Incidence of Cancer in Postmyocardial Infarction Patients Treated with Short-Acting Nifedipine and Diltiazem

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BACKGROUND. Recent reports suggest a possible link between nifedipine (but not diltiazem) and an increased risk of cancer in patients being treated with calcium antagonists.

METHODS. A total of 1054 postmyocardial infarction patients were divided randomly into those being treated with calcium antagonists (n = 566 [nifedipine, 425 patients and diltiazem, 141 patients]) and controls (no calcium antagonist; n = 488). The patients were followed for 26.3 months, and the incidences of cardiac events as well as cancer were compared among the 3 groups.

RESULTS. Thirteen patients (2.7%) in the control group developed cancer, whereas 15 patients in the nifedipine group (3.5%; odds ratio, 1.34; 95% confidence interval [95% CI], 0.63–2.85) and 3 patients in the diltiazem group (2.1%; odds ratio, 0.89; 95% CI, 0.27–2.93) developed cancer.

CONCLUSIONS. Diltiazem appears to present no increased risk of cancer. The incidence of cancer was slightly higher in the patients receiving nifedipine than in those not being treated with a calcium antagonist, which is consistent with earlier reports; however, this increase was not statistically significant. ***Cancer* 1999;85: 1369–74.** © *1999 American Cancer Society.*

KEYWORDS: cancer, nifedipine, diltiazem, myocardial infarction.

Calcium antagonists are one of the most important groups of drugs used in the treatment of patients with cardiovascular disease or hypertension; thus, the efficacy and safety of these drugs is extremely important. Several recently published investigations have raised concern that some calcium antagonists may increase the risk of cancer,[1–5] whereas other reports refute this possibility.[6–12] In the wake of this controversy, the Liaison Committee of the World Health Organization and the International Society of Hypertension formed an ad hoc subcommittee to review the effect of calcium antagonists on the risk of cancer.[12] They announced that the available evidence, gleaned from observational studies, did not indicate an adverse effect of calcium antagonists on cancer risk. This is, in fact, a reasonable conclusion because the majority of studies[3,4] emphasizing the potential of calcium antagonists to increase the risk of cancer are based on observations from a single study population (Established Populations for Epidemiologic Studies of the Elderly [EPESE]).

We have been studying the effect of calcium antagonists on cardiac events in postmyocardial infarction patients since 1986.[13] To determine the efficacy of the drugs, patients were divided randomly to their hospital identification numbers into those who were being treated with calcium antagonists and those who were not. We con-

cluded that short-acting nifedipine and diltiazem did not reduce the incidence of cardiac events in patients with healed myocardial infarctions.[13] For the analysis presented in the current study, we reexamined the data to clarify whether nifedipine or diltiazem influenced the risk of cancer within our study groups.

METHODS

Recruitment of Patients and Drug Assignment

The current study made use of the same subject population used to analyze the efficacy of calcium antagonists in reducing cardiac events in patients with healed myocardial infarctions.[13]

Patient enrollment began in January 1986 and ended in June 1994, a total study period of 102 months. All patients being treated for myocardial infarction in our department were enrolled consecutively. Each patient was assigned an eight-digit hospital identification number on their first visit to our hospital. Whether patients received drug treatment with a calcium antagonist was determined according to the fifth digit of their hospital identification number. If the digit was even (e.g., 9999*2*999), the patient received a calcium antagonist; if the digit was odd (e.g., 9999*1*999), the patient was assigned to the group not being treated with a calcium-antagonist (control group). Among calcium antagonists, short-acting nifedipine capsules (10 mg orally, 3 times a day) or short-acting diltiazem tables (30 mg orally, 3 times a day) were the most widely used standard medications prescribed by our department in the 1980s. Selection of either nifedipine or diltiazem was left to the doctor. Compliance with the calcium antagonist treatment protocol was ensured by regular receipt of prescriptions.

