Influence of Dosage Form on the Gastroenteropathy of Flurbiprofen in the Rat: Evidence of Shift in the Toxicity Site

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Purpose. Gastroduodenal and intestinal permeability were compared after single doses of sustained release and regular release flurbiprofen in the rat to assess possible site-specific formulation-dependent toxicity. Methods. Pharmacokinetics was assessed and gastrointestinal permeability was evaluated using sucrose and ⁵¹Cr-EDTA as gastro-duodenal and intestinal permeability probes, respectively. Results. The two formulations demonstrated equal area under the flurbiprofen concentration-time curve. The sustained release formulation peaked 2–3 h slower with 50–74% lower concentrations than regular release formulation. In comparison, the regular release powder induced greater gastro-duodenal permeability while sustained release granules induced greater intestinal permeability. When S-flurbiprofen concentrations were plotted versus intestinal permeability, a linear relationship and an anti-clockwise hysteresis were observed for regular and sustained release formulations, respectively. Conclusions. Sustained release formulations of flurbiprofen demonstrated reduced gastro-duodenal permeability but shift the site of this side-effect to the more distal intestine.

KEY WORDS: non-steroidal anti-inflammatory drugs; gastro-duodenal; intestinal permeability; flurbiprofen.

Non-steroidal anti-inflammatory drugs (NSAIDs) which are commonly associated with upper gastrointestinal tract side-effects, have recently been shown to cause significant and life-threatening mucosal damage within the small and large intestine (1).

NSAID-induced toxicity in the small intestine was initially observed in animal studies conducted 28 years ago on inflammation and ulcers (2). It has been subsequently suggested that NSAID-induced small intestinal damage in rats resembles NSAID-induced enteropathy of the human intestine (3). It has also been demonstrated that NSAID induced increased gastro-duodenal and intestinal epithelial permeability is a pre-requisite to the development of inflammation and ulceration (4,5). Gastro-intestinal permeability tests, therefore, are considered as facile and sensitive non-invasive markers of NSAID-induced gastrointestinal damage (4–6). These tests are non-invasive and involve determination of the urinary excretion of orally administered non-absorbable probes such as polysugars. We have demonstrated that the rat is a suitable animal model for evaluating NSAID-induced gastro-duodenal (7) and intestinal (8) permeability changes as measured by urinary excretion of sucrose and ⁵¹Cr-EDTA, respectively.

To improve therapeutic efficacy and reduce the severity of upper gastrointestinal side-effects, modified dosage forms of NSAIDs such as enteric-coated and sustained release formulations have been developed. The therapeutic rationale behind these new formulations has not been unequivocally proven, instead it has been suggested that these formulations may increase the exposure of active drug to the mucosa distally to the duodenal bulb, and thereby increase toxicity to this region where the effects are difficult to monitor (9).

The objectives of this work included 1) an examination of the possibility of formulation-dependent toxicity of flurbiprofen, a member of the 2-arylpropionic acid NSAIDs, throughout the gastrointestinal tract as assessed by the urinary excretion of sucrose and ⁵¹Cr-EDTA, 2) delineate the possibility of a relationship between the pharmacokinetics of a sustained release and regular release formulation and increased intestinal permeability.

METHODS

Animals

Male Sprague Dawley rats (250–300 g) were fed with commercial diet (Purina Rat Chow, Ralston Purina, St. Louis, MO). Rats were allowed free access to both food and water for the duration of the experiments and housed at ambient temperature and humidity with a 12 h light-dark cycle. All experimental procedures were approved by the Animal Care Committee of the University of Alberta.

Chemicals

Racemic flurbiprofen and sucrose were purchased from Sigma Chemical Company (St. Louis, MO). Flurbiprofen sustained release 200 mg capsules (Organon Canada Ltd., Westhill, Canada) were purchased from the University of Alberta Health Services Pharmacy. ⁵¹Cr-EDTA (specific activity 570 MCI/mg) was from NEN Dupont (Wilmington, DE).

