ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA

VIII: THE EFFECTS OF ATROPINE AND HYOSCINE

BY

JOHN W. DUNDEE, ROBERT M. NICHOLL AND JAMES MOORE

Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland

In previous papers from this department, the effects of various premedicants on the response to somatic pain have been reported (Dundee and Moore, 1960; Moore and Dundee, 1961a, b). While opinions vary as to the best form of pre-anaesthetic medication, there is unanimous agreement on the need for an antisialogogue drug before general anaesthesia. Although a large number of these preparations are available, the majority of anaesthetists use atropine or hyoscine. In view of this, it was felt that the effects of these two drugs on the appreciation of pain warranted detailed study. This paper reports the results of such an investigation.

The clinical significance of the findings is discussed with particular reference to the action of methohexitone and the relevant literature concerning the mechanisms involved in the effects of these drugs on pain threshold is reviewed.

It has been shown by Mushin, Galloon and Lewis-Faning (1953) that the 0.6 mg dose of atropine leaves much to be desired as an effective pre-anaesthetic drying agent. This finding was confirmed by Galloon (1956) and Wyant and Dobkin (1957) although Diamant and Feinmesser (1959) found 0.5 mg of this drug to be satisfactory. However, there is no reliable information on the comparative potency of atropine and hyoscine other than the work of Wyant and Dobkin (1957) who gave 0.2 mg of each drug to volunteers and found hyoscine to be the more effective and reliable antisialogogue.

METHODS

Atropine was used in the form of the sulphate and the effect of 0.6 mg (1/100 grain) was studied in detail in view of its widespread use as pre-anaesthetic medication in adults. Failure to confirm published findings with this dosage led to a study of the action of 1.3 mg (1/50 grain) in a small number of subjects. Hyoscine hydrobromide (Scopolamine) was studied in a dosage of 0.4 mg (1/150 grain) for two reasons. First this amount is present in the commercially available ampoules either alone or combined with 21 mg papaveretum or 100 mg pethidine. This dose is also employed in obstetric analgesia (Cullhed and Lofstrom, 1961).

The response to somatic pain was estimated by the gradual application of a measurable degree of pressure to the anterior surface of the tibia as described by Dundee and Moore (1960). Two end points were determined on each subject:

(a) when the sensation of pressure changed to pain (threshold) and

(b) when pain became unbearable or the patient moved the limb in response to the stimulus (response).

When the drugs were given intravenously, a control reading was carried out before administration. Further readings were taken at 5 to 10 minute intervals thereafter and the average of the absolute readings in several cases expressed graphically.

When the intramuscular route of administration was employed duplicate control readings were carried out immediately before injection of the drug under study and a further set of observations was made 60 to 90 minutes later. The effect of the drug on each subject was classified as:

(a) decreased sensitivity to pain: rise in readings of more than one pain unit after administration of the drug;

(b) increased sensitivity to pain: fall in readings of more than one pain unit after administration;

(c) no change: second readings within range of control ± 1 unit.
The average effect of each drug was expressed as the analgesia index which is calculated as follows:

\[
\frac{\text{Incidence of rise in readings}}{\text{Total number of observations}} - \frac{\text{Incidence of fall in readings}}{\text{Total number of observations}}
\]

This method of expressing the overall effect of a drug has been described by Moore and Dundee (1961b) but it was not then made clear how the authors decided on the minimum number of cases for calculation of the analgesia index. This is clarified in an appendix to this paper.

RESULTS

Figure 1 shows that the intravenous injection of atropine 0.6 mg and hyoscine 0.4 mg increased sensitivity to somatic pain. However, the effect of atropine was very transient as compared with that of hyoscine.

The effects of these drugs observed 60 to 90 minutes after injection is given in table I. This showed a negligible anti-analgesic action of atropine, even in a dosage of 1.3 mg but hyoscine consistently increased the sensitivity of pain.

To study the difference between the action of the two antisialogogues further they were given intravenously 15 minutes after the administration of pethidine 100 mg (fig. 2). Here again the anti-analgesic action of the atropine was demonstrated but its duration was very much less than that of hyoscine given in a similar manner.

