LYSIVANE THERAPY FOR PARKINSONISM

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The claims made by French workers (Bovet *et al.*, 1947; Sigwald, 1947, 1949; Sigwald *et al.*, 1947) for "diparcol" in the symptomatic treatment of parkinsonism have been confirmed by Duff (1949), Gray (1949, 1950), and Palmer and Black (1949), but the mortality may be in the region of 5%. This paper reports our findings with "lysivane" (N-(2-diethylamino-n-propyl)phenothiazine hydrochloride), a member of the same series of drugs as diparcol.

Both lysivane and diparcol are substituted phenothiazines (the substitution group being the active principle) which have been evolved by Bovet *et al.*, followed by Sigwald *et al.*, whose interest seems to have been derived from the observation that certain drugs of the antihistamine series were capable of benefiting patients suffering from parkinsonism. This benefit they thought was due to the relatively specific action of this series of drugs on the extrapyramidal centres. In addition to this selective action, these drugs (which include such members as "benadryl," "phenergan," diparcol, and lysivane) have a general pharmacological action on the central nervous system, promoting drowsiness, and have other more specific actions, including parasympathicolytic (ganglioplegic) properties. They also have sympathicolytic activity and an anti-acetylcholine and spasmolytic action.

The Parkinson syndrome comprises two main varieties—that which is associated with old age (paralysis agitans), and that which follows encephalitis lethargica. Both varieties have in common a tendency towards muscular tremor which can be coarse or fine (noted in this study to be fairly constant at 5 a second), rigidity and weakness, and an alteration in the psyche. No adequate descriptive term can be given for the change in the mental attitude of these patients, but it includes some apathy, depression, and peevishness, and a paucity of interest, all of which in combination place a peculiar burden on those relatives who are called upon to look after the patients. In many cases this change constitutes the major incapacitating symptom. Parkinsonism following encephalitis lethargica has, in addition, its own peculiar mode of expression, both in the psychical and in the somatic sphere, and in this type oculogyric crises (not encountered in paralysis agitans) are amongst the more troublesome symptoms. In both conditions orthopaedic deformities are apt to develop. Anything one can do to help these patients relieves in turn the despondency which so often descends upon their relatives. In the more practical realm of everyday life a return of the ability to perform the finer movements involved in dressing, writing, feeding themselves, and attending to their toilet is a tremendous contribution to their own and their family's welfare.

This paper reports our experience with 16 patients treated with lysivane, the general purpose of the research having been promoted by the Otago Old People's Welfare Council.

Dosage

The drug is supplied in 0.05-g. tablets. All patients, in the course of one week, were placed on their characteristic effective dose, which varied from 4 to 10 tablets a day. At first we confined our maximum to five tablets daily, but it seems that this leaves a very large margin of safety and some patients did not achieve maximum benefit on this dosage. Up to 20 tablets a day have been used by Sigwald. In view of the fatality encountered with the use of diparcol we have been cautious. We believe that, as further experience is gained and more is known about the clinical toxicity of these drugs, a higher dose may be permissible and better results than those we are recording will be achieved.

The accompanying Table records the effects of our treatment on individual symptoms, as well as the general effect on the patient.

Analysis of Cases

Case No.	Age and Sex	Aetiology	Major Cause of Disability	Disablement	Rehabilitation
1	52 M	Post-encephalitic	Tremor, rigidity, weakness, depression, festination	Walks with aid; fed, shaved, dressed. Partial invalid	Walks, feeds, shaves, dresses unaided. 5 tabs./day for 3 m. (2) Stramonium 15 gr. daily
2	62 M	Senile	Rigidity, weakness, depression, festination	Total invalid	Walks, feeds, shaves, dresses unaided. 10 tabs./day for 3 m.
3	36 F	Unknown	Unilateral tremor	Writing difficult; patient a teacher	Writes normally; tremor absent. 4 tabs./day for 3 m.
4	37 M	Post-encephalitic	Oculogyric crises daily; rigidity, tremor, depression	Crises confine patient to house	Crises 2 a week on diparcol; 1 a week on lysivane 6 tabs./day for 3 m.
5	46 M	Senile	Tremor (arms)	Tremor interferes with fine movements	Can roll cigarette; tremor absent. 6 tabs./day for 2 m.
6	73 F	"	Tremor, rigidity, weakness, festination, retropulsion, extreme retardation	Total invalid; appearance of senile dementia	Walks, feeds unaided. Mental activity restored. 6 tabs./day for 2 m.
7	59 M	"	Tremor, depression, slow indistinct speech	Socially incapacitated	Tremor absent, speech clearer. 4 tabs./day for 1 m.
8	60 F	"	Tremor, rigidity, weakness, depression, retropulsion	Total invalid	Walks, dresses unaided; tremor absent. 6 tabs./day for 2 m.
9	59 F	"	Tremor, rigidity, weakness, depression, deformity	" "	Walks with aid, dresses; deformities reducing; tremor reduced. 8 tabs./day for 2 m. (2) Stramonium 30 gr. daily
10	53 M	"	Tremor, weakness, depression	Difficulty in dressing and writing	Writing and ability to dress regained; tremor absent. 6 tabs./day for 1 m.
11	72 F	"	Tremor, weakness, slow speech, depression, festination	Walks with aid; cannot dress or feed unaided; given up social life. Partial invalid	Walks, dresses, feeds unaided. Loss of depression. 4 tabs./day for 1 m.
12	63 M	"	Tremor (unilateral)	Socially incapacitated	Tremor controlled. 4 tabs./day for 2 w.
13	68 M	"	Tremor, rigidity, weakness, depression, festination	Walks with aid; fed and dressed. Partial invalid	Walks unaided; stronger. 4 tabs./day for 2 w.
14	62 F	"	Tremor, weakness, depression	Foot drags; difficult to manage housework. Given up social life	Improving. 4 tabs./day for 1 w.
15	49 M	Post-encephalitic	Tremor, oculogyric crises, slow speech, festination. Focal epilepsy	Surgical treatment left slowness of speech (and focal epilepsy)	No further improvement on 4 tabs. daily
16	65 F	Senile	Tremor, rigidity, festination, retropulsion, depression	Difficulty with walking and fine movements	Improved on 4 tabs. daily. Treatment not continued owing to isolated home conditions

Results

Rigidity responds better than tremor when the two occur in combination. Tremor alone responds best of all.

