neurotoxicity. Lancet 2:1019–1020, 1974
7. Shields WD, Bray PF: A danger of haloperidol therapy in children. J Pediatr 88:301–303, 1976
8. Gerle B: Clinical observations of the side-effects of haloperidol. Acta Psychiatr Scand 40:65–76, 1964
9. Selye H, Szabo S: Protection against haloperidol by catatoxic steroids. Psychopharmacol 24:430–434, 1972
10. Money J, Drash PW: Juvenile thyrotoxicosis: symptoms and antecedents leading to referral and diagnosis. Journal of Special Education 2:83–91, 1967

Tardive Dyskinesia as a Life-Threatening Illness

BY DANIEL E. CASEY, M.D., AND PETER RABINS, M.D.

The involuntary movements associated with tardive dyskinesia can be a source of social and functional impairment but rarely lead to serious medical complications. This case report suggests that in addition to the typical orofacial and truncal dyskinesias, potentially life-threatening ventilatory and gastrointestinal disturbances may develop that require the reinstitution of neuroleptic therapy.

Case History

Ms. A, a 68-year-old woman, was placed on 300 mg/day of chlorpromazine in 1958 for depression and anxiety after her husband's death. She continued on this dosage in subsequent years because several attempts to decrease the drug resulted in the return of anxiety. In February 1975 the chlorpromazine dosage was decreased by 50 mg every several months. Nine months later, at a dosage of 150 mg/day, an irregular breathing pattern became evident. The chlorpromazine dosage was decreased further, and in February 1976, on 50 mg/day, Ms. A developed orofacial dyskinesias in addition to the irregular respirations. When chlorpromazine was discontinued a month later, the respiratory distress and orofacial dyskinesias increased, and she developed new symptoms of aerophagia, dysphagia, vomiting after meals, and episodes of retching every 2 to 3 hours. Tardive dyskinesia was diagnosed, and treatment with deanol, 200 mg/day was initiated. The dosage of deanol was increased to 1200 mg/day, but the symptoms progressed and the patient was hospitalized. She was discharged 30 days later taking 2000 mg/day of deanol, with modest improvement in all symptoms. However, as an outpatient, she had an increase in symptoms. Papaverine, 450 mg/day, was added for 1 month without benefit.

In June 1976 the patient made several visits to the emergency room complaining of increasing shortness of breath and persistent vomiting. She was admitted when hypoxia and a 13.6-kg weight loss during the previous 10 weeks were documented. Evaluation revealed orofacial dyskinesias, aerophagia, truncal rocking, choreoathetosis in the toes, grunting sounds and irregular respiration synchronous with paroxysmal contraction and distention of the abdominal wall, vomiting after meals, and episodic retching. Her symptoms increased with anxiety but stopped during sleep. All medications were discontinued. Chest X ray, ECG, complete blood count, urinalysis, routine serum chemistries, and electrolytes were within normal limits. Ten attempts at pulmonary function tests were unsuccessful because of an irregular ventilatory movement pattern. Administration of nasal oxygen, 3 liters/minute, improved blood gas values and gave subjective relief, but the abnormal breathing pattern continued. Vomiting after meals and episodes of retching persisted, as did weight loss, and parenteral fluids were required. Gastroscopy was normal. Barium swallow and fluoroscopy demonstrated asynchronous contraction of the lower esophagus with no reflux and a full range of movement of both diaphragms. The final diagnosis was tardive dyskinesia with ventilatory and gastrointestinal complications.

Initially, haloperidol, 35 mg/day, was necessary to control the symptoms, but this dosage produced parkinsonian tremor and rigidity. On 20 mg/day of haloperidol, Ms. A had minimal orofacial dyskinesias, no limb or truncal symptoms, a regular breathing pattern, normal blood gases, no vomiting, normal weight, and a slight parkinsonian tremor in the jaw. Two attempts to reduce the haloperidol below 20 mg/day met with exacerbation of the irregular breathing and subjective shortness of breath. At 1-year follow-up, on 20 mg/day of haloperidol, arterial blood gases remained within normal limits.

