COMPARATIVE STUDY OF THE EFFECTS OF ORAL AND I.M. ATROPINE AND HYOSCINE IN VOLUNTEERS

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SUMMARY
The effects of equivalent doses of atropine and hyoscine following oral and i.m. administration were assessed on salivary secretion, heart rate, arterial pressure, body temperature, pupillary size, near-point of vision and sweat-gland activity. The ratio of oral to i.m. doses of atropine on heart rate and salivary secretion appears to be 2 : 1 and that of hyoscine on salivary secretion about 5-6 : 1. Following oral administration the effects on the eye are minimal even after the highest doses of the two drugs, while the decrease in salivation is adequate.

The results of a recent countrywide survey (Mirakhur et al., 1978) have shown that more than 60% of anaesthetists routinely give atropine or hyoscine in premedication, and that approximately the same number would prefer an oral anticholinergic drug if such were shown to be effective. Although many studies have compared atropine with other antisialogogue drugs (Galloon, 1956; Wyant and Dobkin, 1957; Wyant and Kao, 1974) few have compared the efficacy of the oral and the i.m. administration of atropine and hyoscine. Möller and Rosen (1968) and Murrin (1973) have evaluated the action of atropine on some indices of cholinergic function after oral and i.m. administration, but neither of these was a true cross-over study. Published observations on the oral administration of hyoscine are confined to its antiemetic efficacy.

Mirakhur, Dundee and Jones (1978) undertook recently a detailed study of the antisialogogue and other properties of glycopyrronium, a long-acting anticholinergic drug. In the present study, carried out on the same volunteers, the effects of atropine and hyoscine (each given at three doses) were observed following oral and i.m. administration. The popularity of the oral route for the administration of diazepam as a premedicant drug (Assaf, Dundee and Gamble, 1975; Gamble, Dundee and Assaf, 1975) prompted us to make this current evaluation in an attempt to administer the anticholinergic drugs orally with diazepam.

METHODS
The volunteers in the study were fully conversant with the methodology, having taken part in a previous study (Mirakhur, Dundee and Jones, 1978). Each received atropine and hyoscine on six occasions (table I) administered in random order. At least 1 week elapsed before the tests were repeated in any one volunteer.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral (mg)</th>
<th>I.m. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Control observations were carried out after resting for a minimum period of 30 min. Following the administration of the drug, measurements were repeated at 30 and 60 min and thereafter every hour for a total of 6 h. Heart rate was measured from the radial pulse; arterial pressure was measured indirectly and recorded as mean arterial pressure (diastolic arterial pressure + one-third of pulse pressure) and oral temperature was taken with a standard clinical thermometer. Pupillary measurements were carried out using a transparent pupil gauge and the visual near-point was measured using an R.A.F. near-point scale. Sweat-gland activity was tested using the method of Wada (Wada, 1950) and salivary secretion was measured according to a modification of the method described by Mushin, Galloon and Lewis-Faning (1953).

The results of the effects on salivary secretion and sweat-gland activity were submitted to a Wilcoxon matched pairs signed-ranks test for the determination
of statistical significance. A paired t test was applied to
the other results. Results from various groups were
compared by a Student t test.

RESULTS
The physical characteristics of the volunteers are
shown in table II.

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. M. G.</td>
<td>Male</td>
<td>87.5</td>
<td>31</td>
</tr>
<tr>
<td>S. G. N.</td>
<td>Male</td>
<td>55.0</td>
<td>40</td>
</tr>
<tr>
<td>H. M. L. J.</td>
<td>Female</td>
<td>43.0</td>
<td>30</td>
</tr>
<tr>
<td>M. G. S.</td>
<td>Male</td>
<td>65.0</td>
<td>30</td>
</tr>
<tr>
<td>R. K. M.</td>
<td>Male</td>
<td>57.0</td>
<td>31</td>
</tr>
<tr>
<td>J. K. L.</td>
<td>Male</td>
<td>65.0</td>
<td>29</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>62.1</td>
<td>31.8</td>
</tr>
<tr>
<td>SD</td>
<td>± 14.85</td>
<td>± 4.07</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>± 6.06</td>
<td>± 1.66</td>
<td></td>
</tr>
</tbody>
</table>

