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# The time course of action of (−)-hyoscine after intramuscular injection

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1. Although (−)-hyoscine has been in clinical use for many years, there is little detailed information concerning the speed of absorption or duration of action of the drug after single intramuscular doses.

2. The time course of action of the drug was therefore examined using biological methods, and measurements were made of saliva flow, pulse rate, pupil diameter and mental alertness for up to 8 hr after doses of 0.4, 0.2, 0.1 and 0.05 mg of the hydrobromide.

3. These techniques gave comparable results and peak activity was achieved at 1–2 hr after dose and followed by a gradual decline over the 8 hr period.

4. The results are compared with those of earlier experiments of a similar kind, and discussed in relation to their bearing on both therapeutics and experimental design.

Although (−)-hyoscine has been in widespread clinical use for many years there is very little detailed information in the literature about the speed of absorption or duration of action of this drug after single intramuscular doses. Previous studies of the prevention of motion sickness by drugs have demonstrated that (−)-hyoscine, given by mouth, is the most effective drug available at the present time for protection against symptoms induced by exposure to motion of short duration (Glaser & Hervey, 1951, 1952 ; Glaser & McCance, 1959 ; Brand, Colquhoun, Gould & Perry, 1967). Further, because the drug does not depend for its protective effects on its peripheral parasympathetic blocking action, it has recently been possible to show that the dose level of the drug can be reduced so that side effects are minimized but that a high degree of protection is still maintained (Brand & Perry, 1966 ; Brand, Colquhoun & Perry, 1968). Little is known, however, of the therapeutic value of the drug when given intramuscularly to subjects who have already developed symptoms. It is clear that oral administration of drugs to nauseated or vomiting patients may prove useless, so intramuscular administration could be of great value in the initial management of the condition, followed later by further treatment by mouth. The present investigation was undertaken as a preliminary to studies of the therapeutic efficacy of the drug in patients who had already developed symptoms, in order to gain further information about the time course of action of (−)-hyoscine at various dose levels when given intramuscularly.

**Methods**

Biological methods were used to study the time course of absorption and elimination of the drug because other available techniques are relatively insensitive. The effects of the drug were examined by using groups of eight adult volunteer subjects, each of whom received an intramuscular injection of (−)-hyoscine or an equivalent volume of normal saline according to a double blind randomized crossover design. Four different dose levels were used: 0.4, 0.2, 0.1 and 0.05 mg of the hydrobromide (equivalent to 0.28, 0.14, 0.07 and 0.04 mg of (−)-hyoscine base); observations were then made for up to 3 hr after the 0.4 mg dose and up to 8 hr following the lower dose levels.

Saliva flow was determined by asking the subjects to spit saliva into a 10 ml. beaker for a timed period for 4 min. The saliva was then decanted into a measuring cylinder and the volume determined. The pulse rate was taken for one minute at the radial artery after the subject had been sitting still for 5 minutes. Pupil diameter was measured in standard lighting conditions using a gauge calibrated in 0.25 mm (0.01 inch). A measure of accommodative power was obtained by asking the subject to hold a standard type ($4\frac{1}{2}$ point) at a comfortable reading distance which was then measured to the nearest 5 mm. The subject was asked to indicate his state of mental alertness by making a mark across a 100 mm line, one end of which represented " drowsy " and the other " alert."

**Results**

These are depicted in Figs. 1–4, where they have been plotted as the differences between the mean values which were obtained from the treatment and placebo groups at each time after dose when observations were made. These data were subjected to analysis of variance, and circled points on the graphs indicate that the differences between the means are significant at the 5% level of confidence or better.