Discussion

Tardive dyskinesia is usually characterized by involuntary, repetitive orofacial movements that may be accompanied by limb and truncal dyskinesias and respiratory grunting. However, respiratory distress and persistent vomiting are seldom associated with tardive dyskinesia and raise the question of proper diagnosis. We believe that the ventilatory and gastrointestinal disturbances in this case were either complications or manifestations of tardive dyskinesia, particularly in view of the inverse relationship between decreasing drug dosage and increasing symptoms. The gradual onset and increase of an irregular breathing pattern as-

When this work was done, Dr. Rabins was Resident in Psychiatry, Department of Psychiatry, University of Oregon Health Sciences Center, Portland, Ore., where Dr. Casey is Assistant Professor of Psychiatry. Dr. Rabins is now Fellow, Department of Psychiatry, Johns Hopkins University, Baltimore, Md. Dr. Casey is also Associate Investigator, Departments of Medical Research and Psychiatry, Veterans Administration Hospital, Portland, Ore. 97207. Address reprint requests to Dr. Casey.

This work was supported in part by Portland Veterans Administration Hospital Research Committee grant MRIS 1314-01, and the Grass Foundation.

The authors would like to thank Marian Karr for assistance in preparing the manuscript and Duane Denney, M.D., and John O. Lipkin, M.D., for editorial efforts.

 0002-953X/78/0004-0486$0.40

sociated with abdominal dyskinesias, characteristic orofacial, limb, and truncal dyskinesia, aerophagia, and persistent vomiting concomitant with a steady decrease in neuroleptic dosage were temporally consistent with the clinical emergence of tardive dyskinesia. Further support comes from the fact that no other etiologies could be substantiated to explain the blood gas abnormalities or vomiting and from the improvement in orofacial, limb, and truncal dyskinesias and ventilatory and gastrointestinal functions with haloperidol, a potent dopamine receptor blocker capable of suppressing tardive dyskinesia symptoms (1), and the recurrence of these symptoms when haloperidol was decreased. Thus tardive dyskinesia can present as respiratory distress and persistent vomiting and should be added to the differential diagnosis of these symptoms if the patient has been taking neuroleptics. When these symptoms are severe, accompanying dyskinesias might be overlooked, but their importance in leading to an accurate diagnosis should be emphasized.

The relationship between the specific functional pathology in ventilatory and gastrointestinal activity and typical orofacial and limb signs of tardive dyskinesia is unclear. The patient had irregular movements of the abdominal musculature that correlated with her irregular breathing pattern and were thought to be caused by a diaphragmatic dyskinesia that sufficiently impaired normal breathing to compromise pulmonary gas exchange. This was not unequivocally substantiated because pulmonary function tests could not be performed. However, a return from hypoxia to normal blood gas values after control of the dyskinesias supports the contention that the respiratory distress developed from a disturbance in the breathing pattern rather than in the pulmonary parenchyma. Although the diaphragms were briefly observed to function normally during a barium swallow, a paroxysmal diaphragmatic dyskinesia may have been quiescent or temporarily suppressed during swallowing as other dyskinesias can be reduced during voluntary movements of the affected muscle groups. It was concluded that the patient's vomiting and episodic retching resulted from a combination of asynchronous esophageal movements and gastric distention that occurred from aerophagia associated with involuntary mouth movements. It is doubtful that the gastrointestinal symptoms originated from the alimentary tract below the level of the diaphragm since this is primarily smooth muscle, and tardive dyskinesia involves striated muscle. Therefore, the ventilatory and gastrointestinal symptoms were probably complications of the tardive dyskinesia, but the pathophysiology remains to be defined.

