Pharmacological and pharmacodynamic implications of nonsteroidal anti-inflammatory drug therapy in elderly arthritic patients

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ABSTRACT: There is growing evidence that elderly patients may be more likely to develop adverse drug reactions to nonsteroidal anti-inflammatory drug/analgesic therapy. This may be due to the physiological changes which accompany ageing as well as multiple drug therapies commonly used in the elderly. The elderly may also be more prone to gastrointestinal adverse side effects. There is no satisfactory definition of the elderly. Although age 65 is widely accepted as a chronological definition, many elderly persons remain healthy until the age of 75, and furthermore, healthy elderly subjects differ little from healthy young persons. It is with the frail elderly, ie, those with multiple diseases and multiple drug therapies, that problems of medication occur. Physiological changes, which include reduced muscle mass, total body water and albumin levels, as well as effects on renal and hepatic function, affect pharmacokinetic factors, including absorption, distribution, biotransformation and renal clearance. Assessment of the multiple disease states and resultant organ failure in elderly subjects is therefore necessary. **Can J Gastroenterol 1990;4(3):126-130**

Key Words: *Arthritis, Elderly, Nonsteroidal anti-inflammatory analgesics*

Conséquences pharmacologiques et pharmacodynamiques de la thérapie par les anti-inflammatoires non stéroïdiens chez l'arthritique âgé

RESUME: Il est de plus en plus évident que, comparées aux jeunes sujets, les personnes âgées présentent une sensibilité accrue aux analgésiques. Ces réactions sont peut-être attribuables aux changements physiologiques qui accompagnent

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IN CANADA, ABOUT 10% OF THE population are elderly, defined as age 65 years or older (1). Predictions forecast a doubling of this percentage by the year 2000. At present, the elderly use approximately 75% of doctors' time and require 20 to 40 prescriptions per person annually. Chronic illness, especially rheumatic disease, is common in the elderly. It is therefore not surprising that many nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics and other antirheumatic drugs are prescribed for this group. There is growing evidence that adverse reactions to NSAIDs may be more common in elderly patients, especially women (2). This can be explained, with respect to elderly patients in general, by three basic factors: elderly patients receive an increased number of medications; the physiological changes which occur with ageing may affect pharmacokinetic drug disposition; and ageing tissues may be more sensitive to the pharmacodynamic effects of these drugs. This review is based on these three considerations.

le vieillissement, et à la polychimiothérapie couramment utilisée chez la personne âgée. Celle-ci est peut-être également plus sensible aux effets indésirables affectant les voies gastro-intestinales. Il n'existe pas de définition satisfaisante de la personne âgée. Bien que l'âge de 65 ans soit largement accepté à titre de définition chronologique, de nombreux sujets restent en bonne santé jusqu'à l'âge de 75 ans, et il faut souligner que les sujets âgés en bonne santé diffèrent peu des jeunes sujets sains. C'est donc chez la personne âgée fragile, présentant des affections multiples et soumise à une polychimiothérapie, que surviennent les problèmes associés aux médicaments. Les changements physiologiques, qui incluent une réduction de la masse maigre, de la quantité d'eau contenue dans l'organisme et des concentrations d'albumine, ainsi que la capacité amoindrie du foie et des reins, agissent sur les facteurs pharmacocinétiques - absorption, distribution, biotransformation et clairance rénale, entre autres. C'est pourquoi il est nécessaire de procéder à l'évaluation des affections multiples et des défaillances organiques résultantes chez les sujets âgés.

TABLE 1
Physiological changes that occur with age and may affect drug pharmacokinetics

Pharmacokinetics	Physiological changes
Absorption	Decreased esophageal peristalsis Atrophy of gastric and small intestinal mucosa Decreased gastric and mesenteric bloodflow Increased gastric pH Decreased gastric emptying Decreased active mucosal transport
Distribution	Decreased lean body mass (total body water) Increased fat Decreased plasma volume Decreased plasma albumin concentration
Hepatic biotransformation	Decreased liver mass Decreased function of microsomal cytochrome P_{450} enzymes Decreased enzyme induction Decreased hepatic bloodflow as a result of decreased cardiac output
Renal clearance	Decreased thirst appreciation Decreased functioning nephrons Decreased cardiac output resulting in decreased renal flow and glomerular filtration rate Decreased creatinine clearance*

