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Clonidine in the treatment of vibration-induced white fingers

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PYYKKÖ I, FÄRKKILÄ M. Clonidine in the treatment of vibration-induced white fingers. *Scand j work environ health* 8 (1982) 294-299. The effect of clonidine, a centrally acting drug diminishing the sympathetic activity of peripheral nerves, was examined in a double-blind study of 60 forest workers with vibration-induced white fingers. Clonidine was administered in daily doses of 0.450 mg or 0.100 mg during 30 d. The results were evaluated from a self-administered questionnaire. No significant differences were discerned between the active and placebo groups in respect to either recovery time after an attack or frequency of attacks. Neither did the subjective evaluation of the overall effectiveness of the drug show any differences between the groups. In two subjects clonidine provoked Raynaud's phenomenon, which subsided after the cessation of treatment. The recording of finger pulse plethysmography for two subjects treated with 0.450 mg of clonidine daily revealed comparatively well preserved vascular reflexes, whereas sympathetic mass reflexes such as galvanic skin response were almost absent.

Key terms: clonidine treatment, double-blind, Raynaud's phenomenon, vibration.

Clonidine hydrochloride is a derivative of imidazoline, which is chemically related to tolazoline (6). The drug has both a direct peripheral alpha-adrenoreceptor-stimulating action and a central action probably due to the stimulation of the alpha-adrenergic neurons in the nucleus tractus solitarius (5, 19).

Clonidine has diverse effects on the central nervous system. All of these effects are due to the activation of alpha₂-adrenoreceptors. They include, among others, drowsiness, suppression of spontaneous motor activity, and a decrease in the sensitivity of the thermoregulatory center to environmental temperature changes. Concomitantly an increase occurs in the activity of the parasympathetic nervous system (11, 12). A marked reduction in the discharge of peripheral preganglionic and postganglionic sympathetic nerves has been recorded (10).

Prolonged exposure to the vibration of handheld tools causes disturbances in finger circulation, so-called vibration-induced white fingers (VWF) (20). The vascular symptoms of the vibration syndrome resemble the spontaneous vasoconstrictive disease first described by Raynaud (1, 4). This type of paroxysmal ischemia is provoked by cold. The digits of the hands become white and pale for 5 to 10 min (15). In Finland the symptoms are often caused by chain saws (17).

In Raynaud's phenomenon the elevated output of the sympathetic nervous system has been generally regarded as a primary factor causing the poor regulation of the digital vessels. Subjects with vibration-induced white fingers seem to react to different sympathetic stimuli with stronger vasoconstriction than referents (8, 13, 16). It has been proposed that vibration-induced white fingers occur because of an ailment of the center controlling vasomotor tone (9) or because of an increased sensitivity of the vessel wall receptors to adrenergic stimuli. In the former case the central nervous system expulses sympathetic reflexes that are too strong, and in the latter case the vessel walls react too strongly to a normal amount of sympathetic nerve output.

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Very few investigations have been carried out on the effect of drugs on Raynaud's phenomenon (4). These reports indicate that the blockage of the output of alpha-adrenergic nerves might improve the symptoms of Raynaud's phenomenon. Unfortunately the studies were not carried out with a double-blind design. The present investigation was undertaken to examine whether clonidine would have a beneficial effect on symptoms of vibration-induced white fingers.

Material and methods

The study was carried out in the winter because the symptoms mainly occur in the cold season. Sixty professional forest workers who operated chain saws were selected from a larger, previously documented group (15, 17). All of them had a typical history of Raynaud's phenomenon. The subjects were classified into three groups according to the severity of symptoms based on the so-called VWF index (15). Each group consisted of 20 subjects, and from each group pairs with the same degree of severity were selected. The mean and range of their ages are shown in table 1.

Before the beginning of the trial the subjects were given a questionnaire on symptoms to be filled out during the trial.

Two subjects with especially severe symptoms were additionally examined with physiological tests as earlier described (16, 17).

