ELSEVIER

International Journal of Cardiology 139 (2010) 181 – 186

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Influence of atenolol on coronary artery spasm after acute myocardial infarction in a Japanese population

Manabu Shirotani *, Ryoji Yokota, Ichiro Kouchi, Taku Hirai, Noritsugu Uemori, Kazunao Haba, Ryuichi Hattori

Department of Cardiology, Nara Hospital, Kinki University of Medicine, 1248-1, Otoda-Cho, Ikoma, Nara, 630-0293, Japan

Received 12 May 2008; received in revised form 13 August 2008; accepted 12 October 2008
Available online 18 November 2008

Abstract

Background: Japanese patients with acute myocardial infarction (MI) have a greater incidence of coronary artery spasm than Caucasians. Some beta-blockers have been reported to aggravate coronary spasm. This study sought to assess the effects of beta-adrenoceptor blockade on coronary vasospasm in Japanese patients with acute MI who had been treated with primary angioplasty.
Methods: In 69 patients we analyzed the effect of atenolol 50 mg/day initiated the day after emergency primary angioplasty on the results of intracoronary ergonovine provocation test performed 4 weeks after onset.
Results: Among 35 patients in the atenolol group, the drug was discontinued in 9 (26%) due to hemodynamic compromise. The remaining 26 in the atenolol group and 34 in the control group underwent the spasm provocation test. Atenolol did not significantly increase the incidence of coronary vasospasm (31% vs. 15% in the atenolol and control groups, respectively, $p = 0.135$). Multivariate analysis revealed that only the pre-provocation diameter of the distal segment of the infarct-related artery predicted coronary spasm whereas atenolol did not.
Conclusions: This study showed that atenolol 50 mg/day did not increase coronary spasm in Japanese acute MI patients. It is suggested that beta-blockers can be safely used soon after coronary intervention for acute MI without the risk of increasing coronary spasm; however, attention should be paid to hemodynamic change in the acute phase.

Keywords: Acute myocardial infarction; Beta-blocker; Coronary spasm; Japanese

1. Introduction

Beta-blockers have been found to reduce mortality and morbidity in post-myocardial infarction (MI) patients in the long- as well as short-term period [1–4]. They have been shown to improve stroke volume and left ventricular diastolic filling and to suppress left ventricular remodeling [5–7]. On the other hand, they may induce vascular smooth muscle contraction and thereby promote coronary artery spasm. If this occurs in patients with acute MI, it may cause more extensive myocardial ischemia, leading to serious clinical conditions.

Pristipino et al. [8] demonstrated racial differences in coronary vasoconstrictor response between Japanese and Caucasians in post-acute MI patients. In this study, coronary artery spasm was much more commonly observed in Japanese than in Caucasians (80% vs. 37%). The Japanese Beta-blockers and Calcium Antagonists Myocardial Infarction (JBCMI) investigators [9] reported that the incidence of unstable angina due to coronary spasm was higher in those receiving beta-blockers compared to calcium antagonists among Japanese post-acute MI patients. Therefore, it is important to clarify whether beta-blockers have a deleterious effect in Japanese post-acute MI patients by aggravating coronary spasm and offsetting the above beneficial effects.

* Corresponding author. Tel.: +81 743 77 0880; fax: +81 743 77 0901.
E-mail address: manabu@nara.med.kindai.ac.jp (M. Shirotani).

0167-5273/$ - see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2008.10.017

The present study was designed to evaluate for the first time the effects of a beta-blocker, atenolol, on coronary vasospasm in Japanese post-acute MI patients after treatment with emergency primary angioplasty.

2. Methods

2.1. Patients

The study cohort consisted of 69 acute MI patients (55 men and 14 women, mean age, 62±11 years) who underwent emergency primary coronary intervention (PCI) for an infarct-related artery (IRA) showing a Thrombolysis in Myocardial Infarction trial (TIMI) flow grade of 0 or 1. These patients were recruited from consecutive subjects referred to our hospital within 12 h of pain onset from June 2002 to April 2007. To be included in the study, patients needed to be older than 18 years of age and have had successful PCI obtaining TIMI 3 flow grade with residual stenosis of <50%. Patients were excluded if they had atenolol allergy, bradycardia (heart rate <50 bpm), advanced heart block, Forrester subset ≥2 by right heart catheterization including cardiogenic shock, chronic obstructive lung disease, or arteriosclerosis obliterans. All patients gave written informed consent for participation in this trial.

