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Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance

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Abstract

Several notifications of eye pain and blurred vision associated with treatment with nifedipine were received by New Zealand's Intensive Medicines Monitoring Programme. A questionnaire survey of patients taking nifedipine was undertaken to test the importance of these associations, with disturbance of taste associated with captopril taken as a methodological control. Altogether 961 patients taking nifedipine and 368 taking captopril were sent a questionnaire that asked whether any eye problems and changes in the sense of taste had occurred while they were taking the drug and whether these had resolved after treatment was stopped. Compliance was high: of 922 and 343 questionnaires that were assumed to have been delivered to patients taking nifedipine and captopril, respectively, 770 (84%) and 295 (86%) were returned satisfactorily completed. The distribution of sex was comparable in the two groups; patients taking captopril were slightly younger. Eye symptoms were reported in both groups, but eye pain was significantly more common in patients taking nifedipine (107 (14%) compared with 26 (9%) patients taking captopril). This is a new finding and may be related to ocular vasodilatation. Theoretically, glaucoma is a possible adverse reaction. Loss of taste was significantly associated with captopril, but no other disturbances of taste showed significant associations. Loss of taste persisted in 27 out of 35 patients who continued to take captopril and in three out of eight patients when the drug was withdrawn.

This study showed a method of assessing early signs of adverse drug reactions, which has been used once before and identified previously unrecognised reactions.

Introduction

Nifedipine was approved for marketing in New Zealand in October 1980 and placed in the Intensive Medicines Monitoring

Programme.¹ In this programme the names and addresses of patients being treated with monitored drugs are sent to the Medicines Adverse Reactions Centre by dispensing pharmacists and held on computer file. Doctors prescribing such drugs are urged to report all adverse events experienced by their patients, and this spontaneous reporting is supplemented by surveys that try to complete the recording of all events. The two types of survey used are (a) surveys of reasons for stopping treatment and (b) surveys of the recording of events, in which doctors are asked to record all events noted in their patients' records while the patients are being treated with the monitored drug.

After the first two years of monitoring of nifedipine five records of eye problems had been received, three of painful eyes and two of blurred vision, and it was thought that the possibility of eye problems associated with nifedipine should be investigated. Disturbance of taste with captopril, a drug that was also being intensively monitored, is a known adverse reaction and was selected as a methodological control. Captopril was first marketed in April 1981.

Method

Questionnaires were posted to patients listed in both drug groups after consent was obtained from their doctors. The doctors were also able to advise of any deaths or provide other information about any inability to complete the questionnaires. Patients were asked for the following information. (1) Had treatment been stopped, and if so when? (2) Had their sense of taste changed and any eye problems developed since they started their treatment? (They were not told which drug was suspected of affecting the eyes or the sense of taste.) (3) If their sense of taste had changed they were asked to choose the best answer for the change from sweet, loss of taste, salty, metallic, and other; and for eye problems they selected from painful, stinging or dry eyes, and blurred vision. Some of these choices were included as a blind. (4) Had any of these symptoms caused them to stop taking the drug? (5) Had these symptoms cleared on withdrawal of the drug? (6) If symptoms were current they were asked to grade the severity in one of three categories: severe, moderate, or minor. (7) Did they smoke tobacco? Smoking could relate to taste and possibly eye problems. (8) Date of birth.

The questionnaire had been tested in a preliminary pilot study of about 100 patients; the only change had been the addition of the request for the date of birth. For patients taking nifedipine who said that they had experienced moderate or severe eye pain an ophthalmologist's opinion was requested through their general practitioner.

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The χ^2 test was used to test differences. Differences in totals reflect the fact that not all respondents answered every question.

Results

All doctors allowed their patients to be approached. Table I shows the numbers in each group and the rate of response to the questionnaire. Some questionnaires were returned by the Post Office undelivered; some of these patients had probably died. Over 80% of the remaining questionnaires were returned satisfactorily completed. Only one patient recorded an objection to the inquiry, and 882 out of 954 patients who were asked to supply their date of birth did so.

Table II shows that the distribution of sex was comparable in the two groups and that those in the group taking captopril were slightly younger. About 60% of each group were male, and the overall mean age for patients taking nifedipine and captopril was 62.8 and 56.0 years, respectively. Because of captopril's more recent marketing and its main use soon after release in patients who had not responded to other treatment, patients taking captopril were probably more severely ill. The mortality in patients taking captopril was about double that in those taking nifedipine (table I). Forty five (15%) of the surviving patients taking captopril and 228 (30%) of those taking nifedipine had stopped taking the drug. The mean period of treatment was 19.4 months for nifedipine and 20.0 months for captopril.

