PLASMA PEMPIDINE CONCENTRATIONS IN HYPERTENSIVES

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Pempidine (1:2:2:6:6-pentamethylpiperidine) is a fully saturated heterocyclic tertiary amine with a powerful blocking action on autonomic ganglia. It has the following formula:

It is widely used in treating severe hypertension, and when administered orally as the hydrogen tartrate it is completely absorbed and thereafter excreted rapidly in the urine (Harington *et al.*, 1958). Hitherto, concentrations of pempidine in the blood of patients treated with the drug could not be measured because existing analytical methods were too insensitive. However, a technique described by Muggleton and Reading (1959) has now made it possible to estimate the amount of pempidine in plasma from patients having single or repeated (maintenance) oral doses, which embrace the whole range normally used in clinical practice. Plasma pempidine concentrations have therefore been studied with reference to the hypotensive effect of the drug. Also, data obtained from hypertensive out-patients on maintenance treatment have been compared with plasma concentrations of pempidine found in similar patients treated in hospital.

Materials and Methods

All the patients in this series of studies had severe hypertension with retinitis, hypertensive heart failure, or severe symptoms. Except where otherwise stated, the blood urea was normal.

Preliminary measurements established that the concentration of pempidine in plasma reached its peak some two hours after an oral dose and was negligible at the end of six hours. Throughout the study, except where otherwise stated, blood samples and blood-pressure (lying and standing) were taken just before the dose, and at one, two, four, and six hours thereafter. All blood samples were heparinized, and centrifuged to separate the plasma. The hypotensive response was assessed by the fall in blood-pressure on standing.

Ten fasting patients received their first dose of 2.5 to 10 mg. of pempidine, administered as the hydrogen tartrate either in the standard tablet (eight patients) or dissolved in water (two patients). In three cases urine passed during the six-hour period of observation was collected and the amount of pempidine determined.

Eight patients receiving maintenance treatment in hospital were given 2.5 to 25 mg. of pempidine four times daily, at 6 a.m., noon, 6 p.m., and 11 p.m. The pempidine concentration in plasma and the hypotensive response were measured after the noon dose according to the schedule described above. Two uraemic patients, whose blood-pressures were controlled with twice-daily doses of pempidine, were studied for several days after beginning treatment to find out whether impaired renal function gave rise to progressively increasing concentrations of pempidine in the plasma.

Observations were also made in 30 out-patients during routine visits to the hospital hypertension clinic. Their blood-pressures had all been stabilized with pempidine during a previous stay in hospital. The blood-pressure, lying and standing, was measured, a blood sample was taken, and the time of the last dose (reported by the patient) was recorded. Most of the patients were examined only once, but in four cases estimations were made on two or more occasions.

The methods of analysis of plasma and urine used in the present investigation were largely as described by Muggleton and Reading (1959). Plasma concentrations of pempidine were measured by the eosin fluorescence technique, which was slightly modified to achieve even greater sensitivity than before. A more powerful radiation source was employed (Mazda 250-watt mercury vapour lamp, type ME/D), so that only 1 ml. of plasma was required for the assay. To the plasma was added 0.5 ml. of 10 N sodium hydroxide solution, and the pempidine was extracted with ether (4 × 2 ml.). The base was taken into N hydrochloric acid (1 × 0.5 ml.) to which was next added 0.5 ml. of 10 N sodium hydroxide before extracting the pempidine with xylene (3 × 2 ml.). 5 ml. of this solution and 1 ml. of the eosin reagent were finally mixed in the sample cell and transferred to the fluorescence apparatus. Recoveries were close to 80% and were very reproducible. The blank obtained with plasma which contained no pempidine was rather high ($\approx 0.045 \mu\text{g.}$ of pempidine per ml.) but showed only very small variations from sample to sample. Thus for 26 samples the pempidine equivalent of the blank was $0.045 \pm 0.002 \mu\text{g./ml.}$, and this value was used throughout the present work. The total error in the plasma concentrations of pempidine is thought not to exceed $0.003 \mu\text{g./ml.}$ Estimations of pempidine in urine were carried out by the methyl-orange method.

