COMPARISON OF TEMAZEPAM ELIXIR AND TRIMEPRAZINE SYRUP AS ORAL PREMEDICATION IN CHILDREN UNDERGOING TONSILLETOCYM AND ASSOCIATED PROCEDURES

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Although some anaesthetists believe that the presence of the mother is the most effective "premedication" for young children, the design of modern operating theatres makes this difficult. However, the premedication of children for elective inpatient surgery is an accepted anaesthetic practice (Doughty, 1957, 1962; Binning et al., 1962; Davies and Doughty, 1966; Haq and Dundee, 1968) and it is worthwhile seeking improvements in that practice—particularly since the variety of premedicant agents used by anaesthetists indicates that no one agent has a general advantage over another. The main advantage of the oral route of administration over the i.m. is that the child accepts a drink of a coloured, flavoured syrup more readily than an injection (Doughty, 1959); the main disadvantage is the possible variable timing, and the adequacy of the therapeutic effect as a result of the variable absorption of the drug from the gastrointestinal tract.

The trend of premedication away from basal narcosis to one of anxiolysis and sedation has led to the use of benzodiazepines such as diazepam, lorazepam and, more recently, temazepam (Norris, 1969; Dundee and Haslett, 1970; Galloon, Gale and Lancee, 1977; Amarasekara, 1980; Douglas et al., 1980; Beechey, Eltringham and Studd, 1981; Bradshaw, 1981). Phenothiazines have long been used in children (Binning et al., 1962; Davies and Doughty, 1966; Haq and Dundee, 1968) although, recently, benzodiazepines have also been investigated (Lindgren, Saarnivaara and Himberg, 1980; Furness, Boyle and Fee, 1986; Padfield, Twohig and Fraser, 1986).

SUMMARY

Temazepam 0.5, 1.0 and 1.5 mg kg⁻¹ in an elixir formulation (Euhypnos Elixir), was compared with trimeprazine tartrate 3 mg kg⁻¹ in a syrup (Vallergan Forte Syrup), as premedication in 220 children (ASA grade I) undergoing tonsillectomy and associated procedures. Each patient was randomly allocated to one of the four treatments. The administration was blind to the observers in theatre, recovery room and postoperative ward, who assessed each patient according to a total of 14 criteria. A modelling technique allowed account to be taken of the effects of concomitant variables (e.g. age and duration of anaesthesia) where appropriate. No statistically significant difference was found between the efficacy of the treatments. The only statistically significant differences were that temazepam was associated with more ectopic beats under anaesthesia (P = 0.03 or 0.002, depending on the test applied), more postoperative vomiting (P = 0.04) and more postoperative restlessness (P < 0.0001).


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The phenothiazine, trimeprazine tartrate, has been used widely as an oral premedication and investigated extensively. It has many merits: effective sedation, antialagogue activity and an antiemetic effect. However, it may cause undue postoperative pallor (Davies and Doughty, 1966) and some adverse cardiac responses have been reported in young children (Loan and Cuthbert, 1985).

Temazepam, a relatively new, short-acting 1,4 benzodiazepine, has been used for premedication in adults, with satisfactory results (Amarasekara, 1980; Beechey, Eltringham and Studd, 1981) and has recently become available in an elixir formulation (10 mg in 5 ml, Euhynpos Elixir, Farmitalia Carlo Erba Ltd). A study was undertaken to compare the use of temazepam in this form, with trimeprazine tartrate in a syrup (Vallergan Forte Syrup) as premedication in children. The trial was based on the assumption that trimeprazine is an acceptable premedicant in children which, despite some disadvantages, is widely, although by no means universally, used. The study was not designed to establish whether trimeprazine or temazepam is an effective premedicant but only whether, in an appropriate dose, temazepam is "better" (or at least no worse) than a standard dose of trimeprazine.

The two drugs are an example of the situation where the new drug is believed to produce, in a dose-related manner, many of the effects of the established drug, and there is an accepted "standard" dose of the established drug, at least in local practice, which is thought to produce an optimum compromise between wanted and unwanted effects. In these circumstances, it is desirable to determine, for each relevant response, the dose of the new drug which is equipotent with the standard dose of the established drug. If the new drug has a lower equipotent dose for the desirable than for the undesirable responses, it is to be preferred; if the reverse is true the established drug is preferable.

If the magnitude of a particular response is insensitive to dose, or if the response is very variable between patients, then the confidence limits of the estimated equipotent dose for that response may be too wide to be of any value. The best that can be done then is to determine whether the magnitude of that response is significantly greater for one drug than for the other at the doses used in the trial.