Salivary secretion
All three doses of atropine, when administered
i.m., produced a dose-related decrease in salivary
secretion (fig. 1). This was maximum at 1 h and, at
this time, salivation was reduced to 65, 33 and 16%
respectively following atropine 0.5, 1.0 and 2.0 mg.
The decreases were significant at 1 and 2 h following
0.5 mg, at 0.5 and 1 h following 1.0 mg and at 0.5 and
1 h following 2.0 mg. The maximum decrease in
salivation following oral administration occurred at
2 h. This decrease was minimal with 0.5 mg, but
salivation was reduced to 62% with 1.0 mg and 43%
with 2.0 mg and the decreases were significant at 2
and 3 h following 1.0 mg and between 2 and 6 h
following atropine 2.0 mg.

The effects of hyoscine i.m. on salivary secretion
(fig. 2) were dose-related also. However, the effects
were more pronounced and reached a peak value at
1 h after administration. The mean salivary secretion
was decreased to 42% after 0.25 mg, 21% after 0.5 mg
and to less than 7% after 1.0 mg, and the decreases
were significant from 0.5 to 2 h after 0.5 mg, from
0.5 to 4 h after 0.5 mg and throughout the 6 h after
1.0 mg. Salivary secretion could not be measured at
2 h following hyoscine 1.0 mg i.m. as the volunteers
were deeply asleep. The effects on salivary secretion
following the oral administration of hyoscine were
less marked and reached a peak at 2 h, except with

![Fig. 1. Effect of atropine on salivary secretion by the two routes. Vertical bars represent standard errors of the mean.](image1)

![Fig. 2. Effect of hyoscine on salivary secretion by the two routes. Vertical bars represent standard errors of the mean.](image2)
1.0 mg when the decrease between 1 and 2 h was similar. Doses of 0.25 and 0.5 mg decreased the salivary secretion to a maximum of 83 and 76% respectively. Of these, 0.5 mg produced a significant effect at 2 h only. Following 1.0 mg, however, salivation was decreased significantly, to about 55% between 1 and 2 h. The dose–response curves are shown in figure 3.

**Heart rate**

The maximum effects after the i.m. injection of atropine occurred at 1 h and after the oral administration at 2 h. Atropine 0.5 mg administered by either route induced a slowing of rate which was not significantly different from control. Following i.m. administration of atropine 1.0 mg, the heart rate increased by about 15% after a slight initial bradycardia. Heart rate had returned to near basal values by 3 h. The injection of 2.0 mg increased the heart rate by about 45% without any evidence of an initial bradycardia. The rate was increased significantly from 1 to 4 h after administration. In contrast, atropine 1.0 mg orally did not produce tachycardia; the rate decreased by about 16% at 1 h. However, 2.0 mg orally increased the heart rate by about 13% at 2 h, an effect almost equivalent to that produced by atropine 1.0 mg i.m. at 60 min. The dose–response curves for atropine are shown in figure 4. In contrast, hyoscine produced varying degrees of bradycardia when administered by both oral and i.m. routes. The decreases in heart rate were significant at 2 and 3 h following the administration of all doses of the drug by both routes. The effects of the two drugs on heart rate are shown in figures 5 and 6.

**Sweat-gland activity** (figs 7 and 8)

The effects of the two drugs on sweat-gland activity were similar. The i.m. administration of both agents produced pronounced and significant decreases in the number of active sweat glands which was maximal at 1 h and which returned gradually to basal values over the next 4–5 h. The effects appeared to be dose-related, although the two higher doses of each drug did not differ greatly in their effect. The effects after oral administration were less pronounced and less consistent although they followed the same pattern and were more marked in the case of oral atropine.

**Ocular effects**

Pupillary dilatation, more marked with hyoscine, was noted following the i.m. administration of both drugs. However, this effect had a slower onset and was maximal at 6 h. The i.m. injection of hyoscine 1.0 mg produced the greatest pupillary dilatation in this study. The effects after the greatest i.m. doses of both drugs were significant statistically from 1 h onwards with hyoscine and from 2 h onwards with atropine. The effects of atropine 0.5 and 1.0 mg

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**Fig. 3.** Dose–response curves for effect of atropine and hyoscine on salivary secretion. Doses plotted on a log scale.

