

TARDIVE DYSKINESIA II:

Treatment aspects, Case report

MICHAEL ORR

*Department of Psychiatry
University of Oxford*

Measurement of Treatment Effects

Tardive dyskinesia is a late side-effect of neuroleptic therapy which occurs in up to a fifth of chronic psychiatric patients treated with this group of drugs. As many as 60% of cases could show irreversible symptomatology though outcome studies have often proved to be inconclusive. (Crane 1968). Effective methods of treatment could therefore reduce morbidity in a potentially large number of patients.

Difficulties in the assessment of the efficacy of treatment methods could arise because it may be difficult to measure changes in tardive dyskinesia reliably. Kazamatsuri et al (1972) have used the frequency of mouth movements as a measure in those patients who showed oral dyskinesia and has proved to be a sensitive index of change. Some patients may however present with other forms of dyskinesia and the picture is further complicated by the observation that, in severe cases, parkinsonian symptoms can coexist with tardive dyskinesia, even though they do not share the same immediate aetiology. Electromyographic studies have not proved to be useful and the use of films or other methods of global assessment have shown a very low inter-rater reliability. Cole (1975) has argued for a global clinical approach in patients with diffuse dyskinesia, but the frequency of mouth movements remains a useful measure in those patients with predominantly oral manifestations of the disease.

1. Periodic evaluation of the neurological status of patients on long-term phenothiazines, together with careful and continuous monitoring of the dose of

Prevention

phenothiazines used, and the nature and severity of extrapyramidal symptoms that arise at all stages of treatment could minimise the risk of tardive dyskinesia in vulnerable patients.

2. The routine use of anticholinergic drugs should be discouraged. Not all patients require them and a patient needing anticholinergic drugs early in treatment may develop tolerance to extrapyramidal side-effects later and no longer require an antiparkinsonian agent.
3. High doses of phenothiazines for prolonged periods are known to predispose to tardive dyskinesia. It is not known whether the combination of two drugs in lesser dosage in severely ill patients would involve a lesser risk of tardive dyskinesia than large doses of a single drug, but the possibility is worth exploring. There has been considerable interest recently in the use of high doses of fluphenazine and haloperidol (Howard 1974) in 'drug-resistant' schizophrenia; the long term effects of these doses are difficult to predict, especially as Parkinsonian side-effects do not seem to be a problem in these patients, but an increased predisposition to tardive dyskinesia seems likely.

Treatment

There is no well-established, safe and effective treatment for this syndrome. Most authorities agree that if dopamine hypersensitivity underlines tardive dyski-

nesia, restoration of effective dopamine-blockade or amine depletion with reserpine or tetrabenazine should reverse the dyskinesia. Kazamatsuri et al (1972a) showed that both haloperidol (Serenace) and thiopropazate (Dartalan) had marked anti-dyskinetic effects in a high proportion of cases. The same workers showed that there was no effect of methyl dopa, which competitively inhibits dopa decarboxylase (Kazamatsuri et al 1972b) but that tetrabenazine led to a significant reduction in the frequency of oral dyskinesia (Kazamatsuri et al 1973). Roxburgh (1973) described three patients in whom a marked improvement in dyskinetic movements was shown following the administration of thiopropazate in doses of 30 mg to 60 mg daily, and it was suggested that thiopropazate should be the phenothiazine of choice in the brain damaged, leucotomized or the elderly.

Other treatments suggested have included pimozide, physostygmine (Fann et al 1974), lithium (Dalen 1973, Reda et al 1975) and melanocyte-stimulating-hormone-inhibiting factor (MIF). Physostygmine reduced abnormal movements effectively twenty-four hours after administration and there may be a place for long-acting cholinergic drugs in the treatment of neuroleptic-induced dyskinesia.

The effects of clozapine on tardive dyskinesia are of special interest in that clozapine has been shown to relieve symptoms effectively (Ayd 1974), even though it has no dopamine-blocking action. Clozapine is an effective, non-neuroleptic anti-psychotic drug which enjoyed increasing usage until it was withdrawn from the market recently following reports from Finland of fatal agranulocytosis in a significant number of cases.

None of these treatments is entirely satisfactory as little is known of the long term efficacy of these drugs. Improvement may not persist beyond eighteen weeks (Kazamatsuri et al 1973) though relapse following withdrawal of treatment is not invariable.

A further problem in management is that patients with tardive dyskinesia could

still require maintenance therapy and Cole (1975) has outlined some possibilities of treatment which could provide effective maintenance therapy without exacerbating the dyskinesia. These included the use of lithium, ECT in more severe cases, behaviour modification and raising the dose of neuroleptic. Of these tentative approaches, only the use of dopamine-blocking and amine-depleting drugs have been confirmed as effective and there are strong arguments against the rationale of their use in mild or only moderately severe cases. It is likely that haloperidol and thiopropazate could act by increasing the extent of dopamine blockade to a level where the effects of dopamine-hypersensitivity are 'neutralised', and this could accentuate the extent of neurological damage; nevertheless the symptoms of tardive dyskinesia can on occasions be extremely distressing and indeed endanger life in the elderly by interfering with nutrition and causing exhaustion; in these circumstances symptom relief becomes the main objective of treatment.