Figure 1 shows the effect of the drug on measurements of saliva volume. The depression of salivary flow produced by (−)-hyoscine is shown by an increase in the difference between the mean values obtained from the treatment and placebo groups. After a dose of 0.4 mg of the hydrobromide, a well defined effect was observed after 45 min with a peak action at about 1.5 hr; this was then sustained for up to 3 hr after dose, but circumstances did not permit observations to be made at later time intervals. After dose levels of 0.2 and 0.1 mg, however, it can be seen that peak action began to decline at 3 to 4 hr, although salivation remained significantly depressed for as long as 6 hr after dose. The differences between the mean values obtained after a dose of 0.05 mg were not significant ($P>0.05$) but have been plotted on the same graph because the curve shows the same general trend as that obtained after higher dose levels.

The depressant effect of small doses of the drug on the resting pulse rate is shown in Fig. 2. After a dose of 0.4 mg a significant effect was seen at +30 min and persisted for the 3 hr during which observations were made. (Although this line on the graph lies above that obtained for doses of 0.2 and 0.1 mg, the differences between the means (placebo − drug) are significant from 30 min onwards ($P<0.05$), and the position of the line is a reflection of biological variation in the response of this subject group.) The time course of action of the drug is well seen after dose levels of 0.2 and 0.1 mg, where again a peak effect was achieved within 1 hr, and

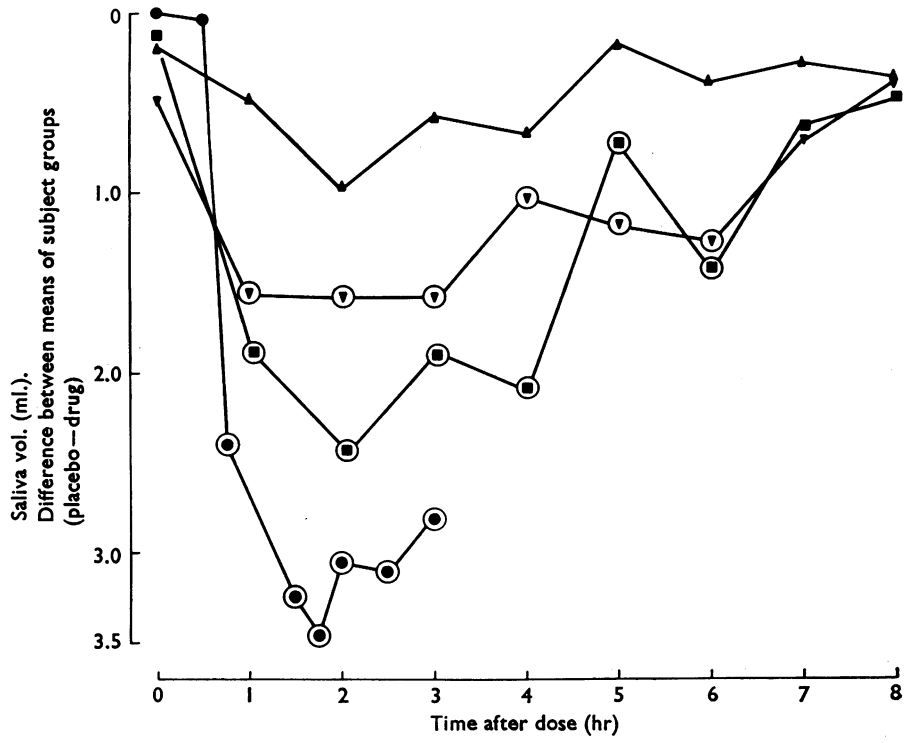


FIG. 1. Time course of action of intramuscular hyoscine on measurements of salivation. ▲, 0.05 mg; ▼, 0.1 mg; ■, 0.2 mg; ●, 0.4 mg. The points represent differences between mean values obtained from two groups of subjects who received drug or placebo at dose levels shown. Circled points indicate differences significant at $P<0.05$ level.

