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PROTOVERATRINE A IN TREATMENT OF HYPERTENSION

BY

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Extracts of the *Veratrum* plants cause a fall in blood pressure and bradycardia through the vagal reflex described by von Bezold and Hirt (1867) and by Jarisch and Richter (1939). Their use for the treatment of hypertension has been limited by the frequent occurrence of nausea and vomiting. Trials have suggested that certain of the pure veratrum alkaloids might lower the blood pressure with less emetic effect (Hoobler *et al.*, 1952a). A study of protoveratrine, the principal alkaloid of *Veratrum album*, was therefore undertaken. This has been shown to be a mixture of two closely related ester-alkaloids, protoveratrine A and protoveratrine B (Stoll and Seebeck, 1953; Nash and Brooker, 1953).

Parenteral administration of protoveratrine to patients with hypertension causes a fall in blood pressure with bradycardia (Meilman and Krayer, 1949). This is accompanied by vasodilatation in the limbs, and the cardiac output is not consistently altered (Hoobler and Corley, 1950). Renal blood flow remains constant or is increased, but with considerable falls in blood pressure the glomerular filtration rate is diminished (Hoobler *et al.*, 1952b).

Methods

The effect of protoveratrine preparations was studied in patients with hypertension admitted to hospital for assessment. All blood pressures were taken by one or other of us and the value recorded was the lowest of three successive readings. Oral test doses were given daily after the patient had been resting for an hour, the blood pressure being observed during that time. Pulse and blood pressure were taken every 30 minutes for the next four hours and hourly thereafter.

The initial amount given was 0.25 or 0.5 mg. of protoveratrine A, and successive doses were increased by 0.25 mg. until a satisfactory response was obtained. With intravenous administration, blood-pressure readings were taken each minute for 15 minutes and at longer intervals thereafter, or, alternatively, a continuous record was made from an indwelling arterial needle. Blood-pressure readings after resting in bed for 10 minutes were taken at 9 a.m. each day throughout the patient's stay in hospital. The average of the first three daily readings before treatment was taken as a baseline for subsequent out-patient assessment.

Out-patients on treatment with protoveratrine A were seen every two weeks at first and later every four or six weeks. The blood pressure recorded was the lowest of three measurements made after resting on a couch for 5, 10, and 15 minutes.

Activity of Protoveratrine A and B

The response to intravenous injection of protoveratrine was studied in nine patients with hypertension. In several of these patients a continuous pressure record was obtained with an indwelling arterial needle. After an injection of 0.15 to 0.21 mg. of protoveratrine the blood-pressure and pulse rate gradually fell, reaching their lowest levels in about 10 minutes. A substantial fall in blood pressure occurred in every case. Blood pressure and pulse rate returned to their original levels in two to three hours (Fig. 1).

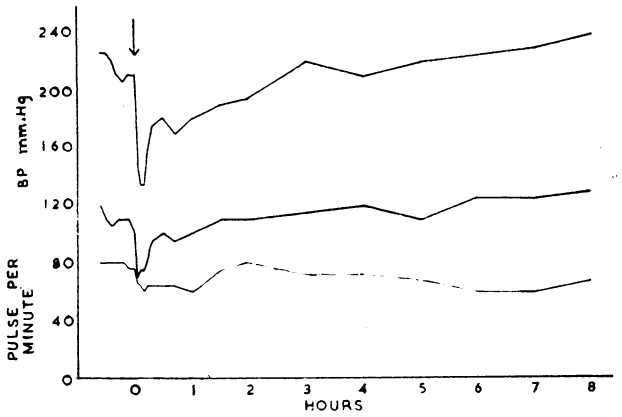

FIG. 1.—Effect of intravenous protoveratrine A (0.18 mg.) on blood pressure and pulse rate in a man aged 55 and weighing 75 kg. (Case 1).