Follow-up and Cardiac Events

Outpatient visits were scheduled for approximately once a month; at the outpatient clinic, routine physical examinations included electrocardiograms and serial blood tests. All other examinations aimed at addressing patients' reported symptoms (e.g., fecal occult blood tests, upper gastrointestinal fluoroscopy, barium enemas, gastrocamera, colonic fiberscopy, chest X-rays, urinalysis, and computed tomography [CT] or magnetic resonance imaging [MRI] of the chest or abdomen were performed as needed. All patients were admitted to the hospital if necessary, including those admitted for the diagnosis and treatment of cancer. The primary endpoints for participation in the study were cardiac death and nonfatal, recurrent myocardial infarction. Cardiac death included fatal, recurrent myocardial infarction, death from congestive heart failure, and sudden death.

Diagnosis of Cancer

A diagnosis of cancer most often was established by histologic findings, either from biopsy specimens, tissue samples obtained during surgery, or autopsy. Those malignancies diagnosed after a patient's enrollment in the study were counted as newly developed cancers. In all instances in which cancer was suspected, a final diagnosis was made during the period of the patients' participation in the study. No patients suspected of having cancer left the study before a final diagnosis was made.

Study Exclusion and Discontinuation

Patients who died within 7 days of the onset of an acute myocardial infarction were not enrolled in the study. Those who for some reason stopped visiting our clinic were contacted so we could determine the reasons for their discontinuation and avoid overlooking cardiac events or any other medical events. If during a follow-up examination a patient was found to have cancer, analysis was discontinued.

Statistical Analysis

Data are shown as the mean $\pm$ the standard deviation. Differences in patient characteristics between any two groups were tested by two-tailed chi-square tests, and a probability value of $P < 0.05$ was considered significant. We also calculated the odds ratios and 95% confidence intervals (95% CI) for all patient risks.

RESULTS

Study Population and Baseline Characteristics

A total of 1054 patients with myocardial infarction (838 males and 216 females, age 60.1 $\pm$ 11.5 years) were included in the analysis. The mean time interval between the onset of myocardial infarction and enrollment in the study was 16.0 $\pm$ 27.2 months; once enrolled, the mean observation period was 26.3 $\pm$ 28.0 months. In the control group the mean observation period was 26.0 $\pm$ 27.7 months, (median, 15.0 months, range, 1–139 months). In the nifedipine group the mean observation period was 27.2 $\pm$ 28.2 months (median, 15.0 months, range, 1–168 months). In the diltiazem group the mean observation period was 24.4 $\pm$ 28.5 months (median, 11.0 months, range, 1–147 months). Among the study participants, 566 were treated with calcium antagonists and 488 were not; 425 received short-acting nifedipine (30 mg/day) and 141 received short-acting diltiazem (90 mg/day). Thirty baseline characteristics of the participants in the 3 groups are listed in Table 1.

TABLE 1
Baseline Characteristics

	No calcium antagonist (n = 488)	Nifedipine (n = 425)	Diltiazem (n = 141)
Gender (Male/female)	386/102	345/80	107/34
Age (yrs)	59.3 ± 11.6	61.3 ± 10.9	58.9 ± 12.4[a]
Blood pressure			
Systole (mm Hg)	126 ± 21	126 ± 21	129 ± 23
Diastole (mm Hg)	76 ± 14	73 ± 11	76 ± 17[a]
Heart rate (beats/minute)	67 ± 12	65 ± 11	69 ± 12[b]
Atrial fibrillation (%)	3.9	5.5	5.5
Inpatient/outpatient (no.)	90/398	71/354	27/114
Time from onset to registration (mos)	17.8 ± 28.3	14.7 ± 26.3	14.1 ± 26.0
Follow-up (mos)	26.0 ± 27.7	27.2 ± 28.2	24.4 ± 28.5
Clinical features during AMI			
Coronary thrombolysis (%)	33.2	31.2	29.7
Forrester class	1.65 ± 1.00	1.49 ± 0.88	1.55 ± 0.96
Killip class	1.32 ± 0.72	1.23 ± 0.61	1.23 ± 0.66
Wall motion index by echo	8.2 ± 6.1	8.1 ± 5.8	6.3 ± 5.2[a,c]
ECG QRS score	6.1 ± 3.5	5.3 ± 4.2	5.0 ± 3.4
Angina after infarction (%)	22.7	37.9[d]	28.3
Variant angina (%)	3.1	6.6[c]	7.8[c]
Coronary risk factors			
Hyperlipidemia (%)	46.7	49.0	42.6
Hypertension (%)	42.3	51.4[c]	44.1[a]
Smoking (%)	68.6	65.1	64.8
Diabetes mellitus (%)	23.9	31.1[c]	30.8
Obesity (%)	21.7	19.9	20.2
Gout (%)	14.5	12.5	16.0
Positive exercise ECG test (%)	36.2	44.9[c]	32.6[a]
Combined medications			
Antiplatelet agents (%)	65.6	58.9[c]	66.7
Cholesterol lowering drugs (%)	31.5	26.3	21.3[c]
β-blockers (%)	58.3	58.7	43.3[b,c]
Warfarin (%)	27.2	24.2	25.5
ACE inhibitors (%)	17.2	8.9[d]	9.9[c]
Nitrates (%)	63.0	73.9[c]	68.1
Antiarrhythmic drugs (%)	13.3	12.8	8.9

