Abstract and Introduction

Abstract

**Background.** Intracoronary (IC) calcium channel blockers (CCB) such as diltiazem and verapamil are frequently utilized during percutaneous coronary interventions to maximize coronary blood flow. Their use, however, may be limited by systemic side effects such as hypotension and bradyarrhythmias. The vasoselective dihydropyridines, such as nicardipine, may be more effective at increasing coronary blood flow with fewer systemic side effects. This study compares the effects of nicardipine, diltiazem and verapamil on coronary blood flow, heart rate and blood pressure.

**Methods.** IC nicardipine (200 mcg), diltiazem (1 mg) and verapamil (200 mcg) were serially administered in a randomized, double-blinded fashion in minimally diseased (< 30% stenosis) left anterior descending or left circumflex arteries in nine patients. Epicardial coronary artery diameter (ECAD) was determined by quantitative coronary angiography and coronary blood flow velocity (CBFV) was measured by Doppler Flowire in each patient before and after each medication.

**Results.** Nicardipine significantly increased CBFV ($p < 0.05$) and had a longer duration of effect ($p < 0.05$), but had no difference in ECAD compared with diltiazem and verapamil. No differences were noted between CCB in changes in heart rate or mean arterial blood pressure. However, two patients had transient episodes of Type I second degree AV block after receiving diltiazem.

**Conclusions.** When compared with diltiazem and verapamil, nicardipine appears to offer more potent and more prolonged vasodilatation with less risk of serious systemic side effects. Future studies are needed to assess the efficacy of IC nicardipine in patients with no-reflow.

Introduction

Intracoronary (IC) calcium channel blockers (CCBs) are administered during percutaneous coronary interventions (PCI) when there is evidence of reduced coronary flow, especially in the setting of nitroglycerin resistance.[1-5] More recently, IC CCBs have been used prophylactically prior to PCI and following interventional procedures. The intracoronary administration of calcium channel blockers maximizes local coronary blood flow while minimizing effects on blood pressure and heart rate. Although IC verapamil[5] and diltiazem[2,9] have been used with excellent results, both have dose-limiting chronotropic, dromotropic and negative inotropic effects on the heart.[10,11]

The dihydropyridines constitute a distinct category of calcium channel blockers that have prominent vasodilatory effects with minimal chronotropic and inotropic action.[29] Thus, dihydropyridines such as nicardipine may be more effective at increasing coronary blood flow with fewer adverse systemic effects. Previous studies have demonstrated that nicardipine induces a marked increase in coronary blood flow,[2,13] No study, however, has directly compared the effects of intracoronary administration of nicardipine to the more commonly utilized calcium channel blockers diltiazem and verapamil. Accordingly, we compared the vasodilator and hemodynamic effects of nicardipine to diltiazem and verapamil to determine the most efficacious drug.
Methods

Patient Selection

All patients enrolled in this study were scheduled to undergo elective PCI of either the left anterior descending artery (LAD) or left circumflex artery (LCX). In order to minimize the risk of bradyarrhythmias and to avoid the need for multiple guiding catheters, the right coronary artery was not utilized. IC CCBs were administered through the PCI guiding catheter into a non-diseased LAD or LCX artery (defined as < 30% stenosis). Patients were excluded from the study if they had an acute coronary syndrome within the last 30 days, left main disease (> 30% stenosis), significant multi-vessel disease (> 50% stenosis), previous percutaneous or surgical revascularization, hypotension (systolic blood pressure < 100 mmHg), bradycardia (heart rate < 50 bpm), 2nd/3rd degree AV block, labile heart rate or blood pressure requiring the need for vasoactive medication during the study, or a left ventricular ejection fraction of less than 45%. Oral calcium channel blockers were withheld at least 48 hours prior to the study and oral nitrates were withheld at least 24 hours prior to the study. Informed consent was obtained from all patients prior to diagnostic coronary angiography. The study protocol was approved by the hospital committee for human research. Nine patients (9 males, mean age 65 years, mean body weight 94 kg) were enrolled in the study.

Diagnostic Coronary Angiography

Patients underwent left heart catheterization after receiving diphenhydramine 50 mg and diazepam 5-10 mg orally as routine premedications. Using ionic contrast (Hypaque, Nycomed Amersham Imaging, Princeton, New Jersey), selective coronary angiography was then performed in multiple projections with 6 French (Fr) Judkins left and right coronary catheters. The study protocol was initiated if the angiographic criteria were met and percutaneous coronary intervention was to be performed.

