active preparation showed no significant improvement in clinical or laboratory findings, compared with a matched group of patients treated with placebo.

We have concluded that lincomycin hydrochloride is of no obvious benefit in the treatment of Reiter's disease.

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Effect of Tetrabenazine on Extrapyrimal Movement Disorders

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Summary: Thirty patients with various extrapyramidal movement disorders were treated for prolonged periods with 75 to 225 mg. daily of tetrabenazine. In patients with choreiform and hemiballistic motor activity the involuntary movements were diminished or abolished. In patients with cerebellar or Parkinsonian tremor the tremor was aggravated in moderately severe cases, but was uninfluenced in severe cases. In all cases the dyskinesia returned when the drug was stopped.

Side-effects were inconsiderable and disappeared on reducing the dose slightly. Hence the drug may be an important alternative to neurosurgical treatment of hyperkinesia and especially suitable for severely disabled patients.

Introduction

Drug treatment of hyperkinetic syndromes aimed at the selective elimination of the abnormal motor movements began with the use of the drug reserpine for the treatment of Huntington's chorea (Farbrot, 1956; Forrest, 1957; Grung and Sundby, 1957; Brandrup, 1960). Nevertheless, even if a sufficiently high dose of the drug can reduce the choreiform activity in nearly all cases, this drug is not suitable for long-term treatment, as side-effects frequently occur in the form of hypotension, depression, and gain in body weight. The search for a less troublesome and more effective drug led to the introduction of tetrabenazine (Nitoman) (Brossi *et al.*, 1958), for Huntington's chorea, hemiballismus, torsion dystonia, and the facial dyskinesias following phenothiazine medication (Brandrup, 1960; Møller-Christensen and Videbech, 1963; Sattes and Hase, 1964; Pakkenberg, 1968).

Tetrabenazine, like reserpine, is a monoamine-depletor and its pharmacological effect is, in principle, similar to that of reserpine. Clinical effects, however, start more quickly and the drug is eliminated in 24 to 48 hours. It is therefore easier to control the dose than using reserpine (Pletscher *et al.*, 1962). The dose given has ranged from 75 to 300 mg. daily. Apart from slight sedation, which disappears on reducing the dose, no side-effects have been encountered in the cases of hyperkinesia treated.

Method

Since 1962 30 patients with extrapyramidal movement disorders have been treated in a trial of the efficacy of tetrabenazine. Fourteen had choreiform movements, four had hemiballismus, two had dystonic torsion syndromes, four had intention tremor, and six had Parkinsonian tremor. The diagnostic classification was as follows: Huntington's chorea (8), cerebral arteriosclerosis (8), epidemic encephalitis (3), Sydenham's chorea (1), paralysis agitans (6), and spinocerebellar degeneration (4).

The results of treatment were evaluated independently by the nursing staff, by the patient's relatives, by the patient himself, and by me. In most cases treatment was given over several periods for one to four weeks alternating with periods of treatment with phenobarbitone or anti-Parkinsonian drugs. Thus the patient acted as his own control, but a placebo technique or a double-blind trial was not performed. In cases where an obvious effect was obtained treatment was extended for periods of three to six months. Two patients were treated for a period of six years without loss of effect.

Films taken of the patients before and during a period of treatment enabled close analysis of the character of the movements initially and of the change occurring during treatment. After discharge from hospital patients who had obtained relief from their hyperkinetic movements were given a choice of tetrabenazine, phenobarbitone, or anti-Parkinsonian drugs. In all cases they chose tetrabenazine. Routine blood tests, urine analysis, and liver function tests carried out during treatment showed no abnormalities.

Results

The Table shows the results of treatment with tetrabenazine in relation to the type of dyskinesia but without regard to the diagnostic classification. "Moderate" means a reduction of abnormal movements by 80-90% as judged by filming the patients. Cases classified as "good" showed complete cessation of the abnormal movements.

