Tetrabenazine Induces Acute Dystonic Reactions

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Four patients suffered acute dystonic reactions caused by tetrabenazine. Because dystonic reactions have previously been reported only after dopamine receptor blockade and not with dopamine depletion, it is likely that the ability of tetrabenazine to induce acute dystonia is due to its dopamine receptor blocking properties. Because tetrabenazine can induce acute dystonia even when combined with α-methyl-*p*-tyrosine, presynaptic dopamine stores may not be necessary for these reactions to occur.

Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S: Tetrabenazine induces acute dystonic reactions. Ann Neurol 17:200–202, 1985

Tetrabenazine (TBZ) is useful in the treatment of movement disorders, including chorea [8], tardive dyskinesia [8], spinal myoclonus [7], dystonia [8], and hemiballismus [13]. TBZ, like reserpine, depletes stores of brain monoamines [14]. Recently we and others have found that TBZ, unlike reserpine, also blocks dopamine receptors in rat brain [11, 15].

We report now that TBZ can induce acute dystonic reactions. This drug-induced movement disorder has previously been observed only during treatment with drugs that have dopamine receptor blocking properties; it has not been reported following treatment with reserpine. The ability of TBZ to induce acute dystonia thus provides clinical evidence of its dopamine receptor blocking properties. The unique pharmacological ability of TBZ to deplete monoamines and block dopamine may be useful for understanding the pathophysiological mechanisms of dystonia and other drug-induced movement disorders.

Case Reports

Patient 1

A 22-year-old woman with Tourette syndrome developed vocal and motor tics at age 6, including coprolalia, echolalia, shouts, hisses, grunts, sniffs, sudden jumps, bending at the waist, tongue protrusions, and sudden dropping to the floor. She had previously been treated with numerous antipsychotic agents and anticonvulsants without benefit. At age 22, while receiving chlorpromazine 200 mg daily, she was given TBZ, increasing to 300 mg per day. Recurrent oculogyric crises lasting minutes to hours developed and ended either spontaneously or following intramuscular diphenhydramine administration. Addition of α-methyl-*p*-tyrosine (AMPT), an inhibitor of tyrosine hydroxylase, 250 mg per day, increased the severity of the dystonic episodes, and medications were discontinued. In the absence of chlorpromazine, she was again treated with TBZ, 300 mg, and up to 750 mg of AMPT per day. Sustained and painful oculogyric crises recurred, with retrocollis as well. Administration of both drugs was stopped, and the symptoms resolved.

Patient 2

A 20-year-old man had had normal development until age 13 months, when he was burned and became apneic. Following this he was unresponsive for a week. Subsequently, development appeared normal except for a speech impediment. At age 18 years he developed dystonia; his speech became more dysarthric and he developed anterocollis, pulling open of the jaw, and dystonic posturing of the hands. At 20 years, after unsuccessful trials of haloperidol, trihexyphenidyl, carbamazepine, ethopropazine, and baclofen, he was given increasing doses of TBZ, to 100 mg per day. Four days later he developed retrocollis and oculogyric crises. Diphenhydramine, 50 mg intravenously, relieved the symptoms. He subsequently resumed taking TBZ at a dose of 50 mg without recurrent dystonia.

Patient 3

A 21-year-old man, the product of a premature, breech delivery, had had delayed acquisition of motor milestones and had been diagnosed as mentally retarded at 5 years. At 18 years he was treated on different occasions with haloperidol, thioridazine, and chlorpromazine without occurrence of acute dystonic reaction. At 19 years he developed tardive dystonia. He had exhibited facial grimacing and both flexion and extension posturing of the trunk. The antipsychotic drugs were discontinued. At age 21 years he was given doses of TBZ increasing to 225 mg per day; he developed episodes

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Received June 20, 1984, and in revised form Aug 16. Accepted for publication Aug 18, 1984.

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of retrocollis, sustained jaw opening, and oculogyric crises. The symptoms resolved after diphenhydramine, 50 mg, was given intravenously.

Patient 4

A 30-year-old woman with idiopathic dystonia had walked with a limp since adolescence, tending to invert the left foot. On examination at age 30, there was scoliosis, torticollis, and dystonic posturing of the left hand and leg. Neurological and laboratory findings were otherwise normal. She was begun on a regimen of TBZ 25 mg twice a day. One hour after the third dose, she developed an oculogyric crisis and her torticollis worsened. The episode abated following intravenous administration of 10 mg of diazepam.

Discussion

Acute dystonic reactions occur in 2 [1] to 10% [16] of patients who receive antipsychotic drugs. The incidence is related to the dose [16] and type of antipsychotic agent; the piperazine phenothiazines and butyrophenones are more frequently implicated [1, 16]. Younger individuals and males develop dystonic reactions more often than do older ones and females [1, 16]. An incidence of 27% has been reported in patients aged 15 to 29 years following intravenous administration of high doses of metoclopramide [10]. The young are also more susceptible to severe reactions.

All drugs previously reported to cause acute dystonic reactions share the ability to antagonize competitively the effects of dopamine, and this property is believed to be fundamental to the pathogenesis. Reserpine, although implicated in one case of persistent dystonia following a stroke [17], has not caused acute dystonic reactions. These observations suggest that TBZ induces acute dystonia by virtue of dopamine blockade rather than catecholamine depletion.

Most dystonic reactions occur within four days of initiation of an antipsychotic regimen [1, 16]. The time course of butaperazine-induced dystonic reactions has been particularly well documented, and most reactions occur 24 to 48 hours following an oral dose [5, 6]. This characteristic time course led Kolbe and coworkers [9] to propose that dystonic reactions may be due to an overlap at 24 to 48 hours of an antipsychotic-induced increase in dopamine turnover, which begins immediately and lasts 48 hours, and dopamine receptor supersensitivity, which begins at 24 hours. This hypothesis accounts not only for the time course of acute dystonia, but also for its characteristic appearance at the start of antipsychotic drug treatment.

The hypothesis has limitations. No clinical pharmacological evidence in humans suggests that acute dystonic reactions are associated with heightened striatal dopaminergic transmission. Methylphenidate, which is believed to enhance dopamine transmission, has been reported to relieve dystonic reactions [3, 4]. Anticholinergic drugs consistently relieve dystonic reactions, a fact not easily understood if such reactions are due to enhanced dopamine transmission when one considers the postulated reciprocal relationship between striatal cholinergic and dopaminergic function. The present observation that TBZ can induce dystonic reactions suggests that presynaptic dopamine stores, which would be depleted by TBZ, are not necessary for reactions to occur. This point was reinforced when the dystonia in Patient 1 worsened after addition of AMPT.

An alternate explanation for dystonic reactions is that they reflect an acute imbalance in striatal dopaminergic and cholinergic systems that leads to relative overactivity of cholinergic transmission [5, 6]. This hypothesis would explain the time course of dystonic reactions, as well as their response to anticholinergic drugs and methylphenidate. The theory is compatible with the recognized inverse relationship between the ability of antipsychotic agents to induce dystonic reactions and their anticholinergic properties. It is also compatible with the present observation that TBZ can induce acute dystonia. The concept that enhanced striatal cholinergic transmission underlies dystonic reactions is supported by the observation that basal ganglia injections of carbachol, a muscarinic agonist, in primates can induce dystonic involuntary movements [2, 12].

Supported by the Dystonia Medical Research Foundation and the Parkinson's Disease Foundation. Dr Traub was supported by The Medical Research Council of Great Britain.

The authors are grateful to Linda DeVard for diligent secretarial assistance.

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