** Corrected for lean body mass using the formula of Crockiff and Gault: Creatinine clearance = ((140–age) x body weight (kg))/(814 x serum creatinine (mmol/L)). The formula should be amended in females by multiplying by 0.85. (Adapted with permission from Ouslander JG. Ann Intern Med 1981;95:711-22)*

DEFINITION OF THE ELDERLY

There is no satisfactory definition of the elderly. Since Otto von Bismarck (1815-98) ordered compulsory retirement of Prussian officers on their 65th birthdays (1), this age has been widely accepted as a chronological definition of the elderly. Many elderly persons remain healthy until the age of 75 (3) and furthermore, healthy elderly subjects differ little from healthy young persons. It is with the frail elderly, ie, those with multiple pathologies and drug therapies (4), that problems of medication occur. A system for assessment of organ failure in elderly subjects is therefore necessary.

PHYSIOLOGICAL CHANGES WHICH MAY ALTER PHARMACOKINETIC DISPOSITION OF ANTIRHEUMATIC DRUGS

Table 1 summarizes the physiological changes which occur with ageing and the pharmacokinetic parameters which they affect, including absorption, distribution, biotransformation and renal clearance (5).

Absorption: NSAIDs are weak acids which are lipid-soluble, with a pK_a of approximately 3.5, ie, the pH at which 50% ionization occurs. Oral bioavailability of NSAIDs is not impaired in the elderly, since NSAIDs are readily absorbed by passive diffusion (6). Substances which are absorbed by active transport mechanisms, such as iron, galactose, thiamine and calcium, may have a reduced rate of absorption in the elderly. It is not known, however, whether antirheumatic drugs, (eg, methotrexate), which are also absorbed by active transport mechanisms, have absorption delayed in the elderly. To date, only one drug, prazosin, has been proven to have absorption diminished in elderly subjects (7). The rate of absorption of many NSAIDs is slower when taken with meals or alkalis; this has no practical significance in the treatment of chronic disease. Enteric-coated and slow release preparations are readily absorbed from the small intestine.

Elderly subjects, especially females, have reduced salivary flow (8) and diminished esophageal motility (5). Normal salivary output has been estimated at 500 to 1500 mL per day. Saliva contains not only a considerable amount of mucin and bicarbonate, but also epithelial growth factor, produced by the submandibular glands (9). Whether the diminution of salivary secretions plays any role in protecting the stomach from NSAID gastropathy is unknown. It is of interest, however, that epithelial growth factor has been shown to be protective in rats (10).

Distribution: The extent to which a drug is distributed and the relative distribution to various organs and tissues depends on the chemical characteristics of the drug. Drugs which are preferentially bound to plasma proteins, as NSAIDs are, are confined to the extracellular fluids. Alternatively, drugs which bind preferentially to tissues have a greater volume of distribution. Changes in body composition such as reduction in total body water and lean body mass might be expected to increase drug toxicity in the elderly (5). Elderly patients, especially if bedridden, often have low serum albumin concentrations as well as a decreased ability

TABLE 2
Half-lives of NSAIDs currently available in North America

Short half-life	Mean (h)	Long half-life	Mean (h)
Acetylsalicylic acid	0.25	Diflunisal	13
Diclofenac	1	Fenbufen	11
Fenoprofen	2.5	Naproxen	14
Flufenamic acid	1.4	Oxyphenylbutazone	70
Flurbiprofen	3	Phenylbutazone	70
Ibuprofen	2.5	Piroxicam	40
Ketaprofen	1-2	Salicylate*	15
Mefenamic acid	2-4	Sulindac† (active metabolite)	18
Meclofenmate	2-4		
Sulindac†	8		
Tiaprofenic acid	2		
Tolmetin‡	1, 7		

** Salicylate metabolism follows mixed phase kinetics, whereby the half-life increases in parallel with the plasma level. This half-life applies to therapeutic doses of 3 g or more daily. With small doses, the half-life is of the order of 2 h. † The active metabolite of sulindate has a long half -life. ‡ Elimination is biphasic. (Adapted with permission from Graham GG, Regan M. Arthritis Rheum 1982;25:1013-5)*

TABLE 3
Cytochrome P450 mixed function oxidase enzyme-dependent drug biotransformation pocesses

N- and O-dealkylation
Aromatic and aliphate hydroxylation
N-oxidation and N-hydroxylation
Sulphoxide formation
Deamination of amines
Desulphation

to bind plasma proteins to certain NSAIDs, eg, phenylbutazone. Thus, elderly patients may have disproportionately high levels of free NSAID, which may explain why drugs such as ibuprofen and naproxen can produce cognitive changes (11).

