INVITED ARTICLE

PHARMACOKINETICS OF NSAID WITH SPECIAL REFERENCE TO THE ELDERLY

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SYNOPSIS

The practicing clinician is faced with prescribing NSAID for their analgesic and/or anti-inflammatory effects to a wide range of the population. This will include not only children and the elderly but patients with liver disease, kidney disease, cardiac disease, etc. NSAID toxicity appears to be particularly prevalent in the elderly in whom deterioration of organ function, concomitant disease and consequently concomitant drug administration are naturally more common. Knowledge of the pharmacokinetics of NSAIDs in normals and in the disease state is therefore essential in modern practice.

The basic characteristics of drug disposition include absorption, distribution, metabolism, tissue receptor interaction and excretion. These are not independent of each other but constantly inter-reacting. The major kinetic variables of NSAID that the practicing clinician should be concerned with are bio-availability, volume of distribution, metabolism and total body clearance.

Although absorption of NSAID is dependent on the fasting or non-fasting state, physical activity, gut motility, gastric pH, and absorptive surface area, absorption problems occur infrequently in day to day practice.

All NSAID are highly albumin bound and soluble in plasma water; therefore changes in volume of distribution with age, renal, liver or cardiac disease may significantly alter blood levels. Drug interaction with highly protein bound drugs such as coumadins and oral hypoglycaemics will therefore be theoretically more common in patients with low albumin.

The two basic pathways of biotransformation are oxidative metabolism and glucuronidation. Phase I metabolism (oxidation) can be altered by drugs (e.g. cimetidine), disease state (e.g. cirrhosis) and with ageing. Piroxicam, isoxicam, phenylbutazone, and indomethacin are examples of drugs which predominatly undergo phase I metabolism and ketoprofen, naproxen, and tiaprofen are drugs which predominatly undergo phase II metabolism. Glucuronidation (phase II metabolism) is rarely affected by age or disease.

The clearance of NSAIDs is generally dependent on renal plasma blood flow, tubular function and glomerular filtration. All can decrease with age and with disease of the renal parenchyma. In the compromised kidney, renal plasma blood flow is partially regulated by prostaglandin activity, therefore interference with prostaglandin production might play a role in renal insufficiency. The presence of renal plasma blood flow may also result in increase of conversion of R enantiomer of propionic acids to the more active S enantiomer leading to a theoretical increase in active drug level. Drugs with short half-lives and rapid plasma clearance will be less affected than those with long half-lives.

In summary, a basic knowledge of the patient's physical health and drug usage are essential for safe NSAID administration. This is particularly evident in the elderly population and those with renal or liver disease.

PHARMACOKINETICS RELATED TO AGEING

It is now recognised that the parameters of drug pharmacokinetics which display the greatest variation with age are: bio-availability, volume of distribution, and drug clearance rates. These variable can be more simply discussed by categorising the pharmacokinetic profile into a process of: absorption, distribution, metabolism, receptor site interaction, drug-drug interaction and excretion.

ABSORPTION

When a drug is administered to the gastrointestinal tract and subsequently absorbed into the blood stream it has to have a reproducible chemical availability. The chemical availability implies that the chemical formulation which reaches the blood stream is equivalent to what has been administered or, as with certain drugs, is an active chemical formulation derived from the administered drug. Chemical equivalence is a reproducible chemical availability between drug formulations from different manufacturers. Physiological availability, now commonly known as bio-availability, is the amount of usable drug absorbed by a particular route relative to the 100 per cent bioavailability which would be achieved by the intravenous route. Thus if 70 per cent of the administered chemical formulation reaches the blood stream via the enteral route and was biologically active one would refer to this dosing as having 70 per cent bioavailability by the oral route (1).

The most important factor, however, is therapeutic equivalence, which implies that all drug formulations administered will have exactly the same therapeutic effect on the patient. When comparing formulations from different manufacturers it is the therapeutic equivalence which must match. It is obvious that therapeutic equivalence is directly related to the physical-chemical form of the drug and environment from which the drug is absorbed (1).

All NSAIDs are weak acids with a pKa in the 2-7 range and thus are lipophilic in the low pH (1-3) of the stomach. Solubility of the product formulation is however greater with increase in available pH (1). This increase in solubility at higher pH and the greater surface area and longer transit time make the small intestine the principal site of NSAID absorption.

