Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration

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Abstract

Background. Although calcium-channel antagonists have been proposed as prophylaxis to prevent radiocontrast-induced nephropathy, the dose and dose interval to achieve a protective effect have not been quantified in humans.

Methods. In a randomized, double-blind protocol we studied urinary enzyme and microprotein excretion in 121 outpatients (mean age 65.3 ± 9.3 years, 62% male) with normal renal function who were to undergo digital subtraction arteriography with iohexol or iopentol. The subjects were treated with a single dose of placebo (group 1) or nitrendipine 10 mg (group 2) or 20 mg (group 3) p.o. 1 h before the procedure. Blood and urine samples were collected 1 h before, 1 h after, and 24 h after contrast administration. Study variables included contrast volume and serum creatinine, and urinary creatinine, osmolality, albumin, alanylamino-peptidase (AAP, a brush border enzyme), N-acetyl-/?-glucosaminidase (NAG, a lysosomal enzyme), and α-1-microglobulin (α-1-micro, a filtered microprotein).

Results. Serum values of creatinine remained unchanged during the study period. Albuminuria was not affected by contrast administration, whereas AAP, NAG, and α-1-micro increased significantly, all except AAP returning to baseline at 24 h. Pretreatment with nitrendipine did not reduce enzyme excretion, although AAP levels were lower in general in the group assigned to the 20-mg dose. Acute renal failure, defined as a 50% increase of serum creatinine 24 h after radiocontrast administration, was found in eight patients: four from group 1 (8.3%), three from group 2 (6.5%), and one from group 3 (3.7%).

Conclusions. Neither the course of enzyme excretion nor the incidence of acute renal failure following radiocontrast administration were affected by single doses of calcium antagonists. AAP levels were lower in general in subjects taking the 20-mg dose of nitrendipine. This study also indicates that a single low or normal dose of nitrendipine per os is not effective prophylaxis before radiocontrast administration.

Key words: radiocontrast-induced nephropathy; calcium-channel antagonists; urinary enzymes

Introduction

Radiocontrast-induced nephropathy (RCIN) is a common cause of hospital-acquired acute renal failure [1], especially in patients with pre-existing chronic renal insufficiency and diabetes mellitus. In the absence of a clear aetiology of RCIN, a number of therapeutic manoeuvres have been proposed to prevent renal damage following contrast administration, including the use of non-ionic agents, the combination of furosemide and saline, mannitol, and others.

Preliminary studies have indicated that calcium-channel antagonists may also have a protective role against a number of nephrotoxins including cyclosporine [2], aminoglycosides and myoglobinuria [3], and in the course of chemotherapy with cis-platinum [4]. The protective action of calcium antagonists at the renal level appears to involve several mechanisms, the two most important being (1) reduction of vascular resistance which results from autoregulation via tubuloglomerular feedback, and (2) a direct effect on tubular transport. Microperfusion of calcium antagonists in peritubular capillaries abolishes tubuloglomerular feedback [5], and calcium antagonists also reduce the vasoconstriction due to angiotensin II [6]. On the other hand several studies have indicated that calcium antagonists inhibit reabsorption of water and sodium without affecting glomerular filtration rate (GFR) or renal plasma flow [7,8]. The dose of calcium antagonist necessary to alter tubular transport is consistently less than that which affects renal haemodynamics [9].

Calcium antagonists have also been used in an attempt to prevent RCIN in humans. Deray and
colleagues [10] have shown that intrarenal verapamil or diltiazem increase GFR significantly following contrast administration in the rat. However, Cacoub et al. [11] retrospectively studied two groups of patients with chronic renal insufficiency following contrast administration, one of which was treated with nifedipine (mean dose 40 mg q.d.) for hypertension. The frequency of RCIN, defined as an increase in serum creatinine of 20%, did not differ between groups. Finally, Neumayer et al. [12] conducted a prospective randomized trial of nitrendipine (20 mg p.o. q.d. for 3 days, beginning 1 day before the radiological procedure) versus a placebo control. Inulin clearance was significantly reduced in the controls but unchanged in the treated patients. In addition, various urinary enzymes were markedly increased in untreated patients. A prospective study designed to determine if calcium antagonists actually reduce the incidence of RCIN has not yet been carried out.

