GUANETHIDINE IN THE TREATMENT OF SEVERE HYPERTENSION

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The ideal drug for the treatment of severe hypertension should be uniform in its effects from day to day and from patient to patient. It should be active when orally administered and capable, by adjustment of dosage, of maintaining the blood pressure at or around a desired level throughout the 24 hours. It should be free from disturbing or dangerous side-effects (Platt and Sears, 1956). As yet, the ideal drug has still to be found, but the advent of adrenergic-blocking agents is a great advance in this direction (Boura *et al.*, 1959, Dollery *et al.* 1960), and at the moment there is little doubt that guanethidine is the drug of choice (Evanson and Sears, 1960).

With the object of trying to learn more about the various advantages, disadvantages, and difficulties in outpatient management of patients with severe hypertension treated with guanethidine, I have recently visited seven other centres in Great Britain. Including the clinic at Manchester this series therefore concerns patients under outpatient supervision in eight centres, and at the time of my investigation the total number of patients being treated with guanethidine in these centres was between 600—700.

The groups of patients undergoing treatment in the various centres were similar in that they all had severe hypertension. Before treatment was started the majority of patients had diastolic blood pressures of over 120 mm. Hg., and a great many had pressures considerably in excess of this. The majority also had started their treatment after an initial period of inpatient observation and investigation. Only a few had been started on guanethidine as outpatients, usually on changing from one of the older ganglion blocking agents and, in these, inpatient investigation had been done on a previous occasion.

In most centres, the first aim was to give guanethidine alone and not in conjunction with other anti-hypertensive agents: for example, an oral diuretic was only given if there was evidence of fluid retention

J. COLL. GEN. PRACT., 1962, 5, 246

due to cardiac failure. The highest dose given was 700 mg. daily, the majority of patients requiring 40—80 mg. Nearly all the patients took the dose at one time, usually in the morning after breakfast. The ages ranged from 7 to 75 years, with the majority in the 40—55 years range.

In seven centres doctors recorded the blood pressures during a single interview. In one hospital the patients spent the whole morning or afternoon at the clinic, and the pressures were recorded at regular intervals by technicians. The other centres might arrange a similar " run through " once or twice a year, or if there seemed to be a specific indication for so doing. Whether a sitting or lying pressure was recorded was a matter of preference. In all patients the erect pressures were taken, and in one centre the standing pressure was also recorded in selected patients after climbing a flight of stairs to the clinic which was held on the first floor.

It was the opinion at all centres that treatment was much more easily managed in the intelligent patient, and could be dangerous in the unintelligent. Serial electrocardiograms, blood-urea estimations, and chest x-rays were done on most patients, and in one or two centres serial retinal photographs were also taken.

The incidence of side-effects seemed much less if the dose of guanethidine was increased slowly, and not more than by 10 mg. weekly. In several centres, and where rapid control was not essential, patients were often discharged on an inadequate dose, and were seen weekly as outpatients so that this slow increase of dose could be carried out without blocking valuable hospital beds.

The commonest side-effect experienced was of lassitude which in some cases amounted to muscular weakness. There was a variety of opinions as to the cause of this weakness. Some physicians felt it was a true muscle weakness due to a specific action of guanethidine, whilst others felt it was an early symptom of hypotension. One abnormal electromyogram was reported.

Diarrhoea was a very common complaint and was treated in many ways, mostly by the addition of one of the ganglion blocking agents, atropine, or propantheline bromide. None of these methods seemed really effective, and there is little doubt that codeine phosphate in a dose of 32 mg. taken half an hour before meals is a most effective remedy (Leishman *et al.*, 1961).

Exertional hypotension was not uncommon, and can be one of the most troublesome features of treatment with guanethidine. In some centres the dose is reduced and less good control accepted, or treatment with guanethidine is discontinued completely. In others, the dose is reduced and other drugs are added. There seems good evidence that oral diuretics such as hydrochlorothiazide have a hypotensive effect *per se*. This being the case, it would seem

logical to expect that the effective dose of guanethidine could be reduced below the dose one would anticipate due solely to a reduced blood volume. This indeed often seems to be the case, and with careful adjustment, the effects of guanethidine on exertion can be greatly reduced or even abolished.

Morning dizziness can be lessened considerably by instructing the patient to sit up in bed for a short time before getting up. Some patients feel they can improve matters by changing their method of taking the tablets: possibly by altering the time of day when they take them, or by splitting the dose. There seemed to be general experience of a small percentage of patients with such severe subjective symptoms suggesting hypotension, that the dose had to be decreased.

