# CLINICAL PHARMACOLOGY SECTION

## Differential effect of atropine and hyoscine on human learning capacity

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Agents used in anaesthetic premedication impair the subject's capacity for subsequent memory recall, and there is evidence to suggest that hyoscine may be one such agent (Gauss, 1906; Pandit & Dundee, 1970). We have applied simple tests of learning capacity and a vigilance task to twelve normal volunteers after administration of hyoscine (0·4 mg), atropine (0·6 mg), or saline (1 ml) by intravenous injection. Each subject received each treatment in a crossover design.

Three tests of learning capacity were applied in order to assess recall after various intervals—a word list learning with immediate recall (3–30 s), a similar test with delayed recall (60–90 s) and a number-colour association test (20 minutes). The results obtained with these learning tests and the vigilance task are shown in Table 1.

TABLE 1. *Mean number of correct responses ± S.E.M.*

| | Immediate recall | Delayed recall | No. colour associations | Vigilance task |
|---|---|---|---|---|
| Maximum score | 50 | 50 | 7 | 27 |
| Saline | 27·9±1·6 | 14·3±1·3 | 7·0±0·0 | 20·3±1·2 |
| Hyoscine | 24·0±1·3† | 10·2±1·3‡ | 5·9±0·5† | 20·5±1·1 |
| Atropine | 25·9±1·3 | 14·1±1·7 | 6·9±0·1 | 20·3±1·2 |

†$P<0.05$.
‡$P<0.001$ for the comparison with results after saline.

Subjects receiving hyoscine showed a significant reduction in performance on both the delayed recall and the number-colour association tests, but no reduction in the vigilance task, and a much smaller reduction in the immediate recall test. There was no impairment after treatment with atropine. An analysis of the results of the immediate recall test showed that at the shortest intervals (3–12 s) there was no difference between the various treatment groups. According to some recent analyses of human learning processes (for example, Baddeley & Warrington, 1970) short term memory can be distinguished from longer term storage and recall in terms of this distinction our results suggest hyoscine may impair the transition from short to longer term storage without impairing either short term recall or intellectual capacity as assessed by a vigilance task.

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## Relationship of plasma concentrations of levodopa to clinical response in Parkinsonism

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There is a striking absence of a dose-response relationship in the treatment of Parkinsonism with levodopa and a considerable variation in the maximum tolerated

intake. Nausea and vomiting are common adverse reactions in the initial stages of treatment, but these symptoms usually regress. New involuntary movement—dyskinesia—of face, arm or leg is the most frequent dose limiting reaction.

We have studied the plasma concentration of levodopa in thirteen Parkinsonian patients on maximally tolerated oral doses of levodopa before and after treatment with L-alpha methyldopahydrazine (300 mg/day), a selective inhibitor of extracerebral decarboxylation. Before addition of the decarboxylase inhibitor the plasma concentration 1·5 h after the last dose ranged from 0·16 to 2·44 $\mu$g per ml (mean 0·877$\pm$ 0·219 $\mu$g/ml) and at 3 h ranged from 0·04 to 0·58 $\mu$g/ml (mean 0·24$\pm$0·073 $\mu$g/ml). After the administration of the decarboxylase inhibitor the plasma concentration at 1·5 h ranged from 0·20 to 2·27 (mean 1·078$\pm$0·214) and at 3 h it ranged from 0·30 to 1·42 $\mu$g/ml (mean 0·85$\pm$0·157 $\mu$g/ml).

The maximum tolerated dose of levopoda after decarboxylation inhibition was 10–28% (mean 18%) of levodopa alone except in two patients who were able to tolerate 42 and 45% of previous dose after decarboxylation inhibition. In these two patients gastrointestinal side effects were markedly improved and there was a clinical improvement. Both these patients, and only one other, had significantly higher plasma concentrations 1·5 h after a dose. In the remaining ten patients the levodopa dose was limited by dyskinetic movements on both regimens and there was no significant difference in 1·5 h plasma concentrations. The plasma concentration of levodopa at 3 h was higher in all patients when taking the decarboxylase inhibitor than with levodopa alone. The mean maximum tolerated dose of levodopa was 2·97 g/day (range 0·75–5·5 g). With alpha methyldopahydrazine, the mean maximum tolerated dose of levodopa was reduced to 0·67 g/day (range 0·1–1·8 g).

We were unable to detect any relationship between clinical improvement and either oral dose or plasma concentration. This may reflect the problem of accurate quantitative clinical assessment, individual differences in the pharmacokinetics of levodopa, or variation in the facility with which levodopa is decarboxylated to dopamine in the brain.

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**Plasma concentrations of fenfluramine and its metabolite, norfenfluramine, after single and repeated oral administration**

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Plasma concentrations of fenfluramine (Ponderax), the antiobesity agent and its deethylated metabolite, norfenfluramine, have been measured using a gas–liquid chromatographic method (Campbell, 1970).

Six male subjects were given an aqueous solution of fenfluramine hydrochloride (60 mg) on an empty stomach and blood samples (15 ml) were withdrawn at intervals over a period of 48 hours. Absorption of the drug was fairly rapid with maximum plasma concentrations occurring between 2–4 h after ingestion. These remained constant for a further 4–6 h before declining exponentially. The mean peak concentration

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