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FROM ANTI-INFLAMMATORY AND ANTI-PLATELET EFFECTS TO GASTROPROTECTION

Ioan DEMETER *
Emergency County Hospital, Deva, Romania

ABSTRACT. Objectives. The study focuses both on the aspects of the anti-platelet – anti-inflammatory treatment in certain cardiovascular disorders and on the major problem deriving from the chronic use of this medication, problems represented by digestive disorders ranging from simple abdominal pain to gastroduodenal ulcer, upper digestive hemorrhage, perforation and stenosis, as well as on the measures of gastric protection required in such situations. Possible and definite risk factors responsible for the development of post-therapeutic side effects have also been analyzed. **Materials and methods.** The study was conducted on 526 patients with various cardiovascular disorders, who were administered minimum-effective doses of aspirin or Clopidogrel (anti-platelet effect). The patients were divided into categories according to their age, risk factors, and the development of possible complications (mainly drug-induced gastrointestinal complications). The study group was monitored clinically, biologically and endoscopically. **Results.** The study focuses on two major aspects: on the one hand, the obvious benefits of the anti-platelet treatment, also indirectly through the occurrence or avoidance of major cardiovascular events and, on the second hand, the risks of anti-platelet treatment in developing gastrointestinal disorders, erosive esophagitis, erosive ulcer, erosive gastroduodenitis, gastroduodenal ulcer, upper gastrointestinal bleeding (UGIB). **Discussions.** The study reveals the benefits of anti-platelet treatment, benefits that definitely exceed the risks of gastrointestinal complications in a certain category of patients with various clinical manifestations of cardiovascular disorders. The results obtained by using anti-platelet treatment are similar to those published in literature. **Conclusions.** The benefits of anti-platelet therapy exceed the risks of gastrointestinal hemorrhagic complications in many clinical situations characterized by moderate- or high- risk vascular or occlusive events. The association of risk factors increases the rate of side effects, mainly of gastrointestinal ones. The prevention of side effects induced by anti-platelet – anti-inflammatory treatment requires therapeutic gastroprotective measures.

Key words: anti-platelet, therapeutic benefits, risk factors, side effects, gastroprotection

INTRODUCTION

Non-steroid anti-inflammatory drugs (NSAIDs) and anti-platelet medication are two of the most widespread classes of drugs used worldwide for their analgesic, anti-inflammatory, antipyretic and anti-aggregating effects.6 Anti-inflammatory drugs appeared about 1874, when aspirin was discovered and marketed for the first time. 7

The major problem connected with the chronic use of NSAIDs and anti-platelet medication is represented by the development of digestive complications, which may range from a simple abdominal pain to the severe complications of gastroduodenal ulcer (digestive hemorrhage, perforation, stenosis). The chronic use of NSAIDs may increase up to tenfold the rate of developing complications, the need for hospitalization, and of ulcer-induced deaths. More than 100,000 patients are hospitalized for NSAID-induced digestive complications in the United States, and the annual rate of deaths due to major gastrointestinal complications exceeds 15,000. Over one third of the chronic users of NSAIDs are aged over 60, and the risk of intestinal complications in these patients is a considerable one. More than 34 per cent of the population over 65 uses NSAID s daily, the percentage increasing even more when we take into account those patients who also use anti-platelet medication.5

The role of aspirin and, generally, of anti-platelet agents in the treatment and prevention of atherothrombosis has been repeatedly revised.8 There are over 300 studies focusing on side prevention which provide updated information on the effectiveness and safety of anti-platelet treatment.

MATERIALS AND METHODS

The study was conducted on 526 patients (during 2006-2008) and focused on two major aspects: the benefic anti-aggregating and anti-inflammatory effects of aspirin and Clopidogrel in certain disorders, and the side effects of these drugs, mainly at gastrointestinal level. The 526 patients were divided in subgroups according to their disease, age and risk factors for developing drug-induced side effects. Clinical monitoring was associated with ECG, biological tests (bleeding time, thrombocytes, occult bleeding), and endoscopy. Upper digestive endoscopy was performed every six months in order to reveal the development of any drug-induced damage (superficial esophageal, gastric and duodenal erosion, mucosal petechia, ulcerations or even UGIB). Digestive endoscopy was accompanied by needle biopsy of the antral mucosa to check for Helicobacter Pylori.

