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CLINICAL COMMUNICATION TO THE EDITOR

Caffeine and Muscle Cramps: A Stimulating Connection

To the Editor:

Muscle cramps are a common medical problem with an estimated 1-year incidence of 36% in the general adult population.[1] As an ingredient of coffee, tea, chocolate, and other dietary products, caffeine is the world's most widely consumed drug. In vitro, caffeine has a well-established stimulant activity and is able to induce muscle contraction.[2] Caffeine's muscle-stimulant effect in humans, although ill understood biochemically, is illustrated by prohibition of its use at the Olympics until 2004. To date, no study of the possible relationship between caffeine and muscle cramps in healthy humans is available. The case reported below suggests that caffeine can increase susceptibility to muscle cramps.

A 54-year-old man complained of muscle cramps in calves and feet, occurring on average every other night. Due to recurrent shoulder pain, he used the analgetic Finimal (Roche Consumer Health, Woerden, the Netherlands) (500 mg paracetamol/50 mg caffeine) 6-7 times a day. No other medication was used. His concomitant dietary caffeine intake averaged 4 cups of coffee and 2 cups of tea (amounting to approximately 600 mg caffeine).[3] He smoked 10 cigarettes daily. Other predisposing factors for muscle cramps were excluded by needle biopsy (muscle histochemistry and electron microscopy assessing presence of tubular aggregates).[4] Considering the stimulant neuromuscular effects of caffeine, we advised the patient to switch to a paracetamol-only compound.[2] Upon this medication change, his muscle cramps disappeared.

To confirm the causal relationship between caffeine intake and muscle cramps, we designed a $n = 1$, double-blind trial. Upon informed consent, the patient received 2 capsules containing 500 mg paracetamol 3 times a day at regular intervals during 1 week; and 2 capsules containing 500 mg paracetamol/50 mg caffeine 3 times a day at regular intervals during the other week. In addition, he received the paracetamol-only compound in the prescribed dose in the weeks before, between, and after the 2 research weeks, amounting to a 5-week trial. During this period, daily dietary caffeine intake was fixed. Intake of medication was verified using vials with caps containing microprocessors that record date and time of vial opening. Intake of medication and dietary caffeine as well as frequency and intensity of muscle cramps, were registered daily. On the 7th day of each week, before first daily capsules and dietary caffeine intake, we measured serum trough concentrations of caffeine with a validated high performance liquid chromatographic method.

At unblinding, the patient appeared to have suffered 3 episodes of muscle cramps during the week he received the paracetamol/caffeine compound, amounting to 300 mg extra caffeine (Table). No cramps were reported during the other weeks. Accordingly, serum caffeine concentration was highest in this particular week (4.99 mg/L) compared with other weeks (0.9-2.7 mg/L). The results of this clinical trial endorse the hypothesis that caffeine can increase susceptibility to muscle cramps in humans.

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Table Trial Results (n = 1)

	Paracetamol-only compound (500 mg)	Paracetamol/caffeine (500 mg/50 mg)	Estimated total caffeine intake (mg/day)	Frequency of muscle cramps (episodes/week)	Serum caffeine concentration (mg/L)
Prior to first research week	X		600	0	2.7
Research week 1	X		600	0	1.7
In between research week	X		600	0	0.9
Research week 2		X	900	3	5.0
After 2nd research week	X		600	0	2.4

Although the exact pathophysiological mechanism of muscle cramping is still subject to debate, potentiation of muscle contraction via induction of sarcoplasmic reticulum calcium release is well established.[2,5] However, in vivo caffeine concentrations are generally considered too low to elicit muscle contraction in this way. Another explanation may be that caffeine causes blockade of the adenosine receptor and subsequent loss of inhibition of neurotransmitter release.[2,6] Finally, it seems unlikely that the muscle cramps were a concentration-related adverse reaction to caffeine, because the caffeine serum levels in this patient remained below concentrations of 50-60 mg/L, which have been associated with serious toxicity.[7]

We hypothesize that caffeine may act in synergy with other metabolites, electrolytes, neuronal excitation and inhibition patterns as well as genetic factors to lower an overall threshold for inducing muscle cramps, where none of these factors per se may suffice.[2] The epidemiological magnitude of both caffeine consumption and muscle cramps may stimulate further study. Until then, the potential influence of dietary and medicinal caffeine intake should be considered in the workup of muscle cramps.

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