Although guidelines can be proposed for the general management of tardive dyskinesia, this case illustrates the need to individualize treatment strategies. A logical approach would be to counteract the striatal influences of hypersensitive dopamine receptors (2) by augmenting the proposed counter-balancing cholinergic system (3). Deanol, which may increase available acetylcholine (4), has been variably beneficial in tardive dyskinesia (5) but was not effective in controlling this patient's symptoms. Papaverine, an opiate alkaloid of unknown mechanism of action, was similarly ineffective, although it has been previously reported to ameliorate tardive dyskinesia symptoms (6). Thus, this 68-year-old patient presented the clinical dilemma of balancing the risks and benefits of no treatment versus palliative treatment with neuroleptics. The symptoms had gradually progressed over 6 months, disrupting the physiological equilibria of ventilatory and gastrointestinal functions to the point of requiring nasal oxygen and intravenous feedings, so rapid spontaneous improvement was unlikely and symptom control was imperative. Haloperidol was started to reverse the patient's deteriorating condition, acknowledging the likelihood that it would suppress symptoms in the short run but possibly lead to increased dyskinesias in the future. Although 35 mg/day of haloperidol was initially required to suppress symptoms, a maintenance dose of 20 mg/day successfully controlled the dyskinesias. Attempts to decrease this maintenance dose resulted in the return of irregular respirations and marked orofacial movements, but there has been no symptomatic breakthrough, as has been previously reported (1).

The coexistence of the presumed pharmacologically opposite neuroleptic-induced tardive dyskinesia and parkinsonism is both clinically and theoretically challenging. Decreasing the haloperidol dosage to reduce parkinsonian tremor led to an increase in tardive dyskinesia, while increasing it to reduce tardive dyskinesia led to an increase in parkinsonism. A similar situation has been described in an attempt to modulate the two coexisting syndromes with anticholinergic agents (7). Although an asymptomatic midpoint could not be achieved, a maintenance dose of neuroleptic gave a tolerable balance of minimum tardive dyskinesia and parkinsonism. The failure to find a point at which neither tardive dyskinesia nor parkinsonism occurred suggests that the concept of a single nigrostriatal dopaminergic system controlling bradykinesia and hyperkinesia should be expanded. Physiological data suggest there are inhibitory and excitatory dopaminergic receptors in the striatum (8), and it has been postulated that these receptors may be differentially affected by neuroleptics to yield pharmacological subtypes of tardive dyskinesia (9). It may also be that both receptor types are involved in causing the simultaneous occurrence of acute and long-term neuroleptic-induced extrapyramidal disorders.

This case also adds to the report (10) of tardive dyskinesia in nonpsychotic patients and speaks against neuroleptic use in illnesses where other nonneuroleptic therapies are available. Chronic use of neuroleptics is necessary in some instances for the continued control of psychotic conditions, but the development of potentially fatal dyskinesias emphasizes the need to withdraw the neuroleptic whenever possible.

REFERENCES

1. Kazamatsuri H, Chien C-P, Cole JO: The treatment of tardive dyskinesia. II. Short-term efficacy of dopamine-blocking agents haloperidol and thiopropazate. Arch Gen Psychiatry 27:100–103, 1972
2. Klawans HL: The pharmacology of tardive dyskinesia. Am J Psychiatry 130:82–86, 1973
3. Gerlach J, Reisby N, Randrup A: Dopaminergic hyper-sensitivity and cholinergic hypofunction in the pathophysiology of tardive dyskinesia. Psychopharmacologia 34:21–35, 1974
4. Haubrich DR, Wang PFL, Clody DE, et al: Increase in rat brain acetylcholine induced by choline or deanol. Life Sci 17:975–980, 1975
5. Casey DE: Deanol in the management of involuntary movement disorders: a review. Dis Nerv Syst 38:7–15, 1977
6. Gardos G, Cole JO, Sniffen C: An evaluation of papaverine in tardive dyskinesia. J Clin Pharmacol 16:304–310, 1976
7. Fann WE, Lake CR: On the coexistence of parkinsonism and tardive dyskinesia. Dis Nerv Syst 35:324–326, 1974
8. Cools AR, Van Rossum JM: Excitation-mediating and inhibition-mediating dopamine receptors: a new concept toward a better understanding of the electrophysiological, biochemical, pharmacological, functional, and clinical data. Psychopharmacologia 45:243–254, 1976
9. Casey DE, Denney D: Pharmacological characterization of tardive dyskinesia. Psychopharmacology 54:1–8, 1977
10. Klawans HL, Bergen D, Bruyn GW, et al: Neuroleptic-induced tardive dyskinesias in nonpsychotic patients. Arch Neurol 30:338–339, 1974