***Correspondence:** Demeter Ioan, Doctor of internal medicine, Specialist in Allergo-Immunology,Competence in Digestive Endoscopy
Address: Ioan Demeter, str. 22 Decembrie, Emergency County Hospital, Deva, Romania, Tel: +40 722 564 003. Fax: +40 254 212 516
E-mail: demeter.ioan@gmail.com*

Table 1

The division of patients according to age groups and predisposing factors for side effects

526 patients CV disorders	Drug	Age			Gender		Smoking		HP	
		25-40	40-60	> 60	M	F	Smokers	Non-smokers	Pos.	Neg.
STABILIZED EFFORT ANGOR	Aspirin	15	25	36	46	30	40	36	35	42
76 patients	Clopidogrel	0	0	0	0	0	0	0	0	0
ATRIAL FIBRILATION	Aspirin	5	40	55	60	40	55	45	30	70
100 patients	Clopidogrel	0	0	0	0	0	0	0	0	0
PERIPHERAL ARTERIOPATHY	Aspirin	0	2	48	35	15	45	5	5	45
50 patients	Clopidogrel	0	0	0	0	0	0	0	0	0
UNSTABLE ANGINA	Aspirin	0	0	0	0	0	0	0	0	0
70 patients	Clopidogrel	0	29	41	52	18	40	30	30	40
ARTERIAL HYPERTENSION	Aspirin	2	45	88	97	58	95	60	50	105
155 patients	Clopidogrel	0	0	0	0	0	0	0	0	0
OLD MYOCARDIAL INFARCTION	Aspirin	0	20	45	55	10	40	25	25	40
75 patients	Clopidogrel	0	10	0	8	2	9	1	2	8

Table 2

Side effects of the anti-platelet treatment + the effectiveness of the treatment by quantifying possible major vascular events

526 patients CV disorders	Drug	Other associated disorders			Side effects
		Erosive esophagitis	Erosive gastro-duodenitis	Gastric ulcer	
STABILIZED EFFORT ANGOR 76 patients	Aspirin	1 (0.19%)	1 (0.19%)	0	1 case UGIB 1 case MVE
	Clopidogrel	0	0	0	
ATRIAL FIBRILATION 100 patients	Aspirin	1 (0.19%)	5 (0.95%)	4 (0.76%)	2 case UGIB 1 case MVE
	Clopidogrel	0	0	0	
PERIPHERAL ARTERIOPATHY 50 patients	Aspirin	0	7 (1.33%)	4 (0.76%)	2 case UGIB 2 cases MVE
	Clopidogrel	0	0	0	
UNSTABLE ANGINA 70 patients	Aspirin	0	0	0	
	Clopidogrel	3 (0.57%)	6 (1.14%)	4 (0.76%)	2 cases UGIB 2 cases MVE
ARTERIAL HYPERTENSION 155 patients	Aspirin	2 (0.38%)	22 (4.18%)	4 (0.76%)	3 cases UGIB
	Clopidogrel	0	0	0	
OLD MYOCARDIAL INFARCTION 75 patients	Aspirin	4 (0.76%)	8 (1.54%)	4 (0.76%)	1 case UGIB 1 case MVE
	Clopidogrel	1 (0.19%)	2 (0.38%)	2 (0.38%)	1 case UGIB

Table 1 shows the division of patients according to age groups and predisposing factors for side effects (smoking and Helicobacter Pylori). Table 2 shows the side effects of the anti-platelet treatment and the effectiveness of the treatment by quantifying possible major vascular events.

As far as the post-therapy side effects are concerned, the situation is as follows: 12 cases of erosive esophagitis (2.28%), 51 cases of erosive gastroduodenitis (9.69%), 22 cases of gastroduodenal ulcer (4.18%) and 12 cases of UGIB (2,.8%), totaling 97 cases with complications (18.44%).

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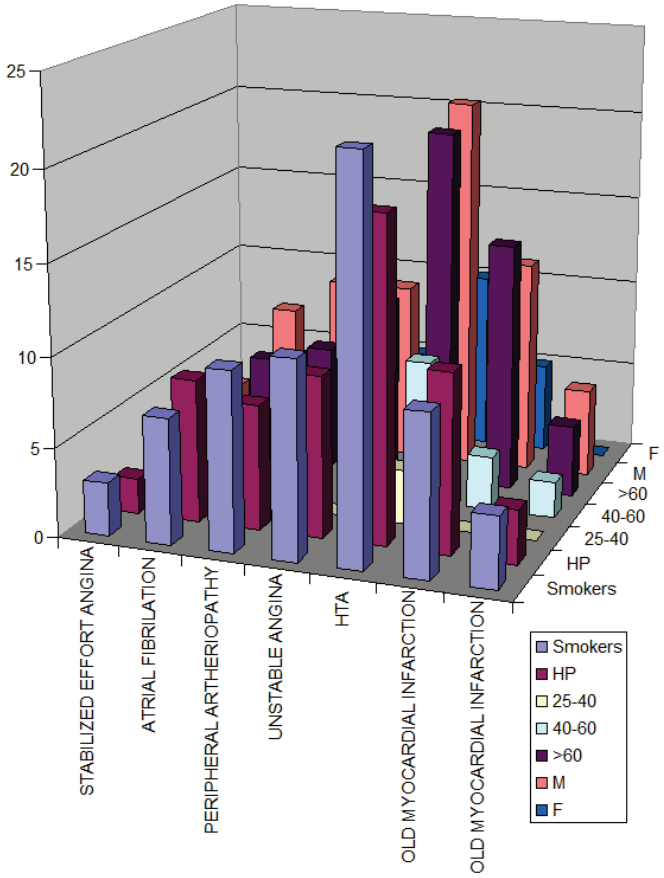

