TREATMENT OF HYPERTENSION WITH "MIO-PRESSIN"

BY

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Numerous compounds have been discovered which affect transmission in the sympathetic division of the autonomic nervous system. Most, if not all, of these compounds have been used in the treatment of hypertension with varying degrees of success. The history of treatment has a ring about it which is familiar to most physicians. The patient is given treatment with a new drug as recommended by the manufacturers and after a variable period of time his diastolic pressure falls, often to within normal limits. But with the passage of time it starts to rise again. Increased dosage of the drug may hold it in check for a while, but eventually the dose reached produces limiting side-effects, after which the diastolic pressure slowly but surely returns to the pre-treatment level or even higher.

Fortunately for most hypertensives the blood pressure usually responds again to a change of treatment. It is also becoming recognized that combination therapy is more effective than single drugs. Combination therapy, however, has some drawbacks for both doctor and patient. It can be very time-consuming in a busy clinic trying to reason out which of three components of a treatment should be increased or reduced, and in my experience it is quite beyond the ability of some patients to take different doses of three sorts of pill three or four times a day.

A combination product, "mio-pressin," has recently been introduced which contains the centrally acting agents rauwolfia and protoveratrine together with the long-acting peripheral agent "dibenyline," now generally recognized as the most specific adrenomotor antagonist. This product has been tested in a controlled trial in hospital and the patients have been reviewed for at least 12 months.

Method

Trials of hypotensive drugs are notoriously tricky. Diurnal changes of blood pressure vary over quite wide limits. So do readings on the same patient taken by different members of the staff. A patient with a labile hypertension is often affected by a change of surroundings.

All the patients in this trial had three days' rest in bed without treatment after admission to hospital. During this period and subsequently the blood pressure was recorded at the same time in the morning and evening. The lowest blood pressure during the rest period was taken as the reference points.

The patients were arbitrarily divided into two groups and were treated with coded capsules for a period of 10 days. Treatment was started with one capsule three times daily and increased at three-day intervals until there was a satisfactory fall in blood pressure or the end of the 10-day period was reached. The blood pressure was taken as the mean of the last three readings—that is, the evening reading on the ninth day and the morning and evening readings on the tenth day. At this point patients who had been on placebo therapy were transferred to known active mio-pressin and the dose built up gradually until a satisfactory result was obtained. The patients were discharged from hospital on this dose as maintenance therapy and were seen at regular intervals in a special out-patient clinic.

Each mio-pressin capsule contained 25 mg. of rauwolfia, 0.2 mg. of protoveratrine, and 5 mg. of dibenyline. The placebo capsules contained lactose.

Results

It is the raised diastolic pressure which produces the main strain on the cardiovascular system of the hypertensive patient. The diastolic pressure has been used as the parameter for observation in this investigation. Readings were taken to the nearest 5 mm. of mercury with a standard sphygmomanometer. Readings in the ward were taken with the patient in a sitting position; at review, they were taken with the patient sitting and standing.

All the readings quoted below are in millimetres of mercury.

In-patients.—There were 24 patients (9 males and 15 females) in the group started on placebo treatment. Their ages ranged from 45 to 71 years. After bed rest the mean diastolic pressure was 122 (range 110–140). After further bed rest and treatment with inert capsules the mean fall in diastolic pressure was 7 mm.; after treatment with mio-pressin the mean fall was 27 mm. There were 28 patients (8 males and 20 females) in the group which started on active treatment. Their ages ranged from 36 to 79 years. After bed rest the mean diastolic pressure was 125 (range 110–150). After treatment with mio-pressin the mean fall was 29 mm.

Out-patients.—All patients have now been reviewed over a period of at least 12 months, extending in eight cases to two and a half years. Thirty patients had a lower diastolic pressure at their last review than when they left hospital; 14 had the same pressure; 8 had a higher pressure. Of the eight with raised pressure only two had returned to the pre-treatment level. Twenty-six patients are being maintained on a dose lower than that on which they left hospital; 24 are on the same dose; and the 2 patients quoted above whose blood pressure returned to pre-treatment level had their dose increased. The maintenance dose varies widely and ranges from 1 capsule daily to 2 capsules four times a day. The doses most commonly used are 1 capsule three times a day and 2 capsules twice a day.

Statistical Check

Measurements of diastolic blood pressure can only be approximate. Individual measurements are given to the nearest 5-mm. interval and may well be subject to an error of one interval. The more refined statistical tests are of doubtful value when dealing with data of this type. A χ^2 test may be made by adopting arbitrary criteria of improvement, but the literature on hypertension is inconclusive on what these should be. It has therefore been decided to apply the simple test of relating the difference of the means to its own standard error. Three comparisons are possible: (1) *Placebo-starting group on placebo against the same group on mio-pressin*:—The average fall of diastolic pressure on placebo was 7 mm. and on mio-pressin 27 mm. The difference is 20 mm. and its standard error 3.0 mm. (2) *Placebo-starting group on placebo against the mio-pressin group*:—The average fall on diastolic pressure of the mio-pressin group was 29 mm. The difference is 22 mm. and its standard error 3.9 mm. (3) *Placebo-starting group on mio-pressin against the mio-pressin group*:—The difference here is 2 mm. and its standard error 4.1 mm.