In patients with choreiform movements, whatever the aetiology, tetrabenazine produced a gradual decrease in the number and amplitude of the involuntary movements, first seen in the axial muscles of the trunk, then in the proximal muscles of the limbs, and lastly in the hands, feet, and face. These results

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were observed after two to three days' treatment with 150–220 mg. of tetrabenazine. If the dose was increased further a slight but distinct sedative effect was produced. In some patients a maximal effect on the choreiform movement was not obtained without unwanted sedation, and the two effects had to be balanced. On complete withdrawal of the drug the abnormal motor activity recurred in all cases in their former frequency and amplitude in the course of one to two days. Patients who had to be protected from trauma inflicted by their involuntary movements were able to get out of bed, to dress, and to eat unaided, so that the difficult nursing problem was greatly diminished. For patients who had only moderate choreiform movements the elimination of the jerks was of great psychological importance, as involuntary and bizarre movements were frequently embarrassing, particularly when dementia was slight or absent.

Effect of Tetrabenazine on Various Extrapyramidal Movement Disorders

	Worse	Unchanged	Moderate	Good
Chorea	0	0	7	7
Hemiballismus ..	0	1	0	3
Dystonia	0	1	1	0
Intention tremor ..	1	3	0	0
Parkinsonian tremor ..	3	3	0	0

The same striking effect was seen in three patients with hemiballismus of arteriosclerotic aetiology, this being arrested completely after two days' treatment with 300 mg. the first day and 200 mg. for the following days. One patient with moderate hemiballismus due to epidemic encephalitis had only a slight improvement.

In contrast to the beneficial effect of tetrabenazine in choreiform and hemiballistic motor activity, patients with Parkinsonian tremor and those with intention tremor due to spinocerebellar degeneration experienced the opposite effect. Patients with moderate and limited tremor developed a severe generalized tremor while on the drug, but those with an initial severe generalized tremor were not influenced by tetrabenazine. Thus in one patient with cerebral arteriosclerosis and generalized choreiform jerks as well as a Parkinsonian tremor of the left hand the choreiform movements disappeared completely, while the tremor became so generalized and severe that the drug had to be withdrawn.

Side-effects of the drug were seen in eight patients and these included fatigue in three, confusion in one, excessive sweating in two, photophobia in one, and amenorrhoea in one. The side-effects disappeared on reducing the dose by 25 to 50 mg. daily.

Discussion

It is tempting to relate these effects of tetrabenazine to the monoamine depletion produced in the brain (Pletscher *et al.*, 1962). The relation between monoamine metabolism and Parkinson's disease has been discussed in several articles since Sano *et al.* (1959) showed that dopamine was present in high concentrations in the caudate nucleus. Curzon (1967) reviewed the subject, but the mechanisms involved are still far from clearly understood. Functionally different monoamines are present in the hypothalamus, the brain stem, and the nucleus caudatus, and are all exposed to the depleting effect of reserpine

and tetrabenazine (Kuntzman *et al.*, 1961; Dahlström and Fuxe, 1964, 1965). A functional block of one or more systems of neurone circuits dependent on monoaminergic mechanisms might underlie the clinical effects. In Parkinson's disease Birkmayer and Hornykiewicz (1961) showed that reserpine aggravated a moderate Parkinsonian tremor but had no influence on a severe universal Parkinsonian tremor. In the present group of patients tetrabenazine aggravated a moderate and limited tremor, but did not influence a severe tremor.

It has been suggested (Curzon, 1967), on the basis of the findings of a low content of dopamine in the caudate nucleus of patients with Parkinson's disease (Ehringer and Hornykiewicz, 1960; Barolin *et al.*, 1964), that in the moderate syndrome dopamine in the caudate nucleus is still so high as to be exposed to the depleting effect of reserpine, thus resulting in a further decrease. In the severe form, on the other hand, the content of dopamine is too low for further depression to take place. Where choreiform movements and hemiballismus occur, however, it is difficult to explain the beneficial effect of tetrabenazine, as the monoamine content has not been reported to be abnormal in these conditions. Hence any explanations can only be speculative, and further work on the biochemical effects of monoamine-depletors is needed to elucidate the problem.

Though tetrabenazine was synthesized in 1956 its use in patients has been limited. The present trial suggests that the drug should be tried in the treatment of hyperkinetic disorders before surgical intervention is considered.

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