Pharmacokinetics and dosage regimens of anti-inflammatory drugs

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Summary— The term anti-inflammatory drug, in its broadest sense, encompasses a number of very diverse compounds, ranging from steroids to non-steroidal anti-inflammatory drugs (NSAIDs) and from disease modifying agents (used in the treatment of canine rheumatoid arthritis) to chondroprotective agents (used in the treatment of osteoarthrosis and traumatic arthritis in the horse). For many of these drugs (*eg,* chondroprotective and disease modifying agents) the mode of action is unknown and even with steroids and NSAIDs there is no universal agreement on mechanism of action. It is therefore in many cases impossible to link pharmacokinetic data to a drug's pharmacodynamics, for example to an effect on a specific biochemical marker. Some agents, including corticosteroids, may have indirect modes of action, so that the pharmacodynamic half-life can be much longer than (and not clearly related to) the pharmacokinetic half-life. In other cases, clinical benefits may only become apparent after several weeks or even months. It can therefore be difficult or impossible to use classical pharmacokinetic approaches to set dosing intervals and dose rates for clinical use. To some extent, the position is more straightforward with NSAIDs. However, even with these drugs simple approaches are not possible and this paper will review briefly some of the studies undertaken in our laboratory which have attempted to utilize NSAID kinetics to set dosage schedules for clinical use.

anti-inflammatory drugs / pharmacokinetics / pharmacodynamics / dosage regimen

Résumé — Pharmacocinétique et posologie des anti-inflammatoires. *Le terme générique d'anti-inflammatoire est utilisé pour un ensemble de substances comprenant des stéroïdes, des anti-inflammatoires non stéroïdiens (AINS), des agents modifiant les processus pathogènes (utilisés dans l'arthrite rhumatoïde du chien), et des agents chondroprotecteurs (utilisés dans le traitement de l'ostéoarthrose et des arthrites traumatiques du cheval). Pour la plupart de ces médicaments (p ex : agents chondroprotecteurs), le mode d'action est inconnu; même pour les stéroïdes et les AINS, il n'y a pas d'accord définitif sur les mécanismes d'action. En conséquence, il est impossible de relier dans de nombreux cas les données pharmacocinétiques aux données pharmacodynamiques. Certains agents, comprenant les corticostéroïdes, peuvent avoir un mode d'action indirect si bien que le temps de demi-vie des effets peut être beaucoup plus long (et mal relié) au temps de demi-vie pharmacocinétique. Dans certains cas, les effets bénéfiques au niveau clinique ne peuvent apparaître qu'après plusieurs semaines ou plusieurs mois. Pour ces médicaments, il est difficile d'avoir recours à la pharmacocinétique pour ajuster la posologie. Avec les AINS, la situation semble plus claire et la présente revue expose les études entreprises dans notre laboratoire pour utiliser les données pharmacocinétiques pour ajuster la posologie des AINS.*

anti-inflammatoires / pharmacocinétique / pharmacodynamie / posologie

INTRODUCTION

Anti-inflammatory drugs comprise very diverse groups of compounds. The principal classes are listed in table I. It is even questionable whether some of these compounds (groups 6, 7 and 9) are strictly anti-inflammatory. For example, polysulfated glycosaminoglycan (PSGAG) is a chondroprotective agent used in therapy of degenerative joint disease in the horse. Since cartilage is an avascular tissue, it cannot exhibit an inflammatory response, and this drug may work as an inhibitor of cartilage degrading enzymes, rather than as a 'true' anti-inflammatory drug.

Other drugs, like the anti-histamines (H_1-receptor antagonists), may be classed as weak anti-inflammatory drugs, mainly because the action of histamine as an inflammatory mediator (pain, vasodilation, edema) is probably restricted largely to the early part of the acute phase of the inflammatory response. As mentioned in the Summary to this paper, the mode of action of some agents (classes 6, 7 and 9) is either unknown or disputed and it is therefore difficult to link pharmacokinetic data to a particular action of the drug. In other cases, with anti-inflammatory steroids, for example, several separate actions probably contribute to the therapeutic effect and these drugs act, at least in part, by indirect means. They induce production of endogenous polypeptides with anti-inflammatory activity (the lipocortins) and there is therefore both a delay in onset and longer duration of action than would be expected from the pharmacokinetics of such drugs (fig 1). For example, the pharmacodynamic half-life of dexamethasone and betamethasone is 36–54 h (Keen, 1987), yet the pharmacokinetic half-life of dexamethasone is approximately 5 h in cattle (Toutain *et al*, 1982) and only 53 min in the horse (Toutain and Brandon, 1983). Thus, classical pharmacokinetic data cannot be used in any simple way to set dosage schedules for anti-inflammatory steroids.

