VIA MEDICA

NEW DRUGS AND TECHNOLOGIES IN CARDIOLOGY

Cardiology Journal
2010, Vol. 17, No. 5, pp. 528–531

ISSN 1897–5593

The 'chest pain kit' study: A 'pill in the pocket' concept to improve the pre-hospital therapy of acute coronary syndrome

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Abstract

The 'pill in the pocket' concept is an established therapy for atrial fibrillation. The current guidelines for the management of patients with ST-elevation myocardial infarction endorse the concept that faster time to reperfusion is associated with important reductions in morbidity and mortality. The mechanical reperfusion and outcome of these patients is significantly supported by dual antiplatelet therapy. There is no data comparing the effect of early self-application by the patient ('pill in the pocket') versus *application by the emergency doctor of dual antiplatelet therapy and a factor Xa inhibitor in case of severe chest pain.*

In patients with a high risk of developing an acute coronary syndrome and previously selected by a cardiologist, early self-application of dual antiplatelet therapy and a factor Xa inhibitor (e.g. fondaparinux) immediately after calling the emergency doctor might be of significance in cases of acute coronary syndrome or pulmonary embolism. In particular, in less developed areas where it might take a long time for the emergency doctor to arrive, this 'pill in the pocket' concept may be significant. (Cardiol J 2010; 17, 5: 528–531)

Key words: acute coronary syndrome, myocardial infarction chest pain, pill in the pocket

Introduction

The current American College of Cardiology and American Heart Association (ACC/AHA) guidelines for the management of patients with ST-elevation myocardial infarction (STEMI) endorse the concept that faster times to reperfusion and better systems of care are associated with important reductions in morbidity and mortality rates [1, 2]. In patients presenting with acute coronary syndrome (ACS), mechanical reperfusion with stenting and the clinical outcome is (among others) significantly supported by dual antiplatelet therapy [3, 4]. Also the factor Xa inhibitor fondaparinux improves the net clinical outcome in patients presenting with ACS [5]. In selected patients, the 'pill in the pocket' concept is an established therapy for atrial fibrillation [6], as is the self-application of insulin s.c.

Hypothesis

In patients previously selected and risk-stratified by a cardiologist, in case of severe chest pain, self-application of some drugs immediately after calling the emergency doctor might improve the outcome in ACS and pulmonary embolism. In particular, in less developed areas where it might take

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Received: 20.07.2010 Accepted: 01.09.2010

a long time for an emergency doctor to arrive, early self-application may be significant. The hypothesis could be tested by a multicenter, randomized, controlled, double-blind study with the following design:

The aim of this study should be to assess the effect of early self-application by the patient ('pill in the pocket') *versus* application by the emergency doctor of dual antiplatelet therapy and a factor Xa inhibitor in cases of severe chest pain.

Study population

The study should include patients with a high risk for developing an ACS, previously selected by a cardiologist, in particular:

— patients with previous history of STEMI or non-STEMI (NSTEMI) or elective percutaneous coronary intervention (PCI), who are currently treated with mono-antithrombotic therapy with acetylsalicylic acid (ASA) 81–325 mg/d.;
— patients without previous history of coronary artery disease (CAD) presenting with a less well-established indication (class IIb) according to the ACC/AHA guidelines for coronary angiography, e.g. patients with a Canadian Cardiovascular Society class I or II angina without high-risk findings on noninvasive testing [7];
— patients with dual antiplatelet therapy, or with anticoagulation with vitamin K antagonists controlled by international normalized ratio (INR) or aortic aneurysms (as the most important criteria among others), should be excluded.

Screening patients for the study, prescription of primary prevention with ASA 81–325 mg/d. according to the ACC Foundation/AHA 2009 performance measures for primary prevention of cardiovascular disease in adults should be initiated. It is recommended for patients at high risk (≥ 20%) for CAD [8].

Study-treatment by self-application

Study medication from the 'chest pain kit' should be taken by the patient him- or herself immediately after calling the emergency doctor (ideally with a button-system allowing localization of the patient). As in the real world, it remains the patient's decision when to call the emergency doctor, and consequently to initialize self-treatment with the drugs. Depending on the continuous medication, pantoprazol 40 mg and atorvastatin 80 mg can also be taken by self-application.

For testing thienopyridine derivatives (clopidogrel, prasugrel or ticagrelor) *versus* a placebo, the 'chest pain kit' used in the study should contain two packages with tablets. Depending on which, the packages should state either: '*Application by Patient*' or '*Application by Emergency Doctor*'.

For testing fondaparinux *versus* a placebo, the 'chest pain kit' used in the study should contain two injections, one with fondaparinux and the other with 0.9% NaCl. Depending on which, the injections should state either: '*Application by Patient*' or '*Application by Emergency Doctor*'.

Study-treatment by emergency doctor

The medication applied by the emergency doctor is located in the 'chest pain kit' and marked '*Application by Emergency Doctor*'. The other procedures of the emergency doctor remain exactly the same as currently recommended in the ACC/AHA guidelines [1, 2]. A possible trial profile is depicted by Figure 1.

Further treatment procedure

In cases of STEMI, deliver directly to a catheter laboratory. In all other cases, deliver to a chest pain unit or emergency department with the aim of definite diagnosis or exclusion of STEMI/NSTEMI/ /unstable angina/aortic dissection/pulmonary embolism. After diagnosis, patients should be treated according to the current ACC/AHA guidelines [1, 2]. The use of glycoprotein IIb/IIIa inhibitors should be at the discretion of the treating physician.

