NSAID use and abuse in gastroenterology : refractory peptic ulcers

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Abstract

With current antiulcer therapies to eliminate H. pylori infection, non-steroidal antiinflammatory drug use is the main factor involved in resistant peptic ulcers which must be defined as those ulcers that do not heal after 6 (duodenal ulcers) or 8 (gastric ulcers) weeks of treatment with proton pump inhibitors, despite H. pylori erradication. NSAID use (especially aspirin abuse) in patients with resistant ulcers is often surreptitious. Ulcers tend to complicate with stenosis and bleeding, commonly change site, are multicentric and have poorly defined margins. These patients should never undergo surgery unless they develop uncontrolled complications, since ulcer recurrence is the rule. Analgesic abuse and personality disorders might present in some of these patients. Refractory ulcers with no evidence of NSAID use and no evidence of H. pylori infection are rare but not exceptional. Smoking and genetic background seem important factors in patients with this type of ulcers. Idiopathic basal gastric acid hypersecretion might be important in a few patients, but the Zollinguer-Ellison syndrome must be ruled out. (Acta gastroenterol. belg., **1999**, 62, **418-420**).

Key words : peptic ulcers, NSAID, aspirin, paracetamol, gastric secretion, Helicobacter pylori, gastric secretion, smoking.

Introduction and definition

Gastroduodenal resistant ulcers are classically defined as those non-malignant peptic ulcers that do not heal with conventional medical therapy (1). Conventional medical therapy has dramatically changed for the last 2 decades and today antisecretory drugs and antibiotics in Helicobacter pylori infected patients are the two nonexclusive options available. However, the problem of resistance is still, in practice, the failure to heal ulcers or the rapid recurrence of ulcers under appropriate acid suppression therapy. Peptic ulcers are considered resistant to medical therapy if healing is not evident after 8 to 12 weeks of therapy and represent no more than 5-10% of all ulcers treated. Patients with these ulcers are frequently sent for surgery, but the proportion of refractory ulcers is decreasing with time because of the introduction of new and progressively more effective antiulcer therapies (1).

Pathogenic factors

In the pre-Helicobacter era several factors were reported as involved in ulcer refractoriness, including the existence of lineal ulcers, deformity, sex, a history of complications, and duration of the ulcer history among others. Today, these factors are of little significance (1), but other factors described are still valid in 1999 and include poor patient compliance with therapy, tolerance to H2 receptor antagonist therapy (2), inadequate acid inhibition with omeprazole (3), smoking (4) and the existence of basal acid hypersecretion (5). Smoking interferes with antisecretory drug effects and increases MAO in DU patients (6). Most studies have also shown that smoking delays the healing rate of peptic ulcers treated with antisecretors (4,7). Basal acid hypersecretion (defined as BAO over 10 mEq/hour) has been reported to be one of the factor responsible for ulcer refractoriness (5), but this has not been confirmed by other authors (1,8,9).

More recently, it has become clear that H. pylori is not only a pathogenic agent for regular peptic ulcers but for resistant ulcers as well. In a more recent prospective study (1) was shown that the frequency of relapses and analgesic-NSAID use were the only independent factors affecting peptic ulcer refractoriness. Since Helicobacter pylori infection is the main factor linked to recurrence in peptic ulcers, it was concluded that H. pylori infection was probably the factor responsible, which was confirmed in follow-up studies in which healing resistance to antisecretory therapy disappeared in most cases where the infection was eradicated (1,10). The study raised the question that if most peptic ulcer patients are infected, why do some patients become refractory to conventional antisecretory therapy while others do not. The mechanisms whereby H. pylori may induce refractoriness in some patients but not in others are not known, but since H. pylori eradication is the first therapeutic option for infected individuals, today, *resistant peptic ulcers must be defined as those H. pylori negative peptic ulcers that do not heal after 6 (duodenal ulcers) or 8 (gastric ulcers) weeks of treatment with proton pump inhibitors.* In these conditions, recent data suggest that NSAID use is the factor responsible in up to 50 or 60% of cases (10).

The role of NSAID use : Ulcer patients are repeatedly advised to avoid NSAID use, however NSAID use must be the first factor to be excluded in patients with resistant ulcers. Several studies have shown surreptitious use of NSAIDs, mainly aspirin, must be excluded in these patients. Isolated reports (11,12) later confirmed in prospective studies (1,13), showed that at least half this population of patients with ulcers resistant to antisecretory therapy and concomitant NSAID use had

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surreptitious use of aspirin, which was uncovered by platelet cycloxygenase activity in platelet rich plasma or blood salicylates tests.

The intervention of NSAID use in resistant ulcers is clear. It is well established that NSAID use delays ulcer healing and that omeprazole heals most (80% in 8 weeks) peptic ulcers despite NSAID use (14,15). However, a small proportion of NSAID-associated ulcers will not heal at all despite prolongation of therapy. In this population the only appropriate treatment is to stop NSAID use. Follow-up of patients with refractory peptic ulcers due to NSAID use showed that 90% of those who continued using NSAID had a morbid evolution, which was fatal in some cases despite being H. pylori eradicated (1,10).