In local practice the dose of trimeprazine is invariably 3 mg kg\(^{-1}\), so this was adopted as the standard dose of the established drug. Therefore, the study was designed to try to determine, for all responses of interest, the dose of temazepam which was equipotent with trimeprazine 3 mg kg\(^{-1}\). Temazepam had not previously been used in children, so a preliminary clinical assessment was undertaken. On the basis of the results, three doses (0.5, 1.0 and 1.5 mg kg\(^{-1}\)) were chosen as being likely to include the equipotent dose for most responses. Therefore, a randomized, observer-blind trial was planned, using these doses, in children undergoing tonsillectomy and associated procedures. The study received the approval of the hospital ethics committee.

PATIENTS AND METHODS

General

Two hundred and twenty children were entered to the trial and randomly allocated to receive trimeprazine tartrate 3 mg kg\(^{-1}\) or temazepam 0.5, 1.0 or 1.5 mg kg\(^{-1}\). The only requirements for inclusion in the trial were that written informed consent had been obtained from the parents and that, at the preoperative assessment performed by Dr David L. Thomas (DLT), the child was judged to be in the ASA grade I category of fitness. Parents were not present at induction.

When a child entered the trial, a sealed, numbered envelope containing the treatment code defining the premedication to be used for that child was attached to the patient's notes. The following day, a qualified nurse on the preoperative ward opened the envelope and administered the specified premedication, without any antialagogue, approximately 90 min before the anticipated start of surgery. Since temazepam elixir is green and trimeprazine is red the treatment was, to that extent, not blind to the patient nor to the administering nurse. However, no traces of the colour difference were visible at the time of the intubation, so that the observations made by the anaesthetist (DLT) were blind. Anaesthesia was induced with sodium thiopentone 5 mg kg\(^{-1}\) (and suxamethonium chloride 1 mg kg\(^{-1}\)) i.v., through a standard 23-gauge Butterfly needle. Anaesthesia was maintained with the child breathing spontaneously through a tracheal tube connected to a Bain coaxial breathing system supplied with 1–2% halothane in a flow of nitrous
Table I. Responses observed, with ranges of scores used or of measurements recorded

Preoperative on the ward
Problems following premedication: 0/1
(None/one or more)

Preoperative in theatre
Salivation on arrival in theatre: 0/1
(Satisfactory/unsatisfactory)
Demeanour on arrival in theatre: 0–5
(Noisy/tearful/apprehensive/serious/cheerful/sleepy)
Response to venepuncture: 0–4
(Abandoned/crying started/audible response/wincing/no response)
Hand withdrawal thereafter: 0/1
(Unsatisfactory/satisfactory)
Preoperative ventilatory frequency: 12–60 b.p.m.

Perioperative
Mean perioperative spontaneous ventilatory frequency: 17–65 b.p.m.
Problems under anaesthesia: 0–2
(None/unifocal ectopic beats/multifocal ectopics)

Postoperative
Duration of stay in recovery room: 4–45 min
Requirement for a postoperative analgesic: 0/1
(nil/some)
Retching: 0–6
Vomiting: 0–6
Restlessness: 0–6
Pallor: 0–6
(All the above four scores indicate the number of 30-min periods, within the first 3 h on the ward, in which the observation was true except that, in the case of vomiting, the score was increased by 1 if vomiting was recorded in the recovery room—but the maximum score achieved was then still only 3.)

Table II. Explanatory variables observed, with ranges of values

Drug and dose
Trimetazaine tartrate: 3 mg kg⁻¹
Temazepam: 0.5, 1.0, 1.5 mg kg⁻¹

Patient
Age: 2 years 9 months–14 years 5 months
Body weight: 13–49 kg
Sex: M/F

Times
From premedication to arrival in theatre: 60–160 min
From premedication to arrival in recovery room: 82–188 min
From premedication to arrival in recovery ward: 100–200 min
Duration of anaesthesia: 12–44 min

Other
Number of operations additional to tonsillectomy: 0–4
Code for grade of surgeon: 0–3
(SHO/registrar/senior registrar/consultant)
Code for identity of surgeon: 0–7
Code for identity of nurse making recovery-ward observations: 0–10

Oxide 6 litre min⁻¹ plus oxygen 3 litre min⁻¹. At the end of the operation the child was transferred to the recovery room and from there, when the nurse deemed recovery to be adequate, to a recovery ward different from that in which the premedication was administered. Thus the nurses who made observations in the recovery ward were unaware of the treatment given.

