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USING ASPIRIN INTRAVENOUSLY

H.-C. Diener

As early as the mid 1970s, an injectible form of LAS (iLAS = Aspisol) was available for the treatment of post-surgical, traumatic, tumor and rheumatic pain conditions. It would be years before iLAS was "discovered" for treatment of acute migraine attacks. Case reports appeared in the 1980s describing iLAS's positive performance in migraine attack treatment. Its evaluation in clinical trials did not take place until the mid-nineties. In these trials, iLAS proved superior to placebo and at least as effective as non-oral ergotamine derivatives. In a double-blind multicenter trial including 278 patients iLAS was compared to subcutaneous sumatriptan 6 mg and placebo for the treatment of severe migraine attacks. Both drugs were superior to placebo. Pain free after 2 hours were 76.3%, 43.7% and 14.3% of the patients following the administration of sumatriptan, iLAS and placebo, respectively. ILAS, however was significantly better tolerated than sumatriptan. Adverse events were reported in 7.6% of patients treated with iLAS and 37.8% treated with sumatriptan. Intravenous aspirin offers a save and effective treatment of acute migraine attacks in the emergency room.

Reference

Diener HC, for the ASASUMAMIG Study Group (1999) Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. Cephalalgia 19:581–588

ASPIRIN PROTECTS THE GASTRIC MUCOSA

H. Schröder

Aspirin is known to cause a multitude of pharmacological actions through inhibition of cyclooxygenase(s) and diminished formation of prostaglandins. Reduced thromboxane generation contributes to the antiplatelet action of aspirin as does a decrease in pro-inflammatory prostaglandins to its effectiveness in pain and inflammation. Recently however, novel mechanisms of aspirin have been identified that are independent of COX-inhibition and relate to the antioxidant potential of aspirin.

Thus, a direct effect of aspirin on the integrity of the vascular wall was reported, which comprises free radical scavenging properties of aspirin and its capacitiy to protect endothelial cells from the deleterious effects of hydrogen peroxide. Antioxidant effects of aspirin leading to the suppression of lipid peroxidation and reduced vascular tone have also been demonstrated *in vivo* in experimental animals and humans. In addition, reduction of oxidant stress and injury by aspirin was documented in extravascular tissues including lung, kidney and neurons.

While the mechanisms responsible for the observed aspirin-induced cytoprotection are largely unknown, we and others have found a very similar profile of cytoprotection evoked by nitric oxide (NO) or NO donors. NO as well as aspirin reduced the sensitivity of endothelial cells to hydrogen peroxide and other pro-oxidant agents in a time-dependent fashion. Both aspirin and NO donors induced long-term protective effects in endothelial cells that occurred following short periods of pretreatment and were sustained after washing out either agent. The similarity in the antioxidant actions of aspirin and nitric oxide led us to assume that NO might have a role as a down-stream mediator in aspirin-dependent cytoprotection.

In a recent study we showed that aspirin directly stimulates activity of endothelial NO synthase activity without affecting expression of eNOS. Increased NO formation was found to be causative of aspirin-induced sustained protection of endothelial cells from oxidant injury. The effects on endothelial integrity and the NO/cGMP system were specific for aspirin and not elicited by other non-steroidal anti-inflammatory drugs such as diclofenac, indomethacin or salicylate. Down-stream targets of NO that mediate tissue protection include the stress proteins heme oxygenase-1 (HO-1) and ferritin. Ferritin and HO-1 have both been identified as targets of, and to be inducible by, aspirin. Moreover, aspirin-induced HO-1 induction was abrogated in the presence of the NO synthase blocker L-NAME (N-nitroarginine-L-monoethyl ester). This observation further strengthens the role of NO as signaling molecule in genomic actions of aspirin that lead to stress gene activation and tissue protection. These effects are not seen with other NSAIDs or selective COX-2 blockers.

HO-1 and its antioxidant product bilirubin were reported to not only be involved in vasoprotection but to have a similar function in gastric tissue. In addition, aspirin-dependent HO-1 mRNA induction was observed in gastric cells and followed by a reduction of free radical formation. An antioxidant effect similar to that observed with aspirin occured when adding bilirubin at physiologically relevant concentrations to gastric epithelial cells suggesting that HO-1 and its enzymatic metabolite bilirubin are indeed of functional relevance in gastric mucosa. It should be noted that stimulation of vascular NO formation through aspirin, as described above, might also help to prevent gastric injury or irritation: NO is recognized as a critical mediator of the gastrointestinal mucosal defence, exerting many of the same actions in the stomach as prostaglandins. In particular, NO functions as a smooth muscle relaxing agent and is thus thought to counteract the reduction in gastric blood flow caused by inhibitors of prostaglandin synthesis. It is conceivable that activation of these pathways in gastric epithelia and microvessels is responsible, at least in part, for the superior gastric tolerability and safety of aspirin compared to other NSAIDs.

