Differential effects of flurbiprofen and aspirin on acetazolamide disposition in humans

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The plasma concentration-time profile of acetazolamide (AZ) following an intravenous bolus dose (5 mg kg⁻¹) was determined during control, aspirin and flurbiprofen (FLU) treatment periods. The unbound fraction of AZ in plasma increased three-fold in the presence of salicylate (SA) while, in contrast, FLU produced consistent, but statistically insignificant, increases in binding. SA caused a two-fold decrease in both unbound AZ renal clearance and apparent volume of distribution at steady-state, while FLU produced a small, but significant, increase only in the latter. The area under the concentration-time curve for AZ in erythrocytes was increased by about 40% during SA treatment while FLU had no effect. Our results suggest that on a pharmacokinetic basis FLU may be a safer nonsteroidal anti-inflammatory drug (NSAID) to co-administer with AZ.

Keywords acetazolamide disposition flurbiprofen aspirin

Introduction

The ability of salicylate (SA) to inhibit significantly the renal tubular secretion of the acetazolamide (Diamox®; AZ) has recently been described and implicated as an important cause of severe toxicity in elderly glaucoma patients receiving these drugs concomitantly (Sweeney *et al.*, 1986). Since concurrent drug therapy for glaucoma and arthritis is common in such a population, determining relative differences among the various NSAID in their ability to interfere with renal tubular drug transport is of clinical importance. The present study was undertaken to test the hypothesis that, compared with SA, an equivalent anti-inflammatory dose of flurbiprofen (FLU) may offer less potential for interfering with the renal tubular secretion of anionic drugs such as AZ in humans.

Methods

Four healthy, nonsmoking, Caucasian, males (mean age 31 ± 5.5 years, mean weight 76 ± 8.0

kg) served as subjects. None had a history of chronic illness or alcohol use and all were medication-free during the study. AZ disposition was studied during three treatment periods in the following order: (1) control period with no NSAID; (2) SA pretreatment; (3) FLU pretreatment. Treatments were separated by washout periods of at least 3 weeks. SA was administered as aspirin using a zero-order release formulation (Zorprin, Boots Pharmaceuticals Inc) at a twice-daily dose adjusted in each subject to produce a nominal serum SA concentration of 200 µg ml⁻¹. FLU was administered as a 100 mg oral tablet every 12 h. This daily dose of FLU is at the upper limit of the recommended dose range and would be expected to produce anti-inflammatory responses comparable with those produced by the SA doses utilised (Lomen *et al.*, 1986). Each drug was administered for 4 days prior to and 2 days after AZ administration.

Following an overnight fast, AZ was administered as an intravenous bolus injection (5 mg kg⁻¹) and blood was collected at approxi-

mately 5, 10, 20, 30, 45, 60 and 90 min and at 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48 and 72 h. Blood samples were heparinized and immediately divided into two aliquots. Plasma was quickly isolated from one and separated into two portions. One portion was frozen for future drug assay, the other was ultrafiltered at 37° C (Amicon Micropartition System) to assess the plasma protein binding of AZ. From the other whole blood aliquot the haematocrit was measured and the sample was stored frozen for assay of AZ concentrations. Urine was collected for 72 h after AZ administration.

AZ concentrations in all sampled body fluids as well as SA and FLU plasma concentrations were measured by h.p.l.c. (Chapron & White, 1984; Cham *et al.*, 1979; Symmons *et al.*, 1983). Creatinine clearance was measured for each subject during the first 24 h of each study phase.

Pharmacokinetic and statistical analyses

Triexponential equations were fitted to the data (Metzler *et al.*, 1974), and areas under the plasma or plasma ultrafiltrate concentration-time curves (AUC) were calculated. Renal clearances of total and unbound AZ were calculated as the ratio of administered dose to the corresponding AUC, extrapolated to infinite time. Clearances were normalised for body weight. Previous studies of AZ disposition in humans have reported quantitative urinary recovery of unchanged drug (Maren *et al.*, 1977; Chapron *et al.*, 1985), and therefore the kidney is the only organ involved in the clearance of AZ. Apparent volumes of distribution based on either total or unbound plasma drug concentrations were calculated according to McNamara *et al.* (1983).

Mean parameter estimates were compared using analysis of variance. Where appropriate, Newman-Keuls pairwise comparison tests were used to identify which mean values differed. Because of the small number of subjects, the probability of failing to detect even moderately large differences was high.

Results

Subject characteristics including steady-state plasma NSAID concentrations and creatinine clearances are presented in Table 1. SA concentrations ranging from 199–213 $\mu\text{g ml}^{-1}$ were achieved in three subjects. One individual could not be titrated to a concentration above 140 $\mu\text{g ml}^{-1}$ without administering an unacceptably high dose. The daily dose range of aspirin in the subjects was 3.2–5.6 g. The steady-state concentrations of FLU covered a much wider range (7.6–20.1 $\mu\text{g ml}^{-1}$) since it was administered at a fixed dose to all subjects. Pretreatment with SA or FLU had no statistically significant effect on creatinine clearance.

The effects of FLU or SA administration on AZ binding to plasma proteins are indicated in Table 2. The free fraction of AZ was increased three-fold in the presence of SA. In contrast, FLU produced consistent, but statistically insignificant, increases in plasma protein binding.

