HYPOTHESIS

Why are non-steroidal anti-inflammatory drugs so variable in their efficacy? A description of ion trapping

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Hypothesis

Our hypothesis is that acidic non-steroidal anti-inflammatory drugs (NSAIDs) undergo ion trapping in acidotic tissue and that this affects not only their gastrotoxicity, which is well known, but also their selectivity for, and their efficacy in, inflammatory joint disease.

Tissue acidosis may not be a feature of all chronic inflammatory disease states, but it does occur in inflammatory joint disease and is highly variable depending on the extent of the mismatch between synovial perfusion and metabolic demand. This mismatch is influenced not only by disease activity, but also by joint movement, which causes transient hypoxic episodes. Interventions, such as rest and drug treatment, would serve to reduce ion trapping and, therefore, NSAID efficacy through their effects on disease activity. The influence of these factors on pH dependent ion trapping may contribute to the variable efficacy of NSAIDs between disease states, between patients within a disease population, and within a single patient over time.

Prostaglandins have been found in increased amounts in many chronic inflammatory states, including rheumatoid arthritis¹ and osteoarthritis,² where they contribute to the severity and persistence of inflammation. They are derived from arachidonic acid by the action of cyclo-oxygenase and it is principally through the inhibition of this enzyme that NSAIDs exert therapeutic effects.³ Despite their mechanism of action NSAIDs are not universally effective in all chronic inflammatory disease states and this may be due, in part, to the pharmacokinetics of the drugs at the cellular level.

To reach their active site within inflammatory cells NSAIDs must be distributed to the extravascular compartment. Passage across the vascular endothelium can be either via gaps between the endothelial cells or by simple diffusion through them. There are, however, restrictions and both routes can be altered by disease.

Normally the gaps between endothelial cells are small, allowing only limited egress of small solutes, but restricting loss of protein. The presence of inflammation weakens the endothelial barrier, and the wider gaps allow the extravasation of water and hydrated molecules and proteins, including albumin.⁴

Non-steroidal anti-inflammatory drugs vary in their aqueous solubility, but most are highly albumin bound and will be co-distributed with this protein. Diffusion of an NSAID into the cell follows Fick's law, as it is dependent on the concentration gradient across the plasma membrane and the lipid/water partition coefficient of the drug molecule.

For weak acids, such as most NSAIDs, the effective concentration gradient is that of the non-ionised form, as ionised molecules are not lipid soluble

The position of the equilibrium depends on the intrinsic ionisation constant of the molecule (pKa) and on the pH value of the aqueous phase. The influence of pH is most profound around the pKa value of the molecule (fig 1).

For acidic NSAIDs, decreasing the pH increases the proportion of the non-ionised form, raises the overall lipophilicity, and enhances transport across the lipid membrane.

The pKa values for several NSAIDs at 25°C are given in the table. Within tissue, the actual values will vary slightly with temperature and the ionisation potential of the environment.

Where pH gradients exist across lipid membranes ionisable molecules are subject to ion trapping. The non-ionised form will tend to equilibrate across the membrane and will move down its concentration gradient into the high pH compartment where it will be ionised.

Figure 1 Ionisation of a weak acid.

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pKa Values of various non-steroidal anti-inflammatory drugs (NSAIDs)

NSAID	pKa Value
Salicylic acid	3.0
Diffunisal	3.3
Acetylsalicylic acid	3.5
Diclofenac	3.9
Mefenamic acid	4.2
Ibuprofen	4.4
Phenylbutazone	4.5
Indomethacin	4.5
Oxyphenbutazone	4.7
6-Methoxy-2-naphthylacetic acid*	5.0
Piroxicam	5.1

*Active metabolite of nabumetone.

More non-ionised drug is then pulled across the membrane and this dynamic process continues until equilibrium is achieved (fig 2).

Ion trapping of NSAIDs within cells therefore occurs in situations where the pH of the extracellular fluid (pHe) is lower than that of the intracellular fluid (pHi), such as in the gastric mucosa and in acidotic diseased tissue. Normally the pHi of a cell is about 7.1 whereas the pHe is 7.5. In vitro studies have shown, however, that the orientation of this pH gradient is reversed when the pHe decreases below approximately 7.1 in cells that have the mechanisms to cope with acidification.^{5 6}

In most situations the magnitude of the measurable pHe–pHi gradient will be small, but nevertheless it can have a considerable effect on the drug concentration at the active site. In human erythrocytes in vitro, decreasing the pHe of the phosphate buffer from 7.4 to 6.8 approximately doubled the concentration of phenylbutazone in the intracellular compartment, without affecting that of the basic compound, antipyrine.⁷ Physical effects can enhance the pH gradient. The electrostatic interaction between negatively charged groups in the plasma membrane reduces the pHe at the external surface of the cell. For example, with a bulk pHe of 7.0 the surface pHe is calculated to be only about 6.2.⁸ In addition, good buffering in the unstirred layer at the surface amplifies the ion trapping effect. Replacing sodium chloride in a buffer solution with sodium citrate produced a 43-fold increase in the ion trapping of salicylate.⁹