Patients were usually aware of a feeling of warmth in the chest and arms as the blood pressure fell, and occasionally hiccup occurred, but there was no nausea or vomiting. A further fall in blood pressure sometimes took place if the patient stood up while the hypotensive effect was at its greatest. The response of the blood pressure and pulse to Valsalva's manœuvre was, however, preserved. The response to intravenous protoveratrine was the same using protoveratrine A, protoveratrine B, or a mixture of the two alkaloids (Table I).

The amount of protoveratrine taken orally which caused a fall in blood pressure varied widely from patient to patient.

TABLE I.—*Response to Intravenous Protoveratrine*

Proto-veratrine	No. of Tests	Average Dose in μg./kg. Body Weight	Average Initial B.P.	Average B.P. Fall
Mixture ..	3	3·2	193/102	81/42
A	5	2·3	197/126	64/44
B ..	4	2·3	231/128	65/24

In earlier trials a mixture of protoveratrine A and B in the ratio of two parts to one was used (" puroverine," Sandoz). Pure protoveratrine A then became available. The minimum effective oral dose of both these preparations was between 0.3 and 1.75 mg. of protoveratrine A.

Protoveratrine B was given to six patients in doses up to 4 mg. In only one was there any hypotensive effect. In this patient the blood pressure fell after 2 mg. by mouth, and 3 mg. caused toxic effects. Since protoveratrine B seemed ineffective by mouth in most patients (Fig. 2) subsequent trials were confined to protoveratrine A.

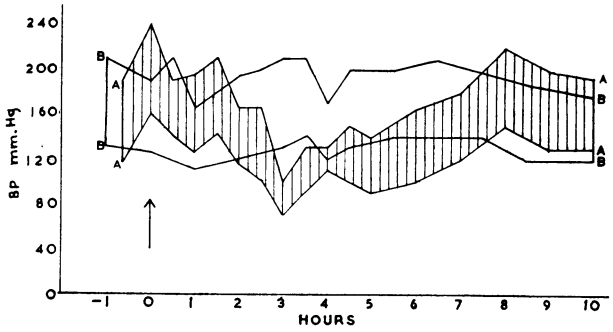

FIG. 2.—Comparison of oral protoveratrine A (1 mg.) and B (2 mg.) in man aged 40 and weighing 81 kg.

Protoveratrine A

The effect of single doses of protoveratrine A was examined in 20 patients with hypertension, a total of 65 administrations being made. A significant fall in blood pressure took place in 48 of these trials, the average fall being from 204/126 to 145/92 mm. Hg. A substantial fall in blood pressure could be obtained with a single oral dose in nearly every case. The blood pressure began to fall about one and a half hours after giving the drug and reached a minimum in about three hours. The hypotension lasted for at least two hours after this and often for much longer (Fig. 3). These findings suggested that effective control of blood pressure throughout much of the day might be expected with oral administration every six or eight hours.

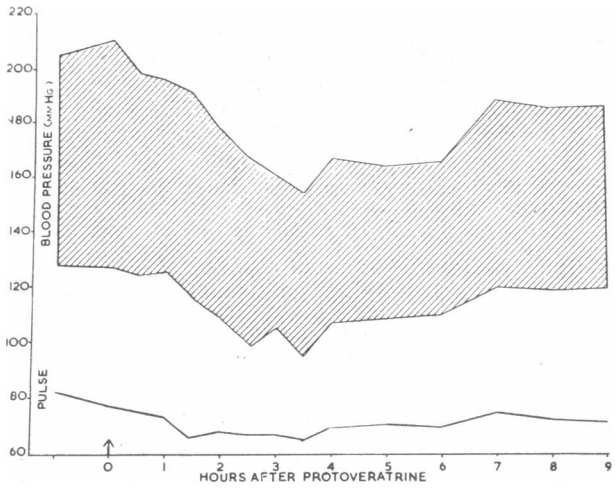

FIG. 3.—Effect of single oral dose of protoveratrine A (mean of 10 patients). Average dose 0.7 mg. P.V.A.