There were marked contrasts between the substantial SA-induced effects on AZ disposition and the minimal effects observed with FLU. Also listed in Table 2 are model-independent pharmacokinetic parameters for AZ disposition during control and treatment periods. SA administration significantly increased the mean residence time for AZ compared with control and FLU treatments. When renal clearance (CL_R) and steady-state volume of distribution (V_{ss}) of AZ were calculated on the basis of total plasma concentration, SA caused significant increases of 34% in CL_R and 60% in V_{ss} . FLU had little or no effect on these parameters. When unbound plasma AZ concentration was used as the basis for calculations, contrasting effects became evident. SA caused approximately a two-fold decrease in unbound AZ renal clearance (CLu_R) and unbound steady-state volume of distribution ($V_{u,ss}$), while FLU produced an opposite effect that achieved statistical significance for the latter. SA produced an increase in the area under the concentration-time curve for AZ in erythrocytes of approximately 40% while FLU had no effect.

Table 1 Patient characteristics and plasma drug concentrations

Subject	Age (years)	Creatinine clearance (ml min^{-1})			Steady-state drug concentrations ($\mu\text{g ml}^{-1}$)	
		Control	Salicylate	Flurbiprofen	Salicylate	Flurbiprofen
1	37	131	132	106	210	8.3
2	30	160	151	132	213	7.6
3	33	134	130	127	199	11.5
4	24	153	130	162	140	20.1
Mean		145	136	132	191	11.9
($\pm$ s.d.)		14.2	10.2	23.1	34.2	5.74

Table 2 Effect of flurbiprofen (FLU) and aspirin (ASA) on the pharmacokinetics and binding of acetazolamide in normal human subjects

<i>Parameter</i>	<i>Control</i>	<i>Mean (s.d.) Flurbiprofen</i>	<i>Aspirin</i>
Total clearance (ml min ⁻¹ kg ⁻¹)	0.59 (0.06)	0.55 (0.04)	0.79 (0.08)
Unbound clearance (ml min ⁻¹ kg ⁻¹)	14.4 (2.43)	18.2 (1.94)	6.53 (1.93)
Intrinsic secretory clearance (ml min ⁻¹ kg ⁻¹)	12.4 (2.52)	16.5 (2.10)	4.73 (2.13)
Steady-state volume of distribution, total (l kg ⁻¹)	0.38 (0.05)	0.36 (0.06)	0.61 (0.19)
Steady-state volume of distribution, unbound (l kg ⁻¹)	8.64 (0.63)	11.7 (2.62)	4.67 (0.25)
Area under erythrocyte concentration vs time curve (µg ml ⁻¹ h)	614 (76.6)	681 (108)	855 (147)
Mean residence time (h)	10.8 (1.54)	11.0 (1.50)	12.8 (3.07)
Percentage unbound in plasma	4.2 (0.7)	3.0 (0.3)	12.7 (3.6)

Means sharing common underlining are not significantly different at $P = 0.05$.

Discussion

Glomerular filtration of AZ, estimated from the product of plasma free fraction and creatinine clearance and expressed as a percentage of total AZ renal clearance was, on average 13.7, 29.6 and 9.6% during control, SA and FLU treatment phases, respectively. Apparently the marked increase in the glomerular component during SA treatment accounted for the significant increase in AZ CL_R observed during this treatment phase.

Since, (1) the renal extraction ratio of AZ is low (Chapron *et al.*, 1985); (2) its reabsorption from the tubule based on physicochemical considerations is unlikely (Maren *et al.*, 1977) and (3) its tubular secretion is restricted to the unbound plasma fraction (Chapron *et al.*, 1985), the CL_R of AZ is numerically equal to the sum of its intrinsic secretory clearance and glomerular filtration components. Together with our observation that GFR was not significantly altered by NSAID treatment, our results imply that the greater than two-fold decrease in CL_R of AZ produced by SA is due to a decrease in the secretory component. This is consistent with a highly significant inhibitory effect on renal tubular transport. In contrast, FLU produced a statistically insignificant increase in intrinsic secretory clearance.

Our findings are consistent with those of Chiba *et al.* (1985) who found a differential effect of various NSAID on the renal tubular secretion of sulphamethiazole in the rat. Ketoprofen and fenbufen significantly depressed the renal clearance of sulphamethiazole while FLU had no effect.

The volume of distribution which most accurately reflects whether drug has shifted between plasma and tissue compartments in the presence of an interactant is the 'corrected steady-state distribution volume for total drug' $\bar{V}_{ss}$ (McNamara *et al.*, 1983). $\bar{V}_{ss}$ was increased by 60% in the presence of SA and unaffected by FLU, consistent with substantial redistribution of AZ into tissues in the former case and with no shift in mass between compartments in the latter. Differences in AZ distribution between control and treatment periods could not be reasonably accounted for by treatment-induced alterations in albumin binding alone, and apparently also involve effects within the 'tissue' compartment. SA appears to be effecting a reduction in tissue uptake of AZ perhaps by decreasing its affinity for tissue components. FLU appeared to have effects on AZ tissue uptake opposite those of SA.

Erythrocytic AZ concentrations may serve as an indicator of availability of AZ to other tissue sites. The net result of simultaneous decreases in

plasma protein binding and CL_{ur} of AZ secondary to SA treatment was a 40% increase in erythrocyte AUC while FLU treatment was largely without effect. Increased erythrocytic AZ concentrations induced by SA may partly account for the toxicity associated with this combination of medications (Sweeney *et al.*, 1986).

These studies illustrate the desirability of determining the specificity of pharmacokinetic processes as they relate to competitive inter-

actions at sites of distribution and elimination. AZ has been shown to be susceptible to competitive interactions at both protein binding and renal secretory sites with a potentially toxic outcome when coadministered with SA. In contrast, our results suggest that FLU may be a safer NSAID to co-administer with AZ and highlight the need to examine further the interaction between FLU and other renally-secreted organic anions.

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(Received 9 August 1988,
accepted 3 February 1989)