ORAL ATROPINE AND PRACTOLOL PREMEDICATION IN DENTAL ANAESTHESIA

W. Ryder, J. E. Charlton and P. B. W. Gorman

SUMMARY

A double-blind controlled trial of practolol and atropine premedication in dental anaesthesia was carried out to determine the effects of small doses of these agents on the incidence of abnormalities of cardiac rhythm and to assess the aetiological role of catecholamines in their production. A worthwhile effect was produced by practolol but not by atropine. The aetiological role of catecholamines is discussed in the light of these findings.

Several papers in recent years (Kaufman, 1966; Annotation, 1966; Meyer, Allen and Hooley, 1966; Rollason and Dundas, 1966; Tuohy, 1968; Ryder, 1970, 1971) have reported a high incidence of abnormalities of cardiac rhythm in association with dental extractions under general anaesthesia. Though a variety of factors may contribute to this high incidence—notably fear and anxiety, the sitting position, respiratory obstruction with its attendant hypoxia and hypercarbia, pain reflexes and anaesthetic "sensitization" of the heart to endogenous catecholamines—the final common pathway for most of them is probably an elevation of myocardial catecholamine levels.

In an attempt to find a safe, simple and effective method of preventing arrhythmias and in order to test the aetiological role of myocardial catecholamines, a double-blind controlled trial was designed using oral premedication. Atropine was used as a vagolytic drug, practolol (Eraldin, ICI) as a cardio-specific beta-adrenergic blocking agent and an identical blank tablet as a placebo.

METHOD

Patient selection.

The nature of the investigation was explained to patients attending the routine lists at the Newcastle Dental Hospital and their informed consent sought. Children under 10 years of age were excluded since the manufacturers felt that insufficient experience had been obtained of the dosage of practolol in this age group. Also excluded were patients already being treated with anti-arrhythmic drugs, diabetic patients, and patients with moderate to severe heart disease. Hypertensive patients were not excluded unless they were receiving beta blocking agents or had evidence of significant heart failure.

Several asthmatic patients were included in the trial. No respiratory function tests were performed on these patients but they showed no adverse effects clinically as a result of taking a beta-blocking agent.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment groups</th>
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<tbody>
<tr>
<td>I</td>
<td>Placebo/placebo</td>
</tr>
<tr>
<td>II</td>
<td>Atropine 0.6 mg/placebo</td>
</tr>
<tr>
<td>III</td>
<td>Practolol 50 mg/placebo</td>
</tr>
<tr>
<td>IV</td>
<td>Practolol 50 mg/atropine 0.6 mg</td>
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Patients agreeing to participate in the trial were randomly allocated to one of four treatment groups and given two identical tablets to swallow with a sip of water. Table I shows the four combinations of tablets used. The doses of atropine (0.6 mg) and of practolol (50 mg) chosen, were deliberately on the small side in an attempt to limit possible side effects to a minimum. At least 1 hour was allowed to elapse after the tablets were taken before anaesthesia was induced. Anaesthesia was induced and maintained in all patients with nitrous oxide, oxygen and halothane using a Walton Mark V demand-flow apparatus of known accuracy and a calibrated halothane draw-over vaporizer capable of delivering up to 3% halothane by volume. The concentration of oxygen used was never less than 20% by volume. Almost half of the anaesthetics were given by or under the supervision of one of the authors (WJL) and the rest by, or under the supervision of, other anaesthetists experienced in dental anaesthesia. All patients were in the sitting position.


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Observations.

Blood pressure and pulse rate and rhythm (regular or irregular) were recorded before premedication and just prior to discharge, by a state registered nurse. Immediately preanaesthesia, at minute intervals throughout anaesthesia and on recovery these measurements were made by one of the authors. A standard oscillometric method was employed for blood pressure measurements.

A continuous e.c.g. trace was observed on an oscilloscope and recorded on magnetic tape from the immediate preanaesthetic period until recovery from general anaesthesia. For ease and speed of application, either lead II or lead I was chosen and was picked up and transmitted through a radiocardiograph system (Medical and Industrial Equipment Ltd). The tape-recorded e.c.g. was played back and analysed at a later date and the events in it correlated with clinical events and observations as recorded by commentary on the second channel of the tape.

Total duration of anaesthesia and surgery were noted. Recovery time, measured with a stopwatch, was noted as the time from stopping anaesthetic administration to the first positive response of the patient to a request to open the eyes.

In 17 randomly-selected patients a sample of venous blood was taken from the cubital fossa during surgery and analysed by ICI for plasma practolol levels.

