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Tetrabenazine in the Treatment of Severe Pediatric Chorea

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Abstract: **Tetrabenazine (TBZ) is widely used to treat adults with hyperkinetic movement disorders; however, published experience with the drug in pediatric patients is limited. We report on 5 children with severe chorea who were treated with TBZ. TBZ effectively controlled chorea in 4 patients, and despite the need for relatively high doses, it was well tolerated.** © 2003 Movement Disorder Society

Key words: chorea; tetrabenazine; children

Chorea is one of the more common movement disorders of childhood, occurring after viral encephalitis, infectious mononucleosis, rheumatic fever, or after exposure to steroids, anticonvulsants, or caffeine.[1] Degenerative diseases such as Huntington's disease may cause chorea,[2] as can metabolic insults, lupus, cardiac surgery, intoxication with thallium and manganese, and fever in the setting of cerebral palsy.[3] The dopaminergic system is likely involved in patients with chorea,[4] as illustrated by the response to treatment with dopamine blockers or depletors.[5] A variety of medications have been employed to treat pediatric patients with severe chorea, including benzodiazepines, anticonvulsants and neuroleptics.[6] Typical neuroleptics may be effective, but the decision to use them incurs the risk of cardiac rhythm disturbances, parkinsonism and the possibility of engendering tardive dyskinesia.[7]

Tetrabenazine (TBZ) is a benzoquinolizine compound that depletes cerebral dopamine and blocks dopamine receptors.[8] It was originally developed in 1960 to treat psychosis, and has since become an important part of the armamentarium to treat hyperkinetic movement disorders. TBZ may occasionally trigger an acute dystonic reaction[9] or even neuroleptic malignant syndrome,[10] but

A videotape accompanies this article.

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TABLE 1. *Clinical features of 5 patients treated with TBZ*

Case no.	Age	Gender	Diagnosis	Daily TBZ dose (mg)	Daily TBZ dose (mg/kg)	Therapeutic response
1	10 yr	M	Cerebral palsy	250	9	+++
2	22 mo	F	Acute encephalopathy	200	17	+++
3	25 mo	M	Trisomy 21	125	10.4	+++
4	27 mo	M	Infantile spasms	100	10	++
5	30 mo	M	Acute encephalopathy	275	25	+

+++, complete resolution of chorea; ++, significant improvement in chorea; +, mild improvement in chorea.

there are no credible cases of tardive dyskinesia after exposure to TBZ. The drug has been used to successfully treat chorea, dystonia, tics and tardive dyskinesia.[11] Jankovic and Orman reported 217 patients treated with TBZ, with effective daily doses ranging from 81.6 mg for Tourette's syndrome to 155.4 mg for tardive dystonia.[12] The mean maximum daily dose was 117 mg, and the most common side effects were sedation, parkinsonism, depression, insomnia, anxiety, and akathisia.[13] These side effects were reversible and disappeared when the dose was reduced.

There are few published cases of pediatric patients treated with TBZ.[14] We present 5 children with severe symptomatic chorea who received TBZ and discuss the clinical implications of our experience.

CASE HISTORIES

Five consecutive patients with severe symptomatic chorea who were hospitalized at Columbia-Presbyterian Medical Center were treated with TBZ as part of their routine clinical care. The parents of each patient signed a written informed consent to use the drug (approved by the Columbia-Presbyterian Institutional Review Board). TBZ was slowly increased until chorea improved, and patients were videotaped with a handheld Hi-8 video camera. Brief clinical summaries appear below and are summarized in Table 1, along with a representative videotape of pre- and post-treatment examinations of Case 2 (see Video).

