sources of mycobacterial infections. It has also been shown that there is a qualitative difference between these two P.P.D. preparations as well as a quantitative difference.

Evidence is presented suggesting that as well as an increase in the incidence of tuberculin sensitivity with age there is also an increase in size or intensity of reactions with age.

There is also evidence from the material presented and from other sources that type-specific P.P.D.s give early intense reactions (24 hours) whereas reactions to a heterologous P.P.D. are delayed, reaching their greatest intensity at 72 hours or later.

Limitations of our knowledge of the materials and the technique of comparative tuberculin-testing of human subjects are reviewed.

Other aspects of comparative tuberculin-testing requiring fuller investigation are mentioned.

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PEMPIDINE FOR HYPERTENSION

EXPERIENCES IN AN AFRICAN HOSPITAL

BY

K. SOMERS,* M.B., B.Ch., M.R.C.P., D.C.H.

From the Department of Medicine, Makerere College Medical School, and the Medical Division, Mulago Hospital, Kampala, Uganda

Ganglion-blocking compounds remain the sheet-anchor of successful therapy in severe hypertension. Until recently the quaternary ammonium derivatives, such as hexamethonium and pentolinium, were the only effective ganglion-blocking agents available for long-term therapy. Their major disadvantage is that they are slowly and incompletely absorbed from the gut after oral administration. Hence therapy is unpredictable and often difficult to control.

The introduction of a secondary amine, mecamlamine (Stone *et al.*, 1956), followed by a tertiary amine, pempidine (Lee *et al.*, 1958; Spinks and Young, 1958), represented a major advance in therapy. They are readily and completely absorbed from the gut (Milne *et al.*, 1957; Harington *et al.*, 1958), and are therefore satisfactory ganglion-blocking agents.

Although mecamlamine has proved very popular in the clinic management of severe hypertension (Doyle *et al.*, 1956; Smirk and McQueen, 1957; Somers and Gitau, 1959) it has several disadvantages. As its excretion is slow and irregular (Milne *et al.*, 1957), toxic effects of overdosage, particularly paralytic ileus and its sequelae, may be prolonged for several days. Patients with ileus due to mecamlamine have been unsuspectingly exposed to the risk of laparotomy (Grant and Boyd, 1957). Intestinal haemorrhage has been reported (Addison and Towers, 1959) and psychosis and incoordination, due to its accumulation within the brain, are known to occur (Schneekloth *et al.*, 1956; Harington and Kincaid-Smith, 1958; Hickish, 1958; Hift, 1958; Connor, 1958; Somers and Gitau, 1959). In contrast, pempidine has a shorter duration of action. Its excretion is more rapid, chiefly because of a lower tissue-affinity for the drug (Harington *et al.*, 1958). Toxic effects of overdosage are not likely to last as long as with mecamlamine because of the rapid elimination of the drug. Favourable reports on the long-term use of pempidine have been published by Botha (1959) and Mathisen (1959). The purpose of this communication is to describe our experience over a period of 16 months with the use of pempidine at a hypertension clinic in the middle of Africa.

Material and Methods

Sex and Age.—The series treated comprised 43 patients (18 males and 25 females). Their age distribution was 19 to 60 years (mean age 40.7 years) (Table I).

*In receipt of a research grant from Makerere College.

TABLE I.—Sex and Age Distribution of 43 Cases of Hypertension

Age in Years:	16-20	21-30	31-40	41-50	51-60	Totals
Male	1	3	3	3	8	18
Female	1	8	6	8	2	25
Total	2	11	9	11	10	43

Aetiological Diagnosis.—The aetiological diagnosis was essential hypertension in 18 cases, post-pregnancy hypertension in 5, chronic pyelonephritis in 12 (including one patient with proved urinary schistosomiasis and one with urethral stricture), chronic glomerulonephritis in 7, and renal hypertension (? cause) in 1. The diagnosis was confirmed at necropsy in three of the four fatal cases, and by needle biopsy of the kidney in four patients. For the remainder the clinical diagnosis is given. Both urinary schistosomiasis and urethral stricture are not uncommon in Uganda. Their rarity in this series is noteworthy. In our experience urinary schistosomiasis rarely results in hypertension, and urethral stricture largely presents as a urological problem.

Clinical Presentation.—All the patients were initially assessed in hospital. The major presenting features, with indications for treatment, are shown in Table II.

