PAPERS AND ORIGINALS

Treatment of Acute Herpes Zoster with Amantadine Hydrochloride (Symmetrel)

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Summary

A double-blind, placebo-controlled trial of amantadine hydrochloride (Symmetrel) in acute herpes zoster (shingles) was carried out in 100 patients in general practice. The cases were serologically proved. There was no difference in duration of pain between the drug and placebo groups when pain disappeared during the 28 days' observation period. However, pain lasted more than 28 days in a significantly greater proportion of patients receiving placebo than of those on amantadine. Patients with pain after the 28-day observation period were significantly older than those whose pain disappeared during the study. The drug had no effect on rate of healing or appearance of new lesions.

Introduction

Amantadine hydrochloride (Symmetrel) has proved to be effective in the prophylaxis and treatment of influenza A₂ (Togo *et al.*, 1968; Galbraith *et al.*, 1969; Hornick *et al.*, 1969). It appears to act by preventing the virus from entering the cell (Davies *et al.*, 1964) or by inhibiting an early stage of virus reproduction (Eggers, 1970), thereby enabling the natural defences of the body to overcome the infection.

After uncontrolled evidence (G. H. Lloyd, personal communication, 1973) that amantadine reduced the duration of pain, produced more rapid healing, and prevented postherpetic neuralgia, a double-blind comparison of the drug with placebo was carried out in general practice to substantiate or refute this observation.

Material and Methods

A total of 99 family doctors volunteered to participate in the study, and each received a box containing instructions for patient and doctor, a record card, sterile syringe and needle, serum specimen tube, preaddressed box to the Virology Laboratory, Oxford, and a code-labelled canister of 56 amantadine capsules or identical placebo capsules containing oil base without the active compound. The canisters were numbered randomly, and if a doctor requested an additional box to treat a subsequent case the random allocation catered for this eventuality.

Patients over 14 years of age, of either sex, suffering from herpes zoster of early onset, preferably within 24 hours of vesiculation, were admitted to the trial. If they were already receiving medication for other conditions they were allowed to take part in the study provided the criteria for inclusion were satisfied, and the routine medication was confirmed.

No patient with a dry herpetic rash was included. In addition, patients suffering from, or with a history of epilepsy, gastric ulceration, or psychosis were excluded from the study.

On including the patient in the trial the doctor entered the clinical details on the record card and noted the time of administration of the first capsule. The dose was one capsule taken twice daily. Pain, crusting of the lesion, the appearance of new lesions, and perfect skin healing were noted daily on the record card for a total of 28 days. All other drugs taken were recorded and the occurrence of postherpetic neuralgia was reported.

Laboratory Study.—In a patient with herpes zoster a high level or rise in complement-fixing antibody provides proof of infection. A 5 ml venous blood specimen was withdrawn from each patient between the 14th and 28th days after diagnosis of the disease. This was placed in a dry plastic container and posted in a preaddressed box to the Virological Laboratory, Radcliffe Infirmary, Oxford. If an equivocal result was observed a second serum specimen was requested by the consultant virologist directly to the general practitioner concerned.

Side Effects.—It is known that amantadine is well tolerated in the recommended dosage and minimal side effects were ex-

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pected. However, any side action was recorded and if a severe adverse reaction occurred the code, held centrally, was broken and the patient was removed from the trial.

Results

Record cards of 117 patients were submitted for analysis. Of these patients fifteen were serologically negative or had low unchanging titres which were no greater than those to *Herpesvirus hominis* in the same serum, one was admitted to hospital, and one had no antibody estimation performed. There were thus 100 patients whose progress could be compared, 54 of whom received amantadine and 46 received placebo.

The age and sex distribution of the two groups are shown in table I. The mean age of the amantadine group was 56.4 years and that of the placebo group 56.6 years. There were 22 males in the drug-treated group compared with 18 in the control group, and 32 and 28 females, respectively. The differences were not significant and the groups may be considered similar. (Statistical significance is achieved only if the probability that it would have arisen merely by chance is less than 0.05—that is, odds of 19 to 1.)

TABLE I—Age and Sex Distribution of both Groups of Patients

Group	Total No. of Patients	No. in Each Age Group								Mean Age (years)	Proportion of Males and Females in Each Group	
		<20	20-29	30-39	40-49	50-59	60-69	70-79	80+		M.	F.
Amantadine	54	3	3	4	6	15	7	11	5	56.4	22	32
Placebo	46	3	4	4	2	9	9	11	4	56.6	18	28

Start of Treatment.—It was observed that there was some variability in the time between the start of the illness and the taking of the first capsule. However, 26% of both drug and placebo groups began the treatment within two days of the start of the illness and 80% began the treatment less than five days from the first symptom. The mean range in the drug group was 3.3 days from first symptoms to first capsule and 3.7 days in the placebo group. The difference is not significant.

Duration of Pain.—In calculating the day pain ended, it was stipulated that if the first capsule was taken before 4 p.m. the day was termed day 1. If it was taken after 4 p.m. the next day was termed day 1. The day on which pain ended for each patient in the trial is given in the graph. (Two patients in the placebo group had no pain at any time.) If all the patients are considered, those receiving amantadine had a significantly shorter duration of pain compared with those on placebo. This is summarized in table II in which the three periods days 1 to 15, days 16 to 28, and over 28 days are given. If only the first two periods are considered the difference between the two

in favour of the drug-treated group. It is also noteworthy that those patients whose pain had not ended by the 28th day of the study were significantly ($P < 0.05$) older on average than the rest of their group, both for those on amantadine and those on placebo. In addition, of those receiving the drug only two out of five aged over 80 years and two out of 11 aged from 70 to 80 years had pain for over 28 days, while of the controls all four aged over 80 years and six out of 11 aged from 70 to 80 years had pain for more than 28 days.