In summary, it has been demonstrated that aspirin increases expression of antioxidant defense proteins via NO-dependent pathways. HO-1 induction by aspirin is followed by inhibition of free radical formation in endothelial as well as gastric mucosa cells. HO-1 induction distinguishes aspirin from conventional and COX-2 selective NSAIDs.

RECOVERING LOST PRODUCTIVITY FROM TENSION-TYPE HEADACHE

T.J. Steiner

According to the World Health Organization, migraine is 19th among all causes of years of healthy life lost to disability. The consequences include significant societal financial cost. In the United Kingdom, for example, 25 million working- or school-days are lost every year because of migraine.

A much more prevalent headache disorder than migraine is episodic tension-type headache (ETTH), affecting two-thirds of adult males and over 80% of females. Unlike migraine, ETTH is widely regarded as merely a "nuisance headache", rarely disabling. This perception is incorrect. Results from a clinical trial comparing two treatments of ETTH [1] suggest that prolonged disability affects a large minority of people affected by this disorder. Over one-fifth of all subjects recorded persisting functional impairment after 4 hours and, in over half of these, the time of regaining normal function was more than 9 hours after treatment. Taken together with the high prevalence of ETTH, this signals that this disorder may be the source of much higher indirect costs than have been recognised – probably similar to those of migraine.

The trial referred to compared acetylsalicylic acid (aspirin, ASA) and paracetamol, each in doses of 1000 mg and 500 mg, with placebo. Both active drugs performed better than placebo and, in each case, there was a dose-response relationship with the higher dose out-performing the lower. Aspirin 1000 mg was best on a number of outcome measures, including functional recovery within the first 2 hours (after this time patients were allowed rescue medication, so later analyses were confounded).

Lost productivity from ETTH has not previously been considered important. Nor has treatment of this very common disorder focused on the potential for reducing the high societal cost this imposes. It is clear that it should. Aspirin, effective in shortening time-to-functional recovery, has much to offer.

Reference

1. Steiner TJ, Lange R, Voelker M (2003) Cephalalgia 23:59–66

TREATING MIGRAINE COST EFFECTIVELY

T.J. Steiner

The acute migraine attack is painful, debilitating and on the majority of occasions disabling. It requires effective treatment, which in almost all cases involves pharmacotherapy.

Migraine is a common disorder. European and American studies have shown that 6%–8% of men and 15%–18% of women have migraine. About 3,000 migraine attacks occur every day in each million of the general population, which translates into 80 million attacks every year in a country such as Spain. This is a very large multiplier of the cost of individual treatment, and should focus the attention of whoever has responsibility for paying for treatment. People may bear the cost personally but, often, it falls on health services, for which competing priorities are a major consideration. Containing cost, without sacrificing effectiveness, becomes important not only for those who have migraine but also for everyone else, since what is spent on one illness is not available for another.

The effectiveness of acetylsalicylic acid (Aspirin, ASA) in acute migraine treatment was the subject of the last presentation. Cost-effectiveness of a particular treatment can be assessed in comparison with other treatments by estimating the cost per successful outcome (however defined) of each. Where drugs differ widely in clinical effectiveness, such comparisons may be difficult to make sense of, but they helpfully guide decisions about which treatment to use for whom, or in which circumstances, when compared treatments produce the same or similar outcomes.

Comparisons in the last presentation between aspirin 1000 mg and sumatriptan 50 mg showed comparable efficacy between the two. Cost differentials on the other hand are substantial when the multiplier identified above is applied. This presentation will review the implications of this.

TREATING MIGRAINE EFFECTIVELY

H.-C. Diener

Acetylsalicylic acid (aspirin, ASA) has been used for more than 100 years as an analgesic, anti-pyretic and anti-inflammatory drug. Evidence for its effectiveness in migraine headache has been shown in several clinical trials using aspirin tablets, aspirin tablets in combination with metoclopramide, intraveneous aspirin and effervescent aspirin. The effervescent highly buffered preparation of aspirin was shown to be effective, safe and well tolerated in comparison with placebo or other treatment options. Effervescent aspirin has improved pharmacokinetics compared to plain aspirin. It is at least as effective as the combination of aspirin plus metoclopramide, but has fewer side effects. The clinical data of aspirin in the treatment of acute migraine attacks with respect to the different galenic formulations are summarised and analysed. The results of an individual patient data (IPD) meta-analysis of trials with 1000 mg effervescent aspirin in comparison with sumatriptan and placebo in acute migraine attacks showed comparable efficacy for 1000 mg effervescent aspirin and 50 mg sumatriptan in headache relief and relief of accompanying symptoms. In a subgroup analysis is was shown that patients with severe headache intensity at baseline responded to the treatment with 1000 mg effervescent aspirin.