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 μg per ml (mean 0·877$\pm$ 0·219 μg/ml) and at 3 h ranged from 0·04 to 0·58 μg/ml (mean 0·24$\pm$0·073 μg/ml). After the administration of the decarboxylase inhibitor the plasma concentration at 1·5 h ranged from 0·20 to 2·27 (mean 1·078$\pm$0·214) and at 3 h it ranged from 0·30 to 1·42 μg/ml (mean 0·85$\pm$0·157 μg/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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in five subjects (weights 59–85 kg) was 63±4·5 ng/ml. The sixth subject (weight 121 kg) had a peak concentration of 24 ng/ml and was excluded from the calculation of the mean. Norfenfluramine was detectable in the plasma of all subjects 2 h after ingestion, attaining a maximum mean plasma concentration of 16 ng/ml within 4–6 hours. A constant level was maintained for a further 24–32 hours.

The biological half-life of fenfluramine estimated graphically from the terminal part of the exponential decay curve showed wide intersubject variation with values ranging from 13·8–30·1 h (mean 20·3 h) using a one compartment system.

The apparent volume of distribution was large (635 l. for a 70 kg subject and 2000 l. for a 121 kg subject) indicating extensive uptake of the drug by the tissues and would appear to be dependent on body weight. Preliminary studies in animals, indicate that the muscle and lung contain a large proportion of the drug.

One female and five male subjects ingested one sugar-coated fenfluramine hydrochloride tablet (20 mg) at approximately 8 h intervals for 9–14 days. Blood samples were withdrawn for analysis at the same time of day for each subject at periods throughout the trial. Plasma concentrations of fenfluramine reached a plateau after 3–4 days in all subjects but varied from 40–120 ng/ml. These intersubject variations in steady state concentrations may be explained by differences in the biological half lives and volumes of distribution found between subjects.

The plateau concentrations of norfenfluramine were reached in approximately 3–4 days with plasma concentrations similar to those of the parent drug. Norfenfluramine produces weight reduction in rats and dogs (Beregi, Hugon, Le Douarec, Laubie & Duhault 1970) and therefore this compound may be an active metabolite in humans.

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Pharmacokinetics of inhaled salbutamol in asthmatic patients

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Salbutamol, 2-t-butylamino-1-(4-hydroxy-3-hydroxymethyl)-phenylethanol, is a non-catechol β-adrenoceptor stimulant. It is selective in man, having more effect on β_2 than on β_1 receptors (Paterson, Courtenay Evans & Prime, 1971), and has become widely used as a pressurized aerosol in the treatment of asthma.

Studies were carried out in four asthmatic patients. The drug was inhaled from a specially prepared pressurized aerosol, which delivered 0·1 mg of ^{3}H-salbutamol per dose. Venous blood samples were taken at appropriate intervals, and urine was collected for 48 hours. Changes in lung function were measured using a Vitalograph.

In two patients who received two doses the peak plasma concentrations were 2·95 and 3·57 nM, and in the two subjects who inhaled four doses the peak concentrations were 4·41 and 5·69 nM. The peak plasma concentrations were seen at 3–4 h after inhalation, and the average half life of plasma activity was 4·6 h (range 3·1–7·1 h).