Study Protocol (Figure 1)

Using a standard 8 Fr guiding catheter, the baseline epicardial coronary artery diameter (ECAD) of the study vessel was determined utilizing biplane coronary angiography. An intracoronary Doppler guidewire (FloWire®, Cardiometrics, Inc., Mountain View, California) was placed in the proximal segment of the study vessel and baseline coronary blood flow velocity (CBFV) was recorded. The coronary blood flow (CBF) was then calculated from the ECAD and CBFV. After confirming a stable Doppler signal, nicardipine (200 mcg), diltiazem (1 mg), and verapamil (200 mcg) were administered in a randomized, double-blinded fashion over 30 seconds. Heart rate, blood pressure and CBFV were continuously monitored and recorded for later analysis. Once CBFV had peaked and then started to fall, biplane coronary angiography was performed. Following angiography, the CBFV continued to be recorded until it reached a baseline steady state for at least five minutes, at which time the second medication was administered. Following the same procedure, the third calcium channel blocker was given. Duration of drug effect was predefined as the time in minutes from drug administration until CBFV declined to 50% of peak effect. Once the recordings for the third medication were completed, the study protocol was concluded and PTCA of the LAD or LCX was performed as planned.
Figure 1. Schema of the study protocol.

Quantitative Coronary Angiography (QCA)

ECAD was measured using biplane quantitative coronary angiography performed at baseline and immediately following administration of each drug. All angiograms were obtained in identical transverse and sagittal inclinations with constant focus-object and object-image intensifier distances. Films were sent to a separate laboratory (University of Washington School of Medicine, Seattle, Washington) for independent QCA measurements. End-diastolic diameters were measured at a constant site in the proximal vessel segment distal to the tip of the Doppler catheter (site of the sample volume). The external diameter of the guiding catheter was used for calibration. ECAD was measured twice in each projection by an independent, blinded investigator resulting in 4 measurements from which the mean ECAD was calculated.

Doppler Measurements

The Doppler angioplasty guidewire (Flowire, Cardiometrics, Inc., Mountain View, California), is a 175 cm-long, 0.014 [hungarumlaut] diameter guidewire with a 12 MHz piezoelectric ultrasound transducer integrated into the tip which has been described and validated previously\(^{16,17}\). Following baseline biplane coronary angiography, the Doppler guidewire was advanced into the proximal segment of the study vessel and maneuvered until a stable high-quality velocity spectral signal was obtained. The spectral display, Doppler audio signals, simultaneous ECG and blood pressure were recorded on a one-half inch videocassette recorder (Panasonic®) for later review.

Calculations

Coronary blood flow (CBF) was calculated by the method described and validated by Douchette et al.\(^\text{[16]}\) Briefly, CBF was estimated as half of the average peak velocity (APV) by assuming a time-average parabolic velocity profile across the vessel. Doppler-derived time-averaged coronary blood flow (CBF) was then calculated as:

\[
\text{CBF} = p \left( \frac{\text{ECAD}}{2} \right)^2 \times \text{CBFV}
\]

with ECAD representing the mean of two angiographic projections measured at the tip of the Doppler FloWire. ECAD, CBFV and CBF were measured and calculated after each medication and compared with baseline values in order to calculate percent change. Each patient served as their own control.

Statistical Analysis

Data are presented as the mean± standard deviation unless otherwise stated. An analysis of variance (ANOVA) with repeated measures on ranks (Sigma Stat Version 2.0, Jandel Scientific, San Rafael, California) was employed to assess treatment effects on hemodynamic, angiographic and coronary blood flow velocity measurements. If significant
changes were noted by ANOVA, a Student-Newman-Kuels post-hoc test was used to identify differences between calcium channel blockers. $P$-values < 0.05 were considered significant.

**Results**

**Patient population**

Forty-eight patients were recruited for potential participation in the study based on either clinical suspicion of or known single-vessel CAD of the LAD or LCX artery. Eleven patients were found to have suitable coronary anatomy. One patient, however, was excluded because of left main disease not appreciated on initial diagnostic cardiac catheterization. A second patient was excluded because of marked hypertension requiring vasoactive medication prior to initiation of the study protocol. Thus, a total of nine patients completed the study protocol.

**Effect on Systemic Hemodynamics**

As shown in Figure 2, there was a trend toward a greater change in heart rate from baseline in the diltiazem group compared with the nicardipine and verapamil groups ($P = 0.06$). Two of the nine patients experienced transient episodes of Type I second degree AV block after receiving IC diltiazem. No difference was noted on mean arterial pressure between calcium channel blockers ($P = 0.19$). Mean arterial blood pressure at peak effect for nicardipine, diltiazem and verapamil were 91 ± 3 mmHg, 92 ± 3 mmHg and 91 ± 3 mmHg, respectively.

![Figure 2](http://www.medscape.com)

**Effect on ECAD**

There was no difference ($P = 0.12$) between baseline ECAD (2.7 ± 0.6 mm) and ECAD following intracoronary nicardipine (2.8 ± 0.6 mm), diltiazem (2.7 ± 0.6 mm), and verapamil (2.8 ± 0.7 mm).

**Effect on CBFV**

As shown in Figure 3, nicardipine produced a greater percent change in CBFV from baseline (123 ± 60%) compared with diltiazem (99 ± 56%) and verapamil (69 ± 27%). The percent change in CBFV with nicardipine was significantly greater than with verapamil ($P < 0.05$). Similar changes were noted with calculated coronary blood flow.
Figure 3. Peak changes in coronary blood flow velocity (n = 9).

