

Source of pain and primitive dysfunction in migraine: an identical site?

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SUMMARY Twenty common migraine patients received a one sided frontotemporal application of nitroglycerin (10 patients) or placebo ointment (10 patients) in a double blind study. Early onset migraine attacks were induced by nitroglycerin in seven out of 10 patients versus no patient in the placebo group. Subsequently 20 migraine patients, who developed an early onset attack with frontotemporal nitroglycerin, received the drug in a second induction test at other body areas. No early onset migraine was observed. Thus the migraine-inducing effect of nitroglycerin seems to depend on direct stimulation of the habitual site of pain, suggesting that the frontotemporal region is of crucial importance in the development of a migraine crisis. This is not consistent with a CNS origin of migraine attack.

Headache is a well known side effect of nitrates which are present in some foods and pharmaceutical preparations. Nitroglycerin or isosorbide dinitrate is commonly administered by the sublingual route to migraine patients as a simple method of inducing a migraine attack.^{1,2} They generally produce a typical throbbing headache, with nausea and photophobia, indistinguishable from a spontaneous migraine crisis. In such cases headache often begins many hours after the drug is administered³ and thus cannot be caused by nitrate induced vasodilatation, in view of nitroglycerin's extremely short half-life and the relatively brief effectiveness of the isosorbide dinitrate metabolites.^{4,5} In the first few minutes after sublingual administration, however, patients often complain of short lasting and sometimes painful pulsations which spontaneously disappear within about half an hour.

Pharmacokinetic studies of nitroglycerin in humans have demonstrated an arteriovenous gradient during intravenous infusion of the drug, due to an avid uptake by venous blood vessels.⁶ Moreover, studies on transdermal nitroglycerin systems have shown marked differences in nitroglycerin plasma concentrations according to the site of blood collection; the concentration is higher in plasma obtained near the administration site than in other body areas.⁷ This

implies that the site of nitroglycerin application greatly influences the drug's bioavailability.

The aims of our study were to show that: 1) nitroglycerin ointment applied to a typical migraine site is able to induce an early onset attack and that 2) the induced migraine attack is triggered from the stimulation of the typical migraine site.

Nitroglycerin ointment applied to the head at the frontotemporal region allowed, for the first time, some observations which were not previously possible using common inductive methods.

Patients and methods

Fifty-three subjects (17 male, 36 female, mean age 33, SD 8, range 20-45 years) suffering from migraine (50 common, three classic), diagnosed according to the "ad hoc committee" criteria,⁸ gave their informed consent to participate in the study. No patient had received any prophylactic treatment for at least three months, and all had been free from headache for at least three days.

Initially, 20 of these subjects (all suffering from common migraine) entered a double blind study to test the first hypothesis. They were randomly allocated into two groups: the first group received a 5 mg dose of nitroglycerin in 2% ointment on a 2 × 4 cm area of hairless and cleansed skin of the frontotemporal region. The ointment was applied to one side only, which was assigned randomly to patients suffering from bilateral or alternating side attacks; in patients with attacks always recurring at the same side that side was selected for application. The ointment was spread in a thin layer and then covered with a strip of cellophane. The choice of a 5 mg dose had been deemed optimal in a preliminary experiment. Patients in the second group (controls) received

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placebo ointment in the same amount and according to the same procedure.

The remaining 33 subjects (30 common and 3 classic migraine) were submitted to a preliminary transdermal nitroglycerin test (as above) in the frontotemporal region; the 20 who exhibited an early onset of migraine were distributed into two further groups of 10 depending on the site of their spontaneous attacks. The third group, suffering from bilateral or alternating side attacks, received 5 mg of nitroglycerin in 2% ointment on the volar surface of the wrist, where a superficial arteriovenous system resembling that of the temporal region of the head is present. The fourth group, with attacks always recurring at the same side, who were previously found to be responders to nitroglycerin applied to the symptomatic side, received the same dose of nitroglycerin ointment on the asymptomatic side.

