STUDIES OF DRUGS GIVEN BEFORE ANAESTHESIA
IV: ATROPINE AND HYOSCINE

BY

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SUMMARY

The effects of intramuscular injection of atropine (0.6 mg), hyoscine (0.4 mg) and a placebo have been compared as premedication. Atropine did not differ from the placebo with regard to sedation and relief of apprehension but did produce a higher incidence of tachycardia. Hyoscine produced a high incidence of good or fair sedation and a very low incidence of tachycardia. The relative slowing of the heart compared with the placebo may be because of the good sedation or may be a specific action of the drug. Anaesthesia with methohexitone and nitrous oxide showed a higher incidence of excitatory phenomena after hyoscine than after atropine. Respiratory upset (hiccough) was reduced by hyoscine, as was the incidence of emetic sequelae in the first hour after anaesthesia.

Atropine has been given for premedication since 1861 (Duncum, 1947) and, during the century since then, its use has become an immutable habit. The main purpose of giving atropine has been to prevent vagal cardiac arrest and to reduce the quantity of secretions in the mouth and respiratory tract provoked by volatile anaesthetics and suxamethonium. It was observed by Dastre in 1890 (quoted by Shearer, 1960) that only in doses of 1 mg/kg could atropine produce complete vagal block. Its value in clinical doses in preventing cardiac standstill was therefore doubtful. Even in doses of 0.6 mg, however, it reduces secretions to some extent (Mushin, Galloon and Lewis-Faning, 1953; Galloon, 1956; Wyant and Dobkin, 1957). Langley (1878) and Wyant and Dobkin (1957) found hyoscine a more potent antialgesic.

Atropine has a transient antanalgesic effect (Dundee, Nicholl and Moore, 1961; Moore and Dundee, 1962) which has passed away about 60 minutes after intramuscular administration. On the other hand, hyoscine has a more prolonged antanalgesic action and antagonizes the analgesic actions of morphine and pethidine used in premedication.

Several authors have recently doubted the value of routine atropine premedication (Ruben, 1961; Eger, 1962; Tomlin, Conway and Payne, 1964) and Holt (1962) has forthrightly condemned such use. The purpose of this paper is to report a study of the value of atropine and hyoscine with regard to pre-operative sedation and relief of apprehension, and also to ascertain the incidence of toxic side effects. Their efficacy in preventing the emetic effects of opiates will be discussed in a later publication.

It is believed (Goodman and Gilman, 1955) that in clinical doses (0.5–1 mg) atropine stimulates only the medulla, having no effect on the cerebral cortex. In toxic doses it has an excitatory effect, causing restlessness, irritability and delirium. Hyoscine, on the other hand, in doses of 0.4 mg causes drowsiness, euphoria and amnesia, and occasionally restlessness and delirium, although opinions differ as to the frequency and degree of amnesia (Lambrechts and Parkhouse, 1961; Hardy and Wakely, 1962). To evaluate these drugs under controlled and identical conditions is clearly desirable and both have here been compared with a placebo.

The anti-emetic properties of atropine are undoubtedly less than those of hyoscine (Isaacs, 1956; Greene et al., 1961; Dundee, Armstrong and Alexander, 1964). Holt (1962) goes so far as to say that the usual dose is "useless" in this context.
respect. Riding (1960), in a clinical study of postoperative vomiting showed that this is not strictly true and that it has a definite anti-emetic action. In the present series the incidence of pre-anesthetic emetic symptoms after medication with placebo, atropine and hyoscine is compared, while postanaesthetic vomiting and nausea are compared after atropine and hyoscine premedication.

**METHOD**

**Pre-operative effects.**

Drugs were made up in quantities of 1 ml, each consisting of saline (placebo), atropine 0.6 mg or hyoscine 0.4 mg. These were given by intramuscular injection in random order to patients before minor gynaecological procedures. The advantages of both the choice of these subjects and the method of study have been discussed by Dundee, Moore and Nicholl (1962a). This latter briefly requires a subjective assessment of the desired effects (drowsiness, apprehension and absence of restlessness or excitement) and an objective evaluation of side effects (persistent pain at injection site, dizziness, emetic symptoms, tachycardia and hypotension). To each of these groups is assigned a score (efficacy or toxic) according to their intensity. The efficacy score varies from 5 (good sedation with no apprehension) to 1 (no sedation and marked apprehension or restlessness). A toxic score of 1 signified absence of side effects and one of 5 indicated the occurrence of very severe complications. The difference between these is referred to as the "net" score.