RESULTS

Two hundred and three cases in all were investigated and were distributed throughout the treatment groups as shown in table II.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of cases</th>
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<tr>
<td>I Placebo/placebo</td>
<td>50</td>
</tr>
<tr>
<td>II Atropine/placebo</td>
<td>52</td>
</tr>
<tr>
<td>III Practolol/placebo</td>
<td>52</td>
</tr>
<tr>
<td>IV Practolol/atropine</td>
<td>49</td>
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</tbody>
</table>

Arrhythmias.

For the purposes of this trial a heart rhythm was classified as abnormal if one or more beats originated outside the sinu-atrial node. Thus "abnormalities" varied from isolated ventricular extrasystoles to runs of abnormal rhythm of nodal or ventricular origin lasting for much of anaesthesia and surgery.

Fifty-one patients developed abnormal rhythms. Table III shows their overall distribution in the various treatment groups. The frequency of occurrence in the placebo group almost exactly matched that of a previous series using the same anaesthetic technique but without premedication (Ryder, 1971). Atropine premedication appeared to increase the frequency slightly but the effect was not statistically significant. Practolol and practolol/atropine premedications both reduced the frequency, the reduction in both cases being statistically highly significant (P<0.01).

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<tr>
<td>I Placebo/placebo</td>
<td>16</td>
</tr>
<tr>
<td>II Atropine/placebo</td>
<td>18</td>
</tr>
<tr>
<td>III Practolol/placebo</td>
<td>7</td>
</tr>
<tr>
<td>IV Practolol/atropine</td>
<td>10</td>
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Table III. Distribution of abnormal rhythms.

Table IV shows the distribution of individual arrhythmias in each group. Practolol premedication appeared to reduce the frequency of nodal rhythm and atropine to increase it, but neither alteration achieved statistical significance. Atropine alone had no effect on ventricular or mixed arrhythmias. The reduction in ventricular and mixed arrhythmias when practolol was used was very striking and was statistically highly significant (P<0.001). Table V groups together all those cases demonstrating ventricular arrhythmias and serves to emphasize this point.

Fourteen per cent of arrhythmias occurred during induction only. These were usually, but not invariably, associated with a stormy induction. A further 23% began during induction and either persisted in the same form into the extraction period or changed

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</tr>
<tr>
<td>II Atropine/placebo</td>
<td>9</td>
</tr>
<tr>
<td>III Practolol/placebo</td>
<td>3</td>
</tr>
<tr>
<td>IV Practolol/atropine</td>
<td>2</td>
</tr>
</tbody>
</table>

Table IV. Distribution of individual abnormal rhythms.

Table V. Distribution of ventricular arrhythmias.
with the onset of surgery to a different form. No definite pattern emerged in these cases, nodal rhythm changing to ventricular in some and ventricular to nodal in others. Fifty-seven per cent of the arrhythmias began with or during extractions. Some were merely transient, one or two persisted into the post-extraction (and post-anaesthetic) phase but most ceased promptly when extractions (and anaesthesia) were stopped. Three arrhythmias (6%) developed after completion of the extractions but were all transient.

A comparison of the duration of anaesthesia and surgery in normal and abnormal rhythm groups is shown in Table VI. Though both anaesthesia and surgery were generally more prolonged in the "abnormals" group, and to a statistically significant degree (P<0.05), the difference was probably of little significance clinically.

Table VII shows the sex distribution of abnormal rhythms. Surprisingly, abnormal rhythms were almost twice as common in males as in females and the difference was statistically highly significant (P<0.01). This pattern of sex distribution contrasts markedly with that of the previous series already mentioned in which abnormal rhythms occurred with equal frequency in both sexes. The difference (table VIII) appeared to be confined almost exclusively to rhythms of nodal origin. We can offer no explanation for this difference.

Arrhythmias were distributed evenly throughout all age groups examined and premedication had no particular effect in any age group.

Recovery times (table IX) were shorter in the "normals" group (mean 97 sec) than in the "abnormals" one (mean 119 sec) but the range in both was wide and similar. Statistically the difference in means was not significant (P>0.05) and perhaps merely reflected the more prolonged anaesthesia of the abnormals group.

Pulse rate changes.

These are expressed graphically in figure 1. The pattern of pulse rate changes in the four treatment groups is shown. The patients given practolol showed an insignificant fall following premedication and a small but significant (P<0.05) rise in response to the stimulus of surgery. Those patients given atropine or placebo had a rise following premedication and a further and significant (P<0.05) rise during surgery. Pulse rates in placebo and atropine treatment groups were similar and were significantly higher during anaesthesia than in the practolol groups. In all patients pulse rates had returned to normal by the time of discharge.

