant l'intervention chirurgicale.

ZUSAMMENFASSUNG

BOOK REVIEW


This book consists of the Proceedings of the First International Symposium on this subject which was held in Graz, Austria, in September 1966. It is divided into three almost equal parts; Part 1 deals with basic research, Part 2 with electrotherapeutic sleep, and Part 3 with electro-anesthesia.

Part 2 deals with the therapeutic applications of the electric currents used—frequency, strength, pulse width, etc. It would only be of interest to someone already deeply involved in this subject.

Part 3 deals with the therapeutic applications of electro-sleep and is therefore not readily open to assessment by an anaesthetist. The list of conditions said to benefit from electrotherapy include hypertension, neurasthenic heart disease, functional disorders, peptic ulcers, enuresis and neurodermatitis. The scarcity of controlled clinical trials in this section further adds to the difficulty of assessment.

After Parts 1 and 2, most anaesthetists will arrive at Part 3 on electro-anaesthesia with a feeling already deeply involved in this subject.

It would be wrong to close this review without mention of the most stimulating opening address by Professor G. Unger in which he deals with the responsibility thrown on man by his own invention—the computing machine. Professor Unger makes these machines ask the question: "Man, we can imitate your thinking; we can imitate your control mechanisms; we can excel you; we can, so to speak, 'Think too'. Man, who are you?"