With each drug, two sets of observations have been carried out as follows:

(a) Index reading. Patients are seen only between 60 and 90 minutes after injection. The desired effects noted at that time only are recorded whereas side effects include those noted by the patient since the time of the injection.

(b) Detailed observations. Patients were seen approximately 20, 40, 60 and 90 minutes after administration of drugs and desired and side effects noted at these intervals. The results from each patient having "detailed observations" were also included in the "index reading".

Table I gives details of patients in these two groups and shows that observations were made on subjects who were broadly comparable as regards age and weight.

**Course and sequelae of anaesthesia.**

Dundee, Moore and Nicholl (1962b) emphasized the importance of studying the effects of premedication on the course of anaesthesia when using a standard technique, and recommended that methohexitone followed by nitrous oxide and oxygen is most suitable for this purpose. These authors describe the anaesthetic technique in detail and list the observations made.

Since the present investigation was carried out in conjunction with studies of other intravenous agents, the number of cases receiving methohexitone is limited. There are no data on patients who received a placebo only.

Emetic sequelae can also be related to the premedication (Riding, 1960), and Dundee, Nicholl and Moore (1962) have described a method for recording and analyzing the incidence and severity of this complication. Data here are limited to those obtained in the cases anaesthetized with methohexitone, nitrous oxide and oxygen.

**RESULTS**

Table II shows a comparison between atropine, hyoscine and placebo when studied 60–90 minutes after administration (index reading). In all the desired effects atropine does not differ significantly from the placebo and the slightly higher efficacy score is due to the higher incidence of

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**Table I**

<table>
<thead>
<tr>
<th>Details of patients for pre-operative studies.</th>
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<tbody>
<tr>
<td><strong>Index only</strong></td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Average age</td>
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<td>Average weight (kg)</td>
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apprehension with placebo. Hyoscine provides significantly better sedation and less apprehension than either of the other agents.

Pooling toxic scores 3, 4 and 5 (because of small numbers) it was found that the placebo was significantly less toxic than atropine ($\chi^2=17.75$; df 2; P<0.01) or hyoscine ($\chi^2=9.64$; df 2; P<0.01). In the case of atropine, tachycardia was the troublesome side effect, while the administration of hyoscine was followed by a high incidence of dizziness, persistent pain at injection site, and emetic symptoms. Heart rate was much slower following hyoscine than after either atropine or the placebo. Even allowing for its increased toxicity, hyoscine gave a much higher net mean score than either of the other two injections.

Results of detailed observations (figure 1) show that about one-fifth of all pre-operative patients become sleepy if left screened off for an hour, even if no active drug is given. In this group the percentage who admitted to being worried about the thought of the operation did not change during the period of the study, although the frequency of restlessness increased slightly with time. These findings were not very much affected by atropine.

The maximum sedative action of hyoscine, as judged by the incidence of drowsiness and lack of apprehension, did not occur until about 1 hour after its administration, although even 20 minutes after injection its effect was significantly different from that of both atropine and a placebo.

Pulse rate remained fairly constant after administration of the placebo, while with atropine tachycardia occurred 20 minutes after administration and reached its peak in severity and frequency 40 minutes after injection. It was surprising to find that this side effect persisted for at least 90 minutes. In contrast pulse rates in excess of 100 beats/min were very infrequent during the first 90 minutes after injection of hyoscine. An unexpected side effect was the higher incidence of persistence of pain at the injection site following hyoscine, as compared with atropine or the placebo.

The study of the effects of hyoscine on the course of methohexitone anaesthesia was limited to 50 cases, because of the high incidence of excitatory phenomena found by Dundee and Moore (1961). Table III confirms that hyoscine is an unsuitable agent for use as sole premedication.