The interaction between H. pylori and NSAID use is now under intense study. Our own data (unpublished) suggest that H. pylori eradication in patients with resistant ulcers due to NSAID abuse makes no differences if patients continue taking NSAIDs, which is in agreement with recent reports showing that H. pylori eradication does not affect ulcer recurrence and delays gastric ulcer healing in NSAID users (16).

The role of analgesic abuse : A particular problem is associated with patients who abuse analgesics. Patients with peptic ulcers are frequently advised to use paracetamol or other non-NSAID analgesics, but some patients go from aspirin abuse to analgesic abuse. The role of paracetamol abuse in patients with refractory ulcers is not defined, but there are suggestions that it is involved in some patients (1). Paracetamol abuse might well be associated with high concentrations of the drug at local levels (e.g. gastric tissues), and in vitro studies with different cell types, including gastric fibroblasts, show that mM concentrations of different analgesics and antiinflammatory drugs are associated with cell growth arrest and absence of proliferation without the induction of cell death (17,18) (Table I). Considering the number of drugs available legally without prescription, the extent of habituation to analgesics may be exceeded only by that of habituation to nicotine and alcohol in many western countries. Some studies suggest that at least half this population of analgesic abusers had long-standing personality disorders in psychiatric evaluations (19).

No evidence of NSAID use and no evidence of H. pylori infection : Refractory patients with no evidence of NSAID use and no evidence of H. pylori infection represent an interesting group that might emerge in the future with the current widespread use of Helicobacter pylori eradication. Patients in this group have normal gastric acid secretion and a positive family ulcer history and half of them are heavy smokers. We have to be aware of this type of patients in the near future, since it has been reported that in areas of some western countries, the proportion of H. pylori negative peptic ulcers might be higher than expected (20) and close to 50% among whites. Hirschowitz (21) reported a high recurrence rate of duodenal ulcer despite H. pylori eradication in a clinical subset of patients with an early ulcer onset and a strong family ulcer history, who might well belong to the same subgroup of patients with refractory Helicobacter pylori negative ulcers.

Refractory post-surgical ulcers

Patients with refractory post-surgical ulcers represent a subgroup of patients with special features. In these patients, it is by no means clear that H. pylori is implicated in recurrence since only 18-25% of postgastrectomy ulcers are H. pylori positive and after fundic vagotomy, H. pylori infection generally persists but relapses of ulcers are uncommon (22). In many of these patients the role of acid is also unclear since only a few show hypersecretion and many do not improve with further surgery (23). NSAIDs might be another cause and it has been suggested that aspirin abuse might be involved in many of these cases.

Hirschowitz and Lanas have recently reported the largest study with thirty such patients (13). Half of them gave a positive history of chronic aspirin abuse from 1-4 grams per day, while the other half, mostly women, denied using aspirin but had recurrent positive salicylate blood levels. Only 6 patients who stopped taking aspirin healed while the rest had a morbid, sometime fatal, evolution, despite undergoing up to 3 and 4 surgical interventions. These ulcers tend to complicate with stenosis and bleeding, commonly change site, are multicentric, often have ill-defined margins and may not respond to proton pump inhibitors.

Table I. — **In vitro cell growth inhibition (human fibroblasts) induced by different concentrations of several anti-inflammatory agents and analgesics. Cell growth was measured by the crystal violet method (see reference 17) and after 6 days of culture in 10% fetal calf serum with/without the drugs tested (unpublished observations). Results expressed in number of cells (× 1000) ± SD ; n = 4 (number of cells plated at day 1 = 40.000)**

[Drug]	Aspirin	Paracetamol	Indomethacin	Ibuprofen
[10^{-3}M]	62 ± 7*	59 ± 10*	—	96 ± 6*
[10^{-4}M]	188 ± 7	204 ± 2.4	99 ± 10*	219 ± 9.2
[10^{-5}M]	187 ± 5.3	211 ± 6.9	234 ± 10	207 ± 25
[10^{-7}M]	227 ± 7.6	224 ± 2.5	199 ± 5	246 ± 13
Control#	254 ± 15	254 ± 15	254 ± 15	254 ± 15

10% fetal calf serum ; * p. 0.0001 vs. control. Paired t-test.

Diagnosis strategy and therapeutic recommendations

Current recommendation for workup of refractory H. pylori negative ulcers is to test for NSAIDs by history and by objective tests including serum levels of aspirin and platelet cyclooxygenase activity. If patients are positive for NSAID use, it should be stopped. If not possible, the dose of proton pump inhibitors should be increased and maintained long-term. These patients should never undergo surgery unless they develop uncontrolled complications. Some of these patients might need psychiatric evaluation. If patients are negative for NSAID use, tests for gastrinoma with fasting serum gastrin and gastric secretion should be performed. Testing for cytomegalovirus must be included if a patient is immunosuppressed. Smoking habits and analgesic abuse should also be checked. Most patients should be controlled by increasing the dose of the antisecretory drugs, which might be monitored by measuring levels of acid secretion on medication. If a patient is submitted for surgery, aspirin abuse should always be excluded.

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