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Review article

Enteric-coated aspirin in cardiac patients: Is it less effective than plain aspirin?

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ARTICLE INFO

Article history:

Received 20 March 2017

Accepted 17 May 2017

Available online xxx

Keywords:

Aspirin

Enteric coating

Coronary heart disease

Resistance

ABSTRACT

The aim of this review article is to make readers aware of the risk of an inadequate antiplatelet effect of enteric-coated formulations of aspirin. Judging by data from studies published to date and exploring the efficacy of various aspirin formulations, there exist sufficient evidences only of a plain form of aspirin absorbed in the stomach. The implication is that patients with coronary heart disease (CHD) should be treated exclusively with the standard formulation of aspirin.

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<http://dx.doi.org/10.1016/j.crvasa.2017.05.011>

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Introduction

Current cardiology guidelines are evidence-based ones. A time-proven drug in antiplatelet therapy of CHD patients is acetylsalicylic acid (aspirin), a cyclooxygenase 1 (COX-1) inhibitor, used both in acute and chronic CHD [1]. Two formulations of aspirin have been available on the market for years, plain aspirin absorbed in the stomach, and enteric-coated (EC) aspirin absorbed in the small intestine. The reason behind the development of EC aspirin was an effort to reduce the number of aspirin side effects on the gastric mucosa. As a result, either aspirin formulation can be encountered in everyday practice of physicians treating CHD patients. However, several questions necessarily remain to be answered such as whether the therapeutic effects of both formulations are comparable in these patients, whether their bioavailability is comparable, whether there is a sufficient body of data from clinical trials of treatment with either aspirin formulation and, last but not least, whether EC aspirin indeed offers gastroprotection.

Resistance and pseudo-resistance to aspirin

A crucial role in the bioavailability of aspirin is played by its absorption. Aspirin is a weak acid little dissociated in the setting of gastric fluid pH and hence quickly resorbed across the various gastric cell membranes. Under physiological conditions, COX-1 is acetylated already in the portal circulation where platelets become deactivated. Aspirin is very quickly (half-life 15–20 min.) hydrolyzed to salicylic acid, 70–90% of which is bound to plasma proteins. Increased pH of intestinal fluid results in increased aspirin dissociation thus slowing down the rate of its absorption. Moreover, aspirin is rapidly deacetylated (already in the intestine) by esterases to salicylic acid which is also absorbed in the intestine and decreases COX-1 activity; yet the inhibition is short-term and reversible. Its antiplatelet effect has not been demonstrated [2]. The degree of aspirin absorption during its degradation in the intestine is unpredictable and its levels in the portal circulation are presumably below the limit of its efficacy [2]. Consistent with this concept are conclusions of a study [3] documenting, in patients with Type-2 diabetes mellitus, a late increase in blood salicylic acid levels and its significantly ($p < 0.0001$) lower plasma levels following the administration of EC aspirin compared with plain aspirin taken orally. Further, the study showed a decreased capacity of EC aspirin to inhibit formation of thromboxane B₂ (TXB₂), a metabolite of thromboxane A₂ (TXA₂), and higher residual platelet reactivity. Both aspirin formulations were administered at doses of 325 mg once daily for 3 days. The ability of both aspirin formulations to inhibit serum TBX₂ formation was assessed by the number of patients in either group reaching 99% inhibition of TXB₂ formation or TXB₂ levels < 3.1 ng/ml when receiving the 3 daily doses of aspirin. The incidence of patients with the lowest observed level TXB₂ (C_{min}) > 3.1 ng/ml for plain aspirin was 18.4% ($n = 38$); this was significantly lower than when the subjects were crossed over to EC aspirin (55.6%, $n = 36$; $p < 0.001$). The time needed to reach 99% inhibition of TXB₂

formation was 16.7 ± 4.5 h ($n = 38$) and 48.2 ± 4.6 h ($n = 36$) in the plain and EC aspirin groups, respectively ($p < 0.0001$). Similar statistically significant differences suggesting a lower antiplatelet effect of EC aspirin were also documented when evaluating maximum arachidonic acid-induced inhibition of platelet aggregation as measured by light transmittance aggregometry. Similar findings were reported from other studies [4–6] showing lower EC aspirin bioavailability compared with plain aspirin both in healthy volunteers and CHD patients. Delayed and reduced EC aspirin absorption results in what is referred to as aspirin pseudo-resistance [5]. In individuals with aspirin pseudo-resistance, the effect of aspirin on platelet aggregation was found to return to normal following the administration of plain aspirin. The authors of the above mentioned study [5] suggested that the phenomenon of pseudo-resistance or resistance from clinical causes was often “hidden”, in other publications, under the item resistance to aspirin occurring in up to 5–20% of studies with aspirin. True resistance to aspirin, this seems to be infrequent, is due to a specific phenotype of pharmacological resistance to aspirin as a result of gene polymorphisms such as the PL A1/A2 polymorphism of the glycoprotein IIIa gene.

Aspirin in clinical trials

Now, what data are actually available from clinical trials regarding treatment with aspirin and use of EC aspirin? The 2015 European Society of Cardiology (ESC) guidelines for the management of patients without persistent STE acute coronary syndromes (ACS) [7] state that “An oral loading dose (150–300 mg) of plain aspirin (non-enteric-coated formulation) is recommended, while the recommended intravenous (i.v.) dose is 150 mg”. The ESC guidelines for the management of STEMI [8,9] state that “Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated indefinitely after STEMI”. However, no explicit recommendations are made on the use of EC aspirin in the above documents.

Several studies with ACS patients were published still in the era prior to the advent of adenosine diphosphate (ADP) receptor antagonists. These were the Second International study of infarct survival (ISIS-2) [10] and the Third International study of infarct survival (ISIS-3) [11] evaluating use of thrombolytics, aspirin, and heparin in patients experiencing acute myocardial infarction (IM). While EC aspirin use was allowed in both of these studies, in ISIS-2 aspirin was administered for only one month and, in ISIS-3 the recommendation for the acute phase was to chew the tablet. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial [12] evaluated four groups of acute MI patients treated by streptokinase alone vs. streptokinase + heparin vs. tPA only vs. tPA + heparin. The study, designed to include the administration of plain aspirin, demonstrated a beneficial prognostic effect of its use. However, the above studies were not designed as head-to-head comparison of plain aspirin versus EC aspirin.

Studies with ACS patients from the era of ADP receptor inhibitors, i.e., the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess

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