Given the diverse mechanisms by which calcium antagonists might afford renal protection in the setting of contrast administration, we were interested in determining the lowest effective dose of nitrendipine which would prevent enzymuria in a cohort of elderly patients with normal renal function who were to undergo digital subtraction arteriography with non-ionic contrast media.

**Subjects and methods**

**Patients**

From October 1991 to October 1992 approximately 3500 patients underwent digital subtraction angiography in the Institute of Radiology of the University of Trieste, Cattinara Hospital, for diagnosis of cerebrovascular disease or claudication. A sample of 100 outpatients was chosen for the study. Exclusion criteria included serum creatinine ≥130 μmol/l, abnormal urinalysis, exposure to other nephrotoxins in the preceding 2 weeks, and current use of calcium antagonists. Demographic variables included gender, age, height, and weight. After randomization to placebo (group 1) or nitrendipine 10 mg (group 2), six patients withdrew from the study, and these data were eliminated from the statistical analysis. At a later date 27 patients (group 3) were randomly chosen to receive nitrendipine 20 mg. Therefore the study base consisted of 121 patients, who gave consent after they were informed of the goals of the study.

**Protocol**

The patients were randomized to undergo angiography with iopentol or iohexol, both non-ionic monomers, which differ by only one side-chain. Both agents have an iodine content of 350 mg/ml and an osmolality of 890 mOsm/kgH2O at 37°C. The patients were randomized to receive nitrendipine 10 mg or 20 mg or placebo per os 1 h before the radiographic procedure. Saline was not administered before the procedure, given that the subjects did not have known renal insufficiency; all patients appeared well hydrated before the study. Mean arterial pressure (MAP) was determined before and after the radiological procedure. Acute renal failure due to RCIN was defined as a 50% increase in serum creatinine 24 h after the procedure. Blood and urine samples were collected 1 h before, 1 h after, and 24 h after contrast administration. Study variables included serum creatinine, and urinary creatinine and osmolality. Urinary enzymes and proteins which were evaluated included alanylaminopeptidase (AAP, a brush border enzyme), N-acetyl-β-glucosaminidase (NAG, a lysosomal enzyme), and α-1-microglobulin (α-1-micro, a filtered microprotein). All urinary enzymes and proteins were expressed as units per gram urinary creatinine. Collateral effects and volume of contrast media were also evaluated.

**Urinary enzyme and protein measurement**

Urine samples were immediately centrifuged at 1500 g for 10 min; the supernatant was filtered through Whatman no. 1 filter paper. A part of the filtrate was dialysed in Visking 8/32 dialysis tubes for 2 h against normal saline in a magnetic Vortex agitator at 4°C. AAP and NAG were determined with a colorimetric technique using kits (FAR, Diagnostic Division, Verona). Albumin and α-1-micro were measured photometrically with kits (Istituto Behring SpA, L'Aquila, Italy) using specific antibodies.

**Statistical analysis**

The data are expressed as mean ± standard deviation. Demographic variables among groups were assessed by Student's t test (age) and chi-square test (gender). Laboratory studies were evaluated with analysis of factorial variance [13], and the variance was divided into 'time' and 'treatment' with nitrendipine. Since there were no significant differences due to the type of contrast agent (iopentol or iohexol) and these groups were homogenous for demographic variables, the results of these two groups were combined for the evaluation of the treatment effect of nitrendipine. Collateral effects were evaluated by chi-square test.

**Results**

The average age of the patients was 65.7 ± 9.3 years, and there were no significant differences among the groups. Males comprised 62% of the subjects; despite the randomization process, the control group contained more males (68%) than the treatment groups. Baseline values of electrolytes and renal function, however, did not differ. Concurrent medical therapy included antiplatelet or anticoagulant therapy (42% of patients), ACE inhibitors (8.5%), diuretics (6.2%), and non-steroidal anti-inflammatory drugs (NSAIDs, 2.1%), which was equally distributed among the groups. Diabetes mellitus affected 14% of the patients, again equally present among the groups. MAP was reduced from 136.71 ± 16.86 before to 129.50 ± 16.86 mmHg after the radiological procedure (∗P = 0.007) in group 3. Collateral effects due to nitrendipine were absent, and the volume of contrast injected did not differ among the groups. Serum values of creatinine remained unchanged during the study period (Figure 1) and were unaffected by nitrendipine pretreatment.