There is little information comparing the effects of anti-arthritic drugs in males and females although in general there is a tendency for females to develop more adverse reactions to drugs (2). It has been shown that the time to reach maximum concentration (Tmax) is delayed in females compared to males for salicylate kinetics (3). This delay in Tmax was not as marked in the middle of the menstrual cycle compared to the end of the menstrual cycle. It is thought that this phenomenon was related to the gastric emptying time which is increased in the middle of the menstrual cycle. There is no difference in the Cmax nor in the area under the curve for salicylate kinetics in the two sexes. It is unlikely that there is any significant intersex differences which occur with respect to NSAIDs in humans, but at present the possibility has not been examined in detail.

The physiological changes potentially relevant to the pharmacokinetic analysis in the elderly have recently been reviewed in detail by Ouslander (4). The major factors which can influence absorption in the elderly are: decrease in gastric surface area and cell number; increase in gastric pH; reduction in splanchnic blood flow; decrease in gastric emptying time and decrease in intestinal motility; and a reduction in active absorption transport (4). The decrease in absorption transport is technically irrelevant since all NSAIDs, which are weak acids, are absorbed by passive diffusion. Studies in the elderly concerning acetaminophen, aspirin, phenylbutazone, indomethacin and ketoprofen have all demonstrated normal absorption patterns (5-8). Problems related to NSAID absorption in the elderly are relatively unimportant clinically and should they occur it is more likely that the alteration in absorption is related to concomitant disease and/or concomitant drug therapy. Data relating to these two important variables is lacking in the general literature since research is rarely done in patients suffering from concomitant diseases who are taking concomitant drugs which might interfere with the process being examined. In studies of absorption, for example, it is uncommon for absorption kinetics to be studied for NSAIDs when the patient is also taking probanthine which will slow gastric and intestinal motility or metoclopramide which will accelerate gastric emptying and intestinal motility. There have been numerous studies undertaken when NSAIDs are administered with food and many significant findings have been documented. For example, the maximum concentration of aspirin (9), diflunisal (10) and flurbiprofen (11) have been shown to be reduced when these drugs are taken with food. But the total absorption as expressed by the area under the curve was not. The rates of absorption namely the Tmax of indomethacin (12), sulindac (13), naproxen (14), fenbufen (15), ibuprofen (16), diclofenac (17), alclofenac (18) and piroxicam (19) are reduced by concomitant food intake. However, it is unlikely that these alterations in absorption kinetics of NSAIDs are relevant to clinical efficacy when these drugs are administered in a chronic dosage regimen. One significant factor which will obviously interfere with absorption is compliance. This has rarely been addressed solely in the elderly patient and the majority of studies to date relate to the general population and non-arthritic disorders (20-22).

There are very few disease states which have been reported to alter the absorption characteristics of NSAIDs, but it is interesting to note that the total area under the curve for tolmetin is reduced (23) as is the Cmax of diclofenac (24) in patients with rheumatoid arthritis. It is most likely that these abnormalities could also be related to a reduction in plasma albumin

and also possible accelerated renal clearance rather than a true absorptive problem.

Theoretically drugs such as cimetidine, ranitidine and antacids which elevate the gastric pH should alter the absorption of NSAIDs in the stomach. However, the majority of NSAIDs are absorbed in the small intestine and concomitant therapy of NSAIDs with H_2 blockers and/or antacids should not be a major problem, specifically with chronic dosing. There are many studies on the influence of antacids on NSAID absorption but the results are varied. The concomitant administration of diflunisal and aluminium hydroxide results in a 26 to 40 per cent reduction in the area under the curve for diflunisal absorption (25). The co-administration of magnesium aluminium hydroxide and indomethacin has been shown to result in prolongation of the Tmax but an increase in the Cmax for indomethacin (12). In contrast concurrent administration of naproxen and sodium bicarbonate resulted in a shortened Tmax (26) for naproxen. The concurrent administration of aluminium magnesium hydroxide and piroxicam did not influence piroxicam absorption (27). Ketoprofen absorption pattern is not influenced by concomitant aluminium phosphate (28). Thus a varied pattern is noted in studies on antacids and the absorption of NSAIDs but in practice it is unlikely that these factors matter when one is considering chronic dosing.