Table III summarises the responses concerning eye problems. Eye symptoms were common in both groups, but painful eyes were significantly more common with nifedipine ($p=0.033$). A significant difference was found ($p=0.031$) when pain and stinging were combined, which was done because these two symptoms are not always easily distinguishable. Eye pain

or stinging resulted in nine of the 156 (6%) patients taking nifedipine having treatment withdrawn. Of the 74 patients with eye pain on taking nifedipine who answered the question about severity, 18 (24%) rated the problem as minor, 41 (55%) as moderate, and 15 (20%) as severe. For patients taking captopril 10 (48%) rated eye pain as minor, six (29%) as moderate, and five (24%) as severe. The mean age of all the patients taking nifedipine with painful or stinging eyes who provided their date of birth ($n=126$) was 63.5 years, which was similar to the mean of 62.8 years for the whole group. The mean age for those with moderate or severe symptoms was 63.4 years.

One hundred of the patients taking nifedipine who had painful or stinging eyes graded the severity of their complaint as moderate or severe. Their prescribing doctors were asked for follow up information and, if symptoms continued, to refer patients to an ophthalmologist for an opinion. Replies were received for 32 patients. Fifteen had either stopped taking nifedipine (13) or died (two). Symptoms had resolved on withdrawal of treatment in eight patients. Only 17 patients had seen an ophthalmologist, and five of them had dry eyes. Four others had red eyes, three complaining of zig zag lights and one of concomitant facial flushing. No cause of eye pain could be identified in the eight other patients examined. Nine patients had had intraocular pressures measured, and all had normal results.

Table IV gives the results for disturbance of taste. The only significant difference between the two groups was the loss of taste in patients taking

TABLE I—Rates of response to questionnaire by patients taking nifedipine and captopril. Values are numbers (percentages)

	Patients taking nifedipine (n=1089)	Patients taking captopril (n=478)
Deaths	126 (12)	105 (22)
Incapable of replying	2	5
Questionnaires sent	961	368
Returned undelivered	39	25
Assumed delivered	922	343
Void or no reply	152	48
Satisfactory replies	770 (84)	295 (86)

TABLE II—Distribution of age by sex. Values are numbers (percentages)

Age (years)	Men		Women	
	Patients taking nifedipine	Patients taking captopril	Patients taking nifedipine	Patients taking captopril
10-19		3 (1)		3 (1)
20-29		3 (1)	2 (<1)	6 (2)
30-39	2 (0.3)	4 (2)	5 (<1)	5 (2)
40-49	31 (5)	31 (12)	17 (3)	19 (7)
50-59	119 (19)	40 (15)	48 (7)	21 (8)
60-69	140 (22)	46 (17)	83 (13)	24 (9)
70-79	103 (16)	31 (12)	67 (10)	20 (8)
≥80	9 (1)		19 (3)	8 (3)
Total	404 (63)	158 (60)	241 (37)	106 (40)
Mean age	62.1	56.1	64.2	55.9

TABLE III—Numbers (percentages) of patients developing eye problems when taking nifedipine and captopril

	Patients taking nifedipine (n=757)	Patients taking captopril (n=289)	Significance (p value)*
Painful eyes	107 (14)	26 (9)	0.033
Stinging eyes	71 (9)	19 (7)	0.19
Blurred vision	238 (31)	88 (30)	0.81
Dry eyes	42 (6)	17 (6)	0.95
Painful and stinging eyes	156 (21)	42 (15)	0.031

* χ^2 test.
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TABLE IV—Numbers (percentages) of patients experiencing disturbance of taste when taking nifedipine and captopril

Disturbance of taste	Patients taking nifedipine (n=770)	Patients taking captopril (n=292)	Significance (p value)*
Sweet	12 (2)	5 (2)	0.92
Loss	70 (9)	44 (15)	0.007
Salty	23 (3)	13 (5)	0.32
Metallic	48 (6)	27 (9)	0.11

* χ^2 test.
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captopril ($p=0.007$). Metallic taste was more common in patients taking captopril, but the difference did not reach significance ($p=0.11$). Thirty patients taking captopril answered the question about the severity of their loss of taste, with 20 (67%) considering it to be a minor problem, six (20%) a moderate problem, and four (13%) a severe one. Only one patient had treatment withdrawn because of loss of taste.

Patients were asked about the persistence of ageusia and 43 patients responded. Among 35 patients continuing treatment symptoms persisted in 27 (77%), and the sense of taste returned to normal in eight (23%). Of the patients who had stopped treatment with captopril, eight complained of loss of taste while taking the drug. Three of them stated that the symptoms had persisted for three, 11, and 23 months, respectively, after treatment had been withdrawn.

Table V shows the effect of smoking on the presence of side effects. Smokers accounted for 114 (15%) patients taking nifedipine and 64 (22%) taking captopril. No significant difference was found between those with and without symptoms.

Discussion

Of the five drugs being intensively monitored at the time of the survey, captopril was the only one suitable as a control for nifedipine. The mean age of patients taking nifedipine was slightly older than that of those taking captopril. Eye pain did not, however,

TABLE V—Effect of smoking on presence of side effects* in patients taking nifedipine and captopril. Values are numbers (percentages) of patients

	Patients taking nifedipine (n=749)	Patients taking captopril (n=297)†
Patients with symptoms	150 (20)	43 (15)
Smokers	114 (15)	64 (22)
Smokers with symptoms	20 (18)	7 (11)
Non-smokers	635 (85)	233 (78)
Non-smokers with symptoms	130 (21)	36 (16)

*Eye pain or stinging with nifedipine; ageusia with captopril.
†Includes two additional patients who completed only the questions on taste.

seem to be related to age because the mean age for those with eye pain was almost identical with that of the whole group. The main indications for both drugs were systemic hypertension and heart failure with, in addition, ischaemic heart disease for nifedipine. These differences were thought unlikely to have any confounding effect in this study.