Addition of Reserpine to Antipsychotic Medication in Refractory Chronic Schizophrenic Outpatients

BY NORMAN M. BACHER, M.D., AND HARVEY A. LEWIS, M.D.

We have followed many treatment-refractory chronic schizophrenic patients over several years in a Veterans Administration outpatient clinic. These patients have failed to improve after prolonged or repeated hospitalization, respond poorly to large doses of antipsychotics, are withdrawn, socially isolated, and have flat affect. They demonstrate overt thought disorder, hallucinations, somatization, and dependency, with marked anxiety about their lack of functioning and impulse control. Increasing the dosage, changing or combining antispychotics, despite negative reports on multiple drug use (1), and adding antidepressants or minor psychotropics have not produced significant results in this group of patients.

Clinical Study and Results

Reserpine, 0.75–6 mg/day, was added to the antipsychotic medication of 13 refractory patients. The antipsychotics they had previously received included chlorpromazine, thioridazine, trifluoperazine, perphenazine, loxapine, and thiothixene. For some patients these antipsychotics were reduced or changed after reserpine was added. Patients were seen at 1- to 4-week intervals. Reserpine was started at a low dose, which was increased but discontinued or reduced at the first appearance of unusual discomfort or side effects. We have a baseline of many years' observation of these patients, so we believe we can detect significant change or lack of change. Seven of the 13 refractory patients continued on the combined medication for at least 4 months and showed slight to marked improvement in mood, affect, and social interaction and a decrease in somatic concern, hallucinations, and withdrawal. Reality orientation and ability to cope with life situations improved. After 8 months there was no evidence of increased depression in this group of patients. In some, a decrease in depression was noted on combined medication. The other 6 refractory patients, who were receiving relatively small doses of reserpine, rejected the combination after a few days to 2 weeks because of tiredness, sluggishness, depression, or other uncomfortable somatic feelings. These patients tended to be younger, less compliant, and more aggressive about discontinuing the medication (see table 1).

Discussion

Reserpine has a complicated molecular structure that is markedly different than that of other antipsychotics. Reserpine is the earliest modern antipsychotic. Three stages of reserpine's action in psychotic patients have been described in the literature: sedation, turbulence, and integration (2). Several articles on combined use of reserpine and chlorpromazine were published in the 1950s when chlorpromazine was new. Small doses of chlorpromazine added to large doses of reserpine were said to induce a smoother antipsychotic action, especially in patients who were resistant to reserpine (3). Reports soon appeared indicating that the newer phenothiazines were more rapid in action

Dr. Bacher is Chief, Loch Raven Veterans Administration Mental Hygiene Clinic, where Dr. Lewis is Staff Psychiatrist, Mental Hygiene Clinic and Drug Dependence Treatment Unit, Federal Bldg., Baltimore, Md. 21201. The authors are also Clinical Assistant Professors of Psychiatry, School of Medicine, University of Maryland, Baltimore.

The authors wish to thank Mental Hygiene Clinic staff members for their support, and Charles Savage, M.D., Chief, Psychiatry Service, Loch Raven Veterans Administration Hospital, for his encouragement.