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Naftidrofuryl treatment for rest cramp

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Summary: A double-blind placebo-controlled study was carried out in 14 subjects to investigate the effect of naftidrofuryl in the treatment of rest cramp. Naftidrofuryl caused a significant reduction in cramp frequency (median naftidrofuryl = 5; median placebo = 17; $P < 0.004$) and a significant 34% increase in cramp free days (median naftidrofuryl = 22; median placebo = 14; $P < 0.004$). Naftidrofuryl is an effective alternative to quinine in the treatment of this painful condition.

Introduction

Rest cramp (sometimes called night cramp) is a common, poorly understood condition characterized by predominantly night-time cramp episodes generally affecting the foot or calf muscles. A tentative model proposed neuromuscular and vascular age-related changes and haemodynamic consequences of sleep as possible inter-related causative factors for muscle ischaemia and neuromuscular instability.[1] Naftidrofuryl has a range of incompletely understood actions resulting in improved cellular oxidative metabolism. Its effects on cerebrovascular and peripheral vascular diseases have been well studied but its possible role in the treatment of rest cramps has not been investigated.

Method

Patients with more than two episodes of cramp per week were recruited. Exclusion criteria comprised: an unstable medical condition, exercise cramps or claudication, receiving a drug known to be associated with cramps,[1] evidence for cardiac, renal, hepatic or neurological disease and plasma electrolyte abnormalities. The study was approved by the local ethics committee and patients gave written informed consent.

The trial used a placebo-controlled double-blind crossover design with a 2 week run-in on placebo, randomized allocation to 4 weeks active or placebo tablets, 2 weeks washout and crossover to 4 weeks of the alternative treatment. The active treatment was one naftidrofuryl slow-release tablet containing the equivalent of 300 mg of naftidrofuryl oxalate twice daily (morning and evening). This formulation was chosen because it provides peak blood levels 4–6 hours post dose (internal report, Lipha Pharmaceuticals) which coincides with the highest incidence of rest cramps between 1 a.m. and 6 a.m.[2] Cramp episodes (number, duration and severity) were recorded by means of a self-completed diary card and compliance was checked by tablet counting. The 2 week placebo run-in was used to ensure a cramp frequency of more than two episodes per week, ability to self-complete the cramp diary card and tablet compliance.

The results are expressed as the number of cramp episodes recorded and the number of cramp-free days for each of the two 4 week treatment periods. The frequency distributions were negatively skewed and therefore median values have been reported with the Wilcoxon matched pairs signed rank test to compare the treatment and placebo medians. Period and carry-over effects were assessed using *t*-tests according to the method of Pocock.[3]

Results

Fourteen patients (three men, 11 women; median age 61, range 39–71 years) participated in the trial. Rest cramp had been present for more than 10 years in 11 patients (range 3–40 years), predominantly affected lower limbs only (eight patients) or both lower and upper limbs (six patients) and mostly occurred at night (12 patients). Self-rating of cramp severity showed that four patients judged their cramps a 'considerable nuisance' and ten patients found them 'very distressing'. Treatment with naftidrofuryl was associated with complete disappearance of cramp episodes in three patients, reduced cramp frequency in eight, caused no change in two and was associated with an increased cramp frequency in one.

The median monthly cramp episodes per patient

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(Figure 1) was significantly reduced by naftidrofuryl (median placebo = 17.0 (range 5–32); median naftidrofuryl 5.0 (range 0–32); $P = 0.004$). The number of cramp-free days per month (Figure 2) was significantly increased (median placebo = 14.0 (range 3–23); median naftidrofuryl = 22.0 (range 8–28); $P = 0.004$). There were no significant period or carry-over effects (Tables I and II). Five patients on placebo experienced minor adverse effects (mild gastrointestinal upset (3), itching (2) and five patients receiving naftidrofuryl reported mild gastrointestinal upset.

Discussion

Several drugs have been proposed as treatment for rest cramps but quinine has been the best studied

Table I Difference in number of cramps and cramp-free days between placebo and naftidrofuryl treatments in 14 patients

	No. of cramps			*Cramp-free days*		
Order of treatment	*Period 1*	*Period 2*	*Difference**	*Period 1*	*Period 2*	*Difference**
Naftidrofuryl/placebo	5	5	0	24	23	−1
	5	11	6	24	22	−2
	23	17	−6	13	16	3
	11	20	9	20	14	−6
	3	13	10	25	23	−2
	0	18	18	28	10	−18
	19	30	11	9	3	−6
	5	20	15	17	14	−3
Placebo/naftidrofuryl	23	14	9	10	16	−6
	17	5	12	13	24	−11
	14	10	4	13	14	−1
	15	0	15	16	28	−12
	32	32	0	7	8	−1
	9	0	9	22	28	−6

*Cramps or cramp-free days on placebo treatment minus those on naftidrofuryl.

