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RECENT ADVANCES IN THE DRUG TREATMENT OF PARKINSONISM

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Introduction

From time to time the progress of pharmacological research results in a spate of new drugs coming under trial in the treatment of a disease or group of diseases which have hitherto responded unsatisfactorily or incompletely to the therapy available. Occasionally the outstanding success of the new preparations ensures them pride of place in the treatment of that disorder, but only too often difficulties of administration, uncertainty of effect or the appearance of unexpected toxic manifestations results in a swing of opinion away from the new drug and the reinstatement of the well-tried, if imperfect, remedies.

Whether such will be the fate of the newer methods of treatment of Parkinsonism remains to be seen, but already the early enthusiasm which greeted the new preparations briefly reviewed below has been dimmed in the light of further experience, and great caution is necessary in assessing their value.

The main disadvantages of the belladonna group of drugs are well known. In particular, the dosage giving maximum therapeutic effect is dangerously close to that which causes severe toxic symptoms, which may take the form of visual accommodation paralysis, extreme dryness of the

mouth in patients not suffering from excessive salivation, giddiness, light-headedness or even marked hallucinations. A preparation capable of producing a comparable improvement in the patient's condition, without these side effects, would have obvious advantages. *Myanesin*, shown to be capable of relieving spasticity of all types (Henneman and Scherrer, 1949), without general depression of the central nervous system and with little toxicity (Henneman *et al.*, 1949), has produced transitory relief in Parkinsonism, without atropine-like side-effects, when given intravenously (Stephen and Chandy, 1947). This method of administration makes its routine use impracticable, whilst there is also danger of intravascular haemolysis, and overdosage may produce irreversible respiratory paralysis.

Of the many other synthetic antispasmodics which have been tried, those found to be most efficacious are *Parpanit*, *Diparcol*, *Artane*, *Lysivane* and the well-known antihistamines.

Parpanit

This is a compound related to *Trasentin* and *Dolantin* and was first brought to prominence by Swiss workers (Domenjoz, 1946; Grünthal, 1946; Hartmann, 1946). Further careful at-

tempts were made to assess its value—an extremely difficult task in a condition such as Parkinsonism where there may be hourly variations in the severity of symptoms—by Dunham and Edwards (1948) and Schwab and Leigh (1949). The former authors studied 25 and the latter 30 cases, post-encephalitic Parkinsonism and paralysis agitans being equally represented. The drug was found to have a beneficial effect. In 62 per cent. of Schwab and Leigh's cases it was thought to be more effective than the belladonna derivatives; the degree of improvement was rarely great (not more than 25 per cent.); the main effect was on the rigidity so that facility of fine movement was improved; tremor was less benefited; the sense of well-being was increased; subjective improvement was greater than objective, and it was possible gradually to withdraw the solanaceous compounds without the usual rapid deterioration.

The best scheme of dosage is to start with 12.5 mg. three times a day and increase by one extra 12.5 mg. dose daily until five such doses are taken. The first is then raised to 25 mg. and each day one of the remaining doses is similarly increased. By 12.5 mg. increments this scheme is continued until signs of intolerance develop, when the dosage should be kept at the previous day's level. The tablets should always be taken with some food, thus reducing the nausea and gastric discomfort which otherwise occurs. On an average 50 mg. five times per day is well tolerated, but a total daily dosage of 600 mg. may be possible.

The chief side-effects are giddiness, light-headedness, a sensation of lightness of the limbs, floating and weakness. All are reduced by avoiding administration on an empty stomach. It seems probable that some degree of tolerance to this drug develops, and in many centres it is no longer used to any great extent, being replaced by more recent and more effective preparations. Schwab and Prichard (1951), however, consider it to be among the most effective of the newer preparations, providing individual dosage is carefully controlled. Schwab and Leigh (1949) found no significant effect on advanced cases of the disease.

Diparcol

Diethazine hydrochloride is a derivative of phenothiazine and related to *Phenergan*, but has little antihistaminic activity. Sigwald *et al.* (1946) reported very optimistically on its effect on 13 patients and obtained particularly dramatic results by its intravenous use. With other collaborators he again wrote of its effect on 168 cases (Sigwald *et al.*, 1947) obtaining good or excellent results in 20 per cent., and similar figures from a larger series two years later (Sigwald, 1949). Duff (1949) found improvement in all of eight cases of post-

encephalitic Parkinsonism particularly in the performance of actions needing finer movements, those with mild disease being much benefited in this respect. Gray (1949, 1950) obtained improvement in three of nine cases mainly in their ability to do common tasks.