Biotransformation: Although the plasma half-life of a drug may be altered by changes in volume of distribution or clearance, it remains a useful pharmacokinetic parameter. NSAIDs can be broadly classified into two groups according to their plasma half-lives: those with half-lives less than 8 h and those with half-lives greater than 8 h (Table 2) (12). The time to reach steady state is approximately five times the half-life; therefore, flurbiprofen would be at equilibrium in 15 h, whereas piroxicam would take 200 h. It is customary to prescribe NSAIDs with short half-lives, three or four times daily. Those with long half-lives, such as piroxicam, are prescribed on a once daily basis; the exceptions are phenylbutazone, oxyphenylbutazone and the salicylates. The former two drugs continue to be needlessly prescribed three times a day, when they would be equally effective once a day.

Acetylsalicylic acid has an extremely short plasma half-life (approximately 10 to 15 mins). Salicylic acid, however, is prolonged, especially with therapeutic doses of 3 g or more per day. It is therefore necessary to prescribe acetylsalicylic acid or a nonacetylated salicylate more than twice a day when high doses are prescribed. The reason that salicylates in low doses have short plasma half-lives and salicylates in high doses have prolonged plasma half-lives is because the drug biotransformation by some of the hepatic enzymes is governed by Michaelis-Menten kinetics. This means that the plasma half-life increases with the dose of the drug (13).

The fact that NSAIDs with short plasma half-lives can be given on a twice daily basis and still be effective is related to the biological duration of action which exceeds the rate of drug elimination, as well as the persistence of the drug in synovial fluid (14). One of the advantages of NSAIDs with long plasma half-lives is that changes in the rate of absorption have little effect on their plasma concentrations. In addition, improved patient compliance is evident when fewer tablets have to be taken (15).

Phase I and phase II: The liver has been aptly described as the great 'poison trap', as it is the principal site of drug biotransformation. Essentially there are two types of drug biotransformation: monosynthetic (phase I) and synthetic (phase II).

Monosynthetic biotransformation is largely carried out by the cytochrome P450 mixed function oxidases, which are present in the microsomal smooth endoplasmic reticulum (Table 3) (16). These enzymes have been shown to have diminished activity in the elderly, as determined by prolongation of the plasma half-life of antipyrine and other drugs oxidized by these enzymes (17). The plasma half-lives of phenylbutazone (18), piroxicam (19) and ibuprofen (20) have been reported to be prolonged; however, this has not been confirmed in all studies (21,22). For example, no prolongation of plasma half-life of isoxicam was observed in elderly versus young patients with rheumatoid arthritis (23). The illfated benoxaprofen has a marked prolongation of plasma half-life in elderly patients, which may explain its toxicity in these subjects (24). There is evidence that the development of aplastic anemia in elderly patients receiving phenylbutazone may be related to slower biotransformation, resulting in increased plasma concentration (25). Whether NSAIDs with long plasma half-lives are more likely to cause gastric complications remains debatable (26).

Synthetic processes, such as glucuronidation, are not affected by ageing. Salicylates are largely biotransformed by such processes, and their plasma half-lives are not prolonged in elderly patients (27). Two of the enzyme processes in the biotransformation of salicylates, however, are saturable, so that a sudden increase in plasma concentration can occur causing acute salicylate intoxication (28).

Renal clearance: There is a steady decline in renal function with age. Consequently, the plasma half-life of an NSAID such as azapropazone, which is largely excreted unchanged in the urine, may be prolonged in elderly patients. Only a small proportion of other NSAIDs are eliminated un-

changed in the urine. Since NSAIDs are weak acids, their renal clearance will rise as urinary pH rises. This is of little clinical significance, however, except in the case of salicylates, for which the plasma concentration may decrease substantially with even small changes in urinary pH above 6.5 (29).