In summary, NSAIDs are principally administered via the G.I. tract either by the oral or rectal route. Almost all are weak acids and hence can be absorbed from the stomach, although the large surface area of the small intestine usually makes this the major absorptive site. For both drug manufacture and research studies, an indepth knowledge of G.I. anatomy, physiology and biochemistry is required. The chemical and physical characteristics of tablets and their interaction with the local environment have to be considered when absorption kinetics are being studied. Variables such as concomitant food and other drugs, co-existent diseases and even the patients' physical activity and emotions may alter drug absorption kinetics. The practising clinician should consider these variables as factors which may reduce or enhance drug absorption and hence potentially influence efficacy and/or drug toxicity.

DISTRIBUTION

Like bio-availability and plasma clearance, the volume of distribution is markedly altered with age and disease. In the elderly, total body water, plasma volume, extracellular fluid, lean body mass and serum albumin are decreased although fat stores are increased (4). NSAIDs are water soluble compounds which are predominantly albumin bound therefore in the elderly one can expect there will be more free drug in equilibrium with the tissues and less drug which is albumin bound. This relative problem of increased free drug is further accentuated by a proportional decrease in renal and hepatic blood flow in the elderly associated with a decrease in cardiac output and increased peripheral resistance. The low albumin concentrations result in high levels of free drug, creating a diffusion gradient to the site of drug action, namely the tissues. Phenylbutazone for example is a highly protein bound drug. Administration of this drug to the elderly will result in greater amounts of free phenylbutazone because of the low serum albumin and hence provide the potential for greater toxicity (29). It is still a controversial topic as to whether there are alterations in the extent of specific protein binding for particular drugs in the elderly since it is well known that concomitant drug therapy with avidly protein bound drugs in the presence of low albumin is potentially hazardous. Almost all NSAIDs have the potential to displace warfarin-like and oral hypoglycaemic drugs from albumin binding. What is known, is that protein binding of NSAID does not seem to be abnormal in rheumatoid disease (30). However, in elderly patients receiving multiple drugs, a rise in unbound salicylate has been demonstrated (29). Since warfarin and NSAID bind to different sites on albumin the problems of increased bleeding during concomitant therapy must be related to some other mechanism: and indeed, it has been clearly demonstrated that phenylbutazone enhances the metabolism of the R (rectus) enantiomer while delaying the excretion of the more active S (sinister) enantiomer of warfarin. Thus, although the total serum concentration of warfarin is not altered, the proportion of the active S-form is increased, so adding to the potential risk for bleeding (31). The other major effect of NSAID which contributes to the risk of bleeding is the inhibition of platelet cyclo-oxygenase activity.

Salicylates can increase the plasma level of chlorpropamide (32) but clinically significant adverse reactions are surprisingly uncommon in our clinical practice. Phenylbutazone prolongs the half-life of tolbutamide, by inducting a 450 cytochrome enzyme which has a decreased capacity for the hydroxylation metabolism of tolbutamide (33). We would recommend that if highly protein bound drugs are to be administered to the elderly that, if possible, individual plasma levels should be established and compared to clinical effect prior to embarking on chronic therapy. An example of this would be the stabilization of the prothrombin time for an elderly patient receiving warfarin-like drugs and a NSAID.

METABOLISM

Liver size is decreased in elderly patients proportional to body size. Hepatic blood flow is reduced to approximately 45 per cent of normal in the elderly subject and creates a significant problem of potential decrease in hepatic clearance for those drugs which require a high hepatic extraction ratio. NSAIDs in general exhibit a low hepatic extraction ratio and therefore are not dependent on splanchnic blood flow for the hepatic clearance. However, changes in metabolism of NSAIDs may be directly related to changes with ageing in the processes of biotransformation. Biotransformation is recognised as two basic steps categorised as Phase I reactions and Phase II reactions. Phase I reactions occur in the microsomal enzyme systems. They are referred to as oxidative biotransformation comprising predominantly of oxidations (hydroxylation, N-dealkylation and sulfoxidation), hydrolyses and reduction (34). The principal reactions of Phase I oxidation results in conversion of active drug to a slightly more polar compound which retains part or all of its pharmacological activity. Phase II reactions or conjugation, on the other hand, result in attachment to the drug by glucuronide, sulphate or an acetate resulting in a more water soluble conjugate which can thus be excreted easily in the urine. Studies in elderly mammals including rats, mice and humans have demonstrated that Phase I oxidative reactions can decrease with old age whereas Phase II or glucuronidation/conjugation type reactions are relatively unaffected by age (35).

In theory those NSAIDs which predominantly undergo conjugation such as ketoprofen, tiaprofen and suprofen usually should have a normal plasma clearance (36) whereas those drugs which undergo predominantly oxidative biotransformation, such as phenylbutazone and piroxicam have the potential to be

retained in the plasma of the elderly (37,38).