From table II it can be seen that atropine 0.6 mg did not appreciably alter the analgesia index of either pethidine 100 mg or perphenazine 5 mg. In contrast to this hyoscine 0.4 mg decreased the analgesic action of pethidine 100 mg and markedly augmented the anti-analgesic action of promethazine 50 mg. The anti-analgesic action of the latter combination was the most marked that the authors have encountered to date in a long-term study of the effects of premedicants on the response to somatic pain. This action is best illustrated when promethazine 50 mg and hyoscine 0.4 mg were given by intravenous injection (fig. 3).

When promethazine 50 mg and hyoscine 0.4 mg were combined with pethidine 100 mg (Pamergan SP.100), the analgesic action of the pethidine was more than neutralized, the resulting mixture having a fairly marked anti-analgesic effect. This was in contrast to the combination of promethazine 50 mg, pethidine 100 mg and atropine 0.6 mg (Pamergan P.100) which had a negligible effect on sensitivity to pain.

| TABLE 1 |
| Results of analgesimetry studies following the intramuscular injection of atropine and hyoscine. |
| Number of patients | Percentage change in readings |
| | Rise | No change | Fall | Analgesia index |
| Atropine 0.6 mg | 53 | 16 | 72 | 12 | +0.04 |
| Atropine 1.3 mg | 18 | 23 | 47 | 28 | -0.03 |
| Hyoscine 0.4 mg | 20 | 12 | 48 | 40 | -0.28 |
Fig. 2
The effect of atropine 0.6 mg (A) and hyoscine 0.4 mg (H) on the analgesic effect of 100 mg pethidine (P).
All drugs were given by intravenous injection.

Table II
The effects of the intramuscular injection of various premedications, with and without atropine or hyoscine on the response to somatic pain.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>No. of cases</th>
<th>Percentage change in readings</th>
<th>Analgesia index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rise</td>
<td>Nil</td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>51</td>
<td>63</td>
<td>29</td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>71</td>
<td>62</td>
<td>31</td>
</tr>
<tr>
<td>Atropine 0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>27</td>
<td>46</td>
<td>33</td>
</tr>
<tr>
<td>Hyoscine 0.4 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine 5 mg</td>
<td>12</td>
<td>15</td>
<td>58</td>
</tr>
<tr>
<td>Perphenazine 5 mg</td>
<td>24</td>
<td>10</td>
<td>66</td>
</tr>
<tr>
<td>Atropine 0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine 50 mg</td>
<td>56</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Atropine 0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine 50 mg</td>
<td>17</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Atropine 0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>14</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Hyoscine 0.4 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>60</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Promethazine 50 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine 0.6 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The action of the intravenous injection of promethazine 50 mg and hyoscine 0.4 mg on response to somatic pain. Upper graph shows alterations in response readings while the lower graph shows the threshold readings.
DISCUSSION

These findings demonstrate that both atropine and hyoscine increase sensitivity to somatic pain in the doses used in clinical anaesthesia. However, the effect of atropine is so brief as to be insignificant when it is given by subcutaneous or intramuscular injection in pre-anaesthetic medication, with or without other sedatives or analgesics.

The importance of the prolonged anti-analgesic action of hyoscine is best demonstrated by considering its effect on the course of methohexitone anaesthesia. Work from this school has shown that the incidence of excitatory phenomena (spontaneous involuntary muscle movements and tremors) following injection of this barbiturate is markedly affected by the analgesic action of the premedication (Dundee and Moore, 1961a; Moore and Dundee, 1961c). With the phenothiazine derivatives, Dundee and Moore (1961c) demonstrated a very close relationship between the analgesia index of the premedication and the incidence of excitatory phenomena which followed a dose of 1.6 mg/kg methohexitone. Dundee and Moore (1961b) also observed that the pre-operative use of hyoscine increased the incidence of this complication as compared with atropine.

These studies of the effect of a fixed dose of methohexitone used for induction for a standard operation have been extended and table III gives the relevant data with regard to the comparison of atropine and hyoscine premedication. This table leaves little doubt about the undesirable sequelae following the pre-anaesthetic use of hyoscine as far as a standard dose of this barbiturate is concerned. Dundee, Riding, Barron and Nicholl (1961) have made a similar observation when a variable dose of methohexitone was used for a variety of surgical procedures. Preliminary unpublished findings suggest that this also applies to other barbiturates, including thiopentone, but with this latter drug the undesirable effects of the hyoscine were not as marked as with methohexitone.

