the permeability of the blood–CSF barrier. Native (barrier-independent) CSF TTR has been shown to be elevated in conditions of decreased CSF turnover [4]. Further study is needed in the newborn period to determine the effect of decreased CSF turnover on CSF TTR and whether CSF TTR is affected out of proportion to other CSF proteins.

In summary, we have demonstrated that increased blood–CSF barrier permeability is not the explanation for increased CSF TTR in the neonate. Other mechanisms must be considered.

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Parkinsonism and Amiodarone Therapy

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We report a case of reversible, dose-related parkinsonian tremor in a patient taking amiodarone. In previous writings by others, basal ganglia dysfunction associated with amiodarone was dose related and reversibility was inversely related to duration of therapy. Patients receiving amiodarone are at risk for the development of basal ganglia dysfunction which may persist if the drug is not discontinued or the dosage reduced.

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Case Report

A 73-year-old man was evaluated for new onset of Parkinson-type tremor of the left leg. He had a history of ischemic heart disease with paroxysmal atrial arrhythmias and ventricular tachycardia refractory to verapamil and tocainide. Amiodarone was initiated at a dose of 400 mg every 6 hours for 2 days, then reduced to 400 mg every 8 hours. On the fourth day of therapy he developed an intermittent, 6-Hz coarse resting tremor of the left leg, indistinguishable from that seen in Parkinson's disease. The tremor was present only on recumbency with both legs at rest. It was abolished with active or passive movement of either leg. Tremor was most pronounced in the foot but at times involved the entire left leg. Superimposed rapid jerks of the left foot were occasionally noted. There was no tremor of the head, jaw, voice, arms, or right leg. There was no alteration of tone, bradykinesia, gait disturbance, or postural instability. Findings on hemogram, routine blood chemistries, thyroid profile, electroencephalogram (EEG), and magnetic resonance imaging (MRI) of the brain were normal. One day after the onset of tremor amiodarone was discontinued, and the tremor stopped 5 days later. The tremor recurred with reintroduction of amiodarone after a latency of 5 days and disappeared when the dose was reduced.

Discussion

Amiodarone is a di-ionated benzofurane derivative used primarily in the treatment of refractory ventricular and atrial tachyarrythmias [1]. Multiple neurological side effects have been reported, including senso-

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Duration of Amiodarone Therapy and Reversibility of Parkinsonian Features

Study	No. of Patients	Daily Maintenance Dose (mg)	Latency	Total Time on Amiodarone	Parkinsonian Features	Drug Discontinued (DC) or Reduced (R)	Reversibility
Werner and Olanow	1	1,200	4–5 days	4–5 days	Parkinsonian tremor	DC	Reversed in 5 days
Lloveras et al [9]	1	100	5–6 days	5–6 days	Extrapyramidal syndrome of dystonic type	DC	Reversed in 24–48 hr
Palakurthy et al [3]	2	800	12 days	12 days	Jaw tremor	DC	Reversed "promptly"
		400	1 mo	1 mo	Jaw tremor	DC	Reversed in 2 wk
Waxman et al [11]	2	600	3 mo	3 mo	Extrapyramidal syndrome	R (to 400 mg)	Symptoms decreased at 3-mo follow-up
		800	4 mo	4 mo	Extrapyramidal syndrome	R (treatment stopped after 3 wk, then 400 mg/day)	Patient had "done well" at 3-mo follow-up
Lombard et al [5]	1	200 × 6 mo, then 600	6 mo	6 mo	Bradykinesia, rigidity, coarse tremor	DC	Partial resolution at 6-mo follow-up
Lustman and Monseu [4]	1	400	1 mo	10 mo	Bilateral rhythmic hand tremor	DC	Partial resolution at 6-mo follow-up
LeMaire et al [10]	1	600	21 mo	27 mo	Akinesia and rigidity	No change in dose	Permanent at 27-mo follow-up

rimotor peripheral neuropathy, gait ataxia, proximal muscle weakness and wasting, and tremor [2, 3].

Tremors are the most common manifestation of neurotoxicity and usually appear early in the course of therapy [2]. The majority are bilateral, 6- to 10-Hz action tremors of the arms, which are indistinguishable from essential tremor. They can be asymmetrical but to date have not been reported to be unilateral. Tremors can involve all four extremities and rarely are associated with Parkinson-like features [3–5].

Manifestations of basal ganglia dysfunction that have been reported in association with amiodarone include myoclonus [6, 7], hemiballism [6], dyskinesias of the extremities [8], orofacial dyskinesias [3], a complex movement disorder with clonus of the jaw and extremities [3], and parkinsonism. Previously reported cases with parkinsonian features include two patients who had a coarse tremor of the jaw [3]; one patient who had bilateral rhythmic tremors of the hand [4]; one patient who had an "extrapyramidal syndrome of dystonic type" [9]; 2 patients who had bradykinesia and rigidity, with "coarse global tremors" in one [5, 10]; and 2 patients who were described as having an "extrapyramidal syndrome" [11]. None of the tremors in these patients was purely unilateral and none involved only the leg.

We describe a case of a patient who had a dose-related, unilateral Parkinson-type tremor that appeared within days after initiation of amiodarone therapy and was completely reversible. A direct relationship to amiodarone therapy appears convincing in view of the onset of tremor 4 to 5 days after initiation of therapy, complete reversal 4 to 5 days after discontinuation, and recurrence 4 to 5 days after reinstitution of the drug.

Based on a review of previously described cases of patients in whom parkinsonian features developed in association with amiodarone, it appears that the reversibility of symptoms is related to the duration of therapy (Table). Patients who were treated for 12 days or less had prompt reversal of symptoms. One patient who was treated for one month had complete recovery, but over a longer period of time [3]. Two patients received amiodarone for 3 and 4 months each [11]. Examination of one patient after the dosage was reduced revealed improvement but not total resolution of symptoms. The second was described as having "done well" but it is not clear if the symptoms totally resolved. The patients who were treated for 6 to 10 months noted improvement after the drug was discontinued but symptoms were still present after follow-up of 3 to 6 months. The one patient who received

amiodarone for the longest period of time (27 months) had persistent parkinsonian features and was found to have depigmentation of the substantia nigra at autopsy [10]. The authors suggested that the patient might have had subclinical Parkinson's disease which was exacerbated by the introduction of amiodarone [10]. However, this patient did not have parkinsonian features prior to the introduction of the drug and was not reported to have Lewy bodies.

Reversible Parkinson-type tremor in our patient who received amiodarone for 5 days is in keeping with the results reported in other patients in whom basal ganglia features developed after they received amiodarone for 12 days or less. The findings in our patient and others suggest that amiodarone treatment is related to the development of basal ganglia dysfunction including parkinsonism in some patients, and that recovery is related to the duration of exposure.

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