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MUSCLE CRAMPS ASSOCIATED WITH VINCRISTINE THERAPY

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Abstract

The course of vincristine-induced neuropathy was evaluated in 14 patients who developed muscle cramps during chemotherapy. Cramps were noticed between 3 days and 4 months after the initiation of vincristine and following a cumulative dose of 1–9.4 mg/m^2 (median 3.1 mg/m^2). All patients reported daytime cramps and only 4 experienced nocturnal cramps. The lower extremities were involved in 11/14 and the upper extremities in 10/14 patients. Duration of cramps ranged from 1 to >9 months. Physical examination revealed signs of peripheral neuropathy in all patients. Cramps were the first symptom of neurotoxicity in 4 patients. Other symptoms were noted in all patients, but only 3 had motor manifestations other than muscle cramps. Although symptoms of neuropathy tended to persist for several months, a rapid symptomatic improvement was noticed after withdrawal of vincristine. We conclude that vincristine-induced muscle cramps are not necessarily associated with severe neurotoxicity and should not automatically indicate interruption of therapy.

Key words: Vincristine, muscle cramps, peripheral neuropathy.

Vincristine is a tubulin-binding vinca alkaloid, widely used in the treatment of various malignant tumors. The major toxic effect of this drug is peripheral neuropathy of a mixed sensorimotor type affecting primarily small fiber function (1). The clinical spectrum of this complication is well-documented and includes decreased deep tendon reflexes, distal paresthesias, sensory loss, motor weakness, muscle wasting and muscle pain (1–4). Muscle cramps are localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration which probably originate in the distal portions of motor nerves (5, 6) and, therefore, are expected to be a prominent symptom of vincristine neuropathy. However, the development of muscle cramps during vincristine therapy has been only briefly mentioned in the literature. Casey et al. (4), who studied 13 patients treated with vincristine, reported that some of their patients complained of muscle cramps and that this complication was related to the individual doses rather than to the total cumulative doses of vincristine. In a recent study Steiner & Siegal (7) prospectively evaluated muscle cramps of various causes in 50 cancer patients and considered vincristine the cause of muscle cramps in 13 of these 50 cases.

It has been our clinical impression that muscle cramps frequently develop during vincristine therapy. In this paper we describe the course of neurotoxicity in 14 lymphoma patients who developed muscle cramps during vincristine-containing drug therapy.

Material and Methods

Fourteen patients with lymphoma, who developed new complaints of muscle cramp during the course of vincristine-containing chemotherapy were identified between September 1989 and March 1990. During that time period a total of 74 unselected patients with lymphoma (16 with Hodgkin's disease and 58 with non-Hodgkin's lymphoma) were treated at our center with various types of vincristine-containing combinations. Patients were not routinely asked about muscle cramps before each course of vincristine. However, patients in whom muscle cramps were identified, were asked about neuropathy-associated symptoms and were prospectively evaluated for such symptomatology. Evaluation of symptoms was performed by the same observer (N.H.) and was repeated every 4–6 weeks during chemotherapy and every 2–3 months thereafter. These patients also underwent a detailed neurological examination which routinely included evaluation of deep

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Table 1

Muscle cramps in 14 patients treated with vincristine (VCR)-containing combinations

Patient No.	Sex/Age (yr)/Type of lymphoma	Cumulative dose of VCR at onset (mg/m^2)	Time of onset from initiation of VCR	Characteristics of cramps	Duration (month) maximal frequency
1	F/83/NHL-IG	4.1	2.5 months	UE-daytime, LE-nocturnal + daytime	> 9.0/ UE-3 per week, LE-1 per day
2	M/69/NHL-HG	3.0	LE-2.5 months UE-3.5 months	LE-nocturnal, UE-daytime	LE-1.0/2 per week UE-3.0/1 per day
3	F/38/NHL-LG	9.4	4.0 months	LE-daytime	3.5/ several times per day
4	F/42/NHL-LG	3.2	1.0 months	LE-daytime + nocturnal	1.0/2 per day
5	F/28/HD	1.4	0.5 month	UE + LE + trunk-daytime	> 8.0/numerous per day
6	F/61/NHL-HG	2.0	1.5 month	UE-daytime	1.0/1 per day
7	M/76/NHL-IG	4.4	2.0 months	UE-daytime	2.0/2 per week
8	M/65/NHL-IG	2.0	1.0 month	UE-daytime	5.0/2–3 per week
9	M/66/NHL-IG	4.7	LE-2.5 months UE-3.0 months	LE-daytime, UE-daytime	LE-2.0/3 per week, UE- > 7.5/4 per week
10	M/42/NHL-HG	UE-2.1 LE-5.3	UE-1.5 month LE-4.0 months	UE-daytime, LE-daytime + nocturnal	UE-2.0/1 per day, LE-1.5/2–3 per week
11	F/59/NHL-LG	6.3	4.0 months	LE-daytime	> 8.0/2 per week
12	M/63/NHL-LG	1.0	3 days	UE-daytime LE-daytime	> 5.0/ UE-6–7 per day, LE-1 per day
13	F/43/HD	3.7	1.0 month	UE-daytime LE-daytime	> 8.5/ UE-4 per week, LE-3 per week
14	M/38/HD	3.0	2.5 months	LE + trunk daytime	LE- > 9.0/1 per day trunk-7.0/2 per week