2.2. Study design

This study was planned as a prospective controlled clinical trial with parallel groups. The study protocol complies with the Declaration of Helsinki, and was approved by the ethics committee of our institution.

Eligible patients were assigned alternatively to either the control group ($n=34$) or the oral atenolol (50 mg tablet once daily) group ($n=35$) after successful PCI. In the latter group, the agent was initiated the day following PCI. Calcium antagonists were not allowed in either group. Four weeks later, patients were scheduled to undergo echocardiography followed by cardiac catheterization. All vasoactive drugs but atenolol were suspended 24 h prior to catheterization. Echocardiographic transmitral flow velocities were recorded from the apical four-chamber view using pulsed Doppler, and the ratio of early flow velocity to atrial flow velocity (E/A ratio) was measured together with heart rate. Coronary angiogram was performed following left ventriculogram by which global left ventricular ejection fraction (LVEF), endodiastolic volume index (EDVI), and endosystolic volume index (ESVI) were measured. Subsequent to control angiogram, the intracoronary ergonovine provocation test for spasm was performed starting with the coronary system, including IRA. Ergonovine was injected at doses of 20 and 30 micrograms into right and left coronary arteries, respectively, over 60 s. The angiogram was taken 4 min after the completion of ergonovine injection or earlier when patients had chest pain with ST-T segment elevation or ST depression of >0.1 mV on electrocardiogram. Unless significant coronary spasm was documented, the test was attempted for the contralateral coronary artery. Sufficient isosorbide dinitrate was then given intracoronarily to fully dilate the arteries and the final angiograms were obtained.

2.3. Angiographic evaluation

Qualitative and quantitative assessments were performed by two independent cardiologists unaware of treatment assignment. Digital angiograms were analyzed offline with an Automated Edge detection system (CMS, Medis Medical Imaging Systems, Nuenen, The Netherlands). Each coronary artery was divided into 3 segments, proximal, middle, and distal, and each was analyzed in its optimal view prior to the provocation test and after each drug administration. For each coronary segment, diameters were measured on end-diastolic frames and percent diameter reduction was also calculated before and after ergonovine injection relative to maximal dilation obtained by isosorbide dinitrate. A diseased vessel was defined as one with >70% narrowing even after nitrate injection.

2.4. Study end points

The primary endpoint was the incidence of coronary vasospasm by ergonovine provocation test, defined as >90% constriction. Secondary endpoints were death, any acute MI, target vessel revascularization, heart failure, anginal attack, stroke, and ventricular arrhythmia.

2.5. Statistical analysis

Continuous variables were compared using the unpaired two-sided Student's t test, and categorical variables were

Table 1
Baseline characteristics of the study population.

	Atenolol group ($n=35$)	Control group ($n=34$)	p
Men (%)	29 (83)	26 (77)	0.510
Age (yrs)	63±10	61±12	0.396
Smoking (C/E/N) (%)	17/12/6 (49/34/17)	20/5/9 (59/15/26)	0.156
Family history of CAD (%)	4 (11)	6 (18)	0.513
Hypertension (%)	26 (74)	19 (56)	0.109
Hyperlipidemia (%)	23 (66)	22 (65)	0.930
Diabetes mellitus (%)	11 (31)	4 (12)	0.048
Hyperuricemia (%)	5 (14)	6 (18)	0.703
Peak CK (IU/l)	3681±2052	3178±2279	0.338
No. of diseased vessels (1/2/3) (%)	23/10/2 (66/28/6)	23/7/4 (68/20/12)	0.554
IRA (LAD/RCA/Cx) (%)	17/12/6 (49/34/17)	15/16/3 (44/47/9)	0.431
Stent implantation (%)	22 (63)	21 (62)	0.925

Abbreviations: C: current smoker; CAD: coronary artery disease; CK: creatine phosphokinase; Cx: left circumflex artery; E: ex-smoker; IRA: infarct-related artery; LAD: left anterior descending artery; N: non-smoker; RCA: right coronary artery.