AMI: acute myocardial infarction; ECG: electrocardiogram; QRS: electrocardiographic wave complex or interval; ACE: angiotensin-converting enzyme.
[a] $P < 0.05$ (difference between the nifedipine and diltiazem groups).
[b] $P < 0.01$ (difference between the nifedipine and diltiazem groups).
[c] $P < 0.05$ (difference from the no calcium antagonist group).
[d] $P < 0.01$ (difference from the no calcium antagonist group).

TABLE 2
Cardiac Events and Total Mortality

	No calcium antagonist (n = 488)	Nifedipine (n = 425)	Diltiazem (n = 141)
Cardiac events			
Nonfatal reMI	10	14	2
Cardiac death	16	10	4
Total	26 (5.3%)	24 (5.6%)	6 (4.3%)
Odds ratio and 95% CI	1.07 (0.60–1.89)		
		0.79 (0.32–1.96)	
Lost to follow-up	7 (1.4%)	7 (1.6%)	4 (2.8%)
Noncardiac death	15 (3.1%)	16 (3.8%)	7 (5.0%)
Total mortality	31 (6.4%)	26 (6.1%)	11 (7.8%)
Odds ratio and 95% CI	0.96 (0.56–1.65)		
		1.25 (0.61–2.56)	

reMI: recurrent myocardial infarction; 95% CI: 95% confidence interval.

Effect of Calcium Antagonists on Cardiac Events and Total Mortality

Of the patients not being treated with a calcium antagonist, 26 (5.3%) experienced cardiac events, whereas 24 patients treated with nifedipine (5.6%; odds ratio, 1.07; 95% CI, 0.60–1.89) and 6 patients treated with diltiazem (4.3%; odds ratio, 0.79; 95% CI, 0.32–1.96) experienced cardiac events (Table 2). There were 15 noncardiac deaths among the patients in the control group (3.1%) 16 in the nifedipine group (3.8%; odds ratio, 1.23; 95% CI, 0.60–2.53), and 7 in the diltiazem group (5.0%; odds ratio, 1.65; 95% CI, 0.66–4.13) (Tables 2 and 3). Total mortalities included 31 control patients (6.4%), 26 patients treated with nifedipine (6.1%; odds ratio, 0.96; 95% CI, 0.56–1.65), and 11 patients treated with diltiazem (7.8%; odds ratio, 1.25; 95% CI, 0.61–2.56) (Table 2).

Incidence of Cancer

During follow-up examinations, a total of 31 patients (2.9%) were found to have newly developed cancers (Table 4). The new cancers occurred in 13 patients in the control group (2.7%), 15 patients in the nifedipine group (3.5%; odds ratio, 1.34; 95% CI, 0.63–2.85), and 3 patients in the diltiazem group (2.1%; odds ratio, 0.89; 95% CI, 0.27–2.93). The final diagnosis was established by biopsy specimen in 15 patients, through surgery in 9 patients, and by autopsy in 5 patients. In 2 patients with hepatic cell carcinoma, the diagnosis was established through clinical findings obtained by scintigram, CT or MRI of the liver, and hepatic angiography. Among the patients in the control group, 6 (1.2%) died of cancer; of these 6 patients, 2 had cancer before enrollment in the study and 4 developed new cancers after enrollment (Table 3). Ten patients in the nifedipine group (2.4%) and 1 patient in the diltiazem group (0.7%) also died of cancer; among these, 2 patients treated with nifedipine had cancer before enrollment, and the remaining 9 patients (8 receiving nifedipine and 1 receiving diltiazem) developed new cancers during the course of the study. There was no significant