Abbreviations: NHL = non-Hodgkin's lymphoma; IG = intermediate grade; HG = high grade; LG = low grade; HD = Hodgkin's disease; UE = upper extremities; LE = lower extremities.

Note: Cumulative dose of vincristine given in prior therapy to patients 5, 11, 12, 13, was 11.2, 13.8, 23.6 and 9 mg/m^2, and the time interval between the last dose and the renewal of vincristine therapy was 21, 83, 44, and 11 months respectively.

tendon reflexes, vibration, pinprick, joint position sensation, muscle strength, and gait. The detailed examination was performed in each patient only once and by the same examiner (S.A.B.). It was performed after cramps had been noticed and before resolution of cramps and withdrawal of vincristine.

To exclude hypomagnesemia and/or primary muscle disorders, serum levels of magnesium and muscle enzymes (creatine phosphokinase and aldolase) were determined.

Results

The characteristics of the 14 patients who developed muscle cramps are shown in Table 1. There were 7 males and 7 females ages 28–83 years (mean 55 years). Eleven had non-Hodgkin's lymphoma and 3 had Hodgkin's disease. In all of them tumor response to chemotherapy was noticed at the time muscle cramps developed and none had evidence of meningeal lymphomatous spread. The drug combinations given to these patients were (8): CHOP (patients 1, 7 and 9), ProMACE/MOPP (patients 6, 8 and 10), MOPP (patients 5 and 13), C-MOPP (patients 3 and 4), CVP (patients 11 and 12), COP-BLAM (patient 2), and MOPP/ABV (patient 14). Procarbazine and vinblastine, drugs with potential toxicity to the peripheral nervous system (1) were, therefore, given concomitantly with vincristine to 9 patients. The schedules of vincristine, procarbazine and vinblastine used in these combinations are shown in Table 2. Other etiological causes that may play a role in peripheral nerve abnormalities, were noticed in 6 patients and included controlled diabetes (patient No. 8), controlled hypothyroidism (No. 6), and prior therapy with Vinca alkaloids (patients 5, 11, 12 and 13). Only symptoms that developed after the onset of chemotherapy were taken into consideration, and their appearance could therefore be attributed to drug-induced neuropathy.

Table 2

Schedules of drugs with potential toxicity to the peripheral nervous system given in the various combinations

Type of combination	Projected dose (mg/m²) in each cycle			Interval between cycles (days)
	Vincristine*	Procarbazine	Vinblastine	
CHOP	1.4, i.v., day 1	—	—	21
ProMACE/MOPP	1.4, i.v., day 8	100, p.o., days 8–14	—	28
MOPP	1.4, i.v., days 1, 8	100, p.o., days 1–14	—	28
C-MOPP	1.4, i.v., days 1, 8	100, p.o., days 1–14	—	28
CVP	1.4, i.v., day 1	—	—	21
COP-BLAM	1, i.v., day 1	100, p.o., days 1–10	—	21
MOPP/ABV	1.4., i.v., day 1	100, p.o., days 1–7	6, i.v., day 8	28

*Maximal dose was limited to 2 mg in all patients except Nos. 9 and 13.