The so-called disease modifying agents (which include penicillamine, gold salts, some cytotoxic drugs like chlorambucil and anti-inflammatory corticosteroids) inhibit the progress of degenerative changes in cartilage in human and canine patients with rheumatoid arthritis. However, the action of these drugs may be extremely slow in onset (weeks or months after initiating therapy) and very difficult to monitor accurately. Clearly, the pharmacokinetics of these drugs also cannot be used in any simple manner to set dosage schedules.

In recent years we and others have carried out studies on the pharmacokinetics of non-steroidal anti-inflammatory drugs in horses, cattle, cats and dogs. Aspects of

Table I. Anti-inflammatory drugs and agents used in the therapy of joint diseases.

1. Anti-histamines (anti-inflammatory action in early phase of acute inflammation)
2. Anti-serotonergic drugs (anti-inflammatory action in some species)
3. Steroids (glucocorticoids)
4. Non-steroidal anti-inflammatory drugs (NSAIDs)
5. Dual inhibitors of cyclo-oxygenase and lipoxygenase
6. Disease modifying and cytotoxic agents
7. Hyaluronic acid
8. Agents with superoxide dismutase activity (*eg*, orgotein)
9. Polysulfated glycosaminoglycan (PSGAG) and other chondroprotective agents

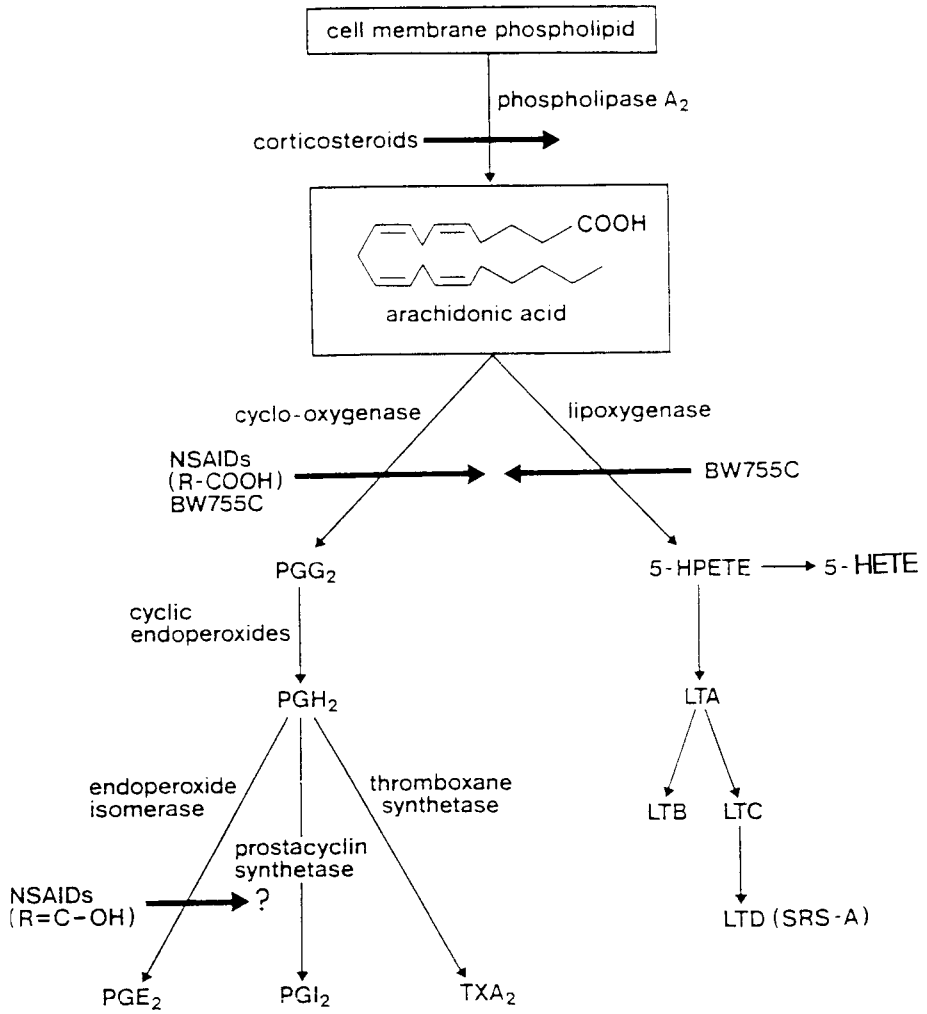

Fig 1. Arachidonic acid cascade, illustrating formation of inflammatory mediators and proposed sites of action of some anti-inflammatory drugs.

particular interest, which have been reported previously are: 1) the very high degree of plasma protein binding (usually 98% or higher, salicylate being the main exception); 2) probably related to this, the low volume of distribution in most species (usually of the order of 0.1 to 0.2 l/kg bw). This is illustrated for flunixin in table II; 3) profound differences between species in elimination half-life and plasma clearance with most drugs and, in some instances, breed differences in half-life (naproxen having twice the half-life in mongrel dogs compared to beagles); 4) the existence of dose-dependent, zero-order pharmacokinetics for some drugs administered at ther-

apeutic or slightly greater dose rates (*eg,* salicylate in the cat and phenylbutazone in the horse); 5) marked delays in absorption following oral dosing of at least one NSAID (phenylbutazone) in the horse, possibly as a consequence of formulation and/or drug binding to fibrous components of feedstuffs. The latter effects may explain both delayed T_{max} values and double (even triple) peaks in plasma concentration–time curves (Lees *et al,* 1986; Maitho *et al,* 1986).