Fig. 1 Complete chart showing the relation of age groups, gender and other criteria with the specified disorders

RESULTS

As far as arterial hypertension is concerned, the charts show that 155 patients were monitored, meaning that they received primary treatment with aspirin. Most of these patients were male, aged around 60, and smokers. This category has a low risk of atherothrombosis and a high risk of gastro-duodenal complications (esophagitis, erosive gastroduodenitis, gastric ulcer and even three cases of UGIB).1,2,3,8 The benefit – risk balance is inconclusive.

The seventy-six patients with stabilized effort angor, mostly male and smokers, had few endoscopic gastro-intestinal signs, one case of UGIB and one case of MVE.

The one hundred patients with chronic atrial fibrillation were mostly males around and over 60, smokers, had two cases of UGIB, a relatively small number of other side effects and one case of MVE.

There were fifty patients monitored for peripheral arteriopathy, all aged over 60, mostly male, smokers, with more side effects of the anti-platelet therapy, two cases of UGIB, four cases of gastro-duodenal ulcer and two MVE.

The patients with unstable angina 4 treated with Clopidogrel, were mostly over 60, males, smokers, with relatively frequent side effects, gastroduodenitis, gastric ulcer, and two cases of UGIB and two MVE.

The seventy-five patients with old myocardial infarction were treated with aspirin (75 mg/day) or with Clopidogrel (75mg/day). The patients treated with Clopidogrel had relatively more side effects and fewer MVEs than the patients treated with aspirin. Of the total of 526 cases, 97 developed side effects (18.44%).

DISCUSSIONS

The study proves the benefits of anti-platelet therapy which definitely exceed the risk of ensuing gastrointestinal complications in a certain category of patients with various clinical signs of cardiovascular disorders. The results obtained by using anti-platelet treatment are similar to those mentioned in literature, except for the number of major vascular events in unstable angina, where the situation seems to have improved. 5

There is also a direct relation between the existence of risk factors (age, smoking, HP) and the increase of gastrointestinal complications (even UGIB).

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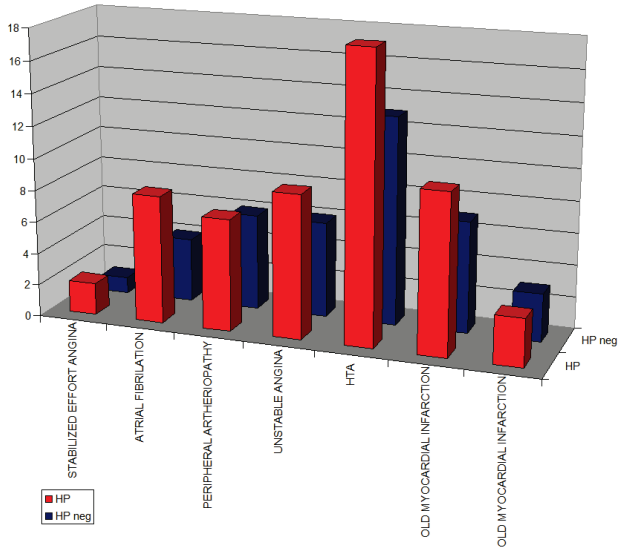