TABLE II.—Clinical Presentation in 43 Cases of Hypertension

Major Symptomatology	No. of Cases	No. with Malignant Hypertension
Cardiac { Left ventricular failure	11	1
{ Congestive cardiac	12	4
Renal { Albuminuria	1	1
{ Uraemia	1	1
Neurological { Headache; giddiness	14	2
{ Encephalopathy	2	2
{ Visual	1	—
Other	1	—
Total	43	10

It will be noted that most cases presented with cardiac failure or neurological symptoms. No patient with asymptomatic or mild hypertension is included in the series. Ten patients were diagnosed as having malignant hypertension. A number of patients had been previously treated with mecamlamine.

Administration and Dosage.—The initial dose of pempidine used was 2.5 to 5 mg. This was followed by increases of 2.5 to 5 mg. eight-hourly until a satisfactory fall of blood-pressure was obtained. In the average case, stabilization was achieved in a week to 10 days. Subsequent increases were necessitated as drug tolerance developed. In patients with renal impairment (blood-urea levels persistently in excess of 60 mg./100 ml.) dosage increases were cautious and small, as the cumulative excretion of pempidine in renal failure is slow (Harrington *et al.*, 1958). Additional hypotensive effect was obtained by the addition of rauwolfia alkaloids, either as reserpine or as whole-root extract.

Results

Duration of Treatment.—Of the 43 patients treated, four died—two within a week, one after four weeks, and one after three months of treatment. All four were cases of malignant hypertension. In three cases death was due to rapidly progressive uraemia. Two of these cases came to necropsy and both showed evidence of chronic pyelonephritis. In two patients treatment was abandoned on account of failure to attend at follow-up. In the remaining 37 patients the period under treatment has ranged from 4 weeks to 16 months

(mean 30.4 weeks). Eleven patients have been on continuous treatment for 12 months or over.

Range of Effective Dosage of Pempidine.—An attempt was made to bring the fall of blood-pressure to normal or near normal levels, usually 135/75 mm. Hg. The final effective daily dose required varied widely. The dosage range was 5 to 120 mg. (average daily dose 28.75 mg.).

Effect of Posture on Hypotensive Action of Pempidine.—The postural fall of blood-pressure was in no way different from that which results from the action of other ganglion-blocking drugs. While the extent of the postural fall varied from one individual to another, our experience was similar to that noted with mecamlamine (Somers and Gitau, 1959) in that the postural fall relative to the non-postural fall in blood-pressure was often slight. Patients experiencing postural giddiness as a result of marked postural fall in blood-pressure were advised to sit down or lie down. They were also helped by a reduction of their dose of pempidine.

Sensitivity and Tolerance to Pempidine.—The results in 19 patients on continuous treatment with pempidine are shown in Table III. Each patient in this group had

TABLE III.—Results in 19 Patients on Continuous Treatment with Pempidine

Patient	Sex and Age	Blood-pressure (mm. Hg.)		Daily Maintenance Dose Pempidine (mg.)	Duration of Treatment (Months)
		Before Treatment	After Stabilization		
E.M.	M 58	230/100	125/90	15	3
N.M.	F 52	210/110	120/100	15	5
A.K.	M 43	170/120	120/100	10	10
Y.K.	M 22	250/170	120/100	45	12
*M.K.	F 25	180/130	160/120	45	16
V.K.	F 48	220/100	130/90	15	15
*N.M.	F 45	180/130	170/110	15	14
*J.T.	M 55	220/110	170/110	120	14
Z.S.	F 30	180/130	140/100	45	9
N.B.	F 51	300+/170	150/110	30	12
M.C.	F 29	180/130	100/90	15	14
*N.J.	F 26	210/140	165/120	120	14
M.N.	F 40	180/120	130/80	15	6
Z.N.	F 39	190/130	160/110	20	12
I.N.	F 35	170/140	100/60	20	4
B.N.	F 50	180/130	150/110	20	4
S.N.	M 54	260/130	120/95	30	3
Z.S.	F 47	210/150	130/90	30	14
J.K.	M 45	190/130	150/120	60	16

* Indicates patients with unsatisfactory response.

been on treatment for three months or more and 11 had had treatment for 12 months or over. The occurrence of or failure to develop drug tolerance was judged by repeated observations at clinic attendance. In 4 out of 19 patients repeated administration of pempidine had led to a gradual development of drug resistance. All four had previously been treated with mecamlamine, to which they had ultimately become resistant. Clearly, pempidine proved no better than mecamlamine in their management, and control was unsatisfactory with either drug. In the remaining cases on continuous treatment tolerance was of slight degree and unimportant in regard to dosage regulation.