Prolongation of Action.—In an attempt to prolong the effect of protoveratrine A taken orally, tablets were prepared by the manufacturers in which some of the drug was in the form of strongly compressed granules which would not dissolve for about two hours. A comparison of these tablets with those not so treated showed no difference in hypotensive action and no prolongation of effect. Tablets were subsequently prepared (" retard " form) in which one-third of the drug content was untreated and the other two-thirds mixed with substances each of which delays absorption to a different degree. No attempt was made to measure the duration of action of these tablets by single oral dose, but they were employed in the therapeutic trial. It was found that somewhat larger doses of the " retard " tablets were needed to produce comparable effects, suggesting that the protoveratrine A in the " retard " tablet might be more slowly or possibly less efficiently absorbed.

Side-Effects.—These resembled those described using mixtures of veratrum alkaloids (Hoobler and Dontas, 1953). A feeling of warmth in the front of the chest and throat occurred most frequently, often with paraesthesiae of the fingers or mouth. Larger doses caused nausea, and sometimes vomiting. This was often sudden in onset with little discomfort. Hiccup was also frequent. Bradycardia was a constant feature. Two subjects with atrial fibrillation changed temporarily to a regular, possibly nodal, rhythm after 0.18 mg. of protoveratrine intravenously, and one patient in sinus rhythm periodically exhibited nodal rhythm over long periods on oral therapy. In the therapeutic trial the dosage was such that side-effects occurred in most subjects, but were not such as to interfere with their normal life. Severe hypotensive episodes occurred on two occasions with vomiting and loss of vision for several minutes but no permanent ill effects followed.

Therapeutic Trial of Protoveratrine A

Prolonged reduction of blood pressure with protoveratrine A given by mouth three or four times daily was attempted in 21 patients (11 males, 10 females) aged 24–69 with hypertension. The hypertension was severe as judged from the fundus oculi, the cardiac and cerebral complications, and the levels of blood pressure.

Evaluation before Therapy.—Left ventricular failure was present in 7 and triple rhythm in 13. Fundus oculi (Keith, Wagener, and Barker, 1939): grade 4 (papilloedema), 5 subjects; grade 3 (exudates and haemorrhages), 6 subjects; grade 2 (arterial changes only), 10 subjects. Radiographs of the chest showed varying degrees of left ventricular enlargement (cardiothoracic ratio, 42–64%—mean 53%). Renal function was investigated in all cases. Blood urea exceeded 50 mg./100 ml. in five patients. Intravenous pyelography was performed in most and was abnormal in three, but in none of these was surgical treatment thought advisable. The electrocardiogram showed evidence of left ventricular hypertrophy in 17 subjects. Complete right bundle-branch block obscured the picture in one subject, but this was lost while the patient was under observation, revealing the typical pattern of left ventricular hypertrophy. Cerebral vascular accidents had occurred in 12 of the 21 subjects and varying degrees of disability persisted. The reasons for attempting reduction of the blood pressure were as follows: retinopathy grade 4 or 3 in 10 subjects; cerebral vascular accidents in 12; left ventricular failure in 7; high blood-pressure readings alone in 2.

In-patient Treatment with Protoveratrine A

Hypotensive therapy was undertaken after an initial period of 5–20 days' rest in hospital. An appreciable fall in blood pressure commonly occurred during this time. After assessment of their response to single doses of protoveratrine A a group of 12 patients were observed in hospital for varying periods so that the effect of regular administration could be judged. The drug was given three to five times daily, the dosage being increased until satisfactory control of the blood pressure was obtained throughout the day or unpleasant side-effects appeared. In these circumstances it was possible to achieve a satisfactory control of the blood pressure in all cases for periods of up to two months. The average fall in blood pressure was from 201/124 to 173/106 mm. Hg, and in seven subjects the diastolic pressure was maintained below 100 mm. Hg. The effective dosage varied widely, from 0.9 to 4.3 mg. daily. In no case did side-effects occur more often than on alternate days.

Protoveratrine was given intramuscularly to two patients, using a mixed preparation of A and B alkaloids in a dose of 0.3 to 0.4 mg. three times a day with an adequate blood-pressure fall in both subjects. Transfer to oral therapy was carried out later without increase in the frequency of side-effects.