There was a similar pattern of changes in systolic blood pressure (fig. 2). A slight fall in all groups following premedication (significant at the 5% level only in Group IV) was followed by a rise during surgery and a return to normal by the
FIG. 2. Mean systolic pressure patterns.

Mechanical ventilation.

Time of discharge. The rise during surgery was significant (P<0.05) in all groups. The differences in maximum systolic pressure during surgery between the practolol and non-practolol groups was also statistically significant (P<0.05).

Conduct of anaesthesia was assessed in relation to treatment group. A small and statistically insignificant tendency for atropine premedication to reduce the incidence of stormy anaesthesia was not obvious clinically.

Plasma practolol levels varied from zero (levels below 0.1 μg/ml are undetectable) to 0.85 μg/ml. Five of the 17 cases had abnormalities of rhythm but only one—a case of nodal rhythm—had a measurable plasma practolol level (0.45 μg/ml).

DISCUSSION

As long ago as 1963 Vaughan Williams and Sekiya, and Murray, McKnight and Davis, showed that the threshold for the development of cardiac arrhythmias in guinea-pigs and dogs was significantly increased by premedication with pronethalol. A subsequent investigation by Payne and Senfield (1964) implied that a similar elevation of arrhythmia threshold in man was associated with the use of that drug. These workers suggested that the administration of pronethalol for premedication should guard against arrhythmias associated with anaesthesia and rightly stressed the very small doses required for this purpose.

The results of the present trial amply demonstrate that the claims Payne and Senfield (1964) made for pronethalol premedication to reduce the incidence of stormy anaesthesia was not obvious clinically. Plasma practolol levels varied from zero (levels below 0.1 μg/ml are undetectable) to 0.85 μg/ml. Five of the 17 cases had abnormalities of rhythm but only one—a case of nodal rhythm—had a measurable plasma practolol level (0.45 μg/ml).

Falls in blood pressure and pulse rate did follow practolol premedication in this series but these were small in extent and clinically insignificant. The ability of the cardiovascular system to respond to stress was not abolished and the values for both variables had returned to normal by the time of discharge.

Stephen, Davie and Scott (1971) reported evidence of quite severe negative inotropic effects following the use of practolol in anaesthetized patients but they used much larger doses than were employed in this series.

Since practolol is a pure beta blocking drug, and since the occurrence of both ventricular and mixed nodal and ventricular arrhythmias was significantly reduced by its use, it seems reasonable to assume that myocardial catecholamines are frequently implicated in the production of these arrhythmias but are of little importance in the genesis of those of purely nodal origin.

Such a simple assumption is difficult to reconcile with the views of Alexander (1971) who believes that many arrhythmias classified as ventricular are in fact of nodal origin. It may be that the difference in classification is unimportant and merely one of definition and that the important differentiation is between those arrhythmias of catecholamine origin and those not. The former, we suggest, are potentially more dangerous; they are the less stable and more likely to progress to ventricular fibrillation; they are those commonly associated with undesirable elevations of blood pressure and pulse required to produce 30% inhibition of exercise tachycardia is said to be about 1.0 μg/ml (Aellig, Pritchard and Scales, 1970); yet of the 17 patients in the present series whose blood was sampled for practolol estimation, a blood level of 0.85 μg/ml was never exceeded and rarely approached.

Moreover, the traditional objections to beta-adrenergic prophylaxis—lack of specificity, local analgesic and quinidine-like properties, bronchospasm, negative myocardial inotropism, and an inability of the heart to respond to stress—cannot be levelled at practolol. It is cardiospecific and without quinidine-like properties (Dunlop and Shanks, 1968; Barrett et al., 1968). It is not contraindicated in asthmatic patients (McDonald and McNeill, 1968; Palmer et al., 1969; Powles, Shinebourne and Hamer, 1969) and in small doses has minimal effects on myocardial contractility and cardiac output (Gibson and Sowton, 1968; Sowton et al., 1968; Gibson and Coltart, 1972).

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intravenous injection of atropine. This finding in progress in which intravenous medication replaces adequate absorption. A further trial is at present in easily, simply, safely and effectively prevented by atropine premedication than without it. We therefore concluded that the dose of atropine used was either inadequate or was given too late for adequate absorption. A further trial is at present in progress in which intravenous medication replaces oral premedication and in which the roles of atropine and salivation can be more surely assessed. Thurlow (1972) reported a significant increase in the production of arrhythmias in dental patients following intravenous injection of atropine. This finding would seem to support our conclusion.

ACKNOWLEDGEMENTS
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REFERENCES