### Table III

<table>
<thead>
<tr>
<th>Percentage incidence of complications and sequelae with methohexitone anaesthesia following premedication with atropine or hyoscine.</th>
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</thead>
<tbody>
<tr>
<td>Number of cases</td>
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<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Course of anaesthesia</td>
</tr>
<tr>
<td>Excitatory phenomena</td>
</tr>
<tr>
<td>Respiratory upset</td>
</tr>
<tr>
<td>Hypotension 20 mm Hg +</td>
</tr>
<tr>
<td>Satisfactory anaesthesia (grades 1 and 2a)</td>
</tr>
<tr>
<td>Awake 2 min after end of operation</td>
</tr>
<tr>
<td>Emetic sequelae</td>
</tr>
<tr>
<td>First hour after operation</td>
</tr>
<tr>
<td>1-6 hours after operation</td>
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<tr>
<td>First 6 hours after operation</td>
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</tbody>
</table>
### Comparison of Placebo, Atropine and Hyoscine

<table>
<thead>
<tr>
<th>EFFECT</th>
<th></th>
<th>PLACEBO</th>
<th>ATROPINE</th>
<th>HYOSCINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apprehension</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Injection-site</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>%</td>
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<td></td>
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<tr>
<td>Heart rate</td>
<td>%</td>
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</tbody>
</table>

**FIG. 1**

Comparison of placebo, atropine and hyoscine, at 20, 40, 60 and 90 minutes after injection.

- **Drowsiness**: Solid area = good and fair. Hatched area = slight.
- **Apprehension**: Solid area = marked and moderate. Hatched area = slight.
- **Heart rate**: Solid area = 140+. Hatched area = 120–140. Stippled area = 100–120.
cant before anaesthesia with methohexitone, nitrous oxide and oxygen, although it is associated with a decreased incidence of cough and hiccough as compared with atropine. There is also some evidence of delay in recovery following hyoscine.

Hyoscine also caused a significant reduction \((P<0.05)\) in the incidence of emetic sequelae following methohexitone, as compared with atropine, but this was entirely due to a lowered incidence during the first hour after operation.

**DISCUSSION**

The findings show that the commonly used dose of atropine does not cause cortical stimulation, and there is no reason to believe that it will decrease the sedative effect of other premedicants. It does not appear to reduce apprehension. As expected, hyoscine had good sedative effects, causing drowsiness and decreased apprehension, with no evidence of restlessness or excitement. The absence of the latter complications may be related to the comparatively young age of the group of subjects in this study.

The persistent pain following hyoscine might be associated with its prolonged antanalgesic action (Dundee, Nicholl and Moore, 1961), since this was also found after promethazine and pceazine (Dundee, Moore and Clarke, 1963).

The study shows that, in the doses used, neither atropine nor hyoscine can be considered as nontoxic drugs. The tachycardia produced by atropine comes on soon after its administration and persists, to some degree, for at least 90 minutes. Dizziness which frequently follows the use of hyoscine also persists for at least 90 minutes after its administration.

There are differences of opinion concerning the effects of atropine and hyoscine on pulse rate. The present study demonstrates tachycardia following atropine and bradycardia following hyoscine, relative to the findings with the placebo. Tachycardia with atropine cannot be attributed to its stimulating action, since the incidence of drowsiness and restlessness was approximately the same after atropine as after the placebo. The slower pulse rates after hyoscine may be in part due to the higher frequency of drowsiness and lower incidence of apprehension after this drug. However, two agents have very different actions on the cardiac vagus as shown by the inability of hyoscine (relative to atropine) to protect the heart from the slowing action of suxamethonium (Bullough, 1959; Foster, 1961; Dundee and Moore, 1961).

The intravenous route was used in most of the reported studies on the effects of the drugs on heart rate, and the findings are not applicable for comparison with the present study. When atropine was given intravenously, Morton and Thomas (1958) demonstrated a biphasic effect manifested by slowing followed by tachycardia, the rapidity of onset of the latter increasing with dosage. Orkin, Bergman and Nathanson (1956) also demonstrated this after intravenous hyoscine. However, they found a more marked and more prolonged tachycardia with atropine 0.6 mg than with hyoscine 0.4 mg. Gravenstein, Andersen and de Padua (1964) studied this action in male volunteers using equal doses of atropine and hyoscine and concluded that low doses of both drugs decreased and large doses accelerated the heart rate.