Results

Single-dose Studies.—The observed concentrations of pempidine in plasma after a single oral dose are summarized in Table I. This demonstrates a striking consistency in the measurements which made it possible to predict quite accurately the amount of

TABLE I.—Plasma Concentrations of Pempidine in $\mu\text{g./ml.}$ for Six Hours After a Single Oral Dose

Case No.	Pempidine Dose (mg.)	Form of Dose	Hours After Dose				
			0	1	2	4	6
1	10	Tablet	0	30	53	—	3
2	10	"	0	26	47	—	6
3	10	"	0	30	59	35	3
4	10	"	0	28	58	26	7
5	5	"	0	17	32	—	3
6	5	"	0	15	29	12	4
7	2.5	"	0	7	16	7	2
8	2.5	"	0	9	18	8	2
9	5	Solution	0	20	53	19	2
10	2.5	"	0	11	20	8	1

pempidine in plasma at any time after a stated dose. After a single oral dose the plasma concentration of pempidine increased rapidly to a maximum in about two hours, after which it fell to a very low value within six hours. The hypotensive response showed a similar variation with time (Fig. 1). The peak value of the

FIG. 1.—Plasma pempidine concentration and hypotensive response after a single 10-mg. oral dose in a previously untreated patient.

plasma concentrations of pempidine were obtained than when it was given in tablet form (Table I).

Maintenance-dose Studies.—With four daily doses of pempidine the peak values in plasma were higher than those found after a single dose (Table II). In addition, the response curve showed considerable broadening. In Fig. 3, curve *a* was obtained after a single 5-mg. dose of pempidine and curve *b* after stabilizing the same patient on a regime of 5 mg. four times daily. Again the plasma concentration increased with the amount of drug given, though the correlation was not so striking as it was with single doses.

Studies on Patients with Renal Failure.—Two uraemic hypertensive patients (blood urea 240 and 250 mg./100 ml.) were studied for four and six days respectively after starting treatment with pempidine. Each received 2.5 mg. twice daily, and blood samples were taken after the morning dose. On this small dose there was no increase in the concentration of plasma pempidine from day to day.

FIG. 2.—The two-hour plasma concentrations after single oral doses of pempidine in previously untreated patients.

TABLE II.—Plasma Concentrations of Pempidine in $\mu\text{g./ml.}$ for Six Hours Following a Maintenance Dose

Case No.	Pempidine Dose (mg.)	Hours After Dose				
		0	1	2	4	6
11	25	115	192	237	204	127
12	10	5	48	68	52	14
13	10	0	21	51	23	2
14	5	3	24	33	27	5
15	5	3	30	49	27	1
16	2.5	0	8	30	15	2
17	2.5	0	7	31	8	3
18	2.5	3	11	30	13	4

Studies on Out-patients.—Using data from the maintenance-dose studies, standard curves were constructed so that a "predicted" value for the plasma pempidine concentration at the time of examination could be computed from the size and time of the last dose reported by the patients. Some patients were receiving chlorothiazide in addition to pempidine, and in such cases different standard curves were used to obtain the "predicted" concentrations, which are about two and a half times those for the same amounts of pempidine without chlorothiazide (Dollery *et al.*, in preparation). The "predicted" values were plotted against the values actually measured. Ideally, all the points should have fallen on the straight line shown in Fig. 4: in fact, 75% of the results were within $\pm 50\%$ of the predicted values, and these limits are indicated by the dotted lines. Only two patients (6%) had no pempidine in the plasma, and a further four (12%) had less than half the predicted value. Three patients (9%) had pempidine concentrations more than 50% higher than the predicted values; of these, two had impaired renal function with blood ureas of over 50 mg./100 ml.

FIG. 3.—Plasma concentrations after a 5-mg. oral dose of pempidine given (a) as a first dose, and (b) as a six-hourly maintenance dose.

FIG. 4.—"Predicted" and "observed" values of plasma pempidine concentration in out-patients.

Discussion

The dose/plasma-concentration relationship observed after single and multiple doses of pempidine is remarkably consistent, and this may well be the most important reason why the drug is so satisfactory in practice. Only if a drug has a constant, and therefore predictable, effect is it possible to achieve the delicate balance between inadequate control of blood-pressure and troublesome hypotension that is so necessary for

successful treatment. The results suggest that the hypotensive response to pempidine when given alone runs parallel to the plasma concentration rather than to the total amount in the body; for, despite the fact that the hypotensive response is small and the plasma concentration negligible six hours after an oral dose of pempidine, more than 75% of the dose must still be in the body, because there is no evidence that the drug is metabolized.

