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Treatment of Persistent Phenothiazine-Induced Oral Dyskinesia

By PETER A. ROXBURGH

Since the first description of persistent oral dyskinesia following phenothiazine treatment by Sigwald in 1956 a good deal of evidence has accumulated indicating the regular occurrence of this syndrome. However there is a disagreement over its incidence and the aetiological role played by phenothiazine drugs. Kline (1968) in a recent review found a total of 114 cases of 'irreversible' oral dyskinesia and concluded that the incidence had been misrepresented since less than two dozen of these recorded cases were previously non-brain damage.

It seems likely that confusion has been created by some of the large scale hospital studies through the inclusion of cases displaying functional habits spasms. Three psychiatric hospital surveys revealed a similar frequency of occurrence. Turunen and Achte (1967) found 6 per cent. in 480 patients; Hunter, Earl and Thornicroft (1964) 5 per cent. in 250 female patients; Demars (1966) 7 per cent. in 488 patients. Pryce and Edwards (1966) however found a 17 per cent. incidence of moderate and severe cases, while ignoring a further 7 mild cases, in 120 female patients. In this latter study oral dyskinesia was associated with total intake of phenothiazines and with female sex, but the results differed from the majority of other studies in the absence of associated 'brain damage' as indicated by leucotomy, 'organicity' or learning deficit.

Reference to the description of small series of cases by various authors (Evans, 1965; Morphew and Barber, 1965; Schmidt and Jarcho, 1966), leaves little doubt of the occurrence, especially in the elderly, of a dramatic persistent oral dyskinesia in response to phenothiazines. In the fully established syndrome, gross, irregular, continual side to side or circular chewing movements of the jaw are present, associated with spasmodic movements of the lips. The tongue writhes continually, is often truly hypertrophied and may be protruded between the lips in a 'fly catching' manoeuvre. Associated screwing up of the eyes with the other facial movements is often evident. Choreiform movements of the neck, trunk and limbs occur to a lesser extent. The irregular spasms of legs and arms interfere with co-ordination and may prevent the individual from feeding himself or walking unaided. There may be a general impression of extreme restlessness which can be considered a form of akathisia. Spasm of muscles of respiration may occur and give rise to grunting irregular respirations. Speech is similarly incoordinate and staccato in quality and a considerable barrier to communication.

This fully developed oral dyskinesia syndrome differs radically from the even well-established chewing habit of the institutionalized long-term manneristic psychotic and cannot be reconciled as a functional development. These functional movements of the mouth which are so commonly seen are likely to be associated with the edentulous state and with the range of psychiatric drugs, including phenothiazines, which depress salivation through their anti-cholinergic action. A further cause for inflation of the number of reported cases is the failure to allow a sufficient period to elapse before designating the condition persistent; 6 months would seem a reasonable period (Kline).

Survey of treatment

Once withdrawal of phenothiazine drugs has failed to result in remission, return to the medication or a change of medication is reported as ineffective or at best slightly effective. This latter partial containment of the movements can result from the Parkinsonian

side effects induced by higher dosage, but the disability the patient experiences is compounded by this additional interference with muscular control (Schmidt and Jarcho).

Anti-parkinsonian drugs such as benztropine methanesulphonate and trihexyphenidyl have been consistently found to be ineffective (Turunen and Achte, Schmidt and Jarcho, Evans).

Antihistamines such as orphenadrine and diphenhydramine have also proved ineffective (Schmidt and Jarcho).

A variety of drugs, such as chlordiazepoxide, reserpine and barbiturates, are reported as having some slight beneficial effect (Druckman, Seelinger and Thulin, 1962).

Bandrup (1961) reports the only fully successful treatment of persistent phenothiazine dyskinesia, using tetrabenacine, a benzochinolizine believed to function by depleting brain catechol amines. This drug is not generally available.

Present study

Two severely affected patients were encountered in surveying a population of 120 long-term mainly middle aged psychiatric patients. A third patient with moderate ill-sustained chewing and tongue movements was regarded as functional and was excluded, as no movements beyond the mouth region were evident. Both patients were severely disabled. Neither had a family history of abnormal movements or dementia.