Table II The carry-over and period effects for the mean cramp episodes and mean cramp-free days shown by a comparison between naftidrofuryl given in period 1 and naftidrofuryl given in period 2. Standard deviation shown in brackets

	Mean cramp episodes		*Mean cramp-free days*	
	Period 1 Naftidrofuryl	*Period 2 Naftidrofuryl*	*Period 1 Naftidrofuryl*	*Period 2 Naftidrofuryl*
Carry-over effect	12.8 (6.7)	14.25 (9.9)	−16.9 (6.1)	−16.4 (6.6)
Period effect	5.5 (5.6)	8.2 (5.4)	−5.1 (5.5)	−5.8 (4.3)

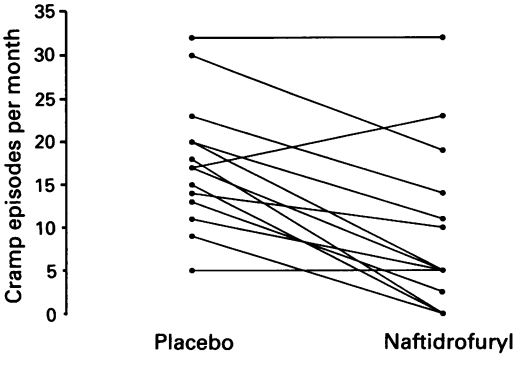

Figure 1 Cramp episodes reported during placebo and naftidrofuryl treatment.

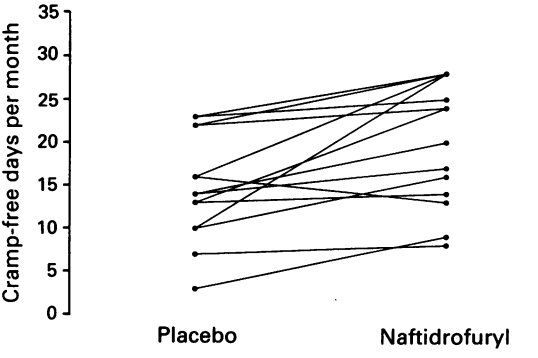

Figure 2 Cramp-free days during placebo and naftidrofuryl treatment.

and is the currently recommended treatment.[4] Although it is of proven value in cramps associated with haemodialysis,[5] evidence for its effectiveness in rest cramp is conflicting. Early open studies suggested a therapeutic potential[6,7] but later more detailed evaluation using randomized placebo-controlled studies indicated a significant reduction in cramp frequency,[8] no effect,[9] or a possible benefit limited to severe sufferers only.[2] Quinine is well tolerated in the doses used for cramp treatment but is a highly toxic compound in overdose causing cardiac arrhythmias and blindness and because of this it has been suggested that a safer alternative should be identified.[10] Several other drugs have been proposed including diazepam, dantrolene, phenytoin and procainamide. However, there is no evidence that these agents are effective. A recent open study of eight elderly patients has suggested that verapamil may be beneficial.[11]

This study has shown that naftidrofuryl is an effective treatment for rest cramp. It significantly reduces the frequency of cramp episodes and increases the frequency of cramp-free days. Naftidrofuryl is a safe drug with a low incidence of adverse effects the most common of which is epigastric discomfort and nausea.[12]

The mode of action of naftidrofuryl in rest cramp is speculative, partly because the pathology of the condition awaits clarification. A recent review which drew together the disparate abnormalities described in rest cramp produced a tentative unifying model for the condition.[1] It was proposed that the uncontrolled tetanic muscle activity resulting clinically in an episode of cramp could be caused by an interaction between impaired neuromuscular control due to neuropathological and neurophysiological changes of ageing; disturbed limb blood flow, again due to age-related changes; and the haemodynamic consequences of sleep (decreased blood pressure and cardiac output and hence the clinical observation that most episodes of rest cramp occur at night). The effects of naftidrofuryl have been attributed to its action on cellular metabolism and regional blood flow.[13] Either of these effects could be beneficial in rest cramp according to the model described above.

Rest cramp is a common, distressing and painful condition whose management is currently unsatisfactory. Naftidrofuryl should be considered as a safe and effective treatment for amelioration of the condition.

Acknowledgement

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