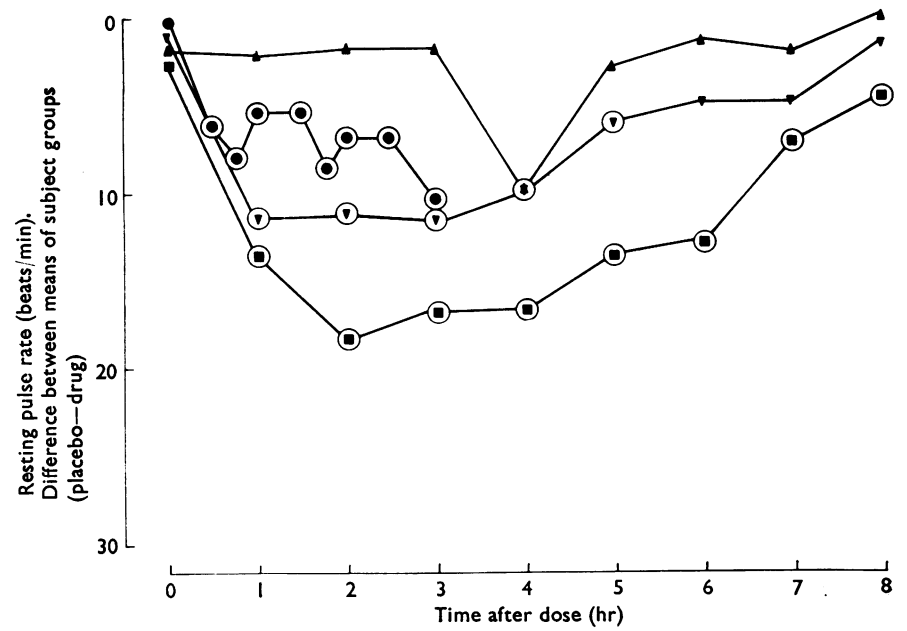


FIG. 2. Time course of action of intramuscular hyoscine on measurements of pulse rate. ▲, 0.05 mg; ▼, 0.1 mg; ■, 0.2 mg; ●, 0.4 mg. Circled points indicate differences from placebo group significant at $P<0.05$ level.

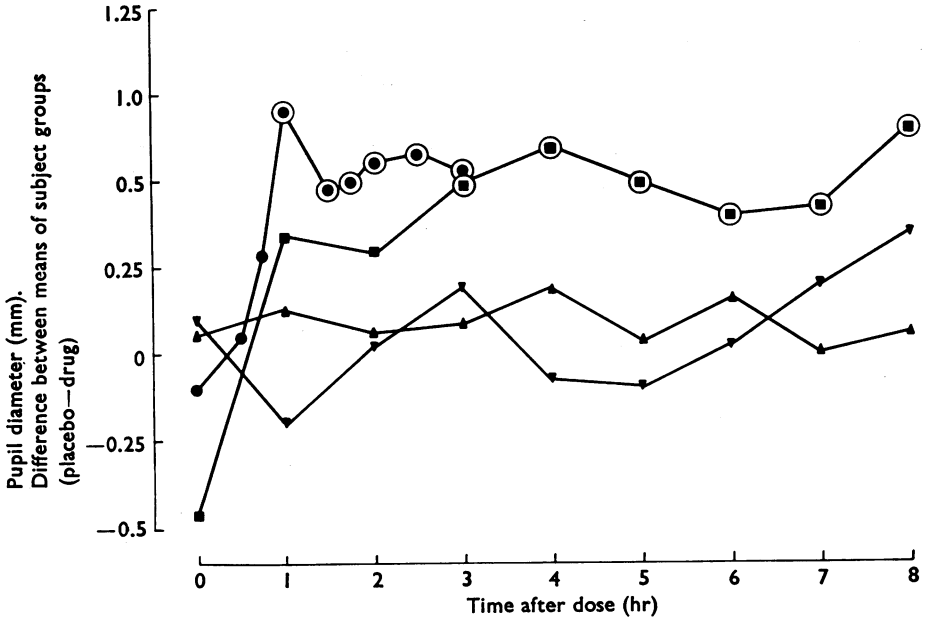


FIG. 3. Time course of action of intramuscular hyoscine on measurements of pupil diameter. ▼, 0.05 mg; ▲, 0.1 mg; ■, 0.2 mg; ●, 0.4 mg. Circled points indicate differences from placebo group significant at $P<0.05$ level.

