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Original article

Low mortality and morbidity of upper gastrointestinal bleeding in Crete. The role of individual non steroidal anti-inflammatory drugs (NSAIDs)

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SUMMARY

Aim: **To estimate the mortality and morbidity of upper gastrointestinal bleeding and to assess the role and relative safety of the common anti-inflammatory drugs (NSAIDs).**

Materials/Methods: **The clinical outcome of 444 patients with upper GI bleeding, admitted to the University Hospital of Heraklion, in relation to the consumption of various NSAIDs was studied prospectively over a 4 year period (1992-1995).**

Results: **The median age of the patients was 62 and the male to female ratio 1.4: 1. In 64.2% of the cases a gastroduodenal ulcer was found. There was a history of NSAID use in 60.6% of patients and NSAID administration was associated significantly with antral erosions (81.7%). Operation and mortality rate were 3.6% and 2.7% respectively. Taking into account the local drug circulation, salicylates, piroxicam and ibuprofen were estimated to have the highest relative risk of bleeding. Drugs used mostly in parenteral or rectal forms were considered safer. No significant association was found between NSAID consumption and age, sex, operation and mortality rate.**

Conclusions: **The operation and mortality rate in patients with upper gastrointestinal bleeding in Crete is remarkably low. NSAID use is strongly associated with upper gastrointestinal hemorrhage and certain brands of NSAIDs have a higher relative risk of bleeding. Parenteral or rectal administration of low-danger drugs is recommended.**

Key words: upper gastrointestinal bleeding, non-steroidal anti-inflammatory drugs (NSAIDs), peptic ulcer

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INTRODUCTION

Acute upper GI bleeding remains a major emergency situation world-wide. The incidence of upper GI bleeding varies between 40 and 150 per 100 000 and increases appreciably with age.[1-4] More than 350 000 patients are hospitalized each year in the United States for upper GI bleeding, 35 to 45% of them being 60 years of age or older.[5,6] Despite the introduction of new acid suppressive drugs and endoscopic intervention modalities, the mortality rate for bleeding from upper GI has remained almost constant during the last 40 years, at approximately 10%.[1,4,7]

The widespread use of NSAIDs, including aspirin, has led to the recognition of their substantial toxicity to the gastrointestinal tract. It is widely accepted that NSAIDs are associated with a spectrum of side effects in the gastroduodenal mucosa.[8] These range from erythema and erosive lesions, to major hemorrhage, perforation and even death. Non-steroidal anti-inflammatory drugs are a well-established cause of peptic ulcer disease and elderly users of NSAIDs are at increased risk of fatal peptic ulcer complications.[9,10] In well-performed studies, the relative risk has been estimated to be three to five. More-

over, the prevalence of peptic ulcers in patients chronically receiving NSAIDs is 10-30% and the relative risk of bleeding is about twofold compared to non-users.[9-13]

The aims of the present study are to estimate the mortality of upper GI bleeding in a group of patients with an acute bleeding episode and to assess the role and relative safety of the common NSAIDs.

MATERIALS AND METHODS

A group of 444 patients with upper GI bleeding, admitted to the Dept. of Gastroenterology of the University Hospital of Heraklion over a 4 year period (1992-1995), was studied prospectively. All patients presented with hematemesis and/or melena or signs of hypovolemic shock. Carcinomas and bleeding esophageal lesions (varices, esophagitis/esophageal ulcers, Mallory-Weiss syndrome) were excluded. Patients with upper GI bleeding that occured while hospitalized were also excluded. All of them were asked about past and present dyspeptic symptoms, history of peptic ulcer disease or previous hemorrhage. A detailed history of smoking and alcohol consumption was obtained. Particular attention was paid to the use of NSAIDs, aspirin and corticosteroids. Patients were considered NSAID users when they had taken one or more drugs at any time during the week prior to admission. The specific NSAIDs and the route of administration (oral, parenteral, rectal), but not the dosage or reason for drug use, were also recorded.

An upper GI endoscopy was performed in almost all patients (92%), and in the majority of them (86.7%) it was done within 24 hours of admission. In a small group of patients (7.9%) with severe coexisting diseases, or advanced age, a radiological examination was preferred. All endoscopic procedures were performed either by an experienced gastroenterologist, or by gastroenterology trainees under supervision. In the minority of cases (5.2%), in which the causative lesion was not endoscopically identified, a small bowel enema and/or a colonoscopy were performed. Endoscopic hemostasis was routinely introduced in our hospital after the second year of the present study and was restricted to 15 actively bleeding ulcers.