Case 1—single male, aged 57, had been hospitalized for 28 years with a schizophrenic illness; improving sufficiently to work at gardening until commenced on phenothiazines seven years previously. He had developed marked dystonia and akathisia on trifluoperazine 5 mgm. twice daily in spite of the addition of trihexphenidyl. Within four or five months he had developed abnormal movements, but over a period of the next three years further trifluoperazine, chlorpromazine, thioridazine and haloperidol were administered. At the time of investigation movements had become extreme and incessant, and he could not safely sit in a chair, function independently or communicate more than his simplest needs. This patient did not respond to further doses of trifluoperazine or perphenazine, to anti-parkinsonian drugs or to withdrawal of phenothiazine drugs for a 12 month period.

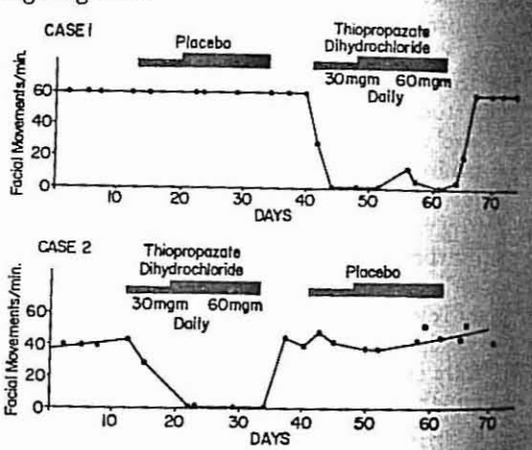
Case 2—married female, aged 54, suffered with long-standing severe deafness, and more recently impaired vision from bilateral cataract. Following a road accident four years previously she had become confused and subsequently developed a sustained paranoid psychosis. The psychosis was presumed to be a response to sensory deprivation, but brain damage from some other cause could not be excluded. She had received chlorpromazine, but did not display abnormal movements until shortly after being given trifluoperazine two years after admission. At the time of investigation continual gross facial movements with less frequent but considerable involvement of the limbs effectively disabled the patient. With this patient also, a return to phenothiazine drugs, including trifluoperazine and perphenazine, had not influenced the clinical picture nor had a 12 month period of withdrawal of phenothiazines.

Thiopropazate dihydrochloride has been reported (Bruyn, 1962) as effective in the superficially similar syndrome of Huntington's Chorea, and on this basis the drug was tried in both cases. It induced an unexpected dramatic improvement in both patients, their movements were reduced in frequency and in amplitude before becoming entirely eliminated.

A double blind trial of thiopropazate dihydrochloride was undertaken and a measure of progress from the frequency of abnormal movements seemed a reliable objective measure. Both patients were withdrawn from medication for a two week period, and two separate treatment periods of drugs and placebo were administered, separated by a seven day interruption. The order of presentation of drug and placebo was unknown to the investigator.

Results

Results were as illustrated in the accompanying diagrams.



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In patient 1, movements more rapid than 60 each minute were continuous and could not be rated. In both patients a decline to zero movements occurred in the treatment phase. This declining frequency was associated with an apparently parallel diminution in strength and amplitude.

During the mid-treatment phase of case 1, a temporary resurgence of low intensity movements occurred, for which no explanation was forthcoming.

Other changes were evident; the tongue, which could not be voluntarily protruded more than momentarily, became freely so in the treatment phase, even though mild rhythmical movements of the tongue were the last abnormal movements to disappear. Speech became fully coherent in one patient and much improved in the other, while the emergence of facial tranquillity allowed spontaneous expressiveness to occur for the first time in both patients.

The irregular leg movements, which had occurred from 8 to 16 times each minute, were eliminated in the treatment phase, and stable independent walking and self-care became possible.

Benefit from the thiopropazate dihydrochloride was evident within 48 hours and relapse 72 hours after withdrawal of the drug. Both cases showed considerable improvement on the lower 30 mgm. daily dose of thiopropazate dihydrochloride, and parkinsonism was not evident on the 60 mgm. daily dose.

Discussion

The use of thiopropazate dihydrochloride in the treatment of a condition probably induced by phenothiazine requires caution and justification. Its efficiency would need to be established by further trials and long term follow-up of treated cases. Findings on the use of thiopropazate in Huntington's Chorea show a successful impact on the abnormal movements, not duplicated with the other phenothiazines, except possibly perphenazine (Pakenham-Walsh, 1960), and indicate that similar differential effects of this type on other extra-pyramidal system disorders might be expected.