It is commonly held (Lees and Higgins, 1985) that NSAIDs produce their principal pharmacological actions (analgesic, antipyretic, anti-inflammatory) by inhibition of cyclo-oxygenase and hence blockade of synthesis of inflammatory eicosanoids, including prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2) (fig 1). This prompted us to develop models of acute inflammation in which NSAID kinetics could be related to: 1) the time course of inhibition in inflammatory exudate of the synthesis of a 'marker' eicosanoid, such as PGE_2 and/or; 2) components of the acute inflammatory response, such as skin temperature rise, degree of edematous swelling and leukocyte numbers in inflammatory exudate (Higgins and Lees, 1984; Lees and Higgins, 1985).

MATERIALS AND METHODS

Models of acute inflammation, based on injection of the pro-inflammatory polysaccharide carrageenan into tissue cages lined with granulation tissue or the insertion of carrageenan-soaked sponges into subcutaneous pouches in the neck, have been described previously (Higgins and Lees, 1984; Lees *et al,* 1987; Lees and Higgins, 1985). Samples of exudate, for analysis of NSAID concentration and concentrations of eicosanoids (PGE_2, 6-keto-$PGF_{1\alpha}$, TXB_2 and LTB_4) are harvested at predetermined times up to 48 h. These models were first developed in the horse, and more recently have been applied in cattle. By using 10–12 exudate sampling times, it is possible both to determine *AUC* values for drug concentration in exudate and compare them with corresponding plasma *AUC* values, and to monitor the magnitude and time course of inhibition of eicosanoids, such as PGE_2, resulting from the blockade of enzymes (*eg,* cyclo-oxygenase) in the arachidonic acid cascade.

Table II. Flunixin pharmacokinetics following intravenous dosing (mean values).

Parameter (units)	*Species*			
	horse [1]	*dog* [2]	*cow* [3]	*cow* [4]
Dose (mg/kg)	1.1	1.1	2.2	1.1
C_p^0 (μg/ml)	11.0	14.6	11.9	16.4
$t_{1/2}\alpha$ (h)	0.14	0.55	0.16	0.29
$t_{1/2}\beta$ (h)	1.9	3.7	6.1	8.1
V_c (ml/kg)	100	79	179	70
$V_{d(area)}$ (ml/kg)	160	348	2290	1050
Cl_b (ml/kg/h)	57	64	263	90
AUC (μg/ml•h)	19.4	18.0	8.5	12.2

[1] Lees *et al* (1987). [2] Hardie *et al* (1985). 3 Lees *et al,* unpublished data. [4] Hardee *et al* (1985).

