Carbamazepine-induced dyskinesia and ophthalmoplegia

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■ Antiepileptic drug-induced dyskinesias are well described with phenytoin but have only occasionally been reported with carbamazepine. We present two patients with carbamazepine-induced dyskinesia, one with ocular skew deviation and down-beating nystagmus associated with a high therapeutic level, and another with systemic dyskinesia with a toxic carbamazepine level, and compare these with previously reported cases.

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ANTIEPILEPTIC drug-induced dyskinesias and ophthalmoplegia may be idiosyncratic or associated with a high drug concentration.[1-19] An extensive study of this subject described the association of limb chorea, orofacial dyskinesia, and dystonia with phenytoin.[5] Phenytoin-induced ophthalmoplegia[16] and abducens nerve palsy also have been described.[11] Isolated cases of choreoathetotic movements have been reported with ethosuximide,[8] methsuximide,[18] phenobarbital,[10] sulthiamine,[5] and primidone.[19]

Relatively few cases of involuntary movements have been reported with carbamazepine. "Flapping tremors,"[20] myoclonic jerks,[21] and "incoordinate ballistic or cramp-like movements"[22] have been attributed to the drug, and carbamazepine toxicity can occasionally cause asterixis.[5] Fifteen cases have been reported of systemic dyskinesias occurring secondary to carbamazepine therapy[2,4,6,7,9,15,23] (*Table 1*). The dyskinesias have been described in association with drug levels in both the therapeutic and toxic ranges. Manifestations have included axial dystonia, appendicular dystonia, opisthotonic posturing, and distal appendicular choreoathetoid dyskinesia.

The association of ocular dyskinesias with carbamazepine therapy is less well recognized[1,3,12,13,14,17] (*Table 2*). There are a few reports of total external ophthalmoplegia,[12,13] ocular skew deviations,[14] and blepharospasm[3] associated with carbamazepine toxicity, but only one report of oculogyric crisis associated with a therapeutic level.[1]

We present two patients in whom dyskinesias occurred during carbamazepine therapy—ocular skew deviation and down-beating nystagmus in one and, in the other, systemic dyskinesia.

CASE REPORTS

Patient A

Patient A, a 42-year-old woman with tic douloureux, was on carbamazepine monotherapy for 3 years. She had been experiencing intermittent double vision for 1 1/2 years. The symptoms usually developed 2 hours after

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TABLE 1
CARBAMAZEPINE-INDUCED SYSTEMIC DYSKINESIA

# Patients	Duration of carbamazepine therapy	Reference	Sex	Age	Duration of epilepsy	Associated disorders	Medications	Serum levels (μg/mL)	Author's description of movements
1	≤1 mo	4	M	11	> 1 yr	None	Carbamazepine	21	Opisthotonic posturing with extension of limbs, flexion of wrists, and severe dystonia
2	≤1 mo	2	F	71	18 yr	None	Carbamazepine Phenobarbital Primidone	19 14.3 3.7	Distal choreoathetoid dyskinesias of all four extremities with gait ataxia and slurred speech
3	≤1 mo	9	F	14	Unknown	Episodic headache with EEG changes	Carbamazepine	20	Lethargy, opisthotonic posturing associated with ballistic movements, athetoid movements, apnea in coma 1½ h later
4	≤1 mo	15	F	42	Unknown	None	Carbamazepine Phenobarbital	54 Unknown	Arrhythmic twitching of face and fingers, slow twisting movements of limbs, absent caloric response, patient in coma
5	≤1 mo	Present pt B	F	36	11 yr	None	Carbamazepine Phenytoin	24.5 32.5	Dysarthria, axial dystonia with opisthotonic posturing, distal choreoathetoid movements of all extremities, dysmetria
6–8	≤1 mo	7		Young adults	Chronic	None	Carbamazepine	Unknown	Transient dystonia of axial muscles
9	≤1 mo	7		Young adults	Chronic	None	Carbamazepine Haloperidol	Unknown	Transient dystonia of hands
10	≤1 mo	6	M	5	3 yr	Mental retardation, spastic quadriparesis	Carbamazepine	Unknown	Dystonic movements of all extremities
11	≤1 mo	6	M	10 mo	Since birth	Mental retardation, agenesis of corpus callosum, cerebral dysgenesis	Carbamazepine Phenytoin Phenobarbital Ethosuximide Clonazepam	Unknown Unknown Unknown Unknown Unknown	Dystonic movements of all extremities, opisthotonic posturing
12	≤1 mo	6	M	4	3⅘ yr	Mental retardation, microcephaly, bilateral cerebral hypoplasia	Carbamazepine Phenytoin Phenobarbital	5.1 11 Unknown	Opisthotonic posturing, grimacing, dystonic posturing of all extremities
13	≤1 mo	4	F	11	>1 yr	None	Carbamazepine	25	Severe dystonic movements of limbs with extension of trunk and neck
14	≤1 mo	24	F	19	5 yr	None	Carbamazepine	35	Stupor, writhing choreiform movements in both arms
15	≤1 mo	24	F	24	N/A	None	Carbamazepine	27	Combative, choreiform movements in both arms
16	≤1 mo	24	F	17	3 wk	None	Carbamazepine	29	Stupor, choreiform movements of the limbs

