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Elderly people taking non-steroidal anti-inflammatory drugs are unlikely to have excess renal impairment

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Summary: The importance of possible adverse effects on renal function of non-steroidal anti-inflammatory drugs has been widely discussed. Elderly people have been thought to be particularly at risk. We therefore studied simple indices of renal function and plasma potassium in 54 patients with a mean age of 85 years, 27 taking these drugs and 27 controls. Twenty five of our 54 patients were also taking diuretics. Non-steroidal anti-inflammatory drugs did not affect renal function or plasma potassium in these patients.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are an effective treatment for arthritic and musculoskeletal pain and are therefore widely used by elderly patients. However renal side effects of these drugs are being increasingly described,[1] It has been suggested that elderly patients are particularly at risk and the risk is increased if patients are also taking diuretics. [2,3]

Data from the Boston Collaborative Drug Surveillance Program suggested that clinical problems may be limited[4] but this data by itself may not be enough to show that elderly people taking the drugs are unlikely to have excess renal impairment.[5] This prompted us to look at a group of elderly patients, some of whom were taking NSAIDs, to see if there was any effect on renal function and serum potassium. Some of these patients, both in the treatment and non-treatment groups, were also taking diuretics.

Patients and methods

We studied 54 patients attending our day hospitals. All were women to avoid any confounding effect of prostatism on renal function in men.[6] They had been attending for at least two weeks. Twenty seven consecutive new patients taking NSAIDs and 27 controls, taken consecutively during the time the patients were collected, were studied. The day hospitals function as multi-disciplinary outpatient clinics and patients may often attend in clinically unstable conditions. Twenty seven had been taking NSAIDs for at least 3 weeks; 12 were taking ibuprofen, 6 were taking fenbufen, 3 were taking naproxen, 2 were taking flurbiprofen and one each were taking ketoprofen, azapropazone and piroxicam. One patient was taking both indomethacin and ibuprofen. The characteristics of the two groups are shown in Table I. Distribution of age, blood pressure (BP) and blood sugar were the same in the two groups. Fifteen of the controls and 10 of the patients taking NSAIDs were also taking diuretics.

Table I Findings in patients on non-steroidal anti-inflammatory drugs and a control group

	Patients (27)		*Controls (27)*		
	Mean	*s.d.*	*Mean*	*s.d.*	*95% confidence interval for the difference*
Age (years)	84	7	85	7	
Systolic BP (mmHg)	132	52	126	32	
Diastolic BP (mmHg)	72	28	74	20	
No. of people on diuretics	10		15		
Blood glucose (mmol/l)	5.8	3.4	6.2	5.3	
Urea (mmol/l)	8.5	4.1	8.1	3.9	−1.8 to +2.5
Creatinine (μmol/l)	106	31	101	3.8	−13.3 to +24.4
Potassium (mmol/l)	4.3	0.5	4.3	0.5	−0.3 to +0.2

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Results

The results are shown in Table I. There was no apparent difference between subjects and controls. The 95% confidence intervals for the differences suggest that adequate numbers of patients were studied and that a real difference between the two groups was not missed. Even if there was a difference and an increase in urea, creatinine and potassium in the patients on NSAIDs was present, this increase would at the most be 2.5 mmol/1, 24 μmol/1 and 0.2 mmol/1 which would have no clinical consequence. Analysis of variance showed no difference between the subjects on diuretics, subjects without diuretics, controls on diuretics and controls without diuretics ($F = 1.61$ with 3/50 degrees of freedom). There was a suggestion that diuretics were associated with a slightly increased blood urea whether or not NSAIDs were taken. The 25 patients on diuretics had a mean blood urea of 9.5 mmol/1 (s.d. 5.1) and the 29 patients not taking diuretics had a mean blood urea of 7.3 mmol/1 (s.d. 3.2). The 95% confidence intervals for the difference were +0.8 to +4.2 ($P = 0.04$).

Discussion

The two main renal side effects of NSAIDs are renal failure and hyperkalaemia. The suggested mechanisms for both are associated with the inhibition of prostaglandin synthesis by NSAIDs. When renal function is normal there is no dependence on prostaglandins. However, when there is renal hypoperfusion, circulating noradrenaline and angiotensin cause renal vasoconstriction aggravating the hypoperfusion and lead to a decline in renal function. Normally this is balanced by these agents also promoting secretion of prostaglandins, especially PGE_2 and PGI_2 (prostacyclin) from arachidonic acid in lipid plasma membranes via cyclo-oxygenase. This balancing process may be blocked by NSAIDs.[7-9] When renal function is normal, it is not prostaglandin dependent unless the patient is salt depleted as can occur when diuretics are taken.[10] However, when renal function is abnormal it may be prostaglandin dependent whatever the mechanism of renal impairment and even in the absence of salt or volume depletion.[11] The renal impairment of normal ageing is caused by a reduction in blood flow due to sclerotic obliteration of the preglomerular arteriole[2,13] and may be dependent on prostaglandins.[14] NSAIDs have been suggested as a cause of chronic renal failure in the elderly.[15]

The mechanism of NSAID-induced hyperkalaemia is said to be related to prostaglandin-dependent vasodilatation of the afferent arteriole affecting the baroreceptors modulating renin release.[16] Plasma potassium rises with age.[17]

Age changes in metabolism of NSAIDs are relatively minor. Protein binding tends to decrease, volumes of distribution tend to show a small increase and clearance, especially of renally excreted drugs, may fall. Any increased propensity of the elderly to suffer adverse reactions to NSAIDs cannot be readily explained on a pharmacokinetic basis.[18]

This study of patients whose mean age was well over 80 shows that in normal use NSAIDs are very unlikely to affect renal function in elderly people. The mean values of urea and creatinine were within the normal range for this age group.[19] The fairly tight confidence intervals for the differences compensate considerably for the relatively small number of patients in each group. An effect in men rather than women is not excluded although this would be more difficult to demonstrate because confounding prostatism is common.

While diuretics may have had some effect on renal function, this was not exaggerated in the patients on NSAIDs. Although renal function deteriorates with age, this study suggests that function of the normal ageing kidney is not dependent on prostaglandins. The use of diuretics by our patients may have caused a slight further rise in blood urea. However, even in this circumstance, the disturbance in renal haemodynamics was not such that there was dependence on prostaglandin synthesis and so further impairment when patients were taking NSAIDs. Similarly there was no effect on plasma potassium.

Nevertheless the results of this study should not be taken to suggest that NSAIDs are safe in elderly patients who are clinically dehydrated or who have renal impairment more than is usual in normal ageing. None of the patients was taking mefenamic acid which can cause dehydration through diarrhoea with associated renal failure.[20] Most of the patients were taking NSAIDs with short half lives and routine use of the drugs with longer half-lives may be undesirable.

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