All patients received antisecretory treatment during hospitalization: 65% an H_2 blocker and 35% a proton pump inhibitor. Patients were studied until discharged from the hospital or until operation or death. Outcome data included transfusion requirements, hospital stay, need for surgery and death rates. The postoperative outcome and length of hospital stay were also recorded.

Statistics

The association between the results of the endoscopic examination and the use of NSAIDs was assessed by Pearson's chi-square test, while the relative risk was estimated by the odds ratio (aproximate relative risk).[14] The association of the various brands of NSAIDs (salicylates, diclofenac, piroxicam, tenoxicam, ibuprofen, corticosteroids, indomethacin, naproxen and niflumic acid) and bleeding episodes was assessed by the corresponding relative risks, estimated by the odds ratios of each drug against the non-users. The calculation of the latter was based on local drug circulation for 1992-1995 (Table 1) projected on a sample of would be 'controls' (with no bleeding episodes) from the general population. In such a case, the frequencies of users of the various drugs among a sample of n such controls, is calculated by assuming that the proportion of NSAIDs is constant at value p. The non-users are regarded as representing a natural zero with which it is reasonable to compare the 9 brands of NSAIDs. Obviously the relative risks are correlated since the non-user figures come into each comparison. Furthermore, they do not depend on n, the sample size of 'controls', but do depend on the unknown proportion p of users of NSAIDs in the general population (although their relative ranking is independent of this proportion). Differences between the relative risks were tested using the large sample estimates of their variances and covariances. Note that the estimates of these variances and covariances change very slowly by varying n or p. To account for the number k say, of multiple tests, the significance level of each test was set at $1-(0.95)^{1/k}$, so that the overall significance level remained at 0.05.

A sensitivity analysis[15] was carried out to test the stability of the conclusions of the relative risk analysis over a range of values of n (5,550, 11,100, 16,650 and 22,200)

Table 1. Local drug circulation in Crete (1992-1995)

	Units (+000)
SALICYLATES	6919
DICLOFENAC	2096
CORTICOSTEROIDS	1062
TENOXICAM	957.4
PIROXICAM	618.5
INDOMETHACIN	577.2
NAPROXEN	540.4
NIFLUMIC ACID	426.7
IBUPROFEN	364.5

and a range of values of p (0.25, 0.30, 0.35, 0.40 and 0.45).

RESULTS

Clinical characteristics and outcome of the patients with respect to NSAID consumption are noted in Table 2.

Of the 444 patients, 291 were men and 153 women. The male: female ratio was 1.4:1.

No significant differences between NSAID users and non-users with regard to the sex, age, alcohol consumption, smoking and history of ulcer/dyspepsia were found. Although there was a tendency towards higher admission rates during spring months (March, April, May), the seasonal variation did not seem to play an important role.

A firm diagnosis based on endoscopy could be assigned to 386 of the patients (86.9%). Endoscopy was performed within 24 hours of admission in the majority of cases (86.7%) and in 285 patients (64.2%) a gastroduodenal ulcer was found. In 23 patients, the initial endoscopy failed to establish a diagnosis. In 35 patients, endoscopy was not done because of very advanced age, or serious coexisting diseases and patients subsequently underwent radiological examination. The endoscopic diagnoses are given in Table 3.

The relation between NSAID ingestion and endoscopic findings is listed in Table 4. There was a significant association between the nature of the endoscopic findings and the use of NSAIDs: erosions were significantly associated with NSAID consumption (81.7% *vs* 18.3%, $\chi 2 = 16.331$ with 1 D.F.; $p < 0.001$).

In table 5, the first column shows, the various individual drugs in association with the absolute number of bleeding episodes. The second column shows the corresponding numbers of $n = 11{,}100$ would be 'controls' (members of the general population with no bleeding episode) based on the local circulation of NSAIDs in

Table 2. Clinical variables and outcome of 444 patients with upper gastrointestinal bleeding

Variable	NSAIDS users n: 269	No NSAIDs users n: 175
Sex (% male)	67	63.4
Mean age (yr)	62	60
Age > 60 yr (%)		
Male (%)	59	38.6
	53	32.6
Tobacco use (%)	68	65
Alcohol use (%)	39	46.3
History of ulcer/dypepsia (%)	32.3	34.8
History of bleeding (%)	25.3	21
Blood units*	3	3
Hospital stay (days)*	6	6
Surgery (%)	2.6	5
Mortality (%)	2.6	2.8