Clonidine (Catapresan®, Boehringer Ingelheim) in two doses, 0.450 mg (divided into three daily doses) and 0.100 mg (divided into four daily doses), and a placebo (divided partly into three, partly into four doses) were administered during a period of 30 d. The groups were randomized, and the medication was given in a double-blind design.

During the trial the frequency of attacks and the recovery time were recorded for every subject. The evaluation of the results was based on a previous analysis of the factors best describing the handicap caused by vibration-induced white fingers (15). In addition an overall evaluation of the effect of the drug on vibration-induced white fingers during the trial period was included. If the questionnaire was incompletely filled out or medication was prematurely discontinued for reasons not linked to the syndrome, the subject was omitted from the study. After the results were classified, the code was opened.

For the statistical calculations the chi-square test was used. The probability level of <0.05 was regarded as statistically significant.

Table 1. Effect of clonidine treatment on subjects with vibration-induced white fingers (VWF).

Classification of the effect of therapy	Recovery time from an attack of VWF (Number of responses)	Frequency of attacks of VWF (Number of responses)	Subjective evaluation of the overall effect of therapy (Number of responses)
<i>Fourteen subjects taking 0.450 mg of clonidine daily (age: mean 42.5 a, range 27–53 a)</i>			
No symptoms	3	3	3
Relieved	2	5	3
Same	9	5	8
Worse	0	1	0
<i>Sixteen subjects taking a placebo (age: mean 40.0 a, range 25–51 a)</i>			
No symptoms	2	2	2
Relieved	3	5	6
Same	11	8	8
Worse	0	1	0
<i>Thirteen subjects taking 0.100 mg of clonidine daily (age: mean 38.5 a, range 24–51 a)</i>			
No symptoms	1	1	1
Relieved	1	5	8
Same	9	5	2
Worse	2	2	2 ^a

^a Provoked Raynaud's phenomenon.

Results

The evaluation of the effect of the treatment is shown in table 1. Because of dropouts the final number of subjects was 14 for the group receiving 0.450 mg of clonidine daily, 13 for the group receiving 0.100 mg of clonidine daily, and 16 for the placebo group. As shown in table 1, some subjects in all groups were asymptomatic during the trial period.

No statistically significant differences between the active and placebo groups could be observed for any of the parameters measured (table 2).

For two subjects the symptoms became worse during the treatment. Both of the subjects received 0.100 mg of clonidine as a daily dose. Their hands became extremely sensitive to cold, and Raynaud's phenomenon appeared even at room temperature. This symptom occurred on the second and third day after the beginning of treatment. After cessation of the treatment the symptoms subsided within 36 h for both of the subjects.

No withdrawal effect was observed. Neither were any signs of orthostatic hypotony reported. Side effects like a dry mouth or drowsiness occurred equally as often in the active as in the control groups. One lumberjack, excluded from further evaluation of the results, stopped taking the medication because he felt too drowsy and was under great pressure at work.

In order to determine the ability of clonidine to inhibit sympathetic responses, the galvanic skin response, finger pulse plethysmography, and the tonic vibration reflex were measured in two of the forest workers. The tests were carried out before and during the treatment. Fig 1

shows the vasomotor, sudomotor, and muscle response to various stimuli before medication. Fig 2 shows the responses of the same subject during the treatment with clonidine (0.450 mg daily). It is noteworthy that the activity of the sudomotor nerves, measured as galvanic skin response, was almost totally absent, though the vascular responses in the finger pulse plethysmography were rather well preserved. The tonic vibration reflexes of the muscle were not affected at all.

Discussion

In the present survey we were not able to show that clonidine would decrease the frequency of or shorten the recovery from an attack of vibration-induced white fingers. Besides, in the overall evaluation of the effectiveness of the drug on this syndrome, no differences could be discerned between the subjects treated with clonidine and those treated with the placebo. Noteworthy was that two subjects with a daily dose of 0.100 mg of clonidine reacted to treatment with strong vasoconstriction, and even a slight cold stimulus could provoke Raynaud's phenomenon in them.