Lomholt (1946) and Pedersen (1963) found cardiac slowing following the subcutaneous and intramuscular injection of hyoscine. The present authors attempted to compare the effects of equal \((0.6 \text{ mg})\) doses of atropine and hyoscine but had to abandon the study because of the intense dryness of the mouth and frequent pre- and postoperative restlessness with this dose of hyoscine. However, the pre-operative heart rate only exceeded 100 beats/min in two out of the twenty patients studied, this is very different from what would have been expected after the same dose of atropine. It must be pointed out that readings taken at 20-minute intervals after intramuscular injection may not detect an initial slowing effect of either atropine or hyoscine, but as far as routine premedicant use is concerned, this study shows clearly that clinical doses of atropine speed the heart more than does the same dose of hyoscine.

Taking into consideration all the factors studied, it would appear that the onset of action and maximum effect of atropine 0.6 mg occurs sooner than that of hyoscine 0.4 mg. The lower incidence of emetic sequelae during the first hour
of anaesthesia when hyoscyamine is used suggests that its action lasts longer than that of atropine. Dundee, Armstrong and Alexander (1964) have shown that this also applies with thiopentone anaesthesia, particularly when these drugs are given in combination with an opiate. The more prolonged analgesic action of hyoscine, as compared with atropine (Dundee, Nicholl and Moore, 1961), also supports the view that the latter has a much shorter action. The very prolonged sedative effect of hyoscine was noted by Gravenstein, Andersen and de Padua (1964) although they found that the cardiovascular effects of atropine and hyoscine given intravenously were of similar duration.

The incidence of excitatory phenomena, when a fixed dose of methohexitone is given after 0.4 hyoscine premedication, is as high as in the preliminary report of Dundee and Moore (1961), and occurred in 95 per cent of the twenty cases given 0.6 mg. This effect, which has been ascribed to the antanalgesic action of the hyoscine, occurs with thiopentone (Dundee, Armstrong and Alexander, 1964), as well as with the two eugenol derivatives, G.29.505 (Riding et al., 1963) and propanidid (Clarke and Dundee, 1965) for this reason hyoscine is less suitable as sole premedicant.

In view of the recent findings of Tomlin, Conway and Payne (1964) that some degree of hypoxia followed the use of atropine premedication, it is important that the need for this and similar drugs be re-evaluated with particular emphasis on their toxicity. It is not the purpose of this paper to suggest the place of atropine or hyoscine in modern anaesthetic practice, but it does show that any benefits they produce are only obtained at the expense of troublesome side effects. If an antisialagogue is really needed in premedication these findings should help to decide the relative merits of the two drugs. Further information is needed on their effects when combined with opiates and other commonly used premedicants.

REFERENCES


ETUDE DES DROGUES ADMINISTRÉES AVANT L’ANESTHÉSIE

IV: L’ATROPINE ET L’HYOSCINE

SOMMAIRE
On a comparé l’effet de l’injection intra-musculaire d’atropine (0,6 mg), d’hyoscine (0,4 mg) et d’un placebo comme prémédication. L’atropine ne se distingue pas du placebo pour la sédation et l’amélioration de l’appréhension, mais elle a produit une incidence plus élevée de tachycardie. L’hyoscine a entraîné très souvent une sédation bonne ou moyenne et très peu de tachycardie. Le ralentissement relatif du coeur, en comparaison avec le placebo, peut résulter soit de la bonne sédation, soit de l’action spécifique de la drogue. L’anesthésie par la méthohexitone et l’oxyde nitreux a causé une incidence plus élevée de phénomènes d’excitation après l’hyoscine qu’après l’atropine. Les perturbations respiratoires (hoquet) ont été réduites par l’hyoscine, de même que les nausées la première heure après l’anesthésie.