Duration of Effect and Effect on Cbfv over 10-Minute Period

As shown in Figure 4, nicardipine produced a longer duration ($p < 0.05$) of effect (5.0 ± 2.0 minutes) compared with diltiazem (2.7 ± 1.3 minutes) and verapamil (1.8 ± 0.7 minutes). Figure 5 depicts the mean CBFV for each of the three drugs over the 10-minute sampling period. Nicardipine produced a greater ($p < 0.05$) mean increase over baseline coronary blood flow velocity (65%) compared with diltiazem (23%) and verapamil (10%).

Figure 4. Duration of drug effect (see text for details).
Discussion

Intracoronary calcium channel blockers are frequently utilized in order to increase coronary blood flow during percutaneous interventions. In distinction to nitrates, which must be converted into vasoactive metabolites, calcium channel blockers act directly on vascular smooth muscle. It has been suggested that nitrate-resistant reductions in coronary blood flow may be due to an inability of microvasculature to metabolize nitrates, especially in the setting of ischemia. This would explain the refractory response to nitrates and the superior response to calcium channel blockers in attempts to reverse the “no-reflow” phenomenon.

The question remains as to which intracoronary calcium channel blocker should be utilized. Ideally, the drug would provide maximal vasodilatory properties with minimal untoward negative chronotropic, dromotropic and inotropic side effects. As a class, the dihydropyridines possess the most potent vasodilatory properties relative to other effects when compared with the other classes of calcium channel blockers such as the phenylalkylamines (e.g., verapamil) and the benzothiazepines (e.g., diltiazem). This vasoselective property was elegantly demonstrated by Magnon et al. They compared the effects of eight calcium channel blockers on in vitro blood vessel and myocardial strip preparations and showed that the dihydropyridines had a more potent "vasoselectivity ratio" (ratio of the negative inotropic potency and the vasorelaxant potency). Furthermore, within the dihydropyridines, nicardipine has been shown to possess more potent vasodilatory effects than first-generation compounds such as nifedipine and appears to be relatively selective for coronary vascular smooth muscle.

In addition to the in vitro pharmacological data supporting the use of the dihydropyridines, several vivo studies have demonstrated the clinical utility of intracoronary nicardipine. Despite this, the majority of published studies have reported results on the less vasoselective compounds diltiazem and verapamil. Most recently, the results of the CARAFE pilot study were published. In this study, the use of a verapamil (10g/ml, total dose 100µg), nitroglycerin (4 µg/ml) and heparin (20 U/ml) "cocktail" during rotational ablation required demand pacing in 15 of 21 patients despite prophylactic administration of atropine. While at least some bradyarrhythmias could be attributed to other factors such as ischemia and endogenous adenosine release, this study nevertheless highlights the attractiveness of a more vasoselective calcium channel blocker. To our knowledge, our study is the first to compare the effects of three different calcium channel blockers in a double-blinded, head-to-head fashion.
Study Limitations

In our study, each patient received the three study drugs, thereby acting as their own control. While our study design does not preclude the additive effects of the drugs, this was minimized by waiting for a return to baseline for at least five minutes prior to the administration of the next medication. Furthermore, each of the calcium channel blockers were administered in random order, thereby eliminating bias created by giving the medications in a particular sequence.

Utilization of a Single Drug Dose

While it is possible that increasing doses of diltiazem and verapamil may have altered our results, our dosages were chosen based on previous studies. In the current study, two of the nine patients displayed transient second degree Type I AV block after receiving diltiazem. AV conduction effects have been reported by other investigators using similar doses of diltiazem as well as verapamil. In our study and others, there were no clinically significant bradyarrhythmias observed following the administration of intracoronary nicardipine.

Treatment of the "No-Reflow" Phenomenon

Many agents, including calcium channel blockers, abciximab (c7E3 Fab, ReoPro, Eli Lilly & Company, Indianapolis, Indiana) and the adenosine triphosphate-sensitive K+ channel opener nicorandil, have been used to treat or prevent no-reflow. Although our study demonstrates the efficacy of IC nicardipine in coronary arteries with no or minimal disease, it was not evaluated in the setting of no-reflow.

Conclusion

In the population studied, the intracoronary administration of nicardipine produced a superior and more prolonged increase in coronary blood flow, compared with diltiazem and verapamil. When compared with diltiazem and verapamil, nicardipine appears to offer more potent and more prolonged vasodilatation with less risk of serious systemic side effects. As this study was performed in minimally diseased vessels, future studies are needed focusing on the efficacy of nicardipine in the no-reflow phenomenon.

References


33. Williams MS, Coller BS, Väänänen HJ, et al. Activation of platelets in platelet-rich plasma by rotablation is speed-dependent and can be inhibited by abciximab (c7E3 Fab; ReoPro). Circulation 1998;98:742-748.