Failure of ejaculation, impotence, unexplained oedema, nasal stuffiness, shakiness, and various other symptoms were reported. Tolerance was, on the whole, unusual. In several centres, this condition was described if only a 10 mg. increase of dose was required, which might be considered a hard criterion by many.

The assessment of success or otherwise of treatment was found difficult to define. In only one centre was there a rigid criterion of a diastolic blood pressure of 100 mm. Hg., or less. It is true that the blood pressure is the only guage that is reasonably accurately assessed instrumentally, but, by and large, most of the other centres aimed at achieving a considerably lowered blood pressure reading consistent with the well being of the patient, an improvement in symptoms such as headache, a retrogression of retinopathy, and increased survival rates.

One of the main reasons of this survey was to see what part might be played by the general practitioner in the whole scheme of management. At the moment it is true that only the severer forms of hypertensions are being treated with guanethidine. It may well be that in the future, some of the milder forms of essential hypertension should receive guanethidine, or some future drug yet to be discovered. Most of us are aware (as indeed are the insurance companies), of the possible significance of chance blood pressure readings that are a little above normal. Many of the patients now being treated for severe essential or malignant hypertension give this kind of history, and I suspect it will not be far off before something other than sedatives should be prescribed for these early mild cases. However this may be, there is no doubt that all cases should be adequately investigated. I have been impressed by the small but steady trickle of cases shown to have unilateral kidney disease or renal artery stenosis. It seems quite definitely worthwhile performing an aortogram in selected cases under 40—45 years of age, and I am sure that it would be wrong to treat any case below this age without a full hospital investigation.

The next point from my own experience in general practice is that if one undertakes to treat a case (having had an intravenous pyelogram, electrocardiogram, and blood urea done), a patient will not tolerate added symptoms being produced by treatment given by their own family doctor. It is a strange but true fact that in my experience and that of several other doctors with whom I have spoken, patients will tolerate a hospital-induced nuisance e.g., diarrhoea, dizziness, impotence, and so on, and are grateful to their own doctors for any efforts they may make to lessen them. They do not, however, tolerate the same effects when induced by the general practitioner. It is my firm opinion that at the moment, all treatment with guanethidine should be initiated in hospital, or under hospital outpatient supervision.

I am sure that patients on guanethidine should be seen at regular intervals in the hospital outpatient clinic, not only for regulation of treatment, but for regular assessment of the underlying condition. At most hospitals I visited, patients are given sufficient instruction about their treatment to know when or whether to lower the dose of guanethidine, and are told to restart in slow stages should they have to stop treatment completely for any reason. On the whole there seemed to be good liaison between the clinic and general practitioners, and in one or two centres the consultants in charge of the clinics have had special discussion meetings with the local general practitioners, and these were well attended. There is a good deal of direct telephone contact between the general practitioners and the clinic doctors, and in this way changes of treatment can be discussed, or arrangements made for the patient to be seen specially at the hospital.

Some hospitals provide only enough drugs to cover the interval between the patient being discharged and the doctor receiving a letter or a copy of the case summary sheet. This sometimes has serious disadvantages in that the letter may be delayed, or else the chemist may not stock the drugs. To overcome this, and to make any changes in treatment more easy, several hospitals provide all the relevant drugs themselves. This is sometimes very necessary when rapid changes in treatment are made, but unfortunately it seems to take nearly all control out of the hands of the general practitioner.

At the present time it seems that these patients should remain under close hospital outpatient control, and that one has to accept this in what was a previously untreatable illness. The rewarding feature is the greatly increased survival rate and, in most instances, the possibility of leading a fairly normal life.

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ABSTRACTS

Obstetrics in General Practice—A Five-year Survey. H. I. HOWARD. *The Practitioner* (Feburary 1962) **188,** 239 and 383.

Dr Howard reports on 419 obstetric patients under his care between 1952 and 1957. He describes the arrangements for antenatal care and the method for liaison with the consultant and hospital service. Part II of his paper is a detailed analysis of his results, and he concludes that childbirth is on the whole still a normal and natural process, with very little interference required, provided great importance is placed on antenatal care.

Meprobamate in the First Stage of Labour. P. S. KERSHAW. *The Practitioner* (February 1962), **188,** 243.

Meprobamate was given to 103 patients in domiciliary conditions in order to allay tension and increase co-operation during labour. The initial dose was 1,200 mg., followed by 800 mg. and further doses of 400 mg. when necessary. This regime produced calm, co-operative mothers and made the labours easier. The need for pethidine was reduced. No untoward side-effects were noted.