Case 1

A 10-year-old boy with cerebral palsy, mental retardation, seizures, encephalopathy, and gastroesophageal reflux required hospitalization for aspiration pneumonia. Severe choreoathetoid movements involving his forehead, mouth, tongue and arms began after he endured a period of hypoxemia. Chorea had previously occurred at age 5, also after an infection. Treatment with clonidine, chloral hydrate, clorazepate, and clonazepam did little to control the chorea, and he required sedation with phenobarbital in the intensive care unit to control the movements. TBZ was begun at 12.5 mg/day and slowly titrated upward, while clonidine and chloral hydrate were tapered. Over a period of 5 weeks, TBZ was increased to a total daily dose of 250 mg (9 mg/kg/day), given in three divided doses. He tolerated these increases without difficulty or side effects and chorea resolved. Total duration of treatment in hospital was 6 weeks. He was maintained on this dose upon discharge to a nursing facility.

Case 2

A 22-month-old girl with neurofibromatosis Type 1 was referred for evaluation of focal motor seizures, encephalopathy and severe chorea. She was admitted to a local hospital and treated with phenobarbital, phenytoin, lamotrigine, and valproate in serial fashion without success. Involuntary movements continued after the drugs were stopped. On transfer to our institution she was hypotonic and obtunded with roving eye movements. Continuous severe ballistic movements of all four limbs were accompanied by opisthotonic posturing. Involuntary movements were severe enough to require padding to be placed on the railings of her crib to prevent her from injuring herself. An extensive evaluation for infectious or inflammatory etiologies of the acute encephalopathy was unrevealing. MRI done on admission noted increased T2 signal in the tectum, cerebellum, and medial temporal lobes. MRA was normal and an EEG was significant for diffuse polymorphic slowing. Workup for the chorea that included a blood smear for acanthocytes and ophthalmic examination for K–F rings was negative. Phenytoin was stopped on admission and TBZ was begun at an initial dose of 25 mg/day, titrating to a daily dose of 200 mg (17 mg/kg/day) given in three divided doses. She was treated for a total of 3 weeks as an inpatient, tolerated TBZ without side effects, and the ballistic movements resolved. She was discharged to a nursing home and continued on the TBZ.

Case 3

A 25-month-old boy with trisomy 21 underwent feeding tube placement at age 15 months, complicated by a wound dehiscence. He required prolonged sedation with fentanyl and benzodiazepines, which likely led to periods of hypoxemia. Chorea began in his mouth with tongue protrusion and jaw deviation, and progressed to involve his neck, trunk, and limbs. At their worst, movements were so severe that he needed to be restrained to prevent him from injuring himself. Treatment with reserpine was only partially successful. TBZ was begun and increased slowly over 5 weeks to a dose of 125 mg/day (10.4 mg/kg/day), with complete cessation of chorea. No side effects were noted. He continues on the TBZ as an outpatient with reductions in dosage causing reemergence of chorea.

Case 4

A 27-month-old boy with treatment-refractory infantile spasms, profound developmental delay, and cortical blindness was treated with zonisamide, primidone, and a vagal nerve stimulator. He was transferred to our hospital for seizure control and found also to have severe choreoathetosis. Etiology of the chorea was unknown. TBZ was started, and the daily dose was increased over 4 weeks to 100 mg (10 mg/kg). TBZ effectively reduced chorea and was well tolerated. The infantile spasms continued necessitating three more admissions over the next 8 months. On the last admission, TBZ was gradually tapered without reemergence of chorea.

Case 5

A 2.5-year-old boy with previously normal development presented with an acute encephalopathy after a viral infection. Over the next several days, he developed continuous severe generalized chorea. On transfer to our hospital 2.5 weeks later, TBZ was begun and titrated to a total daily dose of 275 mg (25 mg/kg/day), with moderate reduction in chorea. Although no side effects were observed, given the lack of functionally significant benefit, TBZ was slowly decreased and eventually discontinued. Chorea did not appear to worsen on discontinuing TBZ and the patient was eventually transferred to a nursing home for further care.