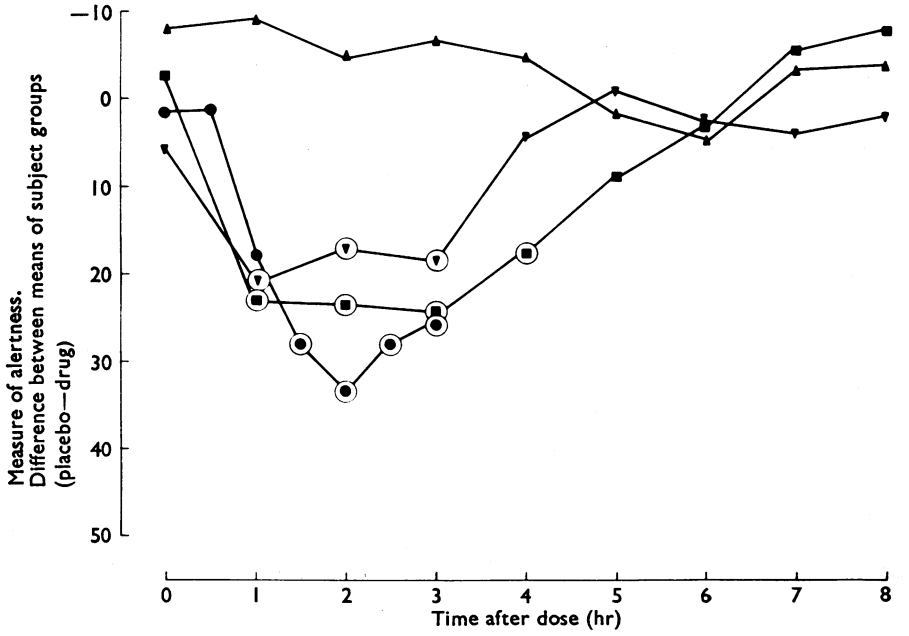


FIG. 4. Time course of action of intramuscular hyoscine on subjective estimate of mental alertness. ▲, 0.05 mg; ▼, 0.1 mg; ■, 0.2 mg; ●, 0.4 mg. Circled points indicate differences from placebo group significant at $P<0.05$ level.

maintained for some 3–5 hr ; the effect begins to tail off after this point, although significant differences were still to be seen at 7 and 8 hr after the 0.2 mg dose. The 0.05 mg dose produced no significant modification of pulse rate.

The results obtained from measurements of pupil diameter are shown in Fig. 3. After dose levels of 0.4 and 0.2 mg, a peak effect was again observed at 1–2 hr after dose: after 0.2 mg this effect was maintained up to 8 hr with no evidence of any diminution of action. Dose levels of 0.1 and 0.05 mg, however, produced no significant effect. The effects of the drug on accommodation were less well defined ; inspection of the data indicates that accommodation for near vision was impaired after the two higher doses, with a peak effect appearing at about 1 hr after dose and lasting for up to 3 hr, but these effects were not significant so they have not been plotted as a graph.

The estimate of the depressive effect of the drug on mental alertness afforded by the line-marking method gave results which were comparable in their time relationships with those derived from the more objective tests. Figure 4 shows that the three higher dose levels exerted a significant effect after 1 hr which was sustained for up to 3 hr, after which there was a rapid decline. No significant effect was produced by the 0.05 mg dose.