The gastric mucosa has the largest pH gradients in the body and is the prime site for NSAID trapping. These drugs accumulate in the cells of this tissue and produce a prolonged

Figure 2 Ion trapping of weak acids. pHe=pH of the extracellular fluid; pHi=pH of the intracellular fluid.

reduction in prostaglandins.¹⁰ Further down the intestinal tract pH gradients may occur but, if correctly orientated, are much smaller as the luminal pH in these regions only varies between 7.0 and 8.0. As a class the acidic NSAIDs have considerable gastrototoxicity and their reduction of endogenous prostaglandins is a major, but not the only, factor in this effect.¹¹ It is interesting that the pattern of ion trapping parallels that of the gastrototoxicity profile. The incidence of endoscopically proved gastric ulcers in patients treated with NSAIDs is estimated to be about 20%,¹² whereas in the intestine the adverse effects of NSAIDs are generally limited to subclinical inflammation, and radiologically demonstrable ulceration and strictures occur only occasionally.¹³

McCormack and Brune¹⁴ considered the physicochemical characteristics of a few acidic NSAIDs with a lower than average gastrotoxic potential. They noted that these drugs did not reach high concentrations in the gastric mucosa. For flufenamic acid, fenclofenac, and diflunisal this was suggested to be owing to their enhanced lipophilicity, whereas for azapropazone it was thought to be because it is a cation at low pH values.

Ion trapping also occurs in tissues made acidotic by pathophysiological mechanisms such as in tumours and in inflammation. Research with ionisable 5-fluorouracil in rat fibrosarcomas in vivo, using nuclear magnetic resonance spectroscopy techniques, has shown that a localised pHe reduction from 7.3 to 6.9 enhanced the cellular uptake of the drug, causing a 2.5-fold increase in the elimination half life.¹⁵ Such direct studies have not been conducted in inflammation. Acidic NSAIDs have been shown to accumulate in inflamed tissue in several animal models, however.^{16 17} In patients with joint inflammation, total NSAID concentrations increase in the synovial fluid and tissue as inflammation becomes more severe and, therefore, more acidotic.^{18 19} Although increased extravasation of albumin bound NSAIDs will contribute to the higher NSAID concentrations, ion trapping could also have a role.

If ion trapping does occur with NSAIDs, it would explain why acidic NSAIDs are more effective in vivo than NSAIDs such as proquazone and indoxole, which, although fairly potent cyclo-oxygenase inhibitors in vitro, are not acidic.²⁰ It might also explain why more than 90% of patients with gout, with its severe synovitis, respond to NSAID treatment within one day, with complete resolution of symptoms in five to eight days²¹ and why the patients with rheumatoid arthritis most likely to respond well to NSAID treatment are those with more aggressive disease.²² The acidosis of osteoarthritis is less severe and probably less persistent than in rheumatoid arthritis.²³ Given this, NSAIDs would be expected to be most effective during inflammatory and acidotic episodes and less so in the intervening periods.

Differences in NSAID ion trapping may account for some of the variation in therapeutic response within a disease group,²⁴ as acidosis

is a dynamic variable and is under the influence of diverse factors. In rheumatoid arthritis the extent of acidosis differs considerably between patients and seems to be compounded by movement.^{19 25 26} Flexion of an inflamed joint produces a small but significant decrease in pH. This correlates with the flexion induced increase in intra-articular pressure, which, in turn, is accentuated by the presence of an effusion.²⁷ Joint movement would, therefore, be expected to have a positive influence on the distribution of NSAIDs and may have contributed to the beneficial effects of physical training observed in patients with moderate rheumatoid arthritis.^{28 29} By the same token, any intervention, be it bed rest or drug treatment, that reduces disease activity would decrease NSAID ion trapping and therefore NSAID efficacy. In fact, NSAIDs could alter the synovial microenvironment in such a way as to attenuate their own efficacy over a period of time. The constantly changing profile of the influences on tissue pH could account for not only some of the variability between patients, but also that within a single patient over time.

The recently developed NSAID nabumetone uses the concept of ion trapping to good effect. Nabumetone itself is not acidic and is without significant pharmacological effects. It does not undergo ion trapping in the stomach and has low gastrotoxicity in animal models.¹⁰ It is metabolised in the liver to 6-methoxy-2-naphthylacetic acid, which is acidic, possesses similar anti-inflammatory activity to other acidic NSAIDs, and can potentially be ion trapped in inflammatory cells.³⁰

In conclusion, we suggest that the variable efficacy of NSAIDs in different diseases, between patients for a selected disease, and within the same patient over time may be accounted for by the acidic nature of NSAIDs and their propensity for ion trapping. Detailed metabolic studies using nuclear magnetic resonance spectroscopy techniques that allow for accurate quantification of tissue pH, and intracellular concentrations of suitably labelled NSAIDs, should be able to assess this hypothesis. In the meantime, should our hypothesis be true, clinical rheumatologists may like to consider some of the more obvious consequences. Movement of the joint may produce beneficial effects on drug distribution and, therefore, efficacy. Also, there may be a rationale for switching between NSAIDs, with their different physicochemical properties, to give continuing anti-inflammatory activity in a constantly changing microenvironment.

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