

Diltiazem for nocturnal leg cramps

SIR—In the prevention of nocturnal leg cramps, quinine sulphate is the most frequently used drug; it has a modest effect [1, 2] but, because of toxicity associated with its use, an alternative is needed. Verapamil can relieve the leg cramps resistant to quinine [3]. Having properties of neuromuscular transmission inhibition [4] and calcium channel blockade in the sarcolemma [5–7], diltiazem hydrochloride may be worthy of investigation.

We have carried out a double-blind, randomized, placebo-controlled, crossover trial on 13 patients (11 women; aged 64 ± 10 years) with typical leg cramps two or more times per week. Subjects with clinically important electrolyte disorders, second- or third-degree atrioventricular block, sick sinus syndrome and uncontrolled congestive cardiac failure were excluded. We prohibited concomitant use of quinine sulphate, vitamins E and B complex and calcium-channel blockers.

This trial had four phases of observation, each lasting 2 weeks. Patients took a tablet containing 30 mg of diltiazem hydrochloride or a placebo tablet before going to bed. Placebo treatment was given during the run-in period (phase 1) and during the washout period (phase 3). We used a random numbers table to randomize the patients and neither the patients nor the investigators

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(except the assistant) knew to which subgroup the patients were randomized. Patients assigned an even number took placebo during the second phase and diltiazem hydrochloride during the fourth phase, whereas those assigned an odd number took diltiazem hydrochloride during the second phase and placebo during the fourth phase. A nightly diary was kept to record each leg cramp and an estimate of its intensity from their own experience with a scale of one (low) to three (high).

The subjects tolerated diltiazem hydrochloride well and none reported side effects. As one patient took felodipine from another doctor to control her very high blood pressure, only 12 patients were included in the final analyses. There was no significant randomization group difference in the frequency [95% confidence interval (CI), -16.96 to 4.96 cramps per phase; $P=0.250$] and intensity (95% CI, -0.709 to 0.142; $P=0.166$) of leg cramps. There was also no carryover effect on the frequency (95% CI, -14.85 to 9.52 cramps per phase; $P=0.636$) and intensity (95% CI, -2.57 to 1.01; $P=0.352$) of leg cramps. Moreover, as for the frequency and intensity of leg cramps, there was neither significant period effect between phases 2 and 4 (95% CI, -4.51 to 4.51 cramps per phase; $P=1.000$ and 95% CI, -0.42 to 0.77; $P=0.551$, respectively) nor significant sequence effect (95% CI, -5.80 to 3.13 cramps per phase; $P=0.542$ and 95% CI, -0.97 to 0.19; $P=0.175$, respectively). The combined data of phases 2 and 4 showed a statistically significant difference (95% CI, -5.84 to -0.16 cramps per phase; $P=0.040$) in the frequency of leg cramps between those on diltiazem hydrochloride and those on placebo. There was no significant difference (95% CI, -0.30 to 0.11; $P=0.347$) in the intensity of leg cramps between those on diltiazem hydrochloride and those on placebo.

The mechanisms of leg cramps are unknown. It is interesting that nifedipine [8] may induce but verapamil [3] and diltiazem may relieve leg cramps. Diltiazem and verapamil (but not nifedipine) can block neuromuscular transmission via inhibition of neurotransmitter release [4]. Nifedipine, diltiazem and verapamil can block the L-type calcium channels in the sarcolemma [5, 6] and interfere with entry of calcium ions into the sarcoplasm via the T tubules, and with calcium-induced calcium release from the sarcoplasmic reticulum. Nifedipine may induce stronger reflex adrenergic stimulation than diltiazem and verapamil [9]. It will then enhance the entry of calcium ions through the dihydropyridine-insensitive T-type calcium channels [7] and thus nullify its net effect on calcium-channel blockade. Such differences either alone or in combination may explain the heterogeneous effects of calcium-channel blockers on nocturnal leg cramps.

In conclusion, this small study suggests that diltiazem is effective and safe in the prevention of nocturnal leg cramps.

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