Side-effects of Pempidine.—As with all other ganglion-blocking drugs, most patients on continuous treatment experienced some parasympathetic side-effects. Their occurrence was directly related to the hypotensive action of the drug. They often varied in the course of several months and generally tended to diminish. Side-effects reported at any time among the 19 patients were: constipation and abdominal distension in 18; muscular weakness in 10; postural giddiness in 9; blurred vision in 8; dryness of mouth in 4; diarrhoea, vomiting,

micturition difficulty, and impotence in 2 each; and ileus in 1. Constipation and abdominal distension usually responded to vegetable laxatives taken at night. In only one case was constipation serious enough to lead to a true paralytic ileus, and this cleared completely after the drug was stopped. The infrequency of complaints of dryness of the mouth is notable in our series. This fact might be related to the local staple diet of steamed unripe banana ("matoke"), which has a soft porridge-like consistency. Matoke is likely to act as a demulcent in a dry mouth. The action of pempidine resembles that produced by mecamlamine on neuromuscular transmission, in that both drugs potentiate the effect of tubocurarine (Corne and Edge, 1958). Clinically, curare-like side-effects of muscular weakness, increased fatigability, and aching in the limbs were reported by 10 patients on continuous treatment. These side-effects do not appear to have occurred in other treatment series (Botha, 1959; Mathisen, 1959). In no case were the side-effects unduly severe. It is uncertain whether the additional fact of tropical heat has a part to play in the production of the curare-like effects recorded in this series. Blurred vision occurred in eight instances and, of the two who complained most bitterly, only one was literate and benefited from the use of glasses.

Effect of Chlorothiazides on the Fall in Blood-pressure due to Pempidine.—As with all other ganglion-blocking drugs (Smirk, 1959), the hypotensive action of pempidine was increased by the addition of 0.5 g. of chlorothiazide or 50 mg. of hydroflumethiazide, twice daily, together with 1.5 g. of potassium chloride. This regime was particularly effective in patients with heart failure.

Comparison of Mecamlamine and Pempidine.—If the effects of different ganglion-blocking drugs are to be compared accurately, it is necessary to make the comparison in the same patient at about the same time after the commencement of therapy. As we were unable to achieve such a comparison and as the side-effects of ganglion-blocking drugs are inclined to vary in the course of several months, an attempt to compare the effects of mecamlamine and pempidine was abandoned. The general impression gained was that there was no constant ratio between the effective dose of mecamlamine and pempidine in controlling blood-pressure. Little difference was noted in the incidence of side-effects in any one patient on each drug; the intensity and duration of side-effects were, however, distinctly less with pempidine.

Summary

Forty-three African patients with severe hypertension were treated with pempidine. Thirty-seven received treatment for from 4 weeks to 16 months—11 of them for 12 months or more. A complex regime proved successful under simple conditions.

Pempidine was shown to be an effective oral ganglion-blocking drug in most patients. In general, the advantages over mecamlamine were that continuous administration produced mild or moderate side-effects. Continuous therapy with pempidine did not lead to significant drug tolerance.

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PORTAL HYPERTENSION AND GROSS SPLENOMEGALY IN UGANDA

BY

H. M. LEATHER, M.D., M.R.C.P.

(From the Departments of Medicine, Makerere College, Kampala, Uganda, and University of Bristol)

Gross splenomegaly is a common condition in Uganda (Trowell, 1950) as it is elsewhere in tropical countries (Fawdry, 1955; Chaudhuri, Saha, Basu, Mukherjee, and Rai Chaudhuri, 1956; Chaudhuri, 1957; Basu, 1958). The aetiology is often unknown. Liver disease, however, is common in Central African natives. A study of African patients with gross splenomegaly was therefore made, with the object of determining what relationship, if any, the splenomegaly bore to portal hypertension and liver disease. The results of this study are here reported.

Methods

All patients in whom the spleen was enlarged to the umbilicus and who were admitted to the medical unit at Mulago Hospital, Kampala, between September, 1955, and February, 1957, were studied. The method of investigation included a history, physical examination, full blood count, and various investigations to exclude splenomegaly due to leukaemia, active malaria, brucellosis, and schistosomiasis. Patients found to be suffering from these conditions were excluded from this study. As an index of portal-venous pressure the intra-splenic pressure was measured (Atkinson and Sherlock, 1954). Liver histology was studied by means of biopsy, and in 19 consecutive cases transplenic portal venography was carried out (Dreyer and Budtz-Olsen, 1952; Walker, Middlemiss, and Nanson, 1953).

Intrasplenic pressure was measured with a simple manometer; the pressure was taken routinely from three sites in the splenic pulp, except in patients with severe anaemia, in whom only one recording was taken. Clotting in the needle in the splenic pulp was troublesome in some of the earlier cases. The clotting-time