It is important to give this drug in very gradually increasing doses and to prescribe it with food. One 50 mg. tablet is given three times a day and one further 50 mg. tablet is added until five doses are taken per day. The increase may be made daily or on alternate days. Each individual dose in turn is then increased by one 50 mg. tablet each day until five 50 mg. tablets are taken five times a day. For convenience sake, each group of five 50 mg. tablets may be replaced by one large 250 mg. tablet. It may not be possible, of course, to complete this scheme owing to toxic symptoms, but one should employ the highest dosage tolerated.

Toxic effects include nausea and vomiting (prevented by taking the drug with food), faintness, feelings of general prostration, paraesthesiae, blurring of vision and drowsiness. Palmer and Gallagher (1950) report a fatality, and one case of Sigwald's developed agranulocytosis, and though this was thought not to be due to the drug it is difficult to dissociate the two, particularly as two further cases of agranulocytosis have since been reported by Pilcher (1950).

Diparcol can be given by injection, either intramuscularly or, very slowly, intravenously. The effect is, of course, temporary, but this mode of administration may be of value in stopping a severe series of oculogyric crises to which some post-encephalitic patients are prone. The dose is 250 mg.

Artane

In experimental testing of over 100 related piperidyl compounds, Cunningham *et al.* (1949) found those containing the 3-(N-piperidyl)-1-phenyl-1-propanol nucleus the most effective as antispasmodics, and of these 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride (275 C) or *Artane* was the strongest. In low dosage it depressed the central nervous system; in high dosage it excited it, and there was a large margin. It had only one-half the mydriatic properties of atropine, only one-eighth its antisialogogue effect and very much less inhibitory effect on the vagus.

Clinical trials were carried out by Doshay and Constable (1949), Canelis *et al.* (1949), Corbin (1949), Schwab and Tillman (1949) and, in this country, by Ellenbogen (1950), Phillips *et al.* (1950) and more recently by Garai (1951). There has been a considerable measure of agreement

between results, improvement being obtained in 65 to 70 per cent. of cases. All agree that the rigidity is most favourably affected, but in many cases tremor is also markedly improved. The improvement in the emotional hebetude seems more striking than with other preparations, but perhaps the most important factor of all is the benefit obtained in the post-encephalitic cases, which are often so resistant to treatment. Oculogyric crises may be completely abolished or drastically reduced in number and duration. All these effects are further increased by the addition of *amphetamine* (Garai, 1951; Ellenbogen, 1951). The improvement is seen as a rule within three days, and owing to the rapid excretion of the drug there is little danger of cumulation.

Again it is wise to start gradually, particularly in the cases of paralysis agitans. An initial dose of 1 mg. three times a day may be increased daily by 1 mg. doses until five doses are taken per day, when each dose in turn is increased by 1 mg. per day. Most authors have considered 2 or 2.5 mg. five times a day to be the highest dosage, though in post-encephalitic cases over 25 mg. per day may be taken without ill-effect. Garai (1951), however, has worked the dose up to 50 mg. daily, and in some cases used between 60 mg. and 100 mg. with additional benefit. Ellenbogen (1950, 1951) has not obtained further improvement in dosage above 12.5 mg. and Canelis *et al.* (1949) found that above 20 mg. per day symptoms did not appear to be so well controlled. It is notable, however, that the objections to the higher dosage are based on doubt regarding their necessity rather than on the production of toxic symptoms.

Side-effects consist of nausea, dryness of the mouth, giddiness, light-headedness, sensations of depersonalization and, in some older patients, confusional delirium or exaggeration of existing confusion. All these symptoms appear to be less frequent and milder in degree than with any of the other newer preparations. It will be seen, however, that the optimum and maximum dosage is not yet certain, and in view of the low toxicity further trials of the higher dosage employed by Garai (1951) seem justified. At the present time *Artane* appears to be the drug of choice for the post-encephalitic case.

Lysivane

This preparation, related to the antihistamines and of the same series as *Diparcol*, was first reported on in English literature by Palmer and Gallagher (1950) of New Zealand, and later by Garai (1951) in this country. The first authors tried its effect on 16 cases and found that rigidity responded better than tremor when both existed together, but that tremor, when alone, responded

best of all. The gait improved as did the mental state. Garai (43 cases) found rigidity improved more than tremor, and in some cases, as has been found with other preparations, the decrease in rigidity may unmask a tremor and make it appear worse. Palmer and Gallagher recommended a dosage of 50 mg. four to ten times a day, gradually attained, while Garai again used much higher dosage even to 1,500 mg. daily, but found *Lysivane* more toxic than *Artane*.