*Median

Table 3. Endoscopic diagnoses of upper GI bleeding (cancers and esophageal lesions have been excluded)

Endoscopic diagnoses	Number of patients (%)	
Duodenal ulcer	175	(39.4)
Gastric ulcer	110	(24.8)
Erosive/Hemorrhagic gastritis	93	(20.9)
No lesion found	23	(5.2)
No data	35	(7.9)
Other/miscellaneous	8	(1.8)
Total	444	

Table 4. Endoscopic findings in relation to NSAIDs ingestion

	Ulcers		Erosions	
NSAIDs users	167	(58.6%)	76	(81.7%)*
No users	118	(41.4%)	17	(18.3%)
Total	285		93	

*p< 0.001

Table 5. NSAIDs ingestion in association with number of bleedings.

	Patients	Controls
No NSAIDs users	175	7770
NSAIDs users		
SALICYLATES	214	1699
DICLOFENAC	17	515
PIROXICAM	12	152
TENOXICAM	8	235
IBUPROFEN	5	89
CORTICOSTEROIDS	5	261
INDOMETHACIN	4	142
NAPROXEN	3	132
NIFLUMIC ACID	1	105
Total	269	3330

Crete during the study period (1992-95). Note that this allocation is further based on the assumption that the proportion p of NSAID users in the general population is 0.40 (so there are 60% non-users) and that users do not take more than one drug at least during the same week. The relative risk of each drug is assessed by its odds ratio against the non-users. These relative risks and their 95% confidence intervals for $p = 0.40$ and $p = 0.30$ (and $n = 11,100$) are shown in Table 6. It is obvious that salicylates have the highest risk, followed by piroxicam, ibuprofen, tenoxicam, diclofenac, indomethacin, naproxen, corticosteroids and niflumic acid, in that order. Tests of significance of the differences between these relative risks reveal two groups: salicylates, piroxicam and ibuprofen, all three of which have high risks (larger than 1) of bleeding, compared to non-users, and indomethacin, naproxen, corticosteroids and niflumic acid, all four of which have small non-significant risks. The remaining two, tenoxicam and diclofenac, occupy a dubious, intermediate position. The above conclusions stayed unchanged in a sensitivity analysis where n was taken as 5,550, 11,100, 16,650 and 22,200 and similarly p was taken as 0.25, 0.30, 0.35, 0.40 and 0.45. Another observation made from our scale is that the drugs with a high relative risk are almost exclusively used in oral tablets, compared with those with low relative risk, which are mainly used in either rectal or parenteral forms (Table 7). Naproxen and corticosteroids are good examples of this point.

Regarding the outcome of bleeding, most of the patients were treated conservatively and only 16 patients (3.6%) underwent emergency surgery. Of the 16 patients operated on for continuous or life-threatening bleeding, 9 were over 60 years old (Table 8). The postoperative mortality was 12.5% (2 patients). As shown in Table 9, despite the fact that 56.7% of all patients were over 60 years old, the overall mortality rate, including post-operative mortality, was found to be unexpectedly low (12 patients - 2.7%). All deaths occurred in patients over 60, and 66.6% of the patients who died were more than 80 years old. No significant differences were noted in either operation rate or mortality rate between consumers and non-consumers of NSAIDs.

Table 7. Prescribing forms of NSAIDs

	PER OS	INJECTION	SUPPOS
SALICYLATES	95%		5%
PIROXICAM	100%		
IBUPROFEN	100%		
DICLOFENAC	26%	58%	16%
INDOMETHACIN	74%		24%
NAPROXEN	41%		59%
CORTICOSTEROIDS	36%	64%	
NIFLUMIC ACID	75%		25%

DISCUSSION

Although the natural history of peptic ulcer disease has changed since the introduction of H_2 antagonists, the overall mortality from acute upper GI bleeding has remained almost stable. However, since the 1940s, the proportion of patients aged over 60 has risen from 15% in 1941 to 21% in 1991 and probably the increasing number of elderly patients with severe comorbidity has been instrumental in maintaining this high mortality.[1]

According to large cohort studies published recently,[1,2,7,16-18] the mortality rates from upper GI bleeding, and