Out-patient Treatment with Protoveratrine A

Following the in-patient observations of the hypotensive effect of protoveratrine A, 8 of the 12 patients studied were followed as out-patients taking three to four doses daily for long periods. To this group were added nine subjects who had shorter periods of in-patient treatment or had been started on protoveratrine A as out-patients. These patients were encouraged, and were indeed able, to lead normal active lives. Periods of treatment alternated with periods either without therapy or on placebos in six of the patients. Since patients were very soon aware of the absence of side-effects with the inert tablets the use of placebos was thought unhelpful. The duration of treatment has been from one month to as long as two years (mean nine months). The total treatment months were 155. The dosage employed varied from 0.5 to 3.6 mg. daily. The drug was taken three times daily after meals and an additional dose often on retiring. It was sometimes possible to give a larger dose after breakfast than later in the day. The aim was to give as large an amount of protoveratrine A as could be tolerated. This generally led to the occasional occurrence of unpleasant side-effects such as nausea or vomiting, but the patient was encouraged to adjust the dosage so that these did not occur more than once a week. Where the dosage had been determined during a period in hospital it was commonly found that alteration was necessary after the patient returned to normal life; the amount tolerated was generally less than while in hospital.

Of the 17 patients in this group, treatment is being maintained in seven. The results as judged by blood-pressure levels and objective improvement may be regarded as good in three and fair in three others (Table II). The case of one patient with an excellent response is described in more detail below.

TABLE II.—*Long-term Treatment with Oral Protoveratrine A*

Case No.	Sex and Age	Duration of Treatment	Initial B.P.	Average B.P. During Treatment	Daily Dosage (mg.)	Remarks
1	M 40	11 months	225/145	175/105	1·8–3·6	Malignant hypertension. Good result (see text)
2	M 56	8 ,,	255/150	210/115	3·6	Good result
3	M 42	16 ,,	200/145	195/105	1·5–3·0	Good result. Diabetic
4	F 41	8 ,,	170/120	140/100	1·4–2·7	Fair result
5	M 39	9 ,,	240/135	200/120	3·0	Malignant hypertension. Fair result. Papilloedema lost
6	F 46	5 ,,	265/150	240/125	1·8	Fair result
7	M 45	19 ,,	185/125	185/120	0·5–1·1	Poor result. Paroxysmal A.F. disappeared

Case 1.—A man aged 40 had had pulmonary tuberculosis successfully treated by a left thoracoplasty in 1936. He attended hospital because of increasing dyspnoea, and the casual blood pressure was 250/160. Pulsus alternans and a pre-systolic triple rhythm were noted. There was papilloedema with many exudates and haemorrhages, and the electrocardiogram showed left ventricular hypertrophy. In hospital the blood pressure fell from 225/145 to 190/120 mm. Hg over a period of 17 days. Treatment with protoveratrine A for 14 days reduced the blood pressure to 155/105 without any side-effects, and improvement in the papilloedema was noted. Out-patient therapy for 14 months with protoveratrine A 1.8 to 3.6 mg. daily has maintained the blood pressure at 175/107 with nausea only two or three times a month. The papilloedema, retinal haemorrhages, and exudates disappeared in five months, and there was marked improvement in the electrocardiogram (Fig. 4).

Treatment was regarded as unsatisfactory in 10 patients. In five of these the drug was stopped because the therapeutic response was inadequate, high blood pressures continuing while the maximum tolerated dose was being given. Two patients who exhibited a fair response over several months' treatment developed complications of their hypertension—one cardiac failure after nine months and the other a cerebral thrombosis after 12 months. Treatment must be judged to have failed in these cases.

Three patients died. One had a fair response to protoveratrine initially, but control of the hypertension became progressively more difficult and he died from cardiac failure and uraemia. One man with malignant hypertension from chronic nephritis responded satisfactorily at first but renal failure supervened. The third was treated for three months with satisfactory control of blood pressure but died from cardiac infarction during a control period without treatment.