Crusting.—There was little difference between the two groups in the average day crusting started. Of those taking amantadine 50% developed crusting of the lesion by day 5 compared with 59% of patients receiving placebo. By day 10 the proportions were 85% and 96%, respectively, a difference which is not significant.

Perfect Skin Healing.—This was a difficult assessment to make, but the groups showed little difference. By day 20 33% of the drug group showed perfect healing compared with 46% in the placebo group. By day 28 74% of the drug group had healed skin compared with 70% of the placebo group, leaving 26% and 30%, respectively, unhealed. This difference is not significant.

New Lesions.—Forty-three patients taking amantadine and 42 controls recorded the appearance of new lesions. These presented with decreasing frequency to day 4. No differences were recorded between the two groups.

Side Effects.—Minimal side effects were recorded in both groups and no patient had to be removed from the trial on this account.

Discussion

This double-blind, placebo-controlled trial confirmed the impression made in an open study that amantadine given early in the infection can reduce significantly the proportion of patients who experience pain of long duration in acute herpes zoster. The mode of action of the drug is not known. It has been shown that amantadine has no analgesic properties and is in fact a mild central nervous system stimulant (Vernier *et al.*, 1969). It might be suggested that the drug is acting antivirally, but this is less likely as it has no effect on *Herpesvirus hominis*—a virus similar to the V-Z virus. In addition, if this was the mode of action it would be expected that the rate of heal-

TABLE II—Day Pain Ended Measured from Start of Treatment

Group	Day 1-15	Day 16-28	Day 28 +
Amantadine	31 (57%)	16 (30%)	7 (13%)
Placebo	17 (37%)	14 (30%)	15 (33%)

$$\chi^2 = 6.580; n^1 = 2; 0.05 > P > 0.02.$$

groups is not significant. Of those receiving amantadine, however, seven were not pain-free after 28 days' treatment compared with 15 receiving placebo. This is a significant difference

ing of the lesions would have been more rapid in the drug-treated group.

A long-term follow-up of patients with pain lasting longer than the 28-day study was carried out. This showed that the group was significantly older than those patients whose pain went during the 28-day observation period and the final disappearance of pain was at about the same time in both the control and treated groups.

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Incidence of Anticonvulsant Osteomalacia and Effect of Vitamin D: Controlled Therapeutic Trial

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Summary

The bone mineral content (B.M.C.) in both forearms (related to total body calcium) was measured by photon absorptiometry for a controlled therapeutic trial in a representative sample of epileptic outpatients, comprising 226 patients treated with one or two major anticonvulsant drugs (phenytoin, phenobarbitone, primidone).

Initially the mean B.M.C. value for all epileptic patients was 87% of normal. During treatment with 2,000 international units of vitamin D₂ daily for three months an average B.M.C. increase of 4% was found, whereas the B.M.C. values remained unchanged in the placebo group and in the control groups. The incidence of hypocalcaemia and raised serum alkaline phosphatase was 12% and 43% respectively. The biochemical indices of osteomalacia were related to B.M.C. These results indicate that epileptic patients should be closely supervised for the occurrence of anticonvulsant osteomalacia, and, possibly, receive prophylactic treatment with vitamin D.

Introduction

Biochemical findings suggesting osteomalacia are quite often seen in epileptic patients treated with major anticonvulsant drugs (Wright, 1965; Schmid, 1967; Kruse, 1968; Dent *et al.*,

1970; Richens and Rowe, 1970; Hunter *et al.*, 1971). The suggestion was made that induction of liver enzymes concerned with hydroxylation of vitamin D might be responsible for this disturbance of calcium metabolism (Richens and Rowe, 1970). Several findings have supported this hypothesis. The urinary excretion of glucaric acid, which is an index of liver-enzyme induction, correlates inversely with the serum calcium levels in epileptics (Hunter *et al.*, 1971). Other investigations have shown low serum levels of 25-hydroxycholecalciferol (Hahn *et al.*, 1972; Stamp *et al.*, 1972), the main circulating metabolite of vitamin D₃ (Ponchon and DeLuca, 1969).

With regard to the clinical significance of these drug-induced phenomena, a number of authors have reported radiological signs of rickets (Kruse, 1968; Berger and Munde, 1970; Lussier-Lazaroff and Fletcher, 1971; Lässker *et al.*, 1971; Stögmann, 1971). However, the published reports disagree considerably as to the incidence of anticonvulsant rickets in epileptic children. This may be due to the inborn qualitative nature of the radiological examination. Bone biopsy has been done in only a few patients (Dent *et al.*, 1970), and this method is similarly difficult to quantitate. It is possible to express the bone mineral content quantitatively by means of photon absorptiometry, and this has been used to show a low bone mineral content in small groups of epileptic patients (Linde *et al.*, 1971; Christiansen *et al.*, 1972, 1973).

Though most epileptics are outpatients the major reports on anticonvulsant osteomalacia have concerned inpatients (Richens and Rowe, 1970; Hunter *et al.*, 1971; Stamp *et al.*, 1972). Naturally, the question arises whether the large number of patients on anticonvulsant therapy should be treated with vitamin D, and if this is so what dose of vitamin D should the patient receive? A subsidiary question might be: which patients should have vitamin D, and how should they be selected?

Before these questions can be answered it is necessary to decide on a method of quantitating bone demineralization in anticonvulsant osteomalacia, and to apply it to a large, representative sample of epileptic outpatients *before* and *after* treatment with therapeutic doses of vitamin D. To minimize unwanted influences the therapeutic trial should be carried out in a

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