Drowsiness and lassitude may occur from half-an-hour to three hours after administration, but may be relieved by amphetamine. Formication and cramps usually disappear spontaneously without reducing dosage. There may be transient diplopia. Light-headedness, confusion and depersonalization may occur on the higher dosage, and ataxia may be troublesome or even dangerous.

Palmer and Gallagher noted a tendency for an initial marked improvement to be followed by a slight relapse and then a final further improvement, and considered the best effects obtained in combination with stramonium.

The Anti-Histamines

In view of the close association of the above drugs with the anti-histamine group, it is not surprising that the better known members of this group have themselves been used. It is unfortunate that so much publicity was given to the early reports by the lay press, for their unreliability has caused the pendulum of medical opinion to swing against them, and the hopes raised in the minds of many sufferers from Parkinsonism have not been fulfilled.

McGavack *et al.* (1947) experimenting with *Benadryl*, found that three of four patients with paralysis agitans were benefited, and Budnitz (1948) obtained improvement in all of his eight cases of Parkinson's disease, four of whom were taking atropine as well. Ryan and Wood (1949) reported consistent improvement in rigidity in 40 cases, with abolition of muscle cramps, but other symptoms were not affected. *Benadryl* is the most effective member of the series (Gair and Ducey, 1950) and better tolerated than *Phenergan*, while *Pyribenzamine* is of doubtful value (Budnitz, 1948).

Benadryl, 50 mg., can be given three or four times a day and there seems little doubt that it is wisest to add this to existing therapy.

The main advantage of this preparation is its comparative freedom from toxic effects, the drowsiness which occurs being relieved by the use of amphetamine. No consistent improvement on the older methods can be expected, however, and initial benefit is often followed by a stationary phase which, if not anticipated, may disappoint patient and physician.

General Remarks

'The effectiveness of a treatment against the symptoms of a disease usually varies inversely with the number of remedies in use.' Schwab and Tillman (1949) after writing this, point out that this situation has applied for many years to the treatment of Parkinsonism, and that the advent of the new preparations has not altered it. None of them is a cure; none can be relied upon to produce alleviation of symptoms in every case, and it is uncertain whether initial improvement will be maintained over the many years during which such patients require treatment.

It is notoriously difficult to assess the value of any preparation in this disease, for not only are there daily, and even hourly, variations in the symptoms, but psychic factors play so large a part in the reaction to any new treatment. The rapid deterioration shown by many workers to occur following the substitution of a placebo unknown to patient and nursing staff, and the improvement on returning to the drug in the same manner, proves their effectiveness to be genuine, and from the information at present available *Artane* appears to be the most satisfactory preparation, and is certainly the least toxic, while there seems little doubt that it is the best drug to use in the post-encephalitic group. In those cases where tremor predominates over rigidity, *Lysivane* may be beneficial. The other preparations have their main effect on rigidity, but the possibility of administering *Diparcol*, very carefully, by injection, should be remembered. There are many patients who seem prone to develop toxic symptoms no matter what preparation is used, and for these *Benadryl*, with its simple scheme of dosage, is well worth a trial.

In a recent study of comparative effectiveness,

Schwab and Prichard (1951) place *Artane* at the head of their list, followed by *Parpanit* and *Benadryl* in that order, but stress the absolute necessity for careful individual regulation of dosage in the case of *Parpanit*.

Most of the authors quoted above have replaced previous therapy, either slowly or abruptly, by the new drugs, in order to compare their effects, but in ordinary practice it is wiser to add the newer preparations to any existing treatment in an attempt to obtain further benefit. It may then become possible to reduce the dosage of the older drugs, but any increase in symptoms will be taken as a warning that this reduction should be stopped.

Owing to the need for increasing dosage very gradually, the use of these drugs in the out-patient department has obvious difficulties, unless the patient is intelligent and co-operative, and the scheme carefully explained. The temptation is to increase more rapidly, for simplicity's sake, particularly in the early stages, and it is these cases which develop the toxic symptoms which have made some of the preparations unpopular. It is necessary to regulate the dosage carefully according to the requirements of each individual case, as one would in the treatment of epilepsy, and the golden rule for the treatment of Parkinsonism by the belladonna group of drugs should be applied to the preparations reviewed above, and the use of any given drug never be stopped abruptly.

It remains for further experience to show us whether these new methods will stand the test of time over as many years as have the belladonna compounds, despite their disadvantages, but the search for even more active preparations continues and an attitude of cautious optimism appears justified.

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