Although there is no documented cause and effect relationship, reports suggest that the elderly are susceptible to toxicity with drugs in the long half-life range such as phenylbutazone, salicylates, piroxicam and benoxaprofen (37,38,39).

RENAL FUNCTION

In the elderly there is a progressive reduction in lean body mass with advancing age with the result that the serum creatinine does not provide a true reflection of renal function status. For example glomerular filtration rate is known to decrease by approximately 35 per cent between the ages of 20 and 90 years and it has been demonstrated that in females over the age of 80 years, serum creatinine below 1.5 mg per cent may correspond with a creatinine clearance of less than 60 ml/min. (40). Concomitant drug therapy, and diseases such as diabetes mellitus and hypertension may seriously diminish glomerular filtration rate in the elderly. Renal function can only be accurately assessed by measuring a 24 hour urine creatinine clearance, although approximation of creatinine clearance can be deducted by using a standard formula recommended by Cockcroft and Gault in which creatinine clearance equals 140 — age × body weight in kilograms — 72 × the serum creatinine. This formula can be adjusted for females by multiplying by 0.85. A correction factor for lean body mass should also be made for both elderly males and females (41). Total drug clearance is not only a function of glomerular filtration but also renal plasma blood flow, tubular secretion and tubular reabsorption. Renal plasma blood flow decreases with age and to a certain extent is dependent on the level of prostaglandin E_2 available. Careful consideration should therefore be given to the fact that NSAIDs will further decrease the availability of PgE_2 (42). In our opinion there is no substitute for knowing the creatinine clearance and plasma levels of drugs being administered.

In patients with renal insufficiency the plasma clearance of most NSADs is delayed and there is an extension of plasma half-life. Appropriate reduction in dosage is recommended. This exercise is easier to achieve with short half-life drugs than with long half-life drugs (Table I).

RECEPTOR SITES

It has not yet been determined whether NSAIDs have a specific receptor site which might be important in determining their efficacy and toxicity. Perhaps one example of tissue sensitivity relevant to NSAIDs is that elderly patients who develop an adverse effect to phenylbutazone are more likely to develop an aplastic anaemia whereas younger subjects are more likely to develop agranulocytosis or thrombocytopenia; however this is mere speculation.

DRUG-DRUG INTERACTIONS

The potential for patients, especially the elderly, to develop drug-drug interactions is astronomical. In clinical practice however, these interactions are relatively infrequent. Table II lists some of the more commonly experienced drug-drug interactions for NSAIDs. These have been reviewed in detail elsewhere by Day and colleagues (43).

TABLE I
HALF-LIVES OF NSAIDs (HOURS)

SHORT HALF-LIFE		LONF HALF-LIFE	
Acetylsalicylic acid	0.25	Diflunisal	13
Diclofenac	1	Naproxen	14
Indomethacin	1 – 1.5	Salicylate**	15
Ketoprofen	1 – 2	Isoxicam	24
Tiaprofenic Acid	2	Piroxicam	40
Fenoprofen	2.5	Oxyphenbutazone	65
Ibuprofen	2.5	Phenylbutazone	70
Fluribprofen	3		
Mefanamic acid	2 – 4		
Meclofenamate	2 – 4		
Tolmetin	4 – 6		
Sulindac***	8		

** In anti-inflammatory dosage i.e. 3 g or more per day. In low dosage half-life of only 2 hours.
*** Active metabolite 18.