each dose and lasted 2 to 3 hours. An ophthalmologist noted that her findings were similar to those seen with lesions of the cranio-cervical junction; the patient had skew deviation with down-beating nystagmus which worsened significantly when looking down and laterally and improved on looking straight down. Her symptoms and signs resolved over a few days after the daily carbamazepine dosage was decreased from 1,200 mg to 500 mg. The carbamazepine serum level was 10.4 μg/mL while symptomatic and 6.0 μg/mL one week later when asymptomatic. Because all of her findings resolved, further diagnostic studies were felt to be unnecessary, given the temporal relationship of the symptoms to carbamazepine use.

Patient B

Patient B, a 36-year-old woman, took an intentional overdose of approximately 25 tablets of carbamazepine

TABLE 2
CARBAMAZEPINE-INDUCED OCULAR DYSKINESIA

# Patients	Duration of carbamazepine therapy	Reference	Sex	Age	Medications	Serum levels (μg/mL)	Author's description of eye findings
1	≤1 mo	13	M	17	Carbamazepine	>24	Stupor, eyes midline, no response to caloric stimulation or doll's head stimuli
2	≤1 mo	12	F	18	Carbamazepine	20	Drowsiness; no response to caloric, oculocephalic, or OKN testing
3	≤1 mo	14	F	16	Carbamazepine	>30	Stupor, skew deviation with absent doll's eye and caloric testing
4	≤1 mo	1	F	8	Carbamazepine Phenytoin Phenobarbital	4.3 "Therapeutic" "Therapeutic"	Intermittent involuntary sustained conjugate eye movements upward (between days 13 and 24 of therapy)
5	>1 mo	Present pt A	F	42	Carbamazepine	10.4	Skew deviation, down-beating mystagmus
6	>1 mo	3	F	42	Carbamazepine Primidone	9.9 trough to 13.7 post-dose Unknown	Episodic forceful eye closure (blepharospasm)
7	Unknown	17	Unknown	Unknown	Carbamazepine	Toxic	Dyskinetic eye movements

(total 5 g) and 25 capsules of phenytoin (total 2.5 g). "Funny movements" of her arms and legs were reported en route to the hospital. The patient had been on long-term therapy with both drugs for 11 years for treatment of an idiopathic generalized seizure disorder.

In the emergency room, approximately 8 hours after her overdose, the patient's vital signs were stable. Her general physical examination was unremarkable. She was lethargic but fully oriented. Her speech was moderately dysarthric with a scanning quality. Bilateral, horizontal, coarse, gaze-evoked nystagmus was noted. Choreoathetosis, more prominent distally, was intermittently observed in all four extremities and increased with sustained posture.

Intermittent axial dystonia with opisthotonic posturing was also seen. In addition, her neurologic examination revealed truncal ataxia, dysrhythmic rapid alternating movements, and dysmetria with finger-nose and heel-knee-shin maneuvers. A moderate cerebellar tremor was noted in the upper extremities. Muscle tone was mildly increased. She had diffuse hyperreflexia with unsustained clonus at the ankles. Babinski signs were absent.

Laboratory results demonstrated a carbamazepine level of 24.5 μg/mL and a phenytoin level of 32.5 mg/mL. Serum and urine toxicology screens were negative for other drugs. Complete blood count, liver function tests, electrolytes, and arterial blood gases were normal. Chest radiograph and electrocardiogram were normal. An electroencephalogram demonstrated generalized theta slowing of the background with no evidence of ongoing epileptic activity.