Work on rats (Harington *et al.*, 1958; Muggleton and Reading, 1959) has shown that pempidine is concentrated in liver, kidney, and spleen, and it is reasonable to suppose that this may also apply in man. After oral administration of pempidine three processes will account for the characteristic shapes of the response curves obtained with isolated and maintenance doses. These are (1) absorption of the drug, (2) passage into the tissues, and (3) renal excretion. For a single dose the peak of the curve is sharp and the steep falling limb represents loss of drug from the blood by both (2) and (3) because the tissues initially contain no pempidine. With a maintenance dose, however, the curve is broader and initially less steep because the tissues already contain pempidine, so that (2) is relatively unimportant and (3) alone is largely responsible for removal of drug from the blood.

The two uraemic patients were given pempidine twice instead of four times a day. In one of them the peak plasma concentration of pempidine after 2.5 mg. was the same (30 $\mu\text{g.}/\text{ml.}$) as that found in patients with a normal renal function after the same dose. The plasma concentrations showed no tendency to rise from day to day, and, despite the severe impairment of renal function, there was no evidence of pempidine accumulating in the body.

Three-quarters of the out-patients had plasma concentrations of pempidine within $\pm 50\%$ of the expected value, many of the values being much closer. Only two patients had no pempidine in their blood, and one of these had a satisfactory level at a later examination. The sample may be unavoidably biased, since patients may be more inclined to take their doses of pempidine before attending the clinic than at any other times, knowing that a satisfactory pressure, with a good postural effect on standing, wins approval. In several cases where blood-pressure control was not satisfactory a low plasma pempidine concentration was expected, but this did not prove to be the case. Such instances of escape from drug control are known to occur from time to time.

The conscientiousness of patients on long-term regimes of treatment is an important problem of present-day medicine. Other studies, most notably with *para*-aminosalicylic acid in the treatment of tuberculosis, have suggested a greater tendency to depart from the prescribed dose regimes than was indicated by our results. Indeed, Dixon *et al.* (1957) concluded that less than half of their tuberculous patients who were supposed to be taking *para*-aminosalicylic acid were in fact excreting it in their urine. Many factors must play a part: the bulk and side-effects of the drug, the severity of symptoms before treatment, and, perhaps most important of all, the patient's attitude to his disease. Our results show a gratifying degree of co-operation by the patients. It must be remembered, however, that all had severe symptoms of hypertension before treatment; they were therefore probably more

conscientious than patients with only mild hypertension, who are less willing to accept the unpleasant side-effects of ganglion blockade. Careful follow-up in a special clinic where the patients always see the same doctors may also help to create a feeling of mutual trust.

Summary

A new sensitive method of estimation has allowed the measurement of plasma pempidine concentrations over the whole range of dosage used in practice. The plasma concentration, which was remarkably predictable for a given dose, was found to be closely related to the fall in blood-pressure on standing. Data from patients in hospital have been used to predict the plasma concentrations of the drug in out-patients: 75% were found to have concentrations within $\pm 50\%$ of the expected values, suggesting reasonably good co-operation by the patients.

We gratefully acknowledge the valuable technical assistance given by Mr. A. F. Ivens, who carried out the fluorescence measurements. Thanks are due also to Dr. H. W. Reading, who examined the urine samples, and to Dr. H. Campbell and Professor J. McMichael, F.R.S., for their interest and support.

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CHLOROTHIAZIDE IN TREATMENT OF HIGH BLOOD-PRESSURE

RESULTS OF A CONTROLLED TRIAL

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Chlorothiazide has been stated by many observers to enhance the effects of a number of agents used in the treatment of patients with hypertension. Others have found that it reduced the blood-pressure when given by itself. A controlled trial of its effect when used with ganglion-blocking agents has not been carried out, nor, at the time when this work was started, had such a trial been carried out in which chlorothiazide was used alone. We present the results of a double-blind trial of the effect of chlorothiazide used both with ganglion-blocking drugs and alone in the treatment of high blood-pressure. Ganglion-blocking agents produce side-effects which are noticed by the patient and are reported to the observer. This difficulty is commonly held to invalidate an attempt at a controlled trial of these drugs, but in the group of patients here presented it proved not to be of importance.

Methods

Seventeen patients with essential hypertension, of whom 10 were being treated with mecamlamine and