The responses observed are listed in Table I, but a few details need explanation. “Problems following premedication” were assessed free-form comments by the nurse on the preoperative ward and were the only observations that were not observer-blind. The scales used for assessing demeanour, response to venepuncture, and hand withdrawal thereafter were those of Doughty (1959). Perioperative ventilatory frequency was expressed as the mean of measurements made at 5-min intervals from the time that spontaneous breathing returned following induction until leaving the theatre. Ectopic beats (a “problem under anaesthesia”) were detected from the ECG which was used as a monitor throughout the operation. (Arterial pressure and heart rate were measured before and at 5-min intervals during the operation, but the results were never a cause of clinical concern, except in relation to the ectopic beats, and were not processed.) When ectopic beats occurred, manual ventilation was instigated until the arrhythmia ceased. No pharmacological therapy was administered.

Variables which were observed in the expectation that they might explain some of the variation in the responses are listed in Table II. Those listed under “Other” were included on the basis that the number of additional operations and the skill of the surgeon might influence the amount of postoperative pain and, hence, restlessness in the postoperative ward. The 11 nurses making the observations on the ward were separately identified on the basis that, for example, what one nurse recorded as “restless” might be recorded by another as “not restless”. The additional operations comprised almost every combination and permutation of adenoidectomy, uni- and bi-lateral myringotomy, bi-lateral antral washout, and “other”. It was not considered worth treating them as separate explanatory variables.

Statistical
For the analysis of the results a modelling technique was developed, based on the statistical computer-package “GLIM” (Generalised Linear
Interactive Modelling) (Baker and Nelder, 1978) and the "bootstrap" technique of Efron (Diaconis and Efron, 1983). This is described in detail elsewhere (Mapleson, 1986), but is outlined here for completeness.

The basis of the method is illustrated in figure 1 for hypothetical data corresponding to the general structure of the present study (three doses of the new drug, one of the old): the response of each patient has been plotted against log dose; a straight line has been fitted to the results for the new drug; and the point A on this line, at which the predicted response to the new drug is the same as the mean response to the standard dose of the old drug, indicates the equipotent dose of the new drug for the type of response in question.

This basic approach has been extended in four ways: to give valid results when the deviations of the responses from the fitted line are not Normally distributed, but can be shown to conform to one of the other distributions available in GLIM; to allow, where appropriate, for the effects of additional explanatory variables from table II by combining them into a single predictor of the response; to allow, where appropriate, for a sigmoid relationship between the response and this predictor; and to provide estimates of the 95% confidence limits of the equipotent dose. The method also allows the inclusion of "interactions" between explanatory variables; for example, the rate of dependence of a response on the time since premedication being different for the two drugs. The criteria for the inclusion of an additional explanatory variable, or an interaction, were that it was thought likely to affect the response in question, that its effect was significant ($P < 0.05$), and that its effect was plausible in direction and magnitude (see Appendix).

The technique can be applied, not only to responses measured on a continuous scale, but also to responses recorded as discrete data: quantal data (e.g. satisfactory/unsatisfactory) or, with some restrictions, counts of events or ordinal data.

For those responses which yielded very wide confidence limits (upper limit more than 10 times the lower limit), recourse was had to a straight comparison of the responses to the two drugs, pooling the results for all three doses of temazepam. The modelling technique was used here if it showed, for a given response, that the difference between the mean magnitudes of response to the two drugs was contributed to
significantly by one or more of the variables in table II. For other responses, appropriate conventional two-group tests were used.

RESULTS

Of the 220 patients entered to the trial, 16 were withdrawn for reasons unconnected with the premedication: “operation cancelled” (four), “procedure not followed” (seven) or “returned to theatre because of excessive bleeding” (five). This left 204 patients for the response “problems following premedication”. In three, the problem was that the child refused the premedication completely. These three patients were, therefore, excluded from the trial except in respect of this one response. The other problems, sometimes more than one per child, included “restless” (six instances), “confused” (four), “fell out of bed” (four) and coughing/hiccuping (three). Any such problem or combination of problems was allocated a score of 1, as opposed to 0 when no problem was reported. This left 201 patients for all the other responses, 54 of whom received trimetazepam 3 mg kg\(^{-1}\), and 47, 50 and 50 of whom received temazepam 0.5, 1.0 and 1.5 mg kg\(^{-1}\), respectively.

Of the responses in table I, salivation was always “satisfactory” and the requirement for a postoperative analgesic was always “nil”. The other 12 responses were analysed by the modelling technique (Mapleson, 1986), in order to obtain an estimate of the dose of temazepam which was equipotent with trimetazepam tartrate 3 mg kg\(^{-1}\). In only three instances was the dependence of response on dose sufficiently significant (\(P < 0.01\)) to lead to 95% confidence limits of the equipotent dose that were close enough to be of any value (table III). Even then, the limits included all three doses of temazepam.