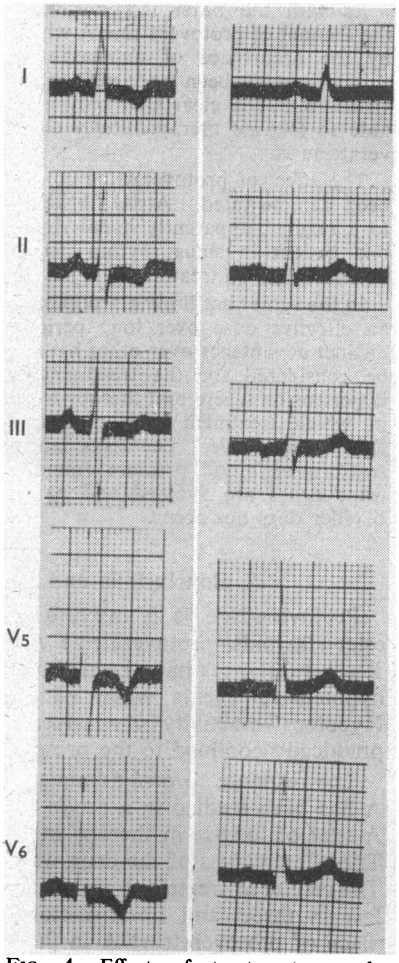

FIG. 4.—Effect of treatment on the electrocardiogram in Case 1. Left, August 19, 1955; right, February 1, 1956.

The effective dosage of protoveratrine A in any single patient was not found to alter greatly either in the first few days or after months of treatment. No evidence was obtained of the development of tolerance to the drug. In two patients subject to paroxysmal atrial fibrillation the frequency of attacks was much diminished during treatment with protoveratrine A. In five subjects reserpine 0.5–1.5 mg. daily was added to the treatment when the full effect of protoveratrine A had been obtained. No further fall in blood pressure occurred, and no change was seen in the effective dose of protoveratrine A or in the frequency of side-effects.

Discussion

The intravenous administration of protoveratrine A and protoveratrine B demonstrated that they were equally effective hypotensive agents by this route. Oral administration of the two substances revealed a marked difference in their activity. While protoveratrine A could be relied upon to cause a fall in blood pressure provided a sufficient amount was given, protoveratrine B was clearly much less potent by this route, and the activity of a mixture of the two seemed to depend solely upon its content of protoveratrine A.

Trials of protoveratrine A given in divided doses to in-patients suffering from hypertension showed that it was possible to lower the blood pressure significantly in the majority of patients without serious side-effects. The prolonged administration of protoveratrine A to a group of out-patients with severe hypertension proved rather

disappointing. The drug had to be given to the limit of tolerance, so that side-effects occurred at some time in all patients, but these in fact were not such as to interfere with their normal lives. In 3 of 17 patients the treatment was regarded as thoroughly satisfactory. Objective improvement and a reduction in blood pressure were obtained over long periods. Another three patients were thought to be improved, but the fall in blood pressure was less impressive. In the remaining 11, although there was sometimes a fall in pressure the overall effect was judged to be unsatisfactory.

As with the other less purified veratrum preparations, the amount of protoveratrine A which can be given is limited by the occurrence of unpleasant side-effects. No direct comparison has been made with the preparations of veratrum viride, but it is clear that only a minority of patients are able to tolerate therapeutically effective amounts of protoveratrine A.

The effect of protoveratrine on the heart has occasionally been demonstrated. Atrial fibrillation temporarily reverted to a regular, apparently nodal rhythm in two patients, and one patient in sinus rhythm periodically exhibited nodal rhythm while on treatment.

In the somewhat limited group of patients who can tolerate an effective dose over long periods protoveratrine A has distinct advantages over other hypotensive agents. It should be considered for the treatment of patients with severe hypertension where oral therapy is preferred, especially those in which treatment with ganglion-blocking drugs is not thought desirable. The risks inherent in the abrupt fluctuations of blood pressure found with effective doses of these drugs are avoided and paralysis of the bowel and bladder does not occur.