Figure 2 illustrates the effect of the single doses of nitrendipine on urinary protein and enzyme excretion after radiointrocontrast injection. Albuminuria was not
changed as a result of the dye load, whereas AAP, NAG, and α-1-micro increased significantly, all except AAP returning to baseline at 24 h. The magnitude of the increased AAP excretion was also greater than the other indicators of tubular damage. Pretreatment with nitrendipine did not reduce the increase in enzyme excretion. The baseline AAP concentration was significantly lower in the group treated with the 20-mg dose; however, also in this group AAP secretion increased significantly after the contrast load.

Acute renal failure, defined as a 50% increase of serum creatinine 24 h after radiocontrast administration, was observed in eight patients (Table 1); four from Group 1 (8.3%), three from group 2 (6.5%), and one from group 3 (3.7%); there were no significant differences among the groups. Age, contrast load, and concurrent ACE inhibitor or NSAID therapy were not significantly different from patients who did not develop RCIN.

Discussion

In the present study two large groups of elderly patients pretreated with single oral doses of a dihydropyridine calcium-channel antagonist before radiocontrast administration did not differ in terms of urinary enzyme excretion increase or the incidence of acute renal failure when compared with an untreated control group. This result contrasts with several smaller studies employing calcium antagonist pretreatment to reduce renal damage following contrast administration. Neumayer and colleagues [12] compared a 3-day treatment with nitrendipine 20 mg p.o. with a placebo group and found an improvement in AAP excretion and inulin clearance with the drug. Russo et al. [14] administered nifedipine 10 mg s.l. before high-osmolality contrast injection and found an increase in inulin and PAH clearances compared to controls during the 2 h after dye injection. Finally, Costanzi
et al. [15] found that pretreatment with felodipine 10 mg p.o. reduced AAP excretion in patients at risk following contrast injection. The incidence of acute renal failure due to the contrast medium is not mentioned in these studies. In the present study the observation that the brush border enzyme AAP was the most sensitive and long-lived indicator of tubular damage following contrast injection agrees well with the previous investigations.

The rationale for the use of calcium antagonists for 'renal protection' stems primarily from the ability of these agents to antagonize preglomerular vasoconstriction in isolated perfused kidneys or in micropuncture studies. Altered tubular transport of water and electrolytes may also provide some protection against tubular toxins. Finally, calcium antagonists have been shown to prevent increased cellular and mitochondrial calcium in the presence of anoxia in cell cultures [16]. In intact animals, however, the renal vascular response is not consistent and depends on the experimental setting—'drug dose, duration of treatment, frequency and route of administration, hydration status, potassium and magnesium homeostasis, sex, strain, species, and race' [16]—and the basal vascular tone [17]. In addition the bioavailability of calcium antagonists may be markedly reduced by first-pass metabolism [18] and increases only after repeated oral doses due to saturation of hepatic metabolic pathways. These factors may explain in part the differences between previous studies and ours, although it seems clear that future studies employing the nephroprotective effect of calcium antagonists per os should use multiple doses to saturate hepatic metabolic pathways. Sublingual administration of these agents for nephroprotection should be abandoned, since calcium antagonists are not particularly well absorbed by the buccal mucosa [18].

Another variable which confounds the comparison of recent studies is the use of urinary enzymes as markers of tubular damage. Reference values for urinary enzymes have not yet been established due to wide inter- and intrapatient differences in urinary flow rate, physical exercise, and circadian rhythms [19]. In fact, baseline AAP levels varied significantly in the present study. In addition, different preservation techniques and enzyme assays can produce important differences in results. In our opinion urinary enzyme values should be expressed per mg urinary creatinine to correct for some of these confounding variables.

In conclusion, our study does not support the use of single doses of calcium antagonists as prophylaxis against RCIN. Repeated doses of these agents per os may prove to be effective in preventing RCIN, but the proof would require a controlled, randomized trial employing serum creatinine as the outcome variable.

Acknowledgements. Part of this study was presented at the 31st Congress of the European Dialysis and Transplant Association—European Renal Association, Vienna, July 1994.
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Received for publication: 18.4.95
Accepted in revised form: 2.11.95