For the other nine responses, dependence of response on dose did not reach even the 5% level of significance, so they were assessed either by the modified modelling technique, if that was appropriate (see above), or by conventional two-group tests. The resulting probabilities are listed in table IV, together with the direction of the difference (where it approached or reached significance) and the statistical test used. It is also worth recording that, although most of the “problems following premedication” were associated with temazepam and not trimetazepam, the difference between the two drugs was less significant for each of the

<table>
<thead>
<tr>
<th>Response</th>
<th>Effect of increasing dose</th>
<th>Equipotent dose (mg kg(^{-1})) Estimate</th>
<th>95% Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroperative ventilatory frequency</td>
<td>Faster frequency</td>
<td>1.2</td>
<td>0.7–3.0</td>
</tr>
<tr>
<td>Duration in recovery room</td>
<td>Longer duration</td>
<td>0.9</td>
<td>0.3–2.4</td>
</tr>
<tr>
<td>Postoperative pallor</td>
<td>Greater incidence</td>
<td>1.0</td>
<td>0.5–1.7</td>
</tr>
</tbody>
</table>

individual problems than the non-significant result given in table IV for all problems taken together.

DISCUSSION

It is disappointing that only three responses yielded equipotent doses with usable confidence limits, and even these are hardly close (table III). This is despite using a sophisticated modelling technique, capable of allowing for the effects of all the explanatory variables in table II. In fact only age and duration of anaesthesia ever met the criteria for inclusion in the model and none of the interactions did so. However, it is interesting that the identity of the nurse did approach significance in explaining the variation in postoperative restlessness.

Sedatives usually depress ventilation. Therefore, it is at first sight surprising that increasing the dose of temazepam increased the ventilatory frequency (table III). However, as with trichloroethylene, this may well be associated with a decrease in alveolar ventilation. This seems likely since, when ectopic beats occurred, presumably as a result of increased carbon dioxide tension in the presence of halothane, they were relieved by manual ventilation.

The wideness of the confidence limits of equipotent dose arises mainly from the non-significance of the dependence of most responses on dose. A number of features may have combined to prevent real dependencies of response on dose showing significantly: the limited range of doses, the wide range of responses to any given dose, and the inclusion of only 200 patients. However, the response “problems following premedication”
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Table IV. Direction and significance of the differences in responses to temazepam and trimeprazine at the doses used. †Given only when the difference approaches or reaches significance. ‡Probability that difference as large as or larger than that observed can be attributed to chance. §Problems v. no problems. *Incorporating allowance for effect of age (Mapleson, 1986)

<table>
<thead>
<tr>
<th>Response</th>
<th>Temazepam compared with trimeprazine†</th>
<th>P‡</th>
<th>Test used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems following premedication</td>
<td>More problems</td>
<td>0.12</td>
<td>Fisher-exact</td>
</tr>
<tr>
<td>Demeanour</td>
<td>—</td>
<td>0.75</td>
<td>Model*</td>
</tr>
<tr>
<td>Response to venepuncture</td>
<td>—</td>
<td>0.79</td>
<td>Model*</td>
</tr>
<tr>
<td>Hand withdrawal</td>
<td>—</td>
<td>0.24</td>
<td>Fisher-exact</td>
</tr>
<tr>
<td>Preoperative ventilatory frequency</td>
<td>Faster frequency</td>
<td>0.05</td>
<td>Model*</td>
</tr>
<tr>
<td>Problems under anaesthesia (ectopic beats)</td>
<td>More problems</td>
<td>0.03</td>
<td>Mann–Whitney</td>
</tr>
<tr>
<td>Postoperative retching</td>
<td>—</td>
<td>0.31</td>
<td>Mann–Whitney</td>
</tr>
<tr>
<td>Postoperative vomiting</td>
<td>More vomiting</td>
<td>0.04</td>
<td>Mann–Whitney</td>
</tr>
<tr>
<td>Postoperative restlessness</td>
<td>More restlessness</td>
<td>&lt; 0.0001</td>
<td>Mann–Whitney</td>
</tr>
</tbody>
</table>

may have been genuinely independent of dose: the green colour of the temazepam preparation may have been less attractive to the children than the red of the trimeprazine and may have had a psychological effect on behaviour before the operation. Alternatively, the nurses, who knew that the usual colour of the premedication was red, might have been biased to notice more problems with tind solution—may, indeed, have thought it their duty to draw attention to them as part of the “experiment”.