Ipecac syrup, 30 mL, was used to induce vomiting and an hour later 50 g of a magnesium sulfate-charcoal slurry was administered via a nasogastric tube. After 12 hours, the carbamazepine level was 4.5 μg/mL, but the phenytoin level remained high, at 26 mg/mL. Her neurologic signs returned to normal except for the previously noted, mild, gaze-evoked nystagmus. She was restarted on her original dosages of carbamazepine and phenytoin prior to discharge, 2 days after her admission.

Two weeks later, the carbamazepine level was 5 μg/mL and the phenytoin level 19.0 mg/mL. Neurologically, she remained asymptomatic over the next 6 months without recurrence of symptoms experienced during her intentional overdose.

DISCUSSION

A total of 21 cases of carbamazepine-induced dyskinesias have been reported, 15 (71%) with systemic dyskinesias and 6 (29%) with ocular dyskinesias. Eleven (52%) of the cases occurred during monotherapy (3 with phenytoin, 3 with phenobarbital, 2 with primidone, and 1 each with clonazepam, ethosuximide, and haloperidol), and the remaining 10 (48%) with polytherapy. Four (19%) of the reported cases were associated with carbamazepine levels in range of 6 μg/mL to 12 mg/mL, 12 (57%) with levels greater than 12 mg/mL, and 5 (24%) with unknown carbamazepine levels. Symptoms developed in 18 (86%) patients 1 month or less after initiation of carbamazepine therapy and in 2 (9%) patients while on chronic maintenance therapy (ie, symptoms began after 1 month). The dura-

TABLE 3
TREATMENT OF CARBAMAZEPINE-INDUCED SYSTEMIC DYSKINESIA

# Patients	Reference	Rx Change	Acute intervention	Time between onset of symptoms and Rx introduction or change	Duration of symptoms after intervention	Rx restarted/ rechallenged
1	4	Carbamazepine, 12 mg/kg, for 2 d (accidental)	Carbamazepine held	2 d	12 h	Restarted on previous dosage with no problems
2	2	Carbamazepine increase after 4 d	Carbamazepine discontinued	4 d	Within 7 d	No
3	9	12–20 g carbamazepine overdose	Carbamazepine discontinued, ipecac, physostigmine IV with success, ventilator support	30 min	3 d	Unknown
4	15	Carbamazepine overdose	Carbamazepine discontinued, gastric lavage, charcoal with cathartic, ventilator support	Soon after discharge	4 d	Unknown
5	Present pt B	5 g carbamazepine overdose, 2.5 g phenytoin	Carbamazepine held, ipecac, charcoal with Mg sulfate	8 h	12 h	Restarted on previous dosage with no problems
6–8	7	Carbamazepine dosage doubled	None	Soon after introduction	Few days	Maintained on same medications with no problems
9	7	None	None	Soon after change	>1 mo	Maintained on same medications with no problems
10	6	None	Carbamazepine discontinued, phenobarbital started	10 d	5 d	No
11	6	None	IV diphenhydramine hydrochloride with success, carbamazepine discontinued	3 wk	10 d	Rechallenged at 15 mo with similar symptoms 3 wk later; symptoms resolved 2 wk after carbamazepine discontinued
12	6	None	Carbamazepine discontinued	3 wk	2 wk	No
13	4	None	IV diazepam with success	1 yr	17 h	Restarted with decreased dosage with no problems
14	24	13.2 g carbamazepine overdose	Carbamazepine discontinued, gastric lavage	18 h	40 h	Unknown
15	24	20 g carbamazepine overdose	Carbamazepine discontinued, gastric lavage 5 times during first 10 hours with activated charcoal after each lavage	18 h	20 h	Unknown
16	24	Carbamazepine overdose	Carbamazepine discontinued; gastric lavage followed by activated charcoal	10 h	14 h	Unknown

tion of therapy prior to onset of symptoms was unknown for one (5%) case.

Our second patient's symptoms resolved rapidly with a fall in the carbamazepine level and despite a persistently elevated phenytoin level. This suggests that carbamazepine was the cause of the dyskinesias. Carbamazepine-induced systemic dyskinesias associated with acute toxicity are known to have their onset from 30 minutes to 4 days after drug introduction or dose change and to resolve within 7 days (*Table 3*). Intravenous physostigmine therapy was beneficial treatment in one case.[9] Based on previously reported cases,[2,4,9,15] it was unclear whether to rechallenge patient B with carbamazepine once the signs and symptoms of toxicity had resolved (*Table 3*). Our patient was restarted on her previous dosage without recurrence of symptoms.