The features of muscle cramps are presented in Table 1. Cramps were noticed between 3 days and 4 months (median 2 months) after vincristine was started, usually after the patients had received several courses of vincristine. In 2 patients (Nos. 5 and 12), cramps were noticed after a single dose of vincristine. Both of them had prior therapy with vincristine. Cumulative vincristine dose prior to the onset of cramps ranged between 1 and 9.4 mg/m² (median 3.1 mg/m²). The cumulative dose of procarbazine that had been administered prior to the appearance of cramps (patients Nos. 2, 3, 4, 5, 6, 8, 10, 13 and 14) ranged between 700 and 5 600 mg/m² (median 1 200 mg/m²) and that of vinblastine (No. 14) was 12 mg/m².

Cramps affected the lower extremities in 4, the upper extremities in 3 and both the upper and lower extremities in 7 patients. In 2 cases the trunk was also involved. Cramps of the lower extremities affected the feet in 10 patients, the calf muscles in 5 and the thigh muscles in one patient. Cramps of the upper extremities mainly affected the flexors of the fingers.

All of the 14 patients experienced daytime cramps, which were usually described as posture or movement-induced. Four patients also reported nocturnal cramps of the lower extremities which awoke them from sleep. Cramps were described as lasting between a few seconds and more than 5 min. The maximal frequency of cramps before their resolution also ranged widely from twice a week to numerous episodes per day (Table 1). The severity of cramps tended to be mild to moderate and only 3 patients (Nos. 1, 5 and 12) described their symptoms as severe. Duration of cramps ranged from 1 to > 9 months (median >5 months).

Chemotherapy was discontinued after the onset of cramps in two patients (6 and 13). In the remaining patients chemotherapy, including all drugs, was continued for 0.5–5.5 months (median 3 months) after the appearance of cramps. All patients were followed after discontinuation of vincristine. The follow-up period ranged from 2–11 months (median 7 months) after withdrawal of vincristine. Cramps resolved before discontinuation of vincristine in 2 patients (Nos. 3 and 4), and gradually resolved in the remaining 12 patients for 0.5–>8.5 months (median > 3 months) after vincristine was stopped. In one of these patients (No. 6) cramps were first noticed 2 weeks after the last dose of vincristine.

Serum magnesium and muscle enzymes were within the normal range in all cases.

Both objective findings and symptoms (other than muscle cramps) were recorded in all the patients during the course of peripheral neuropathy. Complaints included paresthesias in 13 patients (all except No. 11), gait difficulties in three (Nos. 4, 6 and 13), clumsiness of the hands in one (No. 4), muscle pain in two (Nos. 11 and 12), constipation in four (Nos. 5, 6, 11 and 13), and bladder atony in one patient (No. 6).

The detailed neurological evaluation was performed between a few days and 4 months (median 1 month) after the start of cramps. All patients had depression or loss of Achilles reflex and 9 were areflexic. Other sensory objective findings included impaired vibration sensation in the malleoli in seven patients (Nos. 1, 2, 3, 8, 9, 11 and 13), and impaired pinprick sensation in the feet in three (Nos. 1, 4 and 9). Objective signs of motor weakness were found in three patients (Nos. 4, 6 and 13). All of these three had weakness of the dorsiflexors of the toes and feet and patient 4 also developed weakness of the proximal flexors of the lower limbs and the extensors of the fingers and wrists. One patient (No. 6) developed orthostatic hypotension and was unable to walk or stand unassisted, probably due to both motor and autonomic neuropathy.

Muscle cramps were the first symptom of neuropathy in 4 cases and preceded paresthesias by 0.5, 2.0, 2.0 and 4.0 months in patients 2, 5, 7 and 12 respectively. In two patients (Nos. 6 and 10) it was documented that the appearance of cramps and paresthesias was simultaneous. Cramps were preceded by other symptoms of neuropathy in 8 patients. In 7 patients (Nos. 1, 3, 4, 8, 9, 13 and 14) paresthesias appeared between 2 and 4 weeks earlier than

cramps and in one patient (No. 11) constipation preceded cramps by 3.5 months. Symptoms of motor weakness appeared simultaneously with cramps in one case (patient 6) and their appearance lagged by 3.5 months and 1 month after the appearance of cramps in patients 4 and 13 respectively.