Fig. 2 Positive HP vs. negative HP

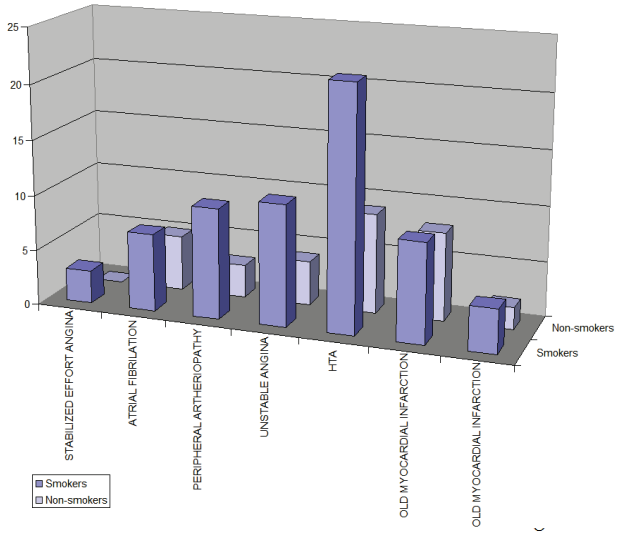

Fig. 3 Smokers vs. Non-smokers

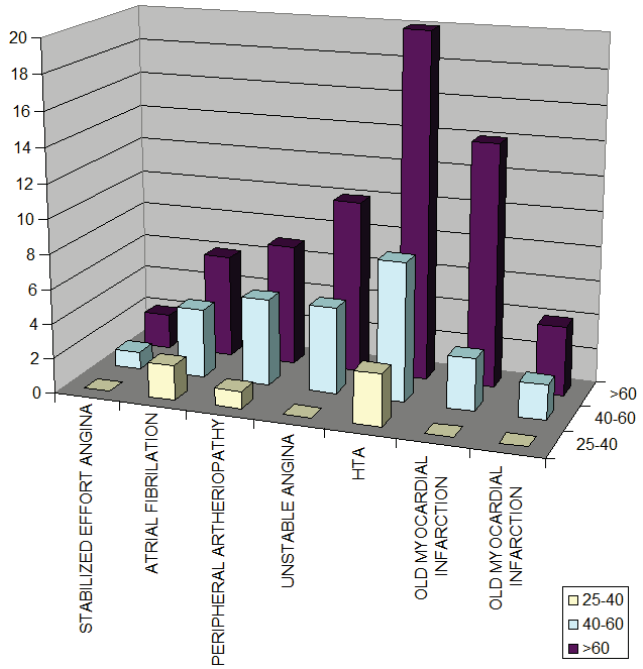

Fig. 4 Age groups

Table 3.

The benefit/risk ratio of anti-platelet treatment in various clinical situations – literature (consensus of the experts on the use of anti-platelet agents in atherosclerotic cardiovascular disorders)

Clinical situation	Benefits (number of patients/1000/year where a major vascular event has been avoided)	Risks (number of patients/1000/year who had a major UGIB event)	
Males with low to high cardiovascular risk	1 —2	1 —2	The benefits and the risks are similar
Arterial hypertension	1—2	1—2	
Stable chronic angina	10	1 —2	The benefits greatly exceed the risks
History of myocardial infarction	20	1 —2	
Unstable angina	50	1 —2	

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CONCLUSIONS

The benefits of the treatment with aspirin and Clopidogrel exceed the risks of gastrointestinal hemorrhagic complications in many clinical situations characterized by a moderate or high risk of vascular or occlusive events.

Although the doses used in anti-platelet therapy were quite small (75 mg/day), gastrointestinal side effects could not be avoided 2 (97 patients out of 526 cases -18.44%).

Administration of aspirin and Clopidogrel in minimum-therapeutic-effective doses prevents MVE; however gastrointestinal side effects should not be overlooked.

The association of predisposing factors (age > 60 – 65, smoking, the presence of HP) increases the rate of gastrointestinal side effects, sometimes leading to wrong conclusions.

The study shows that the results obtained with Clopidogrel are fairly smaller than those obtained by using aspirin, while its side effects are more aggressive than those of aspirin + proton pump inhibitors; however, this should not eliminate the use of Clopidogrel, either alone or associated with other products, according to treatment protocols.

Taking into consideration the quite significant side effects of anti-platelet – anti-inflammatory treatment, such treatment obligatorily needs taking certain gastroprotective measures, measures which are still subject to debate. Thus:

- anti-H2 – they may prevent duodenal ulcers but not gastric ones, studies generally pointing to their ineffectiveness in preventing NSAID-induced damage.
- proton pump inhibitors (PPI) – prevent both duodenal and gastric ulcer (the latter to a lesser degree), being currently the treatment of choice in ulcer prophylaxis.
- prostaglandins (CYTOTEC) also have a protective role of the gastric mucosa.
- protection barrier agents (sucralfate) protect the gastric mucosa against drug aggression.
- entero-soluble products may also slightly protect the gastric mucosa.
- it is mandatory to eliminate risk factors involved in the development of gastrointestinal side effects, one of the most important aspects being the effective treatment of Helicobacter Pylori.
- last but not least, patients who suffer from cardiovascular disorders associated with rheumatoid disorders might associate low doses of aspirin with COX-2 inhibitors with anti-inflammatory effect and a strong analgesic, without overlooking the thrombo-embolic risk. Such an associated therapy has a pro-aggregating effect by reducing prostacyclin synthesis, thus requiring an extremely careful monitoring of this category of patients.

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