Table 6. The relative risks (RR) and their 95% Confidence Intervals (CI) of the various NSAIDs, for $p = 0.40$ and $p = 0.30$ and $n = 11,100$

	p = 0.40		p = 0.30	
	R.R.	95% CI	R.R.	95% CI
SALICYLATES	3,60	2,93 - 4,41	5,59	4,55 - 6,88
PIROXICAM	2,26	1,24 - 4,12	3,51	1,91 - 6,43
IBUPROFEN	1,59	0,64 - 3,95	2,48	1,00 - 6,18
TENOXICAM	0,97	0,47 - 1,99	1,51	0,74 - 3,11
DICLOFENAC	0,94	0,57 - 1,56	1.47	0,88 - 2,43
INDOMETHACIN	0,81	0,30 - 2,19	1,25	0,46 - 3,42
NAPROXEN	0,65	0,20 - 2,04	1,00	0,32 - 3,18
CORTICOSTEROIDS	0,55	0,22 - 1,34	0,85	0,35 - 2,09
NIFLUMIC ACID	0,27	0,04 - 1,96	0,42	0,06 - 3,05

Table 8. Relation between NSAIDs ingestion, age, operation rate and post-operation mortality (number of post-operative deaths in parentheses)

	Number of operations		
Age (yr)	**NSAIDs users**	**No NSAIDs users**	**Total**
< 40	2	-	2
40-50	-	1	1
50-60	1(1)	2	3(1)
60-70	3	4	7
70-80	1	1	2
> 80	-	1(1)	1(1)
Total	7(1)	9(1)	16(2)

Table 9. Relation between NSAIDs ingestion, age and overall mortality

	Number of deaths		
Age (yr)	**NSAIDs users**	**No NSAIDs users**	**Total**
60-70	2	1	3
70-80	1	-	1
> 80	4	4	8
Total	7	5	12

especially from bleeding peptic ulcers, varies between 5 and 15%. Patients over 60 years of age have a higher mortality (10-15%), that increases to 25-30% in patients aged over 80.[6,19,20] A recent epidemiological study in the United Kingdom[1] has shown that the incidence of acute upper GI hemorrhage is twice that previously reported in England, with an overall mortality of 14% if hospital inpatients are included and 11% in those admitted with bleeding. It is also known that in 60-80% of patients, hemorrhage stops spontaneously with conservative measures.[21] Although a marked decline in elective surgery has occurred, the frequency of emergency operations has been constant with a high operative mortality of 10 to 30%.[4,6,17,21]

In our study, a remarkably lower operation (3.6%) and mortality rate (2.7%) than that reported in similar series from other European or USA centers was found.[1-7,16-21] Moreover the bleeding stopped spotaneously in 90.7% of cases. One factor which could only partly explain this discrepancy, is the exclusion from our study of bleeding episodes occurring in inpatients. It is well established that patients who bleed while being treated for other reasons in intensive care units or surgical departments have a higher morbidity and mortality rate. We have not included such patients because their death could not be directly attributed to their bleeding and because of inadequate data for the purposes of the study of patients treated in other departments. Another possible explanation could be based on the H. pylori status of the Cretan population. According to the findings of the Eurogast Study Group, although H. pylori infection has a rather high prevalence in Crete compared to other European countries, the virulence of the organism, as indicated by CagA seropositivity, is very low.[22,23] Whether or not this could influence the outcome of bleeding is not yet established. Finally, another hypothesis could be the kind of diet and eating habits of our study population. In Greece, and especially in Crete, unlike in other European countries, olive oil is still the principal source of fat and for cooking, is used more or less to the exclusion of animal or other edible fats.[24] Consumption of margarine, rich in either saturated fatty acids or trans-fatty acids, is virtually unknown in the traditional Cretan diet (only 2 gr/day) and the trans-fatty acids in the adipose tissue of this population is two times lower than that of US Americans.[24,25] Recent experimental and epidemiological studies have shown that diets rich in polyunsaturated fatty acids enhance the resistance of the duodenal mucosa to acid by potentiation of adaptive cytoprotection and suggest a relationship between the incidence of peptic ulcer and the consumption of dietary polyunsaturated fatty acids.[26-28] Grant et al found that the mean percentage of linoleic acid in adipose tissue was significantly lower in patients with ulcer disease.[29] Therefore, they suggest that the diets of duodenal ulcer patients are deficient in linoleic acid and this could be of aetiological importance. Dietary essential fatty acids can be rapidly converted to prostaglandins of the E group by the gastroduodenal mucosa. These fatty-acid-derived prostaglandins are able to protect the gastroduodenal mucosa against injury by alcohol, aspirin and NSAIDs. Furthermore, the reported decline in incidence and virulence of peptic ulcer disease that has occurred during the past few decades in the United States and England, is likely to be in strong relation to the 200% increase in the dietary availability of vegetable oils during the same time span.[27-28] Obviously, prospective epidemiological studies are required to verify this hypothesis.

