ATROPINE AS AN ANTISIALOGOGUE, COMPARED WITH L-HYOSCYAMINE (BELLAFOLINE), SCOPOLAMINE BUTYLBROMIDE (BUSCOPAN) AND OXYPHENONIUM (ANTRENYL)

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The belladonna alkaloids are commonly used in anaesthetic premedication because of their ability to depress salivary activity. This effect is achieved by blocking the response to acetylcholine at the effector organs innervated by postganglionic cholinergic fibres. The drug which is best known and most commonly used is atropine. In recent years another drug of the belladonna alkaloids group has been introduced as an antisialogogue, namely 1-hyoscyamine (Bellafoline, Sandoz), a preparation which contains the pure laevorotatory alkaloids of belladonna leaves. Griggs, Adriani and Berson (1953) reported that 1-hyoscyamine was clearly superior to atropine as a depressor of salivary activity—a conclusion based on their clinical experience. Their finding was confirmed by other authors using more objective methods (Galloon, 1956; Wyant and Dobkin, 1957). Galloon compared the effect of atropine and 1-hyoscyamine by stimulating salivary secretion with lemon juice and collecting the saliva in a measuring cylinder. Wyant and Dobkin stimulated the secretion by injection of carbaminoylcholine chloride (Carbachol), and collected the parotid secretion by means of a plastic suction cup applied to the opening of Stensen’s duct.

Our experience with anticholinergic drugs in the treatment of poisoning indicated that atropine was the most active antidote (Diamant, 1954). Its excellent effect as an antisialogogue was then observed but was not measured exactly. In subsequent experiments, using an exact method for stimulation of the salivary flow, the antisialogogue action of atropine was studied (Diamant and Holmstedt, 1957). Since the results were inconsistent with the conclusions both of Galloon and of Wyant and Dobkin, it was thought worth while to compare atropine with 1-hyoscyamine and two other widely used anticholinergic preparations—scopolamine butylbromide and oxyphenonium—using the method of Diamant, Diamant and Holmstedt (1957).

MATERIAL AND METHODS

Eight patients were selected, ranging in age from 33 to 50, and having no disturbances of the salivary glands or disorders of the circulatory system. The technique, described by Diamant, Diamant, Holmstedt (1957), consists of stimulation of the salivary secretion by intravenous infusion of acetyl-β-methylcholine iodide (Betacholyl; Vitrum) in 0.02 per cent solution. This will be referred to hereafter as methacholine. The infusion is given over two 5-minute periods separated by an interval of 5 minutes. The antisialogogue agent is administered by slow intravenous injection 1 minute after the beginning of the second infusion period. The latter is followed by 5 minutes’ rest and a third infusion period. Throughout the experiment the pulse rate is registered by an automatic electrocardiographic recorder ad modum Johanssen (1958). Figure 1 shows a typical experimental chart.

Drugs.

The drugs used were as follows:

(1) Atropine sulphate 0.05 per cent solution
(1 ml = 0.5 mg) in a dose of 0.5 mg in all experiments except one, in which 1 mg was used.

(2) 1-Hyoscyamine (Bellafoline, Sandoz) in doses ranging from 0.05 mg to 0.5 mg.
(3) Scopolamine butylbromide (Buscopan, B.C.H. Boehringer Sohn) in a dose of 20 mg.
(4) Oxyphenonium (Antrenyl bromide, Ciba) in a dose of 1 mg.

In all experiments the above doses were given regardless of body weight (table I).

RESULTS

Atropine.

Atropine was used in each of the nine cases, the dose being 0.5 mg in eight and 1 mg in one. In all experiments the typical excellent antisialagogue effect of atropine was noted. The pulse rate, which was raised by the infusion of methacholine, dropped after the injection of atropine and remained normal during the second rest period as well as the third methacholine infusion period. In the patient in whom 1 mg of atropine was injected, the pulse rate fell to normal after the injection of atropine. However, it rose again, and remained at a fairly high level as a sign of slight atropine overdosage. These observations were in agreement with earlier experiments (Diamant and Holmstedt, 1957).

1-Hyoscyamine (Bellafoline).

1-Hyoscyamine was used in all subjects, though in varying amounts. In five cases in which 0.5 mg was injected the antisialagogue effect was excellent. Where 0.3 mg was administered, the effect on the salivary secretion was good, but in two other cases in which the dose was 0.1 mg and 0.125 mg respectively the corresponding effect was very slight. In four of the five patients who received 0.5 mg, the pulse rate rose and had not returned to normal 30 minutes after the end of the methacholine infusion, a fact which pointed
to slight overdosage (fig. 2). In the five cases in which 0.3 mg or less of l-hyoscyamine was injected, no toxic effect on the circulation was noted.