Although it is not mentioned frequently in the anaesthetic literature, the effect of the antisialogogues on appreciation of pain has already been studied in some detail. In the early papers on pain sensations in man from the Cornell University Medical College, Wolff, Hardy and Goodell (1940) found that a combination of morphine 8 mg and hyoscine 0.4 mg had less effect on the pain threshold than morphine 8 mg alone. Using the same radiant heat method of analgesimetry (Hardy, Wolff, and Goodell, 1940), Christensen and Gross (1948) found that the subcutaneous or intravenous injection of 0.3 mg of atropine or hyoscine did not alter the pain threshold in three subjects. However, this dose shortened the effective analgesic action of morphine 10 mg, methadone 2.5 mg or pethidine 100 mg. When atropine 0.3 mg was injected intravenously 40 minutes after a subcutaneous dose of methadone, the intensity of analgesia immediately began to decrease and the total duration of analgesia was greatly shortened compared with the normal effect of a similar subcutaneous dose of methadone alone. The intensity of pethidine analgesia was not affected by com-

<table>
<thead>
<tr>
<th>Pre-anaesthetic medication</th>
<th>Analgesia index</th>
<th>No. of cases</th>
<th>Per cent incidence excitatory phenomena</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative</td>
<td>Antisialogogue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine 0.6 mg</td>
<td>Hyoscine 0.4 mg</td>
<td>+0.04</td>
<td>146</td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>Atropine 0.6 mg</td>
<td>-0.28</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Hyoscine 0.4 mg</td>
<td>+0.55</td>
<td>150</td>
</tr>
<tr>
<td>Promethazine 50 mg</td>
<td>Atropine 0.6 mg</td>
<td>+0.25</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Hyoscine 0.4 mg</td>
<td>-0.66</td>
<td>60</td>
</tr>
<tr>
<td>Pethidine 100 mg</td>
<td>Atropine 0.6 mg</td>
<td>-0.96</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Hyoscine 0.4 mg</td>
<td>-0.03</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.50</td>
<td>15</td>
</tr>
</tbody>
</table>

BRITISH JOURNAL OF ANAESTHESIA
bining it with atropine or hyoscine, although both drugs decreased the efficacy of morphine and methadone. With the same method of analgesimetry Gross and others (1948) found that atropine 0.3 mg abolished the analgesic action of 25 per cent nitrous oxide and 3 per cent cyclopropane although neither atropine nor hyoscine affected the rise in pain threshold produced by dextramphetamine 10 mg.

Slaughter and Gross (1939) demonstrated that the analgesic action of morphine was potentiated by neostigmine in cats. This finding has been confirmed by Flodmark and Wrammer (1945), and by Komlos, Porszasz and Knoll (1950) in other animals and in man and has been put to clinical use by Slaughter, Parsons and Munal (1940) and Abaza and Gregoire (1952). These latter workers found that the concurrent injection of neostigmine 0.5 mg markedly increased the efficacy of doses of 5 to 10 mg morphine. Christensen and Gross (1948), and Slaughter (1950) have shown that this potentiation applies to codeine, papaveretum, methadone and pethidine, while Bitter (1953) reported good pain relief from levorphanol and neostigmine in patients who were resistant to the analgesic action of the opiate alone. Pyridostigmine was also shown to intensify and prolong the analgesic action of levorphanol (Oehlandt, 1955) while both physostigmine and pilocarpine potentiate the action of pethidine, morphine and methadone (Porszasz, Knoll and Komlos, 1951). It can thus be seen that a variety of widely used anticholinesterases are capable of increasing the analgesic action of the commonly used opiates. Flodmark and Wrammer (1945), and Christensen and Gross (1948) have also demonstrated that neostigmine alone is capable of increasing the pain threshold.

It has been suggested by Slaughter and Gross (1939) that the analgesic action of morphine is due to a depression of the cholinesterase system since it is increased by parasympathetic stimulant drugs. They also found that the morphine-neostigmine potentiation was antagonized by atropine and explained this on the grounds that this agent prevented the cholinergic action of both drugs. This might be considered a reasonable explanation of the findings of the present study also, particularly since atropine and hyoscine and other cholinergic compounds are known to antagonize other cerebral effects of anticholinesterase drugs, such as convulsions (Holmstedt, 1959) and paralysis of the respiratory centre (Krivoy, Hart and Marrazzi, 1951; Douglas and Matthew, 1952) resulting from organophosphorous poisoning. However, more recent work has failed to substantiate the basic premises on which the hypothesis is founded.