Study endpoints and data capture

Efficacy can be assessed by rates of the composite of death, myocardial infarction (MI) and refractory ischemia at 30 days. Troponin levels from the arterial sheath using a high sensitivity assay, before and immediately after revascularization of the infarct-related artery, as well as serial and maximum elevation of creatine kinase and creatine kinase-myocardial band, should be measured. Safety could be assessed by rates of major bleeding and non-fatal stroke. Net clinical outcome can be assessed by composite of death, MI, refractory ischemia or major bleeding at 30 days.

Other parameters routinely evaluated in ACS studies (such as TIMI flow at baseline/final, door--balloon time, etc.) could be recorded. Further, the incidence of NSTEMI and pulmonary embolism by admission to hospital, subjective quantification of chest pain 1–10, etc. could be evaluated. Cardiac magnetic resonance imaging could be used to evaluate the incidence of transmural infarction, extent of peri-infarction zone, and ejection fraction percentage (at baseline and after cardiovascular event).

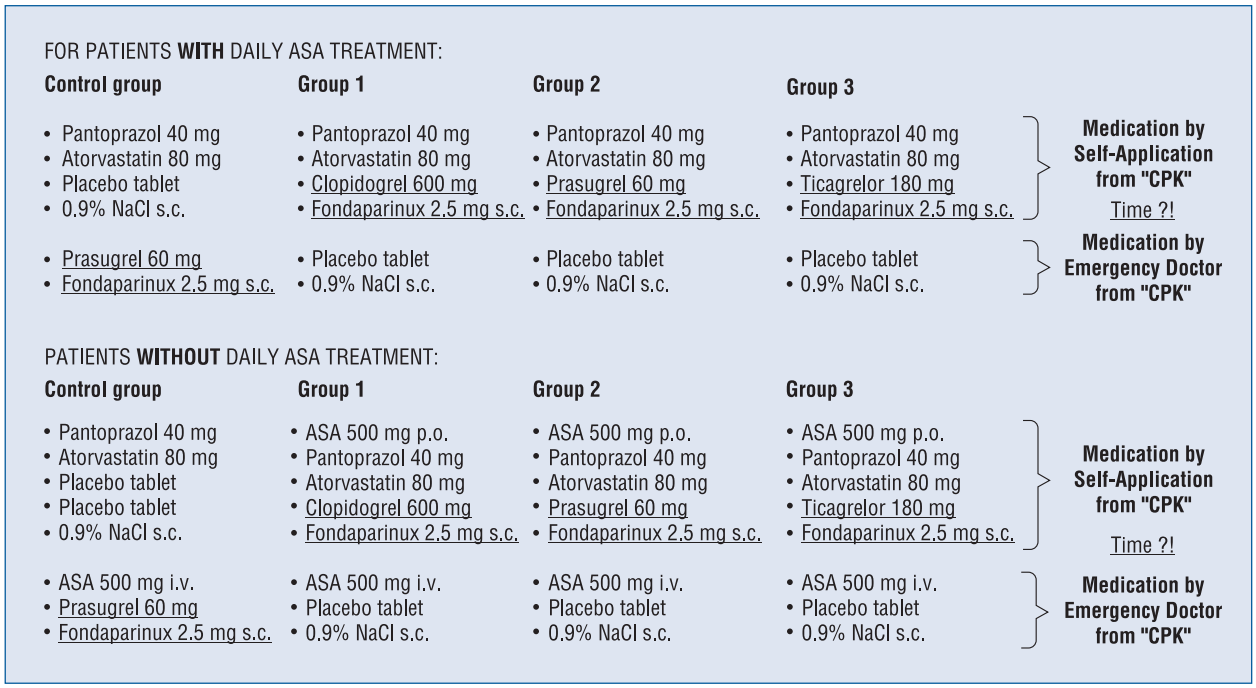

Figure 1. Possible trial profile — first draft; ASA — acetylsalicylic acid, CPK — chest pain kit, NaCl — sodium chloride

Discussion

Many important aspects of this proposed study design need careful consideration. Primarily, the careful selection of patients is ocrucial. Secondly, focusing on the main aspect (early initiation of effective anticoagulation by self-application), a routine use of a platelet function test in the catheter laboratory should be considered to assess the incidence of non-responders and allow early off-blinding and optimizing of the thienopyridine derivate therapy.

Further, depending on the exact study design, the effect of an early application of statins, proton pump inhibitors (PPIs), beta-blockers, nitro derivates and sedatives could be investigated. Nevertheless, the main benefit is expected to result from the dual antiplatelet therapy and the factor Xa inhibitor. The availability of pre-hospital 12-lead electrocardiography, and of physicians who could be contacted by telephone before self-application, would additionally improve the study design.

Of note, the focused update of the ACC/AHA guidelines [2] states that additional data from randomized controlled trials is needed before an official recommendation can be made about the use of PPIs in the setting of ACS. This is a question which could also be partly addressed by the study design described here. A complete study protocol is currently in progress.

Conclusion and clinical perspective

In patients previously selected by a cardiologist, early self-application of dual antiplatelet therapy (ASA plus thienopyridine) and a direct thrombin (II) inhibitor or a factor Xa inhibitor (e.g. fondaparinux) immediately after calling the emergency doctor might be of significance in cases of ACS or pulmonary embolism. The combination of drugs inside the 'chest pain kit' should be individually adapted by a cardiologist to allow exclusion/inclusion of ASA, thienopyridine, factor Xa inhibitor, statin, beta-blocker, PPI etc. A combination tablet with these drugs could improve the compliance of the patient and simplify the intake.

The 'chest pain kit' should be designed to be easy to use (maybe as a pen) and might also provide useful information for the emergency doctor ('*Patient takes/does not take ASA*', for example). It should ideally allow the patient's location to be identified. In particular, in less developed areas where it might take a long time for the emergency doctor to arrive, this 'pill in the pocket' concept may be significant.

Acknowledgements

The author has no conflict of interest to declare.

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