Endoscopic hemostasis was attempted only in 15 of our patients. This figure does not reflect mild episodes of bleeding, since this therapeutic modality was routinely introduced in our hospital after the second year of the study and was applied only in actively bleeding ulcers. All cases were treated conservatively with blood transfusions as required and administration of either an H_2 receptor antagonist (65%) or, more recently, a proton

pump inhibitor (35%). However there is no convincing evidence that the administration of acid suppression therapy influences significantly the outcome of bleeding. In a similarly designed study carried out in Greece, comparable results in terms of morbidity and mortality were reported in a group of patients without any antisecretory treatment during the acute episode.[30] According to the literature, apart from one study[31] reporting the beneficial effect of omeprazole, the results of a meta-analysis by Collins and Langman[32] suggested that treatment with H_2-antagonists may only marginally decrease the surgery and death rate in acute upper GI hemorrhage.

Overall, the diagnostic profile of our patients is similar to that in other studies from Europe and USA; gastroduodenal ulcers account for 64.2% of the cases, followed by erosive/hemorrhagic gastritis.[1,4,16,33] However, we found a slightly higher proportion of benign gastric ulcers (24.8% *vs* 12-20%). In 23 patients (5.2%) no evident endoscopic site of bleeding was identified. This proportion is probably related to small bowel ulceration and bleeding, as has recently been proved by enteroscopy.[34] Another possible explanation could be early healing of antral erosions in association with a relatively late arrival at the hospital on some occasions.

There are several prospective and retrospective case-control studies demonstrating a causal relationship between upper GI bleeding and NSAID use, although the risk varies in these studies. In a large-multicenter study, Langman et al[10] found an odds ratio for gastrointestinal bleeding of 4.5 and a recent meta-analysis[35] calculated an odds ratio of 2.39. In our study 60.6%of patients had a definitive history of NSAID consumption, which is in accordance with most recent data.[8-13,36-38] This association was evident regardless of whether the underlying pathology was a peptic ulcer or antral erosions, although erosive or hemorrhagic gastritis was strongly associated with NSAID consumption.

Considering the association of NSAIDs with the outcome of upper GI bleeding (mortality rate, need for surgery, transfusion requirements and length of hospital stay), the results of previous studies have been conflicting. In agreement with previous studies,[7,39,40] the present study has demonstrated no difference in mortality rate between NSAID users and non-users. Moreover, no significant associations of NSAID use with other important variables, such as need for surgery, transfusion requirements and length of hospital stay were found.[7,38,39,41]

It is of interest that a high proportion of these patients were men. While two meta-analyses found the relative risk to be similar for both sexes,[35,42] several other studies have found the female sex to be associated with high relative risk.[43,44] The latter phenomenon has been attributed to higher NSAID consumption by women over 60, due to excessive osteoporosis, which is not the case in our series. Incidence of osteoporosis in elderly Greek women has not been documented and therefore we cannot exclude the possibility that a lower osteoporosis rate in women is responsible for this discrepancy. Our results are consistent with a recent case-control study from Denmark,[11] in which male rather than female sex is indicated as a risk factor for NSAIDs-related ulcer complications.

Considering the use of various NSAIDs, certain findings are of special interest. Salicylates are responsible for most of our cases with upper GI bleeding and they have the highest risk, followed by piroxicam and ibuprofen. Our results are completely different from a recent British study[10] and a meta-analysis from Australia,[36] where the odds ratio for aspirin was lower than for other NSAIDs and ibuprofen had the lowest odds ratio for bleeding. When comparing these studies, it is worth noting that the odds ratio for aspirin is roughly similar to ours. However it is the generally lower odds ratios for the other NSAIDs in our study that seems to cause this discrepancy. Similarly, indomethacin and naproxen, which have a relatively low odds ratio in our series, are associated with a much higher risk of bleeding in the above studies. These discordant findings possibly indicate that no general recommendations applicable to all populations can be made and probably local studies are required. This assumption is verified when our results are compared with studies from other Mediterranean countries like Italy and Spain.[45,46] Indomethacin appears relatively safe in Spain but not in Italy, while the opposite is true for diclofenac.

In terms of the relative safety of orally administered drugs, our data suggest that corticosteroids and niflumic acid seem to be relatively safe, as has been supported by a previous study.[47] Finally, the rectal or parenteral administration of NSAIDs seems safer than the oral route. Therefore, the recommendation that rectal or parenteral administration is preferable in high risk patients is justified on the basis of the present data.

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