TABLE II
CLINICALLY ESTABLISHED INTERACTIONS WITH ANTI-RHEUMATIC DRUGS

Interacting Drug	Effect	Mechanism and Comments
	Aspirin and Salicylates	
Acetazolamide	Increased CNS toxicity of acetazolamide	Increased plasma un-ionised salicylate with increased brain concentrations
Alcohol	Erosive gastritis	Additive
Antacids	Decreased plasma concentrations	Increased renal clearance of salicylate
Aminosalicylic acid	Decreased salicylate levels (PAS)	Increased renal clearance
Bumetanide	Decreased diuretic effect	Inhibition of prostaglandin synthesis
Captopril	Decreased antihypertensive effect	Possible inhibition of prostaglandin
Dipyridamole	Increased effects on platelet function	Synergism
Heparin	Potential increased bleeding risk, especially with aspirin	Inhibition of platelet function Theoretical rather than proven risk
Methotrexate	Increased methotrexate toxicity	Displacement of methotrexate from protein binding sites, and decreased renal excretion of methotrexate. Latter probably more serious effect.
Moxalactam	Increased bleeding risk	Addition effect, but risk is only potential
Oral anticoagulants	Increased bleeding risk	Inhibition of platelet function with aspirin additive effect. With high doses of salicylates increased hypoprothrombinemic effect
Oral hypoglycemics	Increased hypoglycemia	Additive effect with displacement of hypoglycemics from protein binding sites, especially chlorpropamide
Probenecid	Decreased uricosuric effect	Mechanism not established but important in the treatment of gout
	Indomethacin	
Antacids	Decreased indomethacin effect	Decreased indomethacin absorption
Beta-adrenergic blockers	Decreased antihypertensive effect	Possibly by prostaglandin inhibition
Diuretics	Decreased antihypertensive and natriuretic effect	Possibly by prostaglandin inhibition. Seen with thiazides and furosemide
Lithium	Increased lithium toxicity	Decreased lithium renal excretion
Oral anticoagulants	Potential increased bleeding risk	Inhibition of platelet function
Sympathomimetic	Hypertension and hypertensive crisis	Inhibition of nonepinephrine uptake
	Naproxen	
Probenecid	Increased naproxen effects	Probenecid inhibits hepatic metabolism of naproxen

	Pheynylbutazone and Oxyphenbutazone	
Oral anticoagulants	Increased anticoagulant	Inhibition of metabolism S-isomer and displacement from protein binding sites
Oral hypoglycemics	Increased sulfonylurea hypoglycemia	Inhibition of microsomal enzymes
Methotrexate	Increased methotrexate effect	Not established
Phenytoin	Increased phenytoin toxicity	Inhibition of microsomal enzymes

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COMPLIANCE

Since many patients with joint disease are elderly it is important to know how compliant they will be with prescribed medications. Studies of how rheumatic patients use medicines in their homes leave little room for confidence that the elderly will take their medication in the proper dose and at the proper time (44). Gatley (20) has clearly shown that compliance is better if only one tablet has to be taken each day compared to four tablets a day. However, there is no information on compliance in this regard in elderly subjects. Taking one tablet with a prolonged half-life each day would be ideal for the elderly if one could be sure that the patient would not take more than one tablet a day if their pain was severe. With a short half-life drug ($t\frac{1}{2} < 6h$), however, taking extra tablets would not theoretically be so serious as with a long half-life drug ($t\frac{1}{2} > 24h$). Compliance in rheumatic disease is largely determined by pain, those patients with more severe pain being more compliant than those with less severe pain (45). This is probably why patients with rheumatoid arthritis are more compliant than those with osteoarthritis (21,22). This might be considered as the 'disease stimulus' compliance factor. On the other hand there are other significant variables determining compliance in elderly subjects such as cognitive function. Elderly patients are notoriously forgetful and frequently cannot remember whether they took a tablet at a specified time. Thus, there is a danger of them taking several "once-a-day" tablets in the one 24 hour period. Social mobility also may determine compliance in the elderly, since frequently they will complain that they are homebound due to weather, lack of transport, or social commitments e.g. to the cat or dog or an elderly spouse. Compliance may however, be improved in the elderly by an emphasis on education regarding disease state, drug necessity, the purpose of the drug, and how it should be taken. This can be reinforced by the family doctor, district nurse, social worker or intelligent relative by means of frequent visitation and/or phone calls.

It is clearly obvious that compliance is one of the major variables of pharmacokinetics and hence pharmacodynamics of drug therapy in the elderly.

CONCLUSIONS

Although a great deal of research has been done on the NSAIDs it is somewhat sobering how little this is, in contrast to the advances in knowledge of the biochemistry and immunology of rheumatoid arthritis in the 20th Century. This reflects a paucity of interest, among doctors regarding the drugs which they use to treat patients, and also of the granting agencies who tend to defer the onus of drug research to the major pharmaceutical companies. Quite clearly the major advances in drug therapy during the past two or three decades has been the result of the generous funding by the pharmaceutical industries as well as their own in-house research.

It behooves the educationalists to offset this discrepancy both at the undergraduate and postgraduate level lest we fall prey to the acidic comments of the 18th Century French philosopher Voltaire's description of physicians as "men who prescribe medicine of which they know little, to cure disease of whichgthey know less, in human beings of which they know nothing".

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