A primary aim in premedicating children is to ensure that the child is in a satisfactory state on arrival in theatre. The three responses which reflect this: demeanour, response to venepuncture, and hand withdrawal, all showed non-significant differences between the two drugs. This indicates that, in these respects, any of the three doses of temazepam (0.5, 1.0 or 1.5 mg kg⁻¹) chosen on the basis of the preliminary clinical assessment, may be equipotent with 3 mg kg⁻¹ of trimeprazine. This is broadly supported by the fact that Furness, Boyle and Lee (1986), comparing the effects of trimeprazine 3 mg kg⁻¹ with temazepam 1 mg kg⁻¹, found no significant difference in efficacy or apprehension. Also, Padfield, Twohig and Fraser (1986), comparing a larger dose of trimeprazine (4 mg kg⁻¹) with temazepam 1 mg kg⁻¹, found a better “attitude” (approximately equivalent to our “demeanour”) with trimeprazine (P = 0.025) but a non-significant difference in “behaviour” (approximately equivalent to our “response to venepuncture”). Therefore, the estimated equipotent dose for pallor (1.0 mg kg⁻¹, with confidence limits of 0.5–1.7 mg kg⁻¹) (table III) does not provide any support for the hope that there would be less postoperative pallor with temazepam. On the other hand, at the doses given, temazepam was associated with significantly more problems under anaesthesia (ventricular ectopic beats) (P = 0.03 or 0.002 depending on the test applied (table IV)), more postoperative vomiting (P = 0.04) and more postoperative restlessness (P < 0.0001). Furness, Boyle and Lee (1986) found no cardiac arrhythmias with either temazepam or trimeprazine, but this was probably a result of the substitution of isoflurane for halothane for maintenance of anaesthesia. Padfield, Twohig and Fraser (1986) also found more postoperative vomiting with temazepam than with trimeprazine.

CONCLUSION

In this study, the only significant differences between the two drugs seem to favour trimepr-
zine rather than temazepam, although the wide confidence limits may conceal some differences in favour of temazepam.

APPENDIX

CHOICE OF ADDITIONAL EXPLANATORY VARIABLES

In both methods of using the model, the criteria for including an additional explanatory variable were: (1) that the variable should have been selected as a candidate for inclusion before commencing the analysis; (2) that the effect should be significant ($P < 0.05$ was used in this study); and (3) that the effect should be plausible in direction and magnitude. In most instances in the present trial, if an additional explanatory variable had a significant effect on a response, the effect was clearly plausible; a greater age led to a more restrained demeanour, a more controlled response to venepuncture, and to lesser pre- and peroperative ventilatory frequencies; a greater duration of anaesthesia led to more problems during anaesthesia and to a longer stay in the recovery room.

In one instance the predicted change was not obviously plausible: the peroperative ventilatory frequency was greater for a greater duration of anaesthesia ($t = 3.36, d.f. = 196$) or for a greater number of operations additional to tonsillectomy ($t = 3.12, d.f. = 196$) when both were included in the model (along with drug, log dose and age) both were of only borderline significance ($t = 2.26$ and $1.91$, respectively; $d.f. = 195$). However, the tonsillectomy was always performed first and anaesthesia was then lightened for any subsequent, less painful operations. Therefore, the greater the number of additional operations the longer the duration of anaesthesia, the lighter the mean depth of anaesthesia and, arguably, the greater the mean peroperative ventilatory frequency. Since the dependence on duration of anaesthesia was the more significant, this variable was retained and the other rejected.

In the remaining instance the plausibility of the predicted change was equivocal. The demeanour on arrival in the anaesthetic room showed a highly significant dependence on the time since the premedication was administered, provided that separate gradients against time were allowed for the two drugs. Qualitatively, this could be explained on a pharmacokinetic basis: in adults, the time of peak plasma concentration of temazepam is about 1 h (Pickup, Rogers and Lauchbury, 1984) (the shortest time from premedication to arrival in theatre) while, for trimetrazine, it is about 3 h (Johnson and Masters, 1962) (more than the longest time). Quantitatively, however, the explanation fails: in the model, when the two drugs are allowed separate dependencies of demeanour on time, the implication is that a 20-min change from the mean time of 99 min since premedication produced a 10-fold change in the calculated potency ratio; whereas, when the results of Pickup, Rogers and Lauchbury and those of Johnson and Masters were plotted on a common graph, this showed only a 1.2-fold change in concentration ratio in the same circumstances. Therefore, time was rejected as an explanatory variable. This does not imply that demeanour is independent of time since premedication, only that the predicted difference in time dependence, between the two drugs, is much too large to be plausible.

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