AUSTRIAN DOSAGE SCHEDULES

Dr. W. DANIELCZYK (Vienna): Even when amantadine therapy was continued for more than a year, we saw no reason to modify the 200 mg dosage. After about four weeks' treatment, and later after nine months or so, a period of deterioration may occur, lasting from one to two weeks. We tell the patient that this negative phase is only temporary, and that it is unwise to discontinue the drug, as this would cause a further deterioration. In these phases, combination with L-dopa is usually beneficial. Symmetrel only has to be discontinued if the patient develops a severe organic psychosis with confusion. These confusional states are sometimes aggravated by atropine or similar preparations, but they may also be induced by Symmetrel alone, especially in arteriosclerotic patients. The best results were observed in 60 patients with idiopathic forms of Parkinson's disease.

The results in 12 cases of post-encephalitic Parkinsonism were less satisfactory, and the drug was least effective in 18 patients suffering from arteriosclerosis. As, however, arteriosclerotics also respond poorly to other drugs—for example, L-dopa—it is worth trying amantadine therapy. I saw no evidence that post-encephalitic crises responded to amantadine or, it must be admitted, L-dopa.

I imagine that psychoses may be activated by amantadine. A patient with post-encephalitic Parkinsonism and a tendency to hallucinations of a paranoid nature showed slight improvement in Parkinsonian symptoms on amantadine, but the psychotic disturbances became more pronounced. Particularly in long-term therapy, Symmetrel should, wherever possible, be administered alone. Only when absolutely necessary should it be supplemented with small doses (a quarter to a half of the usual) of anticholinergic agents. Combination with L-dopa is well tolerated if its dose is kept low—to a maximum of 1.5 gm daily. We do not reduce the Symmetrel dosage. Symmetrel intensifies the action of L-dopa, thus increasing the efficacy of small doses, with the result that fewer side-effects are observed.

Patients suffering from arteriosclerotic Parkinsonism tolerate the combination less well. The more severe the degree of arteriosclerosis, the poorer the response to both L-dopa and Symmetrel. In most cases where there is a good response to Symmetrel, a good response to L-dopa may also be expected, but a combination should be given, especially in phases of reduced response to Symmetrel. Of course,

there are patients who respond best to the administration of Symmetrel alone, though the benefit is unpredictable.

Dr. F. GERSTENBRAND (Vienna): We have experience of treating 54 patients with Parkinson's syndrome of idiopathic and post-encephalitic origin. In 80% of our patients the best effect was achieved with a daily dosage of 200 mg. This is true of treatment with Symmetrel alone, as well as in combination with conventional drugs and with L-dopa. In 50% of our cases, it was necessary to increase the dose of Symmetrel to 300 mg daily. Most of the patients in this group, which contained four post-encephalitic cases, showed a better response on this dosage.

In only two cases—both with idiopathic Parkinson's syndrome—did we prescribe 400 mg daily. In patients with additional arteriosclerosis cerebri, dosage should be limited to 200 mg daily, because larger doses may provoke hallucinations, without producing further benefit. I should mention here that in our opinion we have to distinguish patients with idiopathic Parkinson's syndromes who later develop cerebral arteriosclerosis from those whose arteriosclerotic brain damage is the cause of their Parkinsonian symptoms.

An increase in daily dosage from 300 to 400 mg of Symmetrel was necessary, especially in patients whose main symptom was akinesia and rigidity. In post-traumatic cases, we treated 12 patients with a daily dosage of 200 mg. This proved enough, an increase to 300 mg often provoking an increase of the cerebellar symptoms which commonly affect these post-traumatic cases.

In a study of 10 patients with mild idiopathic Parkinsonism, previously untreated, we gave 200 mg Symmetrel daily for 2½ months. It then seemed necessary in four cases to increase the daily dosage to 300 mg. This increase alone was without effect, but combination with other therapy gave good results. We always find combined therapy necessary in moderately severe to severe cases, which have always been treated beforehand with conventional drugs or L-dopa.

To summarise our experience, in 80% of cases we used 200 mg Symmetrel daily. In some cases, especially in post-encephalitic Parkinsonism, it was necessary to increase the dosage to 300 mg. In two cases we achieved a better effect by further increasing the dosage to 400 mg. In patients with Parkinsonism and arteriosclerosis cerebri, no more than 200 mg daily should be ordered, because of possible side-effects, especially hallucinations.

DISCUSSION

CHAIRMAN: You are saying that the presence of cerebrovascular disease reduces the patient's tolerance, are you not?

GERSTENBRAND: Yes. These cases which have a combination of Parkinson's symptomatology and signs of arteriosclerosis cerebri are likely to get side-effects, especially with L-dopa. I am sure you will all have had this experience. From this point of view, L-dopa can be a very dangerous drug. It would be wrong to leave this treatment in the hands of general practitioners.

CHAIRMAN: This was always the case with the anticholinergic drugs too, was it not?

GERSTENBRAND: But not to such a serious degree.

Dr. D. G. IEZZONI (Endo Laboratories, New York): We are doing drug dynamic studies with amantadine in older patients. In some preliminary results the half-life of amantadine appears to be somewhat longer (up to 30 hours) in the geriatric patient than in younger patients or normal adults, in whom the normal half-life of amantadine is about 15 hours.

CHAIRMAN: You say "older patients". What diseases had they got?

IEZZONI: They were just older. Amantadine is excreted in urine unchanged. I wonder whether, in some of the patients where arteriosclerosis has been described, the side-effects may have been due to accumulation of the drug. There may be some impairment of renal function. Or it may be that certain patients are particularly sensitive to the drug.

TISSUE LEVELS, DOSAGE AND EXCRETION

Prof. J. OFFERMEIER (Potchefstroom University, South Africa): The important factor in a dosage scheme, generally speaking, is that the tissue level of the drug which gives the desired therapeutic response must be reached and maintained. Many side-effects of drugs are also pharmacological responses, and are usually obtained by

higher drug tissue levels. Too high a dose, or giving the drug too often, leads to its accumulation, giving tissue levels at which side-effects are produced, whereas too low a dose, or dosage intervals which are too far apart, produce a tissue level which is too low or too variable to be clinically effective. To find the correct dosage schedule one should, generally speaking, know what concentration is necessary for the therapeutic response. Secondly, the biological half-life of the drug should be studied. When these two factors are known, a dosage scheme which produces a constant and therapeutically effective level can be calculated. If the tissue level at which side-effects develop is also known, then these may be excluded, as far as possible.

IEZZONI: The reports of withdrawal symptoms are interesting. We have always felt that the side-effects described with Symmetrel could be alleviated in a matter of hours by stopping medication immediately and forcing fluids to increase urinary excretion of the drug.

OFFERMEIER: How does the pH of the urine affect excretion of amantadine? This would, of course, affect the half-life.

IEZZONI: Acidification of the urine produces a rapid increase in excretion, whereas alkalinisation results in retention of the drug.

GERSTENBRAND: In 10 patients, in all of whom it had been combined with conventional antiparkinson drugs, we stopped Symmetrel therapy. Two of them developed a confusional state. If we resumed Symmetrel treatment this confusional state ceased almost immediately—after 24 hours in one patient and 48 hours in the other.

Dr. P. B. JØRGENSEN (Newcastle, England): We saw one patient who developed a hallucinated state after withdrawal, but did not subsequently receive amantadine.

SENSITIVITY DUE TO IMPAIRED RENAL FUNCTION

Dr. J. PEARCE (Hull Royal Infirmary): I agree very much with various colleagues about the increased sensitivity to amantadine with increasing age, and I think this is likely to be related to decreasing renal function. I think this is a much more sensible interpretation

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