RESULTS

Several studies, using the tissue cage and polyester sponge models of acute inflammation in horses, have been undertaken in our laboratory and reported in the scientific literature. Drugs investigated for anti-inflammatory activity and pharmacokinetics have included NSAIDs, steroids and dual inhibitors (table I). In this paper, data are presented on recent studies on intravenously administered flunixin in calves. With doses of 2.2 and 8.8 mg/kg, flunixin pharmacokinetics followed a biexponential decay pattern. It was of interest to note, consistently, a small secondary peak in the plasma concentration–time curve, possibly as a result of enterohepatic recirculation. Flunixin did not penetrate well into tissue cage fluid (transudate); *AUC* values were approximately one fifth of corresponding plasma values. However, the drug penetrated very readily into acute inflammatory exudate (probably because of a high degree of binding to plasma protein). *AUC* values for flunixin in exudate exceeded corresponding plasma values. The slow release of flunixin from the exudate proteins probably explains the longer duration of action of flunixin than would be expected from its relatively rapid plasma clearance. With both 2.2 and 8.8 mg/kg doses, exudate PGE_2 inhibition was high (95–100%) relative to placebo-treated PGE_2 concentrations for 12 h after dosing. Partial inhibition persisted up to 24 h, particularly with the higher dose of flunixin. Insofar as the analgesic and anti-inflammatory actions of flunixin are due to cyclo-oxygenase inhibition, these findings suggest that the 2.2 mg/kg dose is likely to be clinically effective and a 24 h dosing interval is probably suitable. The higher 8.8 mg/kg dose might provide a greater clinical effect, but this is likely to be restricted to the period between 12 and 24 h after dosing.

DISCUSSION

The starting point for establishing dosage schedules for NSAIDs is to determine, in each target species, classical pharmacokinetic parameters, such as Cl_b $V_{d(area)}$, $t_{1/2}\beta$, *etc.* The fact that marked species differences do exist, especially in $t_{1/2}\beta$ (approximate half-lives for phenylbutazone are 4–6 h in the horse and dog, 72 h in man and 40–60 h in cattle), clearly will permit longer dosing intervals in certain species. It has, for example, been shown that similar plasma concentrations of salicylate are obtained following oral aspirin doses of 25 mg/kg at 8 h intervals in the dog and at 24 h intervals in cats.

Secondly, in some instances it is necessary to take account of the formation of metabolites with biological activity. Phenylbutazone is an example. The ring-hydroxylated metabolite, oxyphenbutazone, has been shown to be approximately equipotent with the parent drug in laboratory animal studies. In the horse, plasma and extravascular fluid concentrations are achieved which might provide up to 25% of the activity following phenylbutazone administration.

Thirdly, it is necessary to attempt to relate pharmacokinetic parameters to some biochemical or whole body marker of the drug's action, *eg,* inflammatory mediator concentration in exudate and degree of edematous swelling, respectively. The rapid penetration into and slow clearance from inflammatory exudate of NSAIDs highly bound to plasma and presumably to exudate proteins may account for the longer duration of action than might be predicted from studies of plasma concentration–time relationships.

This approach is still in its infancy and much further work is required before drug action in models of pain perception (for an-

algesic activity), pyrexia (for anti-pyretic activity), endotoxemia (for anti-shock activity) and inflammation (for anti-inflammatory activity) can be usefully related to the pharmacokinetics of unbound or 'free' drug concentrations in such body fluids as plasma, inflammatory exudate, synovial fluid, *etc.*

Another aspect of pharmacodynamic–pharmacokinetic relationships which will be explored in future researches is the differing biological activity of enantiomers of NSAIDs. Some agents are supplied as a mixture of two enantiomers in equal proportions. The pharmacokinetic disposition and metabolism of each enantiomer is known in some cases to differ, and in this circumstance conventional analytical (usually high pressure liquid chromatography) methods measuring only total drug concentration may either over- or underestimate the concentration available for exerting pharmacological actions. This will arise if biological activities of enantiomers differ.

Finally, we noted in two recent investigations of novel NSAIDs in the horse that agents with relatively weak activity, as cyclo-oxygenase antagonists in the carrageenan–sponge model of inflammation, have, nevertheless, exerted significant anti-edematous actions. These findings highlight a limitation in using 'markers' of cyclo-oxygenase inhibition (*eg,* PGE_2) to predict anti-inflammatory activity for some NSAIDs and point towards other mechanisms of action.

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