Thiopropazine, although possessing a piperazine side-chain as do perphenazine and trifluoperazine, produces less parkinsonism. In its use in Huntington's Chorea frank chorea is first controlled, then, as the optimum dose is exceeded, signs of parkinsonism appear which are not beneficial to the patient (Lyon). A similar sequence might be observed in treating oral dyskinesia and might be equally disadvantageous for the patient's co-ordination and functioning as well as having the added possibility of inducing further permanent extra-pyramidal damage.

Many case reports in the literature are incomplete, but the oral dyskinesia syndrome often clearly follows extra-pyramidal side-effects, particularly dystonia and akathisia, the presence of which may be used as an indication for modification of the offending phenothiazine therapy at an early stage. It is a reasonable precaution to take considerable care not to induce parkinsonism in a patient with oral dyskinesia who is either receiving thiopropazate or who has been replaced on phenothiazines for exacerbated psychotic disturbance, as may be sometimes necessary (Demars, 1966).

Up to the present thiopropazate has not been reported in association with the development of oral dyskinesia. In our present state of knowledge, therefore, it can be recommended as the phenothiazine of choice in the brain damaged, leucotomized or elderly.

Summary

A comparison of the features of persistent oral dyskinesia and functional oral movements is made. The literature on the drug control of oral dyskinesia is reviewed. In a double-blind interrupted cross-over trial in two established cases of oral dyskinesia, thiopropazate dihydrochloride was found to be highly effective.

Acknowledgement

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References

Bandrup, E. (1961). 'Tetrabenacine treatment in persisting dyskinesia caused by psycho-pharmacea.' *Amer. J. Psychiat.*, 118, 551–2.

Bruyn, G. W. (1962). 'Thiopropazate dihydrochloride (Dartal) in the treatment of Huntington's chorea.' *Psychiat. Neurol. Neurochir.*, 65, 430–8.

DEMARS, J. C. A. (1966). 'Neuromuscular effects of long-term phenothiazine medication, electro-convulsive therapy and leucotomy.' *J. nerv. ment. Dis.*, **143**, 73–9.

DRUCKMAN, R., SEELINGER, D., and THULIN, B. (1962). 'Chronic involutionary movements induced by phenothiazines.' *J. nerv. ment. Dis.*, 135, 69–76.

EVANS, J. H. (1965). 'Persistent oral dyskinesia in treatment with phenothiazine derivatives.' *Lancet*, *i*, 458–460.

HUNTER, R., EARL, C. J., and THORNICROFT, S. (1964). 'An apparently irreversible syndrome of abnormal movements following phenothiazine medication.' *Proc. Roy. Soc. Med.*, 57, 758–762.

KLINE, N. W. (1968). 'Rarity of irreversible oral dyskinesias following phenothiazines.' *Amer. J. Psychiat.*, 124:8, Feb. Suppl. 48–54.

LYON, R. L. (1962). 'Drug treatment of Huntington's chorea.' *Brit. med. J.*, *i*, 1308.

MORPHEW, J. A., BARBER, J. E. (1965). 'Persistent oral dyskinesia in treatment with phenothiazine derivatives (Letter to the Editor).' *Lancet*, *i*, 650–1.

PAKENHAM-WALSH, R. (1960). 'Perphenazine in Huntington's chorea.' *Lancet*, *ii*, 767.

PRYCE, I. G., and EDWARDS, H. (1966). 'Persistent oral dyskinesia in female mental hospital patients.' *Brit. J. Psychiat.*, 112, 983–7.

SCHMIDT, W., and JARCHO, L. W. (1966). 'Persistent dyskinesias following phenothiazine therapy.' *Arch. Neurol.*, 14, 369–77.

SIGWALD, J., BOUTTIER, D., and COURVOISIER, S. (1959). 'Les accidents neurologiques des médications neuroleptiques.' *Rev. Neurol.*, 100, 553–95.

TURUNEN, S., and ACHTE, K. A. (1967). 'The bucco-linguo-masticatory syndrome as a side effect of neuroleptics therapy.' *Psychiatric Quarterly*, 41, 268.

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