The following conclusions may be drawn from these tests: (1) there is a significant difference between the

fall in diastolic pressure in patients on placebo treatment and the same patients on mio-pressin treatment; (2) there is a significant difference between the fall in diastolic pressure in patients on placebo treatment and a different group of patients on mio-pressin treatment; and (3) there is no significant difference between the fall in diastolic pressure in the two groups of patients on mio-pressin treatment.

Discussion

It is not surprising that a combination of hypotensive drugs produced a satisfactory initial fall in diastolic pressure or that treatment with active material was significantly better than treatment with inert material. It would have been more remarkable if the results had been otherwise.

The most interesting observations from this trial would appear to be those on the out-patients. Of the 52 patients treated, 44 maintained their blood pressure at the lowered level or even further reduced it. In no instance was it necessary to increase the dose of mio-pressin, and in 26 patients the daily dose has been greatly reduced from the original level.

Side-effects were negligible and there was no postural hypotension. One patient complained of dizziness, one of anorexia, and one of blurred vision, but these disappeared without alteration of the treatment.

Summary

Mio-pressin, a combination of rauwolfia, proto-veratrine, and dibenylamine, has been used in a controlled trial in hospital. Out-patient reviews have been made over periods from one to two and a half years.

In the controlled trial there was a satisfactory fall in diastolic pressure on active treatment and a significant difference between the results of active and inert treatment.

Of the 52 patients, 44 maintained or reduced the lowered blood pressure. None had the dose of mio-pressin increased, and 26 have had the maintenance dose reduced.

DOES SERUM GONADOTROPHIN CURE ACNE VULGARIS?

BY

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Acne vulgaris starts at puberty and ends in late adolescence or early adult life. This close connexion with the major period of hormonal imbalance has been recognized by the lay public as well as the medical profession for a very long time. Even to-day many doctors use the old cliché, "It's your age; you'll grow out of it," as an excuse for treating acne sufferers lightly, and this mentality has so affected the general public that large numbers of young people suffer agonies of embarrassment in the belief that nothing can be done, and a regrettably high proportion end up with severe scarring of the face, chest, and back.

What, then, can be done for these patients? As most of them have a very greasy skin, measures to counteract this should be of value, and dietary restrictions should be advised, associated with local degreasing by soap and water, application of detergents *N.F.*, or 1% cetrimide lotion. Exfoliation of the hyperkeratosis may

be obtained by local applications of sulphur or resorcinol or by weekly erythema doses of ultra-violet light. The control of the pustular element has been made much easier in the past few years by the prolonged administration of antibiotics at low dosage, the results of which were summarized by Cronk *et al.* (1956).

None of these treatments can expect to be curative, but with their prolonged administration the patient can be guaranteed that while the acne is present it will be less cosmetically unpleasant, and ultimately there will be much less scarring than might otherwise have occurred. This is useful for the patient but time-consuming for everybody, and better treatments must still be sought.

Theory

The closer investigation into the problem of hormonal imbalance was initiated by Pick (1921); a stream of articles followed this over many years until the work of Hamilton (1941) stimulated dermatologists to use oestrogens. Gradually the inadvisability of prescribing these for the male has been recognized, but there has remained a definite place for their use in women during the second half of the menstrual cycle. This is of most value in those whose acne is predominantly of the comedone type. This satisfactory advance led most people to assume that the androgen/oestrogen ratio was at fault, and that this was a fact of prime importance in the causation of acne. Few dermatologists were rash enough to claim that the administration of hormones could effect a permanent cure, as puberty is a dynamic disequilibrium of all hormones, whose ratio alters far too often to be affected by the physician's ministrations.

In 1950 Aron-Brunetiere and Fitoussi widened the scope of the theories about hormones by postulating that the imbalance was a result of the interrelation between androgen, oestrogen, and progesterone in the following ratio: $\frac{\text{androgen} + \text{progesterone}}{\text{oestrogen}}$. Following the work of

Vignes (1937) and Jausion *et al.* (1941) they produced evidence to show that the administration of 20–30 mg. of progesterone in two or three doses between the 21st and 25th days of the menstrual cycle aggravated acne. They also claimed that chorionic gonadotrophin did the same thing. From this they postulated that the

disequilibrium of the $\frac{A+P}{OE}$ ratio was due to a parallel

disequilibrium in the hypothalamopituitary mechanism responsible for the secretion of sex hormones. A series of experiments based on this concept led them to use serum gonadotrophin as a treatment, first by injection (Aron-Brunetiere, 1954) and later by oral administration and transmucosal absorption (Aron-Brunetiere, 1956). This treatment is claimed to give a 61% cure rate in women and 35% in men, with another 25% in women and 43% in men much improved. Only two brief annotations have appeared in British journals: MacKenna (1957) and Cohen (1957) each claim that about 60% of their cases showed considerable improvement.

Such claims warrant further investigation, most particularly when the word "cure" has slipped into the journals, and, unfortunately, into the literature of a pharmaceutical company.

Method

It is always difficult to decide how to investigate the effects of a new drug, especially when there is some