Dosage Forms and Administration

Rats were dosed orally with 10 mg/kg flurbiprofen via gastric intubation. The formulations were either flurbiprofen powder suspended in 0.5 mL of 2% (w/v) methylcellulose or sustained release granules contained inside a commercially available capsule (Organon, Westhill, Canada) followed by 0.5 mL of 2% (w/v) aqueous methylcellulose solution. A single dose of 10 mg/kg racemic flurbiprofen was chosen since it had previously been shown to induce significant and measurable intestinal permeability at approximately 50% of the maximum effect (8).

Pharmacokinetic Studies

As described elsewhere (11) male Sprague-Dawley rats were cannulated in the left jugular vein. Two groups of rats (n = 4 for each group) were dosed orally with flurbiprofen powder or sustained release granules. Whole blood samples were withdrawn from the cannula at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h after drug administration, plasma separated and stored at −15°C until analysis. A stereospecific
assay was used for quantification of flurbiprofen enantiomers (10) and pharmacokinetic indices were calculated (11).

Pharmacodynamic Study

To establish baseline permeability values, control rats received either sucrose or $^{51}$Cr-EDTA in the absence of flurbiprofen. The effect of the NSAID on the permeability was examined using rats, which received flurbiprofen followed by either sucrose or $^{51}$Cr-EDTA.

Assessment of Gastrointestinal Permeability

Gastrointestinal permeability was assessed using a previously described method using the urinary excretion of orally administered sucrose as a marker (7). Flurbiprofen dosage forms were administered orally to each group of rats ($n = 4$) at the same time of day (9 a.m.) 1 h prior to the sucrose solution (predetermined time of maximum effect (7)). Urine was collected 0 to 8 h following the administration of the sucrose solution and individual volumes measured. Permeability was determined by calculating the sucrose present in each urine sample as a percent of the administered dose after correcting for baseline levels of glucose and sucrose present in urine for each individual rat (7).

Assessment of Intestinal Permeability

Intestinal permeability was assessed using $^{51}$Cr-EDTA as a surrogate marker (8). Urine was collected from 0 to 8 h following oral administration of $^{51}$Cr-EDTA and counted directly in a Gamma counter. The relative permeability was calculated as a percentage by dividing the count/min present in 0 to 8 h samples by that of the dosing solution after correcting for background radiation. To study the time course of the permeability changes, $^{51}$Cr-EDTA was administered 0, 1, 2, 3, 4, 6, 12, 24, 36, 48, or 72 h ($n = 4$ at each time point) after flurbiprofen administration to individual rats and the 0–8 h urinary excretion of the marker was measured.

Statistical Analysis

Differences between two means were determined by Student's unpaired t-test. Differences between more than two means were determined by one-way ANOVA followed by Duncan's multiple range test at $\alpha = 0.05$. Data are presented as mean ± standard deviation.

RESULTS

Pharmacokinetics

Following administration of the regular release suspension, the plasma concentration of both enantiomers of flurbiprofen peaked rapidly in 0.25 to 0.5 h (Fig. 1a). Following administration of the sustained release formulation, on the other hand, both enantiomers of flurbiprofen exhibited slow absorption rates as reflected in significantly longer $T_{\text{MAX}}$ values (2.25–3.5 h) and lower $C_{\text{MAX}}$ values as compared with the regular release form (Fig. 1b). There was no significant difference between the AUC$_{0-\infty}$ values between the powder and the sustained release granules (R, 76 ± 20; S, 215 ± 55 and R, 84 ± 12; 225 ± 46 mg.h.L$^{-1}$, respectively). The plasma concentration of the S enantiomer was significantly higher than that of the R enantiomer. The S:R plasma concentration ratio was not significantly different between the two formulations. The terminal $t_{1/2}$ of R and S were approximately 5.0 and 7.5 h, respectively, with no significant differences between the products. The observed pharmacokinetic indices were very close to those reported earlier (11).

Gastrointestinal Permeability

Both the regular release and sustained release flurbiprofen treatments significantly increased gastroesophageal permeability above baseline values 1 h post-dose (Fig. 2). This effect was, however, significantly greater for regular release as compared with the sustained release formulation.

The urinary excretion of $^{51}$Cr-EDTA as a measure of intestinal permeability was significantly increased following administration of both formulations (Fig. 3). Both treatments resulted