**Fig. 4.** Dose–response curves for effect of atropine on heart rate. Doses plotted on a log scale.
given i.m. had similar effects and pupillary dilatation was observed from 3 h onwards and was significant at 5–6 h. The smallest i.m. dose of hyoscine had minimal effects, but 0.5 mg did produce noticeable effects (fig. 10) which were significant at 5 and 6 h. Following oral administration, only the largest dose of atropine (2.0 mg) produced appreciable pupillary dilatation and the effects were broadly comparable to atropine 1.0 mg administered i.m. The two lower doses of atropine and all doses of orally administered hyoscine had negligible effects (figs 9 and 10).

The measurements of pupil size, with a light shining on the eye, showed these effects to be similar to those observed in ordinary room light. However, the pupils reacted sluggishly at 5 and 6 h following the highest dose of hyoscine.

The effects on the visual near-point were similar in their course and intensity to those on the pupil size. Hyoscine i.m. seemed to produce more intense effects which persisted. Oral administration of both drugs produced only minimal effects on near-point vision (figs 11 and 12).

**Subjective impressions**

The most common initial symptom was dryness of mouth and this reflected the decreases in salivary secretion. Drowsiness was the next most common subjective feeling and its intensity was dose-related. The highest i.m. dose of hyoscine produced such intense drowsiness that it was not possible to measure salivary secretion, near-point of vision and sweat-gland activity at 2 h. This was associated with intense restlessness in three volunteers, with an inability to walk without stumbling and irrational behaviour. Surprisingly, the volunteers had hardly any amnesia when questioned later. The i.m. administration of atropine was associated also with drowsiness in all the volunteers. Oral administration of both drugs produced less intense drowsiness, but it occurred later and persisted well after the 6 h of the study. The most persistent subjective effect was blurring of vision. This seemed to be more intense and prolonged with hyoscine. Reading was difficult for more
ORAL AND I.M. ATROPINE AND HYOSCINE

than 16 h after administration of the highest doses of hyoscine i.m.

The effects of the two drugs on mean arterial pressure and oral temperature were minimal, and although statistically significant changes were observed with both drugs, they were small in magnitude.

DISCUSSION

This study was designed to assess the effectiveness of atropine and hyoscine when administered orally and to determine a ratio of oral to i.m. dose. Both atropine and hyoscine are tertiary compounds and should be absorbed well from the gastrointestinal tract. Beermann, Hellstrom and Rosen (1971) showed that atropine was absorbed well from the upper gastrointestinal tract, with the exception of the stomach, between 1 and 2 h after administration. Möller and Rosen (1968) in an earlier study found also that atropine was absorbed well from the gastrointestinal tract, although quaternary anticholinergic compounds were shown to be absorbed poorly. These are not absorbed from the stomach, as both atropine and hyoscine are almost completely ionized at the acidic pH of the stomach contents. Murrin (1973), in a comparison of the effects of atropine administered both orally and i.m., found the ratio for the same peak effect to be 1.86. From our studies we feel that the oral to i.m. ratio for atropine appears to be 2 : 1 as judged by the effects of this drug on salivary secretion and heart rate (figs 3 and 4). Joseph and Vale (1960) thought that the effects were equally satisfactory when 1.3 times the i.m. dose was taken by mouth, while Unna and colleagues (1950) thought the ratio of 3 : 1 more appropriate. Our finding of a 2 : 1 ratio is closer to that reported by Murrin (1973). His study was carried out in adults and consisted of objective measurement of salivary secretion, as in our case, whereas the other two studies were in children and obviously open to errors of measurement. Lomholt (1946) showed that six to eight times the i.m. dose of hyoscine was needed orally for an equivalent effect. His findings were, however, more subjective than objective. Our dose–response curves for the effect of
hyoscine on salivary secretion show a similar ratio for hyoscine. It would appear that hyoscine hydrobromide is not as well absorbed from the gastrointestinal tract as is atropine. This is supported further by the fact that the effects on the eye after oral administration were minimal as maximum doses are needed to produce such effects (Innes and Nickerson, 1975).