## Discussion

A search of the literature reveals very little accurate or detailed information about the measurable effects of (−)-hyoscine after parenteral administration at various dose levels and related to time after dose. Tonndorf, Hyde, Chinn & Lett (1953), however, examined the effects on salivation of 0.65 mg of the hydrobromide given subcutaneously for up to 2 hr after dose, and reported a time course of action similar to that observed after the 0.4 mg dose given in the present experiment. These effects may be compared with those seen when the drug is given by mouth, when, as might be expected, the rate of absorption is somewhat slower and a peak effect does not appear until 2–3 hr after dose and is followed by a rapid decline to baseline levels (Brand *et al.*, 1968). It is also of interest to attempt to relate measurable depression of salivation to subjective complaints of "dry mouth": whereas this symptom was readily recognized by all subjects after doses of 0.4 and 0.2 mg it was much less noticeable after the 0.1 mg dose although significant differences could still be demonstrated between the measured saliva volumes of the treatment and placebo groups.

The effect of the drug on pulse rate has likewise received little attention. Apart from the investigation of Smith & Hemingway (1946), who measured the effect of pulse rate at 1.5 hr after a single oral dose of 0.7 mg of the hydrobromide, no other similar observations could be found. In the present study the effect on pulse rate was similar in its time course to that on salivation, and a peak effect was achieved about 1 hr earlier than when comparable doses were given by mouth (Brand *et al.*, 1968). Once again the effects of intramuscular injection were sustained and significant differences could still be recognized up to 8 hr after a dose of 0.2 mg.

The effect of single intramuscular doses of the drug on pupil diameter was studied by Leopold & Comroe (1948) and by Mehra, Chandra & Khare (1965), who reported a mean increase in pupil diameter of 1 mm at 1–2 hr after doses of 0.4 and 0.6 mg of the hydrobromide ; these findings are comparable with those of the present experi-

ment. The few studies which refer to the effect of the drug on the eye after parenteral administration suggest that larger doses are needed to modify pupil size or power of accommodation for near vision than to depress salivation or pulse rate and that the effects on the eye are relatively prolonged. Thus Chinn *et al.* (1956) reported severe blurring of vision when 0.5 mg of the drug was given by mouth at 6–8 hourly intervals for 2 days, and Glaser (1953), who gave 0.5 mg of the drug twice a day on 5 consecutive days to a group of subjects under controlled conditions, reported a decline in all subjective side effects except blurred vision. In the present investigation, a dose of 0.4 mg of the hydrobromide gave rise to paralysis of accommodation and dilatation of the pupil within 1 hr after dose. Reduction of the dose level to 0.2 mg resulted in the disappearance of any measurable effect on accommodation. It is of particular interest to note, however, that the effect of the drug on pupil diameter persisted and remained significantly different from the placebo group even at 8 hr after dose. This suggests that the effect of the drug on the sphincter pupillae is of relatively long duration and possibly explains the severity of this side effect which was reported in previous studies when repeated doses were given.

Earlier studies of the depressant effects of the drug on mental functions have made use of objective measurements such as the ability to maintain vigilance over a 60 min period or the speed of arithmetical computations (Brand *et al.*, 1968). Drowsiness is a common complaint when the drug is given therapeutically. Doses of (−)-hyoscine base of up to 0.7 mg, however, failed to produce any measurable effect on vigilance or speed of computation at time intervals ranging from 1 to 7 hr after dose. It is interesting to compare these observations with the present findings when subjective drowsiness was readily measurable at 1–3 hr after doses of 0.4, 0.2 and 0.1 mg of the hydrobromide but showed a sharp decline to baseline levels soon afterwards.

All the measurements used in the experiment display comparable time relationships except that the effect of the drug on measurements of pupil size was unexpectedly prolonged and this underlies the need for caution if repeated doses of the drug are to be given. The speed of action and therapeutic value of the drug given parenterally for the treatment of motion sickness in the nauseated subject awaits more precise definition, but the evidence derived from the present experiment should serve as a useful guide to absorption and elimination rates and to the selection of a suitable dose level in further investigations.

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