Case Report

The following case report illustrates the response of a severe phenothiazine induced dyskinesia to thiopropazate.

The patient was an 86 year old woman who was referred to hospital a year previously because of difficulties in her management at home. She had become garrulous, quarrelsome and showed marked paranoid ideation. She had been treated at home by her general practitioner with trifluorperazine 10mg three times a day (chlorpromazine equivalent: 600 mg/day) and this was continued for several months. Her medication in hospital was subsequently changed to chlorpromazine 25 mg three times daily with benzhexol 5mg twice daily; her behaviour improved but she remained querulous and there was some evidence of organic cerebral deterioration.

Nine months after admission she started to exhibit an oral dyskinesia which increased in severity and subsequently generalised to the neck and upper limbs

and which eventually led to her referral for management of tardive dyskinesia.

She was a thin, emaciated, pale woman who appeared dehydrated and there was evidence of hypovitaminosis. She was grossly dyskinetic with writhing, rolling movements of the tongue and mouth, repetitive blinking, jerking of the head and athetoid movements in both arms. She was unable to talk, eat or drink and her attempts at communication were restricted to weak strangled cries.

Her blood pressure was 90/60 and her pulse was 78/minute and regular; there was minimal congestive cardiac failure but there were no focal neurological signs.

The frequency of mouth movements was taken as a measure of her dyskinesia and the following plan of treatment was agreed: her benzhexol would be stopped and, if no improvement occurred, chlorpromazine would be withdrawn and substituted by thiopropazate 10 mg three times daily. The stopping of benzhexol led to no improvement and there was no worsening of her dyskinesia following withdrawal of chlorpromazine.

Figure 1 shows the response of the oral dyskinesia to thiopropazate. Results were dramatic and the frequency of mouth movements dropped sharply. On the second day of treatment she could talk intelligibly and could eat, though the choreiform movements in the arms were relatively unaffected. By the fifth day she could feed herself and converse. Her medication was reduced to thiopropazate 5gm three times a day on the fourteenth day; she also developed diarrhoea and the dyskinesia reappeared in full force three days later. Her medication was therefore restored to thiopropazate 10 mg t.d.s. and the dyskinesia responded immediately once more. Her mental state suggested a significant degree of organic cerebral deterioration.

She was followed-up until her death from pneumonia nine months later; the dyskinesia had remained well controlled, her mental state had not changed and there was some evidence of a mild parkinsonian syndrome, with minimal rigidity

and moderate hand tremor.

Similar results have been observed in two severely affected elderly female patients with drug-induced dyskinesia. Thiopropazate effectively controlled oral dyskinetic movements but effects on dyskinetic movements elsewhere were less marked. It proved to be a valuable drug for immediate symptom relief in very severely affected patients and could have a place in the management of the disorder in selected cases.

References

- AYD, Jnr. F.J. (1974). "Clozapine — a unique new neuroleptic". *International Drug Therapy Newsletter* 9: 5.
- COLE, J.O. (1975). "Tardive dyskinesia — legal and therapeutic aspects", in "Neuropsychopharmacology" Eds. Boissier J.R., Higgins H., Pichot, P. Excerpta Medica, Amst.
- CRANE, G.E. (1967). "Prevention and management of tardive dyskinesia". *Am. J. Psychiat.* 129: 466.
- CRANE, G.E. (1968). "Tardive dyskinesia in patients treated with major neuroleptics — a review of the literature". *Am. J. Psychiat.* 124: 8 Suppl: 40.
- DALEN, P. (1973). "Lithium Therapy in Huntington's chorea and Tardive Dyskinesia". *Lancet* 1: 107.
- FANN, W.E., LAKE, C.R., GERBER, C.J. & MCKENZIE, G.M. (1974). "Cholinergic suppression of tardive dyskinesia". *Psychopharmacologia (Berlin)*. 37: 101.
- KAZAMATSURI, H., CHIEN, C.P. & COLE, J.O. (1972a). "Treatment of tardive dyskinesia: II: Short term efficacy of dopamine-blocking agents haloperidol and thiopropazate". *Arch. Gen. Psychiat.* 27: 100.
- KAZAMATSURI, H., CHIEN, C.P. & COLE, J.O. (1972b). "Treatment of tardive dyskinesia: III: Clinical efficacy of a dopamine-competing agent, methyl dopa". *Arch. Gen. Psychiat.* 27: 824.
- KAZAMATSURI, H., CHIEN, C.P. & COLE, J.O. (1972c). "Therapeutic approaches to tardive dyskinesia". *Arch. Gen. Psychiat.* 27: 491.
- KAZAMATSURI, H., CHIEN, C.P. & COLE, J.O. (1973). "Long term treatment of tardive dyskinesia with haloperidol and tetrabenazine". *Am. J. Psychiat.* 130: 479.
- REDA, F.A., ESCOBAR, J.I. & SCANLAN, J.M. (1975). "Lithium carbonate in the treatment of tardive dyskinesia". *Am. J. Psychiat.* 132: 277.
- ROXBURGH, P.A. (1970). "Treatment of phenothiazine-induced oral dyskinesia". *Br. J. Psychiat.* 116: 277.