DISCUSSION

We present 5 pediatric patients who developed severe, acute, generalized chorea occurring in the setting of encephalopathy. Our patients were acutely ill and required hospitalization to control involuntary movements. Several similar cases have been described in the literature. Harbord and Kobayashi reported 2 patients with cerebral palsy who developed acute generalized chorea associated with an intercurrent febrile illness.[15] Chorea was associated with a marked elevation in creatine kinase and was resistant to treatment with standard neuroleptics. Beran-Koehn described 2 children with cerebral palsy who experienced recurrent episodes of violent ballism triggered by infection or minor surgical procedures.[16] Chorea was severe enough to require sedation with intravenous pentobarbital and was relatively resistant to treatment with dopamine blocking agents. Okun and associates[17] presented a similar patient whose recurrent episodes of chorea were associated with antiphospholipid and anticardiolipin antibodies, again resistant to treatment with neuroleptics. Chorea has also been reported with the use of phenytoin[18,19] and, given the temporal relationship of this drug to the appearance of chorea in Case 2, the possibility that her chorea was related to phenytoin use cannot be ruled out. In such a situation, discontinuing the offending drug may be sufficient. The severity of the chorea in our patient, however, necessitated treatment. These patients and ours are similar to dystonic patients who experience acute exacerbations of dystonia (dystonic storm),[20] and the condition of our patients might appropriately be named choreic storm.

Four of our patients experienced dramatic improvement in chorea with TBZ, and the drug was well tolerated. Controlling involuntary movements prevented self-injury, and patients were able to transfer out of the intensive care unit. It was also possible to reduce the dose of other medications, including sedative medications that complicated their care. We did not observe adverse events with TBZ, although our patients' encephalopathy may have prevented recognition of mild parkinsonism or sedation.

The mean dose of TBZ required to control chorea was 190 mg/day (14.28 mg/kg/day), higher than the doses employed by Jankovic and colleagues[12] in their adult patients. Although doses required to control involuntary movements were high, patients tolerated the drug without incident. Nevertheless, the prospect of using 200 mg of TBZ in a 22-month-old child is intimidating. In published cases of severe pediatric chorea, high doses of neuroleptic have also been used, often without success.[15–17] The reason pediatric patients require higher doses of TBZ as compared to adults is unclear, and requires further study.

TBZ is not currently approved in the United States, and patients' families must bear the cost of the drug. We chose not to try to treat our patients with standard neuroleptics before resorting to TBZ because of the potential risks of neuroleptic treatment. It is unknown whether

TBZ is superior to typical neuroleptics or reserpine in patients with severe chorea, however the failure of neuroleptics in the published case reports referenced above suggests that TBZ might be preferable. TBZ's dual mode of action, depleting synaptic vesicles, and blocking the dopamine receptor, may confer an advantage. It is also possible that the long half-life of TBZ's metabolite, dihydrotetrabenazine, may contribute to improved symptom control.[21]

LEGEND TO THE VIDEO

Case 2 is shown before and after treatment with TBZ. Before treatment, continuous generalized chorea is present with opisthotonic posturing. Protective padding needed to be placed around her crib to prevent self-injury. After treatment with TBZ, chorea has resolved.

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Unusual Phenotypes in DYT1 Dystonia: A Report of Five Cases and a Review of the Literature

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Abstract: **Since the advent of widespread testing for the presence of the DYT1 gene mutation, the range of phenotypes that have been associated with this genetic abnormality has expanded. We report on 5 DYT1 gene-positive patients with unusual phenotypes. Two of them had late presentation, one of these after peripheral injury. Three additional patients had late progression of symptoms, onset after exposure to haloperidol, and severe bulbar involvement, respectively. The clinical heterogeneity of this condition raises problems for clinicians in selecting appropriate patients for diagnostic testing. Also, because of the low phenotypic penetrance of DYT1 dystonia, the discovery of the DYT1 mutation in a patient with an atypical clinical syndrome may not necessarily suggest a causal relationship. We have, therefore, analysed all published clinical studies of DYT1 dystonia to guide clinical decision making concerning DYT1 gene testing based on current information.**

Key words: DYT1 dystonia; phenotype; phenotypic variability

A videotape accompanies this article.

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