In all the groups nitroglycerin ointment was left on the site of application for two hours. During the test blood pressure was recorded to detect the occurrence of orthostatic hypotension. Because of the possibility of topical applied nitroglycerin causing redness of the skin and a tingling sensation, patients' responses were recorded during the test by a physician unaware of the aim of the trial and of the drugs employed. For the same reason we decided to avoid a cross-over randomised study. So far as the effect of site of application was concerned we also avoided a double blind design, because patients in the last two groups had been previously submitted to a preliminary nitroglycerin test at frontotemporal level.

Response to the test was considered positive when headache occurred closely resembling the patients' typical attacks such as the type, site, and intensity of pain, and to accompanying symptoms.

All patients were asked, 24 hours later, if any event possibly related to the test had occurred after the drug had been removed. To obtain such details patients were requested to avoid taking analgesics.

Results

The results of the double blind study are the following: of the 10 patients in the first group, migraine was induced in nine, of whom seven experienced early onset and two delayed attacks. In the seven patients who developed early onset migraine, pain began at 30, 24 min (mean, SD) and reached the peak at 104, 53 min. In the two patients who developed delayed migraine, pain began at 315, 106 min and reached the peak at 338, 117 min. No migraine attack was induced among the 10 patients in the control group ($p < 0.01$, chi square test).

Among the 10 patients in the third group (wrist group), seven did not develop any headache, while three developed delayed migraine (beginning at 420, 120 min, peak at 530, 176 min); of the 10 patients in the fourth group (asymptomatic side group), eight developed no headache and only two developed delayed migraine (beginning at 437, 95 min, peak at 575, 35 min), which occurred at the symptomatic side.

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Statistical comparisons between the first group and, the third and the fourth group respectively, showed significant differences ($p < 0.01$). No significant difference was found between the double blind and the open study with frontotemporal applied nitroglycerin. Of the 33 patients who entered the open study 20 developed early onset migraine, five delayed migraine and eight had no migraine attack.

The overall number of patients submitted to the nitroglycerin test in the frontotemporal level was 43 (10 patients of the double blind study plus 33 tested in open regimen), of whom nine did not develop migraine (they were eight common and one classic case of migraine) and 34 developed migraine: respectively, early onset migraine in 27 (25 common and two classic cases of migraine) and delayed migraine in seven (common migraine cases).

Headache was induced without significant difference in both unilateral and bilateral sufferers.

In the 27 subjects who developed early onset migraine, pain began at 35, 18 min and reached the peak at 92, 48 min. In the seven subjects who developed delayed migraine pain began at 381, 133 min and reached the peak at 440, 142 min. Accompanying symptoms were present in 23 of them. Almost all complained of nausea. Photophobia, lachrymation, shivering and yawning also occurred. Prodromal symptoms (nausea, drowsiness, blurred vision and photophobia) were also reported by four patients suffering from common migraine. Nitroglycerin failed to produce aura symptoms in any classic migraine patient. Finally, one patient with common migraine complained of mild and transient weakness of the right arm during an early onset induced migraine.

After the ointment was removed pain disappeared within one hour in five out of the 27 subjects who exhibited early onset migraine. In the others, headache was long lasting, as in their spontaneous attacks. Fourteen of these patients had to take analgesic medication, but only four reported some benefit from it.

Orthostatic hypotension was not observed in any patient throughout the study.

Almost all subjects tested with transdermal nitroglycerin exhibited a slight local redness of the skin when the ointment was removed. Only two reported a burning sensation at the fronto-temporal region during the test.

Discussion

Our findings can be summarised as follows:

(1) Nitroglycerin ointment applied to the fronto-temporal region of migraine patients induced an early

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onset migraine attack virtually identical to a spontaneous attack.

(2) In patients whose attacks always occur at the same side, an early onset induction was obtained only when nitroglycerin was applied to the symptomatic side.

(3) Nitroglycerin ointment applied to the wrist was not able to cause an early onset attack.

Undoubtedly, the induced attacks produced by nitroglycerin ointment were clinically similar to the patients' spontaneous migraine crises with the exception of aura in classic cases of migraine. Moreover, in unilateral sufferers, only the stimulated side was affected, whereas in people with bilateral migraine pain began at the stimulated side and then spread to the opposite one, sometimes remaining more severe at the stimulated side.

