Assessment of Lumiracoxib Bioavailability from Targeted Sites in the Human Intestine Using Remotely Activated Capsules and Gamma Scintigraphy

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Received September 24, 2003; accepted November 10, 2003

Purpose. To determine the bioavailability and pharmacokinetic profile of lumiracoxib from different sites in the gastrointestinal tract.
Methods. Subjects (11 healthy adult males) were randomized to receive a 100 mg lumiracoxib dose, via a site-specific radiolabeled delivery capsule, to the stomach (internal reference), proximal small bowel, distal small bowel, or ascending colon. Gamma scintigraphy was used for real-time visualization of capsule location, and a radiofrequency signal was used to activate capsules at target site.
Results. Ten subjects completed the study. The mean capsule activation times for the stomach, proximal small bowel, distal small bowel, and ascending colon were 0.22, 1.52, 3.43, and 11.46 h post dose, respectively. Lumiracoxib was well absorbed from the proximal and distal small bowel, with $AUC_{0-\infty}$ ratios 104% (86, 127)% and 110% (89, 136)%, respectively. The highest C_{max} (2413 ng/ml) and $AUC_{0-\infty}$ for lumiracoxib were in the distal small bowel (6842 ng·h/ml). Effective absorption was observed from the ascending colon, with an $AUC_{0-\infty}$ ratio of 85% (69, 104)% vs. the reference.
Conclusions. Lumiracoxib is rapidly and efficiently absorbed throughout the gastrointestinal tract.

KEY WORDS: absorption; gamma scintigraphy; lumiracoxib; site-specific delivery.

INTRODUCTION

In the drug development process, a thorough understanding of the human bioavailability process is of value when optimising immediate release (IR) formulations and is of assistance in developing alternative formulations. Knowledge of the bioavailability profile for a drug from various regions within the gastrointestinal (GI) tract can best be achieved by undertaking a regional drug absorption (RDA) study in healthy subjects (1,2).

Historically, the most common approach for obtaining information on drug bioavailability from the human GI tract has been to use perfusion or intubation methods (3). These procedures involve the placement of tubes via the mouth or rectum into relevant areas of the GI tract. Once the tube is located in the appropriate region, a drug solution or suspension is infused at a predetermined rate. The invasive nature of such procedures not only results in significant discomfort for subjects, but also alters the physiological function, in particular the absorption and secretion balance of the GI tract (4).

In contrast, site-specific capsule delivery provides a novel, easy to use, noninvasive methodology for assessing RDA from the GI tract (5). The procedure uses gamma scintigraphy to track the location of the capsule in the GI tract and to identify when the active substance has been released. Scintigraphic evaluation requires significantly lower radiation doses than radiological methods and thereby enables frequent imaging and more accurate assessment of anatomical location (6).

Lumiracoxib is a novel cyclooxygenase-2 (COX-2) selective inhibitor (MW, 294 Da; pK_a, 4.7; log P, 1.2; water solubility, 0.03 mg/ml) that has been developed as an oral formulation for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and the management of acute pain (7–9). Single-dose studies using an IR formulation indicate that lumiracoxib is rapidly absorbed with a T_{max} of 1–4 h post dose and a relatively short plasma half-life of 3–6 h (10). As a COX-2 selective inhibitor, lumiracoxib demonstrates anti-inflammatory and analgesic characteristics similar to traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) (11), while having a superior GI safety profile (12).

The aim of this study was to assess the bioavailability profile of lumiracoxib following delivery at specific sites along the GI tract (stomach, proximal small bowel, distal small bowel, and ascending colon) using a remote-controlled capsule. The results of this study should provide insights into the pharmacokinetic characteristics of lumiracoxib in an IR form.

METHODS

The study was conducted at Pharmaceutical Profiles according to U.S. and European Good Clinical Practice guidelines and in accordance with the Declaration of Helsinki (1964 and subsequent revisions). All subjects provided written informed consent before receiving any study medication. The Clinical Protocol was approved by an independent ethics committee and by the ARSAC secretariat of the U.K. Department of Health.

Study Design

Eleven healthy, nonsmoking male subjects were selected to participate in a four-treatment, open-label, randomized, crossover study. Single 100 mg doses of lumiracoxib were delivered orally via remote-controlled capsules (5) to the stomach (regimen A), proximal small bowel (regimen B), distal small bowel (regimen C), or ascending colon (regimen D). Each subject received each of the four site-specific capsules in a randomized order, with a minimum of 4 days washout between doses. After an overnight fast, study medication was administered with 200 ml of water between 07:30 and 09:00 h. Standard meals were provided to all subjects 5 h and 9 h post dose.