It is less well known whether certain NSAIDs which are glucuronidated, including diflunisal, fenoprofen, indomethacin, ketoprofen and naproxen, have decreased renal clearance in renal failure. This is because their acyl glucuronides are readily hydrolyzed back to the parent drug in a 'futile cycle' (30). Many of these drugs are racemic, consisting of R (rectus) and S (sinister) enantiomers. Naproxen is an S enantiomer which is active, whereas all other propionic acid derivatives are a mixture of R and S enantiomers. The R enantiomer can be considered somewhat of a prodrug since stereo-inversion occurs in the body, converting it to the S enantiomer. In renal failure, not only are the acyl glucuronides hydrolyzed back to the parent drug, but the R enantiomer is converted to an S, with a potential for toxicity. This may have contributed to benoxaprofen toxicity in elderly patients who had renal failure.

Prostaglandins are important in maintaining renal bloodflow; drugs which inhibit them, such as NSAIDs, may have deleterious effects on renal function (31,32). Although sulindac has been claimed as renal-sparing, acute renal failure has been reported in the elderly with the use of this drug (33). The rare occurrence of interstitial nephritis in association with NSAID therapy is idiosyncratic, but interestingly, has not been reported as a result of salicylate therapy. The celluria which occurs with acetylsalicylic therapy clears after 10 to 14 days (34). Whether the same occurs with non-acetylated salicylates is not known.

Receptors: Animal studies have shown that there are fewer corticosteroid binding sites in the adipocytes and leukocytes of elderly animals compared to younger animals (35,36); no comparable data exists for humans. There is, however, a decreased number of isoprenaline receptors on the lymphocytes of elderly patients (37). It remains to be determined whether such altered receptor function has relevance in the toxicity of antirheumatic drugs.

ANALGESICS

Acetaminophen is widely prescribed as an analgesic in elderly patients. The overall incidence of adverse effects is low, especially in terms of gastrointestinal irritation. There is, however, a potential for hepatotoxicity, particularly in patients with a history of chronic alcoholism or other conditions which result in hepatic glutathione deficiency. Hence, any elderly patient who presents with unexplained hepatocellular disease should be carefully questioned regarding the amount of acetaminophen they are taking (38).

Stern et al (39) have claimed that acetaminophen protects the gastric mucosa from the effects of both acetylsalicylic acid and ethanol in healthy subjects. This protective effect was, however, abolished by pretreatment with indomethacin, suggesting that the effect of acetaminophen is likely to be prostaglandin-mediated.

Pharmacodynamic considerations: It is not clear whether healthy elderly subjects are more prone to adverse effects of NSAIDs and other antirheumatic drugs than younger patients. Drug monitoring studies of NSAIDs have shown no increase in side effects, including gastrointestinal complications, in patients with rheumatoid arthritis (40). Likewise, no evidence has been found that elderly persons with rheumatoid arthritis develop more adverse reactions to injectable gold complexes or D-penicillamine (41,42). It should be noted, however, that these studies involved relatively healthy patients, rather than frail elderly patients in extended care institutions with multiple organ failure and receiving a plethora of medications (43). Fries et al (2) showed that elderly females were at particularly high risk of gastrointestinal complications of NSAIDs. The study consisted of a univariable analysis, and, as the authors carefully pointed out, the variables were interdependent.

Elderly females are more likely to develop osteopenic crush fractures when prescribed oral corticosteroids, although such patients have a low bone mass before treatment is begun. Tinnitus occurs less frequently in elderly patients receiving salicylate therapy, especially those with hearing loss; consequently, salicylate toxicity is more likely to occur (44). The studies of Grigor et al (45) suggest that elderly patients with rheumatoid arthritis are more likely to develop side effects with salicylate therapy.

CONCLUSIONS

Overall, pharmacokinetic disposition does not appear to be a significant factor in drug toxicity in the elderly. Likewise, pharmacodynamic effects of NSAIDs may be altered only slightly in healthy elderly subjects. Elderly patients with multiple disease and multiple drug therapies may, however, be very much at risk with antirheumatic drug medication.

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