In an attempt to explain the findings, pKa values of atropine and hyoscine were determined by the potentiometric method (Albert and Serjeant, 1971) and found to be 7.9 and 9.8 at 25 °C respectively for hyoscine and atropine. Thus atropine is more ionized than hyoscine at the pH of the upper small intestine (7.5–8), yet it seems to be absorbed better. This is contrary to one basic principle of drug absorption. A possible explanation could be the greater lipid solubility of atropine. Also, it could be postulated that hyoscine is metabolized quickly before it reaches its site of action. The metabolism of hyoscine is not well understood.

The delayed onset and the prolonged effect of these drugs on the eye has been explained by Herzheimer (1958) on the basis that the aqueous humor acts as a reservoir. However, clinically it would be an advantage to give hyoscine 1.0 mg by mouth, decrease the salivary secretion, yet minimize the uncomfortable effects on the eye. The same is true for atropine.

The peak effects for both drugs occur after 2 h following oral and 1 h following i.m. administration.

Tachycardia was noted only after the 2-mg oral dose of atropine. While smaller doses are necessary for depression of salivary secretion, higher doses are required for the action on the heart. In this study, inhibition of sweating was accompanied by minimal changes in temperature. The absence of change in arterial pressure may be a result of the fact that the peripheral vascular system has little cholinergic innervation.

Contrary to popular belief, atropine caused drowsiness and hyoscine caused restlessness, especially with the higher doses, an effect assumed to occur only in the elderly. In this regard, quaternary drugs like glycopyrronium could be advantageous on account of their prolonged action and lack of action on the eye (Mirakhur, Dundee and Jones, 1978). Also glyco-
pyrronium has no marked cardiovascular action although neostigmine-induced bradycardia is prevented effectively (Mirakhur, Dundee and Clarke, 1977). Unfortunately, its quaternary structure limits gastrointestinal absorption.

From this study we believe that atropine and hyoscine can be effective premedicants when given orally in the appropriate dose of atropine 2 mg and hyoscine 1 mg. If the antisialogogue action is the main objective, oral administration of either drug is effective, as the degree of tachycardia is less and the effects on the eye are minimal.

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REFERENCES


ETUDE COMPARATIVE DES EFFETS DE L'ADMINISTRATION ORALE ET DE L'ADMINISTRATION INTRA-MUSCULAIRE DE L'ATROPINE ET DE L'HYOSCINE SUR DES VOLONTAIRES

RESUME

On a évalué sur la sécrétion salivaire, la fréquence cardiaque, la tension artérielle, la température du corps, la dimension des pupilles, la vue et l'activité des glandes sudoripares, les effets de doses équivalentes de atropine et d'hyoscine après leur administration par voies orale et intramusculaire. Le rapport entre les doses orales et intra-musculaires d'atropine sur la fréquence cardiaque et la sécrétion salivaire semble être de 2 : 1 alors que celui de l'hyoscine sur la sécrétion salivaire est d'environ 5–6 : 1. Après administration orale, les effets sur l'œil sont minimaux, même après les plus fortes doses des deux médicaments, alors que la diminution de la salivation est adéquate.

VERGLEICHENDE STUDIE DER WIRKUNGEN BEI FREIWILLIGEN VON ORAL UND INTRAMUSKULÄR VERABREICHTEN ATROPIN UND HYOSCIN

ZUSAMMENFASSUNG


ESTUDIO DE COMPARACION ENTRE LOS EFECTOS DE ATROPINA E HYOSCINA ORAL E I.M. EN VOLUNTARIOS

SUMARIO

Se evaluaron los efectos de dosis equivalente de atropina e hioscina, siguiendo su administración oral e i.m., sobre las secreciones salivales, latidos del corazón, presión arterial, temperatura del cuerpo, tamaño de pupila, punto de visión mas cercano y la actividad de las glándulas sudoríparas. La relación entre los efectos que las dosis de atropina oral e i.m. ejercen sobre los latidos del corazón y las secreciones salivales parece ser de 2 : 1 y que la de hioscina sobre la secreción salival es de aproximadamente 5–6 : 1. Siguiendo la administración oral, los efectos ejercidos sobre el ojo son mínimos, aún después de administrarse las mas elevadas dosis de las dos drogas, mientras que la disminución en la salivación es adecuada.