The compliance in returning the questionnaires was high. The significantly higher incidence of ageusia in patients taking captopril ($p=0.007$) validated the method and also allayed fears of collecting spurious replies from direct questioning of patients that would affect the significance of the results. The high compliance (93%) for supplying dates of birth indicated that patients had little objection to giving personal information to an authority monitoring drugs.

Painful eyes associated with nifedipine has not been reported. Eye symptoms are common in the age group in this study, and dry eyes are not unusual. The small number (17) of opinions received from ophthalmologists did not show any other signs of eye disease that could be responsible for the pain, apart from some sign of haemodynamic disturbances. Topical administration of three different calcium channel blockers, including nifedipine, to the eyes of rabbits can cause a transient rise in intraocular pressure and ocular blood volume, which is probably due to ocular vasodilatation.² Topical verapamil has also been shown to raise intraocular pressure in healthy human volunteers.² No patients in our study were found to have raised intraocular pressure, so eye pain associated with nifedipine may be due to similar changes in ocular blood volume without important changes in intraocular pressure, although, theoretically, glaucoma should be considered to be a possible reaction.

A well known side effect of nifedipine is headache, resulting from its vasodilatory action, and patients may at times find difficulty in discriminating between headache and eye pain. The alerting reports were, however, made by doctors who clearly indicated eye pain, and, in addition, all reports of moderate or severe eye pain from the patients surveyed were referred back to the prescribers. Some of the patients were then referred to an ophthalmologist. As well as the ophthalmologists' reports comments were received from the prescribing doctors when they advised of a withdrawal of treatment or death. In all, comments were received from doctors about 32 patients and the presence of eye pain was confirmed in 23 patients and denied in one. For the eight others no comment was given, which was taken as tacit confirmation, but in none of the replies was headache mentioned. This and the fact that the questions were specifically about the eyes suggest that any difficulty in discriminating between eye pain and headaches related to nifedipine probably had no important effect on the results.

This survey was designed to test an association between nifedipine and eye pain or blurred vision, or both. The questionnaire was deliberately kept simple with as few questions as possible to enhance compliance and achieve accuracy. It did not try to delineate clinical features other than whether symptoms developed after nifedipine was prescribed, whether they caused withdrawal of treatment, and whether they persisted after withdrawal. Now that an association has been found prospective clinical studies should be undertaken to elucidate the problem. Doctors' comments about patients with moderate or severe eye pain or stinging eyes showed some features in addition to the expected symptoms and signs of keratoconjunctivitis sicca or other common diseases. Three patients were confirmed as having red eyes associated with the pain. In one pain and redness were intermittent and regular, starting 20 minutes

after the patient took nifedipine and lasting for half to one hour. Although little specific information was given about the time of onset, it was about two months after the start of treatment in three patients. Replies from doctors indicated that symptoms cleared in eight of 10 patients whose treatment was stopped. As these numbers are small the total number of patients with eye pain related to nifedipine was probably small. If the incidence of 9% in the group taking captopril is taken as the background value for eye pain in a group with similar ages and morbidity the incidence of 14% in the group taking nifedipine probably includes about 5% with symptoms related to nifedipine. This would be about 38 patients with all grades of pain. There is inadequate information for comment relating symptoms to indication for use.

The association of loss of taste with captopril was confirmed but not an association of other forms of taste disturbance. The incidence of ageusia was 15%, much higher than that of 1.4-2.1%³ or 2.7%⁴ reported for the broader category of dysgeusia. Much of this difference may be because two thirds of the patients considered ageusia to be a minor problem and would not normally have reported it to their doctor unless asked; it has been considered to be a self limiting side effect,³ but in only 23% of the patients studied here did the problem clear while treatment continued and three out of eight patients had persistent symptoms after withdrawal of treatment. Thus some permanent damage to the perception of taste may be possible.

This study showed a method of assessing early signs of possible adverse drug reactions in a specialised scheme of postmarketing surveillance and highlighted an adverse reaction not previously reported, even though nifedipine was available in Europe for five years before being marketed in New Zealand. Eye pain had not been reported spontaneously but was indicated from the routine additional procedures of the intensive monitoring programme. One survey reported 60 new systems of postmarketing surveillance as alternatives to voluntary reporting and concluded that none had identified any side effects or hypotheses about the drugs studied different from those already observed in premarketing clinical trials.⁵ This study identified a new side effect, as did a similar study of labetalol.⁶ The side effects identified seemed to be of little clinical importance, but the methodology used was effective in identifying new reactions.

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