TABLE 3
Causes of Noncardiac Death

	No calcium antagonist (n = 488)	Nifedipine (n = 425)	Diltiazem (n = 141)
Cancer	6	10	1
(Before registration)	(2)	(2)	(0)
(After registration)	(4)	(8)	(1)
Infections	3	0	0
Cerebrovascular	3	2	2
CABG surgical	1	2	0
Others (no.)	GI bleeding (1), GI perforation (1),	Renal failure (1), Unknown (1),	Bronchial asthma (1), Death on arrival (1), Unknown (2)
Total	15 (3.1%)	16 (3.8%)	7 (5.0%)
Odds ratio and 95% CI	1.23 (0.60–2.53)		
	1.65 (0.66–4.13)		

CABG: coronary artery bypass grafting; GI: gastrointestinal; 95% CI: 95% confidence interval.

TABLE 4
Cancer Diagnosed after Registration among Three Groups

	No calcium antagonist (n = 488)	Nifedipine (n = 425)	Diltiazem (n = 141)
Stomach	4	4	2
Colorectal	2	3	0
Lung	2	3	0
Kidney	2	0	0
Ureter	1	0	0
Urinary bladder	1	0	0
Liver	0	1	1
Pancreas	1	0	0
Lymphoma and leukemia	0	2	0
Skin	0	1	0
Larynx	0	1	0
Total	13 (2.7%)	15 (3.5%)	3 (2.1%)
Odds ratio and 95% CI	1.34 (0.63–2.85)		
	0.89 (0.27–2.93)		

95% CI: 95% confidence interval.

difference in the site specific incidence of cancer among the three groups.

Subgroup Analyses

To exclude possible effects resulting from differences in baseline characteristics, subgroup analyses were performed on all 30 strata. Alterations in the risk of cancer among the three groups were not associated with any of the baseline characteristics. To exclude the possibility that the duration of exposure to calcium antagonists influenced the risk of developing cancer, 446 patients enrolled in the study for $>$ 1 year were analyzed. Of the 202 patients who were not treated with a calcium antagonist, 4 (2.0%) developed cancer, whereas 8 of 200 patients treated with nifedipine (4.0%; odds ratio, 1.95; 95% CI, 0.61–6.21) and 2 of 44 patients treated with diltiazem (4.5%; odds ratio, 2.60; 95% CI, 0.53–12.61) developed cancer.

DISCUSSION

In this study, we found that the incidence of cancer was slightly higher in patients treated with short-acting nifedipine (3.5%) compared with those not treated with a calcium antagonist (2.7%), but this difference was not statistically significant (odds ratio, 1.34; 95% CI, 0.63–2.85). Subgroup analysis also revealed no significant effects on cancer development. In addition, we found that diltiazem had no effect on the risk of cancer.

Recently, several reports suggested that there may be a link between treatment with calcium antagonists and an increased risk of developing cancer;[3–5,14,15] however, other studies have found no such association between cancer and these drugs.[5–11,16,17] Not surprisingly, much discussion also has been published regarding this controversial topic.[12,18–22] Among those suggesting that there is a link between calcium antagonists and cancer risk are Hardell et al.[15] who analyzed the incidence of colon carcinoma with respect to previous diseases and drug intake; they found an increased risk of cancer associated with treatment with verapamil (odds ratio 22; 95% CI, 2.4–480). However, the principle report postulating a possible association between cancer and calcium antagonists comes from