We believe that restoration of that controlled background of muscular tone upon which all voluntary movement is based determines the favourable response to lysivane, though some degree of tremor may persist. Festination and retropulsion disappear, the patient ceases to be the important claimant on his relatives' attention, and the tremor becomes a matter of the transient emotional tension to which even normal individuals are prone.

In our opinion the most striking case, and one which illustrates the importance of viewing a patient as a whole as opposed to estimating the effect of the treatment on symptoms, is Case 6. On admission to hospital this patient resembled a senile dement. She was confined to bed in a rigid, hopeless state, with little contact with the outside world, and with all the implications which this state of affairs had for the nursing staff of the home for the aged where she was being nursed. She walked out of hospital unaided, had assumed quite a charming personality, and returned to the home to gladden the hearts of her fellow patients and to encourage the staff in their humanitarian care of the ageing and chronic sick. In a case like this we do not feel disposed too narrowly to estimate benefit in terms of isolated symptoms alone.

Of our 16 cases 12 were treated as out-patients, receiving no other form of therapy. We mention this fact since the remainder whilst in hospital may have derived benefit from rest in bed and the physiotherapy which was given. One patient (Case 15) suffering from post-encephalitic parkinsonism and showing tremor, oculogyric crises, and festination, who had received surgical treatment in the U.S.A. which relieved all symptoms, except bradyphasia and depression (partly due to a post-operative complication of focal epilepsy), obtained no benefit from lysivane.

Toxicity

The laboratory findings of the French workers place the available drugs in the following descending order of toxicity (in rats) : phenergan, diparcol, lysivane.

As we have had no deaths with lysivane in spite of one patient stopping the treatment suddenly, and in view of our one fatality with diparcol, we infer that our experience bears out the laboratory findings.

Clinical toxic events are as follows : (1) Drowsiness and lassitude, with or without vertigo, appearing half an hour after dosage and lasting one to two hours, most apparent early in treatment. These effects eventually disappear and are countered effectively by strong coffee or by amphetamine sulphate. (2) Formication, irritation, and cramps are paraesthesiae related to parkinsonism rather than to drug therapy. These are perhaps, strictly speaking, not toxic effects so much as release phenomena consequent upon the treatment of the basic condition. They are relieved by aspirin and disappear in some weeks. (3) Dryness of the mouth, transient diplopia, vasomotor reactions ; these are rarely found, and disappear spontaneously.

In the present study only the first group of toxic symptoms was observed and in no case was it necessary to discontinue treatment. In Sigwald's series six out of 106 patients treated suffered vertigo or cramps, necessitating discontinuation of treatment.

An interesting feature was the tendency for patients to show a marked initial improvement followed by some relapse and then a final upward movement until stability had been reached. This probably refers to the placebo effect of encouragement which operates at a maximum initially.

One case (No. 4) previously treated with diparcol gave an improved response to lysivane.

Sigwald has recorded, however, that lysivane was greatly superior to all other forms of treatment in 46 out of 106 cases, identical in 29, and inferior in 4.

Relation to Other Forms of Treatment

One of the advantages of lysivane therapy is that the drug can be combined with other forms of treatment—for example, stramonium. Indeed, in two of our cases which had previously derived benefit from stramonium, lysivane alone was to some extent disappointing, though improvement undoubtedly occurred. When, however, the two drugs were given in combination the final effect was far superior to that achieved by stramonium, or, indeed, by either one separately. It would seem, therefore, that patients suffering from parkinsonism should also be tried with lysivane in combination with stramonium.

With lysivane alone one patient who suffered from oculogyric crises, and who formerly had had attacks daily, had the attacks reduced to one or two a week.

All the remarks concerning withdrawal which apply to diparcol apply by inference to lysivane, but one old lady stopped her treatment while having five tablets a day, with no untoward result. For the time being, however, it would seem to be mandatory that all patients should be carefully instructed never to withdraw the drug suddenly.

Conclusion

Lysivane is capable of affecting beneficially any symptom or complex of symptoms from which the parkinsonian patient is suffering—notably his mentality. We would estimate our findings in general as follows : complete alleviation, 1 ; good result, 10 ; improved, 4 ; and no change, 1 (patient and relatives concurred in cessation of further treatment).

We wish, however, once more to reiterate the dangers of attempting to evaluate results on too narrow a symptomatic basis and are content to assert that in our opinion lysivane does all that is claimed for it in a manner which is safe for the patient. It may confidently be recommended, therefore, as a valuable remedy in the treatment of this condition.

We propose to extend our work to the other drugs for which claims have been made, and this will be reported in a subsequent paper.

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A booklet on the *Superannuation Scheme for Those Engaged in the National Health Service* has been prepared by the Ministry of Health. It will be issued to new entrants to the Health Service free of charge, and is also obtainable from H.M. Stationery Office for 3d. The scheme is described in plain language, and specific examples are given on how it works.