It is evident that treating vibration-induced white fingers with a centrally acting drug (like clonidine) causing a reduced discharge to the peripheral sympathetic nerves is not beneficial. The lack of response may be due to different factors. According to the present results the inhibitory effect of clonidine on the galvanic skin response was marked, whereas its effect on vascular reflexes was weaker. Thus clonidine seems to inhibit generalized reflexes better than specific sympa-

Table 2. Statistical significance of the effectiveness of the treatment.

	Recovery time ^a		Frequency of attacks ^a		Subjective evaluation ^a	
	χ^2	Degrees of freedom	χ^2	Degrees of freedom	χ^2	Degrees of freedom
0.450 mg of clonidine vs placebo	0.47	2	0.76	3	1.07	2
0.100 mg of clonidine vs placebo	3.26	3	1.06	3	5.97	3

^a None of the values are significant.

thetic reflexes, a result which has earlier been reported by Zaimis (22). Clonidine reduces the discharge of peripheral sympathetic nerves, especially in the splanchnic area, but the effect becomes weaker in cardiac nerve fibers and is the weakest in the cervical sympathetic nerves (19). This variety of responses may be attributed to the organization of the sympathetic nervous system, which is capable of expelling both general and localized reflexes (7). For instance, in the case of conditioned reflexes, specific organization occurs in the spinal cord and sympathetic ganglia (18). Thus the highly organized outflow of the sympathetic impulses, together with the

different synaptic mechanisms, may explain the weak inhibitory action of clonidine on the responses recorded during finger pulse plethysmography. This outflow might also be the reason for the poor effect of clonidine on the symptoms of vibration-induced white fingers.

The adverse effects of clonidine were negligible in all but two subjects, in whom clonidine, at a daily dose of 0.100 mg, provoked Raynaud's phenomenon. An adverse effect of this kind has been reported earlier for two subjects with elevated blood pressure (22). In one subject the reaction was connected with skin rash, arthralgia, and bulla formation resembling

Fig 1. Vasospasm in a forest worker with white fingers caused by simultaneous body cooling, vibration of the hand, and loud noise. The potentiating action of these different stimuli led to the disappearance of the pulsewave recorded by an air-filled piezoelectric finger plethysmograph. The activity of the sudomotor nerves is recorded as the galvanic skin response (GSR). The GSR shows moderate responses to various stimuli. Vibration is also followed by activation of the tonic vibration reflex.

Fig 2. A recording from the same subject as in fig 1 after one month's medication with clonidine. The vasomotor responses to vibration and noise have become weaker, but the extent of the vasomotor response to the cold towel test is the same. Galvanic skin response is reduced to an almost negligible level. The tonic vibration reflex is unchanged.

an allergic manifestation (21). Neither of the men with clonidine-induced Raynaud's phenomenon in this study exhibited hypertension or any symptoms which could be related to drug allergy.

The extreme tendency towards vasospasms may be attributed to the direct alpha-adrenoreceptor stimulating action of clonidine on the digital vessels. In fact, during the intravenous administration of clonidine, significant vasoconstriction occurs (22). The flow of the skin vessels may be temporarily reduced 50–60 % (14). The vasoconstriction subsides within a few minutes and is followed by dilatation (22). In this study the vasoconstrictions of the two forest workers increased gradually at the beginning of the treatment. It is possible that the receptors of the smooth muscle of the vessel wall were more sensitive to alpha-adrenergic stimuli than normally, and hence the theory of Azuma et al (2, 3) is supported, ie, that the reason for vibration-induced white fingers is exaggerated responses of alpha-receptors to the normal outflow of the sympathetic nervous system.

Conclusions

The findings of the present study indicate that clonidine, despite strong centrally mediated diminution of sympathetic nervous activity, is not effective in the prevention of the vascular spasms occurring with vibration-induced white fingers and may even cause Raynaud's phenomenon.

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