The high incidence and remarkably early onset of headaches induced by nitroglycerin ointment are of great interest. In fact, migraine usually started within an hour of the beginning of the induction test, whereas the brief, initial stage of painful pulsations was rarely observed. These data are made more significant by the lack of placebo responses and the ability of the induced migraine to persist until an analgesic medication was needed, even if the nitroglycerin ointment had been removed, suggesting that the frontotemporal region is an important site for the development of a migraine attack.

This suggestion is supported by the lack or marked delay of induced crises when the drug was applied to the wrist. In fact this finding renders unlikely the hypothesis that nitroglycerin ointment in the frontotemporal region induces an attack via systemic absorption by cutaneous vessels. It has been reported that the systemic absorption of topical nitroglycerin applied to the mid-forehead is higher than when the drug is applied to the wrist.^{9,10} However, in our study, no haemodynamic change (such as hypotension) was observed with nitroglycerin applied to either the frontotemporal area or the wrist. Moreover, results from nitroglycerin applied to the asymptomatic side in patients with unilateral migraine provide further evidence that systemic absorption of the drug is not involved in the genesis of early onset attacks.

We suggest that the induced attack results, on the contrary, from a selective, direct action of the drug on the site of spontaneous head pain in any given subject. This is supported by the fact that early onset pain was induced in patients with attacks always recurring at the same side only when they received the ointment at the symptomatic side. In the same subject, nitroglycerin ointment applied to the asymptomatic side was, on the contrary, not able to cause migraine. Interestingly, in the few cases in which headache developed many hours later (when the drug is administered by the sublingual route) the pain was always

localised to the symptomatic side.

Our findings suggest therefore that the superficial branches of the external carotid artery, the venous vessels and the periosteum below the frontotemporal region, all richly innervated by trigeminal fibres, are of crucial importance in the development of a migraine crisis. It is possible that, when applied to the frontotemporal region, the drug induces early onset attacks because of its continuous and constant delivery to that crucial region. However, the intimate mechanism by which nitroglycerin acts remains unclear.

Nitroglycerin induced migraine could theoretically result from vascular effects of the drug, for example vasodilatation of intra- and extracranial vessels,¹¹ or from increased intracranial pressure.^{12,13} However, our data imply that such mechanisms are improbable; the former effect should be produced more readily and efficiently by sublingual nitroglycerin administration, while the latter is usually obtained by iv bolus administration.¹³

We do not know whether nitroglycerin acts directly on the abundant perivascular trigeminal nerve endings, influencing, for example, the delivery of pain producing mediators such as substance P. In fact, the site of the pathogenetic alteration responsible for migraine could well be here. The mechanisms by which trigeminal nerve fibres activation may lead to migraine attacks have been thoroughly studied by Moskowitz.¹⁴

Our results cannot at present indicate whether a vasogenetic or a peripheral neurogenetic hypothesis is more likely. However, they seem to be in contrast with the classic central neurogenetic theory, which assigns a major role to hypothalamic function¹⁵ which periodically would give rise to migraine by activating some brainstem nuclei (nucleus raphe magnus, locus coeruleus) involved in intra- and extracranial circulation control¹⁶ and in pain perception.¹⁵ Supporters of the central neurogenetic theory see nitroglycerin's migraine inducing effect as a non physiological stimulus to the final stage of the complex central mechanism mentioned above: the trigeminovascular system.¹⁵ Our data render this hypothesis improbable: when nitroglycerin ointment was applied to the asymptomatic temple in cases with unilateral migraine, attacks were never induced on that side. This suggests instead a differing "activation" of the trigeminovascular system from each of the two sides of the head. This could be the pathogenetic factor, as yet not understood, responsible for migraine.

Our study suggests that, acting on the peripheral structures at the frontotemporal region, centrally elaborated physiological stimuli (such as hunger, sleepiness, stress) could trigger spontaneous migraine; in the same way, non physiological, artificial stimuli (for example nitroglycerin) could trigger induced attacks.

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