Six patients have been reported to have systemic dyskinesias following initiation of therapy with carbamazepine and unreported serum levels.[6,7] Symptoms occurred soon after introduction or change in dosage of carbamazepine and persisted up to 3 weeks. Five of these patients were maintained, or later restarted, on the same treatment without recurrence of dyskinesias. In one report, symptoms were transient and resolved spontaneously.[7] Intravenous diphenhydramine hy-

TABLE 4
TREATMENT OF CARBAMAZEPINE-INDUCED OCULAR DYSKINESIA

# Patients	Reference	Rx Change	Acute intervention	Time between onset of symptoms and Rx introduction or change	Duration of symptoms after intervention	Rx restarted/ rechallenged
1	13	6 g carbamazepine overdose	Carbamazepine discontinued, supportive care	Several h later	*	*
2	12	Carbamazepine dosage increased from 200 mg/d to 1,600 mg in 8 h	Carbamazepine discontinued	At least 8 h	36 h	Unknown
3	14	5.8 g carbamazepine overdose	Carbamazepine discontinued	36 h	4 d	Unknown
4	1	None	IV diphenhydramine hydrochloride with success	13 d	12 d	No
5	Present pt A	None	Carbamazepine decreased from 1,200 mg to 600 mg/d	18 mo	Few d	Maintained on 600 mg/d with no problems
6	3	None	Carbamazepine decreased from 1,800 mg to 400 mg/d	9 mo	Few d	Maintained on 400 mg/d with no problems
7	17	None	Unknown	Unknown	Unknown	Unknown

*Patient died 30 h after ingestion

drochloride was used acutely with good success in one case.[6] There is only one report of systemic dyskinesia associated with a high carbamazepine level during chronic maintenance therapy (starting more than 1 one month after initiation of the drug).[4] The symptoms began after 1 year of treatment and resolved 17 hours after treatment with intravenous diazepam therapy. The patient was restarted on carbamazepine at a lower dosage but at a therapeutic level without further problems.

Only one case has been reported of carbamazepine-induced ocular dyskinesia in a patient with therapeutic levels on chronic therapy.[3] Symptoms occurred 9 months after introduction of the drug. In our case, symptoms developed after 18 months of therapy. The symptoms in both patients resolved a few days after the dosage was decreased.

One case of ocular dyskinesia following initiation of therapy and associated with a normal therapeutic carbamazepine level has been reported.[1] The patient responded well to intravenous diphenhydramine hydrochloride. Acute carbamazepine toxicity associated with ocular dyskinesias has been described rarely [1,3,12–14,17] (*Table 4*). Three of the patients had decreased levels of consciousness and responded to neither caloric testing nor oculocephalic maneuvers.[12–14] One of the patients died 30 hours after drug ingestion.[13] Marked horizontal nystagmus has been reported in four patients recovering from massive carbamazepine overdose.[24]

The mechanisms of action of carbamazepine-induced systemic and ocular dyskinesias remain unclear. The drug is a tricyclic compound related to imipramine, and both are structurally related to the phenothiazines. Crosley and Swender suggested that carbamazepine may be a dopamine antagonist, and this property might account for the production of dystonia.[6] Consolo and associates reported that carbamazepine selectively increases acetylcholine levels in the striatum of experimental animals.[23] Jacome proposed that the dyskinetic effects of the drug may be related to the increased acetylcholine level in the striatum.[7]

Regarding ocular dyskinesias, Bousounis and associates suggested that carbamazepine-induced increased central catecholaminergic activity might have produced blepharospasm in their patient, as is seen in Meige syndrome.[3] Carbamazepine has been shown to decrease catecholamine uptake and probably enhances its action. Thus, previously tolerated doses may cause a dystonic reaction because of enhanced central transmitter activity. Spector and associates stated that total external ophthalmoplegia induced by phenytoin might be related to effects on the vestibulo-oculomotor pathway.[16] As an additional mechanism, effects of cerebellar activity on the vestibulo-ocular reflex must also be considered.

Despite the large number of patients who have therapeutic or toxic levels of carbamazepine, dyskinesia develops in only a few. In most reported cases, symptoms developed following initiation of carbamazepine therapy, so carbamazepine-induced dyskinesias are probably idiosyncratic reactions. No clear precipitant for dyskinesia could be identified in the two patients who

developed symptoms while on chronic therapy.[3,4] An almost equal number of reported cases have been reported with monotherapy and polytherapy, which suggests that concomitant medications do not contribute significantly to the incidence of carbamazepine-induced dyskinesia.