Conclusions and Summary

Protoveratrine is a mixture of two closely related ester-alkaloids, protoveratrine A and protoveratrine B. These substances have been shown to be equally potent hypotensive agents when administered intravenously. Hypotensive activity when given by mouth seems to be practically confined to the protoveratrine A fraction.

The response to oral administration of protoveratrine A has been studied in a group of hypertensive patients. A trial of long-term therapy in 17 patients is described. The effectiveness of the drug was limited by side-effects. The results of treatment were judged to be good in three, fair in three, and unsatisfactory in 11 patients. The place of protoveratrine A in the treatment of hypertension is discussed.

We thank Dr. D. Evan Bedford for his encouragement in this work and Dr. H. Holgate, of Sandoz Ltd., for much assistance and generous supplies of protoveratrine. We are grateful to Mrs. Connolly, of the photographic department of the Institute of Cardiology, for her help in preparing the illustrations.

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The Ministry of Health has issued a new leaflet on dental care, "Sound Teeth Mean Good Health and Good Looks." Free supplies are obtainable from the Ministry of Health, Public Relations Division (Room 121), Savile Row, London, W.1. Also available, free on application, are copies of a 12-panel picture set "Take Care of Your Teeth," and a 4-panel picture set "Shield Your Child."

SUPERFICIAL GLANDULAR TUBERCULOSIS

TREATMENT WITH CHEMOTHERAPY

BY

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Much has been written for many centuries about superficial glandular tuberculosis. Several theories regarding its pathogenesis have been suggested and many treatments have been tried, but, in general, glandular tuberculosis is a notoriously chronic relapsing disease which is unsatisfactory to treat. While the number of cases is now probably falling, it can still be a serious and often disfiguring condition.

Interest has been aroused in antituberculous drugs for the treatment of glandular tuberculosis by the satisfactory results which can be achieved by their use in the treatment of other forms of tuberculosis, and this paper is a report of our experience of 52 cases of superficial glandular tuberculosis treated by antituberculous chemotherapy.

Material and Methods

The 52 cases comprise a heterogeneous collection derived principally from two Edinburgh hospitals. They were seen between 1952 and June, 1955, and have been followed up to June, 1956: all have therefore been observed for at least one year. The age extremes of the 52 patients (37 females, 15 males) were 4 and 67 years, 13 (8 females, 5 males) being 15 or less. The cervical region was affected in 50 and the axillary in two. In six of those with cervical adenitis the glands were bilaterally involved. Of the 44 with unilateral disease the right side was affected in 30 and the left in 14. The proneness of tuberculous glands to relapse is shown by the history obtained from 46% of our patients (24 out of 52) of at least one previous glandular episode. Radiological evidence of either active or inactive pulmonary tuberculosis was found in 26 cases (50%). A persistently negative Mantoux test was recorded in two patients; one, a girl aged 17, had histologically proved tuberculous granulation tissue in a neck gland removed surgically, while the other, a girl aged 8, was one of a series of cases which comprised a small epidemic of tuberculosis traced to an infected cow.

Only two patients had had previous antituberculous chemotherapy before coming under our observation and in each case it was for a short period of time. In all but three of the cases the glandular disease was present when the patients were first seen. The exceptions were three females aged 18, 26, and 37 with miliary tuberculosis in whom tuberculous cervical adenitis *developed* while they were under observation in hospital and after they had had five, six, and five months' good chemotherapy.

In most cases the diagnosis of tuberculous adenitis was originally made on clinical grounds, but in 23 it was confirmed either bacteriologically or pathologically. The assessment of progress in patients with tuberculous adenitis is not easy, and, though we have personally seen most of the patients at regular intervals, the recorded happenings can only be clinical impressions. In general, fluctuation, discharge, the persistence of large gland masses, or sinus formation has been regarded as an unsatisfactory result. Satisfactory treatment, in addition to causing a retrogression of the glands, must reduce the relapse rate, and to show this a long-