**Oxyphenonium (Antrenyl bromide).**

In three patients oxyphenonium was used in a dose of 1 mg and had a very good antisialogogue effect. In one of them a major rise in the pulse rate was observed.

**Scopolamine butylbromide (Buscopan).**

This substance was used in four experiments. The salivary secretion was but little affected and there was an evident, though not marked, effect on the pulse rate.

**DISCUSSION**

**Atropine compared with l-Hyoscyamine.**

As illustrated by table II, atropine in a dose of 0.5 mg was invariably effective as an antisialogogue without producing any toxic side effects. It should be pointed out that the duration of the relevant action was recorded only for 30 minutes after injection of the antisialogogue. The same doses of l-hyoscyamine also had a good antisialogogue effect. No difference was found between the two drugs in their effect on the salivary secretion.

Doses of 0.5 mg atropine and 0.3 mg l-hyoscyamine were almost equivalent in their antisialogogue action; the same applied to 1 mg atropine and 0.5 mg l-hyoscyamine (fig. 2). As regards the side effects of the two drugs, 0.5 mg l-hyoscyamine (the contents of one ampoule) raised the pulse rate, as a sign of slight overdosage. The same was true in most subjects tested with 1 mg atropine, as shown by Diamant and Holmstedt (1957, 1959), and in one of our cases. We used the intravenous route in all our experi-
TABLE II
Effect on the pulse rate and the salivary secretion of atropine, l-hyoscamine, oxyphenonium and scopolamine butylbromide counteracting intravenous infusion of methacholine iodide.

<table>
<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>l-Hyoscamine</th>
<th>Oxyphenonium</th>
<th>Scopolamine butylbromide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 mg (a)</td>
<td>0.05 mg (a)</td>
<td>0.1 mg (a)</td>
<td>0.125 mg (a)</td>
</tr>
<tr>
<td>E.W.</td>
<td>++</td>
<td>++</td>
<td>(a)</td>
<td>(a)</td>
</tr>
<tr>
<td>G.K.</td>
<td>++</td>
<td>(+)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>T.O.</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>S.T.</td>
<td>++</td>
<td>++</td>
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<td>++</td>
</tr>
<tr>
<td>D.W.</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>E.G.</td>
<td>++</td>
<td>– (+)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>A.E.</td>
<td>– (+)</td>
<td>++</td>
<td>– (+)</td>
<td>++</td>
</tr>
<tr>
<td>E.K.</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

= no
(+) = slight
++ = considerable
++ = marked
(a) overdosage affecting the pulse rate
(b) antismologogue effect exerted on the salivary secretion.

ments, since with that mode of administration there was no need to consider all the absorption factors associated with the intramuscular or subcutaneous routes. Other experiments have shown that the effects of atropine administration other than intravenous are far more varied (Diamant and Holmstedt, 1959).

As far as can be judged from our experiments l-hyoscamicine is in no way superior to atropine as an antismologogue. On the contrary, there is a chance of overdosage, since l-hyoscamine is produced in ampoules of 0.5 mg.

Atropine in comparison to Oxyphenonium and Scopolamine butylbromide.

Oxyphenonium and scopolamine butylbromide were used only in seven experiments. Oxyphenonium was evidently an excellent antismologogue, and small doses would probably be as good as atropine. Yet even with this compound there is a risk of overdosage that is not offset by any advantage over the action of atropine (fig. 2).

In our experiments we did not consider the duration of action of the drugs. Nevertheless, we feel that during a long operation repeated injections of an antismologogue are necessary. Other experiments have shown that injected atropine has an effect lasting some 40 minutes. Thereafter a second, smaller, dose should be injected.

Scopolamine butylbromide is a rather weak anticholinergic drug with respect to its action on the salivary glands; but even in the fairly small doses used in our experiments it has a marked action on the pulse rate. This, in conjunction with its slight antismologogue effect, makes it unsuitable as an anaesthetic premedicant.

CONCLUSIONS AND SUMMARY

As far as can be judged from our experiments which, though relatively few, seem conclusive, atropine has a very good antismologogue action in doses which produce no toxic effects. None of the other drugs with which it was compared, i.e., l-hyoscamicine, scopolamine butylbromide and oxyphenonium, was found superior to atropine. Hence, there seems no reason to replace it with any of the other drugs here tested.
REFERENCES


Diamant, H., and Holmstedt, B. (1959). Absorption of atropine as judged by disappearance of cholinergic symptoms. (In manuscript.)
Johanssen (1958). Personal communication.