Carbamazepine serum levels do not appear to predict the development of dyskinesias, but the reactions occur more frequently in individuals with toxic concentrations (greater than 8 μg/mL).

Based on the review of the literature for both systemic and ocular dyskinesias, if the carbamazepine level is in the therapeutic range, we recommend stopping the drug and prescribing another antiepileptic medication in its place. If the serum level is in the high therapeutic or toxic range, we recommend withholding carbamazepine until the symptoms resolve, and then restarting therapy at a lower dose.

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REFERENCES

1. Berchou RC, Rodin EA. Carbamazepine-induced oculogyric crisis [letter]. Arch Neurol 1979; **36:**522–523.
2. Bimpong-Buta K, Froescher W. Carbamazepine-induced choreoathetoid dyskinesias. J Neurol Neurosurg Psychiatry 1982; **45:**560.
3. Bousounis DP, Konkol RJ, Keller AH. Blepharospasm induced by carbamazepine. Epilepsia 1986; **27(5):**592 (abstract).
4. Bradbury AJ, Bentick B, Todd PJ. Dystonia associated with carbamazepine toxicity. Postgrad Med J 1982; **58:**525–526.
5. Chadwick D, Reynolds EH, Marsden ED. Anticonvulsant-induced dyskinesias: a comparison with dyskinesias induced by neuroleptics. J Neurol Neurosurg Psychiatry 1976; **39:**1210–1218.
6. Crosley CJ, Swender PT. Dystonia associated with carbamazepine administration: experience in brain-damaged children. Pediatrics 1979 **63:**612–615.
7. Jacome D. Carbamazepine-induced dystonia [letter]. JAMA 1979; **241:**2263.
8. Kirschberg GJ. Dyskinesia—an unusual reaction to ethosuximide. Arch Neurol 1975; **32:**137–138.
9. Lehrman SH, Bauman ML. Carbamazepine overdose. Am J Dis Child 1981; **135:**768–769.
10. Lightman SL. Phenobarbital dyskinesia. Postgrad Med J 1978; **54:**114–115.
11. Manlapaz JS. Abducens nerve palsy in dilantin intoxication. J Pediatr 1959; **55:**73–77.
12. Mullally WJ. Carbamazepine-induced ophthalmoplegia. Arch Neurol 1982; **39:**64.
13. Noda S, Umezaki H. Carbamazepine-induced ophthalmoplegia [letter]. Neurology 1982; **32:**1320.
14. Salcman M, Pippenger CE. Acute carbamazepine encephalopathy. JAMA 1975; **231(9):**915.
15. Sethna M, Solomon G, Cedarbaum J, Kutt H. Successful treatment of massive overdose of carbamazepine. Epilepsia 1987; **28(5):**581 (abstract).
16. Spector RH, Davidoff RA, Schwartzman RJ. Phenytoin-induced ophthalmoplegia. Neurology 1976; **26:**1031–1034.
17. Troupin AS, Green JR, Levy RH. Carbamazepine as an anticonvulsant: a pilot study. Neurology 1974; **24:**863–869.
18. Stenzel E, Boenigk HE, Rambeck B. Methsuximid in der Epilepsiebehandlung. Nervenarzt 1977, **48:**377–382.
19. Schmidt D. Die Behandlung der Epilepsien mit Hilfe der Blutspiegelbestimmung von Antiepileptika. Nervenarzt 1977, **48:**183–196.
20. Lefevre JP, Gablain J. Ataxie aigue et dibenzoaze'pine. Quest Med 1967; **20:**1181–1183.
21. Wendland KL. Myoklonien nach Gaben von Carbamazepin. Nervenarzt 1968; **39:**231–233.
22. Gruska H, Beyer KH, Kubicki S, et al. Klinik, Toxikologie und Therapie einer schweren Carbamazepin-Vergiftung. Arch Toxicol 1971; **27:**193–203.
23. Consolo S, Bianchi S, Ladinsky H. Effect of carbamazepine on cholinergic parameters in rat brain areas. Neuropharmacology 1976; **15:**653–657.
24. Weaver DF, Camfield P, Fraser A. Massive carbamazepine overdose: clinical and pharmacologic observations in five episodes. Neurology 1988; **38:**755–759.