After withdrawal of vincristine all patients reported rapid improvement (within 2–6 weeks) in paresthesias. Mild paresthesias, however, persisted for 1–>8.5 months (median > 4 months) after discontinuation of vincristine. Cramps resolved before paresthesias in 6 patients (Nos. 2, 3, 4, 7, 8 and 10), continued after the disappearance of paresthesias in one patient (No. 5) and resolved simultaneously with paresthesias in one patient (No. 6). In 5 patients (Nos. 1, 9, 12, 13 and 14) both cramps and paresthesias persisted at the time of the last follow-up.

The symptoms related to motor weakness and to orthostatic hypotension (patients 4, 6 and 13) considerably improved 6 weeks after vincristine had been withdrawn.

Discussion

The complaint of muscle cramps is common in cancer patients and could be caused by both the underlying disease and its treatment (7). To the best of our knowledge, the characteristics of muscle cramps and the relationship between this symptomatology and the course of neuropathy in vincristine-treated patients have not been described in the English literature. Such information is important in view of the fact that neuropathy is the dose-limiting toxicity of vincristine.

Our patients developed new complaints of muscle cramps which were associated with typical manifestations of vincristine neuropathy and which tended to gradually resolve after withdrawal of vincristine. Laboratory investigation failed to detect non-neurological causes of cramps such as hypomagnesemia and primary muscle disease. Therefore, muscle cramps in these patients were most probably vincristine-related, although an additional role of the other cytotoxic drugs such as vinblastine and procarbazine cannot be ruled out.

Muscle cramps were detected in 14 out of 74 (19%) lymphoma patients treated with vincristine-containing combinations during the study period. It should be emphasized that our vincristine-treated patients were not routinely asked about muscle cramps. Therefore, the real incidence of this complication among this patient population is probably higher than that observed in the current study.

In contrast to the cramps observed in otherwise healthy individuals (benign cramps) and which tend to occur at night and involve the lower extremities (6, 9), the cramps in the present group of patients with vincristine neuropathy were predominantly posture or movement-induced, occurring at daytime, and frequently involved the upper extermities. All the patients experienced daytime cramps compared to only 4 out of 14 (29%) who reported nocturnal cramps, and the frequency of involvement of the upper extremities (10/14) was similar to that of the lower extremities (11/14).

Cisplatin is another commonly used antineoplastic agent which is toxic to the peripheral nervous system (1). The occurrence of muscle cramps in cisplatin-induced neuropathy has been recently reported (10). In comparison to the present group of patients, cramps in a group of 14 patients with cisplatin neuropathy occurred more frequently at night (9 had nocturnal and 10 had daytime cramps) and more frequently involved the lower extremities (the lower extremities were involved in 13 and the upper extremities in 6) (10).

The onset of muscle cramps in our patients was usually noted during a relatively early phase of neuropathy and in four patients cramps were the first symptom of neuropathy. Since muscle cramps are a manifestation of motor neuropathy, it is important to note that only one patient had symptoms of motor weakness at the time cramps were first noticed.

Furthermore, vincristine was continued after the onset of cramps in 12 patients, and only 2 out of these 12 later developed symptoms of motor weakness.

In this regard, it is worthy to mention the study of Bradley et al. (3) showing electromyographic signs of denervation after 2 months' therapy with vincristine and before muscle wasting became apparent. Our clinical observation that muscle cramps occur at an early stage of motor neuropathy is, therefore, in accordance with the findings of early electromyographic abnormalities.

The course of neuropathy in our patients was not prospectively compared to that of a control group of vincristine-treated patients without muscle cramps. Nevertheless, the symptoms and signs observed in our patients were typical for vincristine neurotoxicity and the appearance of muscle cramps was not associated with a rapidly progressing course of neuropathy. Although symptoms of neuropathy tended to persist for several months, a rapid symptomatic improvement was noticed after withdrawal of vincristine. Thus, the course of neuropathy in the present series was similar to that reported in the literature (1). In comparing the clinical significance of muscle cramps in vincristine neurotoxicity to that found in cisplatin neuropathy (10) it is interesting to note that in cisplatin-treated patients, the symptomatology of cramps was usually associated with a relatively advanced symptomatic stage and with a deteriorating course of the peripheral neuropathy.

We conclude that the symptomatology of muscle cramps in vincristine-treated patients is not necessarily associated with severe neuropathy and should not automatically indicate interruption of therapy. However, careful neurological evaluation is recommended in these patients. In cases with

severe cramps, modification of vincristine dose and/or treatment with drugs such as phenytoin or quinine should be considered.

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