Using modern methods of determination of cholinesterase activity, Young and co-workers (1956) were unable to demonstrate a relationship between the analgesic action of a group of opiates and their anticholinesterase activity. Furthermore, they found that levallorphan which has no analgesic action whatever had a greater anticholinesterase activity than any of the opiates studied. It was found by de la Lande and Bentley (1955) that certain concentrations of morphine inhibited acetylcholine synthesis in whole cell preparations of brain and this action was shared by many of the morphine antagonists described by Shaw and Bentley (1952, 1955). Knoll and Komlos (1951) not only found no relationship between the pain relieving effect and degree of cholinesterase inhibition produced in the cerebral cortex by several analgesics but observed that the simultaneous injection of morphine and neostigmine did not increase the cholinesterase-inhibitory activity of the former in the brain. Komlos, Porszasz and Knoll (1950) and Porszasz, Knoll and Komlos (1951) found that one of the most potent anticholinesterases, tetraethylpyrophosphate, was incapable of potentiating the effect of any analgesic substance and concluded that the cholinergic mechanism could not play an important part in synergism either directly or by inhibition of cholinesterase.

It is of interest to consider alternative explanations for the morphine-neostigmine synergism although one cannot say how much they apply to the findings of the present study. Knoll and Komlos (1952) found that the subcutaneous injection of peptone reduced or neutralized the effects of several analgesics. It also minimized the synergism between analgesia and parasympathomimetic drugs. Further studies by Knoll, Komlos and Tardos (1953) implicated a reduction in plasma binding by the anticholinesterase as a possible cause for the morphine-neostigmine synergism. In a series of careful ex-
experiments Komlos and Komlos-Szasz (1954) found that the action of morphine and pethidine was considerably decreased after perfusion through mammalian liver. This action was less marked when liver previously damaged by carbon tetrachloride was used and it was also considerably inhibited by perfusion of the liver with neostigmine. However, if, after its passage through the liver, the weakened analgesic solution was autoclaved for 3 hours it regained its pre-perfusion potency. These findings led the authors to postulate that parasympathomimetic agents potentiate the analgesic drugs by inhibiting those enzymes which normally inactivate a part of the analgesic molecule. This theory was supported by the observation that injection of the neostigmine 25 minutes after morphine—when its inactivation could not be markedly affected—produced a negligible increase in its analgesic action.

Thus it would appear that anticholinesterases may potentiate analgesics by some interference with the normal processes by which they are inactivated but there is no evidence to show that either atropine or hyoscine antagonizes these drugs by hastening their inactivation.

APPENDIX

CALCULATION OF THE ANALGESIA INDEX

Drugs were studied using the "double blind" technique and with the large number of preparations under study at the same time, it was unlikely that any single operating list would include more than two cases who received the same premedication. The changes in threshold and response readings produced by each preparation were noted at the end of the operating session and the analgesia index of the cumulative total was calculated. The study was continued until the analgesia index, calculated on five or six successive occasions (with an increasing total number of observations) was fairly constant. Thus it could be ensured that this index gave an accurate reflection of the overall action of the drug.

Figure 4 illustrates the results obtained when atropine 1.3 mg and hyoscine 0.4 mg were studied. At the beginning of the study, when the number of cases was small, the analgesia index, calculated on successive days, fluctuated widely. As the series increased so the denominator in the formula for calculation of the analgesia index became greater and eventually a constant value was obtained on five successive occasions with each drug.

ACKNOWLEDGMENTS

We are indebted to the many surgeons who co-operated in this study, to Mr. D. T. Smith for the illustrations and to Mr. R. A. Wood for the photographs. Generous supplies of hyoscine (Scopolamine) were provided by Roche Products Ltd., while May and Baker Ltd. prepared the ampoules containing pro-methazine and the perphenazine was supplied by Allen and Hanbury Ltd.

REFERENCES


RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA—VIII

571


CORRECTION

It is regretted that in the September issue of the Journal the following figures were inverted:

Page 437: figure 4
Page 477: figure 2