the cohort study of the EPESE.[1,3,4] These investigators found that, compared with β-blockers, the relative cancer risk presented by calcium antagonists was 2.02 (95% CI, 1.16–3.54).[4] Analyzing the same study population, they found that patients treated with verapamil or nifedipine, but not diltiazem, were at a greater risk of developing cancer than those not treated with calcium antagonist.[3] However, issues arising from the limitations of the EPESE studies have been raised. Messerli[18] pointed out that 1) the studies were based on too small a number of cancers, 2) there were higher rates of hospitalization in patients treated with calcium antagonists, 3) information regarding only one drug was supplied, and 4) it was unlikely that such a relation, if it existed, would have gone unnoticed under the intense scrutiny of the medical community. Several others also criticized the fact that the both studies were observational and originated from the same selected EPESE population.[12,22]

Our analysis, conducted on a Japanese sample population receiving the same medical care, revealed a slightly higher risk of cancer in patients treated with nifedipine compared with those not treated with a calcium antagonist, but the increase was not statistically significant. In contrast, no effect on cancer risk was found with diltiazem. Fitzpatrick et al.[5] also reported an elevated risk of breast carcinoma associated with the use of immediate-release calcium antagonists. Their protocol included a 1-year time lag from the initiation of drug treatment to allow for tumor growth and diagnosis. In the current study, we also considered the effect of exposure duration, and a patient population who had been treated with nifedipine for a period of > 1 year was analyzed separately. Once again, the risk of cancer was found to be slightly higher in the nifedipine group than in the control group, but again the difference was not statistically significant.

Several studies have failed to find an increased cancer risk associated with calcium antagonists, despite being based on larger sample populations than the current study.[7–11] Olsen et al.[11] concluded that there was no evidence of a tumor-promoting effect among calcium channel blockers, although their period of follow-up after enrollment was relatively short. Jick et al.[9] studied a group of hypertensive patients and found a slightly increased risk for the development of all cancers among users of calcium antagonists compared with a group using β-blockers (adjusted relative risk, 1.27; 95% CI, 0.98–1.63). Nevertheless, they suggested that this slight increase in cancer risk should not be interpreted casually as being associated with the calcium antagonists. In the Shanghai Trial of Nifedipine in the Elderly (STONE),[7] death from malignancy occurred in 8 of 746 patients in the placebo group whereas it occurred in only 2 of 787 patients in the nifedipine group. However, cancer risk cannot be evaluated properly in that study or in certain others[7,8,10] because surviving patients who developed cancer while participating in those studies were not counted. Indeed, in the current investigation, the number of cancer patients who were alive at last follow-up exceeded the number who died.

Pahor et al.[3] showed that treatment with diltiazem was not associated with an increased risk of developing cancer, in contrast to nifedipine (odds ratio, 1.74; 95% CI, 1.05–2.88; $P < 0.01$). Similarly, with diltiazem, we did not observe even a small increase in cancer risk. In that context, it may be too early to ignore the slight increase in cancer risk observed in the nifedipine group, even though it was not statistically significant. After considering the findings of Pahor et al.[3] along with our own, it was apparent that detailed analysis of a larger number of patients than has been studied to date will be required to resolve the relation between nifedipine and cancer conclusively.

Mechanisms by which calcium antagonists may be associated with cancer are discussed in detail elsewhere.[3,4,20] Pharmacologic blockade of calcium channels is believed to inhibit apoptosis, a process of programmed cell death by which organisms may eliminate "unwanted" cells.[20,23] In addition, calcium is involved in the activation of endonucleases, which leads to DNA fragmentation. Taken together, these data suggest that, in some tissues, the use of calcium antagonists possibly could act as a tumor promoter by interfering with the programmed death of DNA damaged cells.[20] Correale et al.[24] reported that low doses of verapamil increased the growth of breast carcinoma cells. However, the data from several other basic research studies suggest that no association exists between calcium antagonists and increased cancer cell growth.[6,16,25,26] Thus, the results from both clinical and basic research currently remain inconclusive with respect to the relation between calcium channel blockade and cancer. This circumstance emphasizes the need for further analysis.

Study Limitation

It should be noted that the mean observation period of the current study was 26.3 ± 28.0 months. This relatively short follow-up period may limit the ability of the current study to detect the potential increased risk of cancer development.

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