Gastric safety and tolerability of aspirin

Key points

- New insights into the gastric effects of aspirin are still being reported
- OTC aspirin is as well tolerated as other OTC analgesics
- Side effects reported in scientific studies of aspirin should not all be attributed to it
- Aspirin remains a valuable analgesic with a strong record of tolerability

Introduction

The issue of the gastric safety and tolerability of aspirin has been a cause of misunderstanding for many years. It is well established that aspirin may be associated with an increased risk of gastric irritation, increased occult blood loss and, occasionally, serious gastric bleeding (for more information, see *Undesirable Side Effects* at www.aspirin-foundation.com/uses/cardio/undesirable.html). However, these risks must be balanced against the substantial benefits from taking aspirin. Recent research, considered in the context of what is already known about aspirin, casts doubt on some common misconceptions about its tolerability.

Evidence base

It is now clear that there is still much to learn about the gastric safety of aspirin. A recent epidemiological study in the United States concluded that over-the-counter use of aspirin carries little risk of gastrointestinal (GI) toxicity in most people. When problems do occur, they are most likely in people known to be at high risk because of other factors (for example, in those also taking oral corticosteroids); in others, there was no difference in the incidence of GI events between aspirin, ibuprofen and paracetamol[1].

It's therefore surprising that aspirin is sometimes said to have the worst side effect profile of all OTC analgesics. Laboratory research has shown that aspirin - unlike some other NSAIDs but like vitamin E - may actually protect cells against the damaging effects of highly reactive metabolites of oxygen[2,3]. A review by the US Food and Drug Administration concluded there are no safety grounds to prefer one OTC analgesic over another[4], a finding confirmed by a large epidemiological study in Italy[5]. Single-dose studies in patients using aspirin for typical OTC indications have revealed few, if any, serious GI events[6-8].

People who take low-dose aspirin to reduce their risk of heart attack may experience gastric bleeding and this is commonly attributed to the effects of aspirin. This is unjustified. The background rate of severe gastric bleeding in the population as a whole is about 1 per 1,000 people annually and in people taking low-dose aspirin the risk increases slightly to 1 - 2 per 1,000 annually. It is not known whether this additional risk is due to aspirin because of the presence of confounding factors such as *Helicobacter pylori* infection, advanced age and excessive use of alcohol or tobacco[9-11]. Similarly, it is not possible to state categorically that the side effects reported in clinical trials are always caused by the treatment under investigation: it can be difficult to determine whether symptoms are due to the condition being treated or the effects of a drug used to treat it (e.g. nausea during a migraine attack), and providing information about possible side effects may increase the rate at which they are reported[12,13].

It is also widely believed that gastric irritation associated with aspirin is a systemic effect that cannot be influenced by changing the formulation. However, gastric irritation and subjective tolerability are modified by enteric-coating, buffering, modifying solubility[14] and including vitamin C in the tablet[15,16]. Many trials have shown that single OTC doses of aspirin are well tolerated with a minimal risk of severe side

effects[6-8,17,18], and this is supported by many years' experience in hundreds of millions of people.

Despite the introduction of many new NSAIDs, aspirin still has an important role in the management of osteoarthritis and rheumatoid arthritis. This is because aspirin is a well-established treatment and there is strong evidence that it is well tolerated in the treatment of arthritis, pain and inflammation[1] and better tolerated than some NSAIDs[19]. The introduction of COX-2 selective NSAIDs does not mean that aspirin has become redundant. Despite evidence for their gastric safety, increasing use of these agents has been associated with a rise in the number of gastric haemorrhages among older people[20]. This is partly due to their use in patients at increased risk and it demonstrates the importance of caution with high doses and during long-term use[21,22].

References

1. Fries JF, Bruce B. Rates of serious gastrointestinal events from low dose use of acetylsalicylic acid, acetaminophen, and ibuprofen in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol 2003;30:2226-33

2. Grosser N, Schroder H. Aspirin protects endothelial cells from oxidant damage via the nitric oxide-cGMP pathway. Arterioscler Thromb Vasc Biol 2003;23:1345-51

3. Podhaisky HP et al. Aspirin protects endothelial cells from oxidative stress--possible synergism with vitamin E. FEBS Lett 1997;417:349-51

4. Majority of aspirin GI adverse events reported in users with multiple risk factors - FDA Review. Health News Daily 2002. August 27, p. 2

5. Motola G et al. Over-the-counter oral nonsteroidal anti-inflammatory drugs: a pharmacoepidemiologic study in southern Italy.Advances in Therapy 2001;18:216-22

6. Steiner TJ, Lange R, Voelker M. Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. Cephalalgia 2003;23:59-66

7. Diener HC, Eikermann A, Gessner U et al. Efficacy of 1,000 mg effervescent acetylsalicylic acid and sumatriptan in treating associated migraine symptoms. Eur Neurol 2004;52:50-6

8. Diener H, Bussone G, de Liano H, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. Cephalalgia 2004;24:947-54

9. US Preventive Task Force. Aspirin for the primary prevention of cardiovascular events: recommendations and rationale. Ann Intern Med 2002;136:157-60

10. Task Force on Use of Antiplatelet Agents in Patients with Atherosclerotic Disease of the European Society of Cardiology. Expert Consensus Document on the Use of Antiplatelet Agents. Eur Heart J 2004;25:166-81

11. Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. Gastroenterology 2004;127:395-402

12. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. J Am Med Assoc 2002;287:622-7

13. Hahn RA. The nocebo phenomenon: concept, evidence, and implications for public health. Prev Med 1997;26:607-11

14. Drug and Therapeutic Bulletin, (1997), 35(1), 7-8

15. Elfstrom C, Amin D, Nilsson LG et al. Subjective gastrointestinal tolerability of acetylsalicylic acid and paracetamol after single dose treatment. Eur J Pharm Sci 1999;8:141-5

16. Dammann HG, Saleki M, Tors M et al. Effects of buffered and plain acetylsalicylic acid formulations with and without ascorbic acid on gastric mucosa in healthy subjects. Aliment Pharmacol Ther 2004;19:367-74

17. Edwards JE, Oldman AD, Smith LA et al. Oral aspirin in postoperative pain: a quantitative systematic review. Pain 1999;81:289-97

18. Lange R, Schwarz JA, Hohn M. Acetylsalicylic acid effervescent 1000 mg (Aspirin) in acute migraine attacks; a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 2000;20:663-7

19. Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1991;34:1353-60

20. Mamdani M, Juurlink DN, Kopp A et al. Gastrointestinal bleeding after the introduction of COX 2 inhibitors. Br Med J 2004;328:1415-6

21. Hinz B, Brune K. Cyclooxygenase 2 - 10 years later. J Pharmacol Exp Ther 2002;300:367-5

22. Arzneimittelkommission der Deutschen Arzte. Infomration: Zur Sicherheit von COX-2-Inhibitoren. Deutsches Arzteblatt 2002. Nr. 22

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