Capsule Methodology

Study capsules were filled with 0.75 ml of lumiracoxib solution (133.3 mg/ml in PEG 4000) at the study site. In order to establish drug release from the desired site of activation, 25

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0724-8741/04/0300-0443/0 © 2004 Plenum Publishing Corporation

μl (4 MBq) of radiolabeled marker [99mTc-diethylenetriaminepentaacetic acid (DPTA)] was added to the drug reservoir within the formulation. Movement of the capsules through the GI tract was assessed by incorporating a ^{111}Indium (1 MBq) marker in the radioactive tracer port in the end cap of each capsule. Device activation occurred when the capsules reached their target site.

Real-time visualization of capsule location in the GI tract was achieved via gamma scintigraphy using a gamma camera with a 40-cm field of view fitted with a medium-energy collimator. Images (50 s in duration) were recorded at 10-min intervals until capsule activation. Further images were collected after activation to assess release of the reservoir contents and continued transit of the capsule. This was undertaken every 10 min until 4 h post capsule activation, then at 20-min intervals until 8 h post capsule activation. Further imaging was performed 12, 16, and 24 h post capsule activation.

The images were analyzed visually as they were acquired. Once the capsule had reached its target site, the device was activated via application of a radiofrequency magnetic signal. This caused the memory alloy elements within the capsule to reach 40–43°C, at which point they underwent transition to their original shape, aligning the slots in the InteliSite capsule, and allowing the drug and its radiolabeled marker to be released from the reservoir compartment.

Assessments

Venous blood samples for pharmacokinetic evaluation were withdrawn using an indwelling cannula or by venepuncture. Samples were taken pre-dose, pre–capsule activation, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post capsule activation. Additional post-dose samples were collected at 1 h after dosing for capsules activated in the proximal bowel, at 2–3 h after dosing for capsules activated in the distal bowel, and at 4–5 h after dosing (approximately 1 h prior to activation) for capsules activated in the ascending colon. Concentrations of lumiracoxib were assessed in plasma samples using a validated HPLC-UV assay method with a lower limit of quantification of 10 ng/ml (9). Pharmacokinetic parameters were determined using noncompartmental methods (WinNonlin Pro, version 3.1).

Safety assessments including physical examinations, 12-lead electrocardiogram (ECG), vital signs, laboratory evaluations (biochemistry, urinalysis, hematology), and adverse event (AE) monitoring were made during the 12 h prior to baseline and 24 h post capsule activation, at which time subjects were discharged from the unit until the next treatment period. A study completion evaluation was undertaken at 14 days or a minimum of 2 days after the last dose.

Statistical Methods

Analysis of variance (ANOVA) was undertaken on log-transformed values for $AUC_{0-\infty}$, AUC_{0-t} and C_{max}, and non-transformed T_{max}. Corresponding 95% confidence intervals were computed for the antilogged geometric treatment means for the test sites relative to the stomach. Cases where the confidence interval included "1" were used as evidence to suggest that there was no difference in the relative bioavailability at the test compared to the control site.

Table I. Capsule Activation in the Gastrointestinal Tract Assessed Using Gamma Scintigraphy

	Mean time post dose (hours) ± SD	
	Arrival at target site*	Initial release of drug
Stomach	0.22 ± 0.19	0.35 ± 0.20
Proximal small bowel	1.52 ± 0.83	1.60 ± 0.84
Distal small bowel	3.43 ± 1.04	3.61 ± 1.14
Ascending colon	11.46 ± 7.13	11.93 ± 8.15

* Defined as activation

RESULTS

Study Population

Eleven subjects aged between 19 and 54 years (mean, 35.5 ± 10.9 years) entered the study: body weight ranged from 62 to 93 kg (mean, 77.3 ± 8.8 kg) and height from 158 to 183 cm (mean, 173.7 ± 8.2 cm). No relevant clinically significant medical history or medical conditions were reported. Drug or alcohol abuse and HIV and hepatitis screening were negative for all subjects.

Capsule Performance

Ten subjects completed the study; one subject withdrew consent after the second dose. In 37/42 instances, the Intelisite capsule was correctly and successfully activated on the first attempt. Three subjects received the distal small bowel preparation twice, two because it activated at the wrong site, and one because it failed to activate at all. In each case, the second dose was given during a fifth period at the end of the scheduled randomization sequence. The capsule was activated in the descending colon (rather than the ascending colon) in one subject and in the stomach rather than the distal bowel in another subject. There were no signs detected scintigraphically of any capsule leakage prior to activation. This was confirmed by analysis of lumiracoxib in the preactivation plasma samples.

Gastric emptying times for the capsules ranged on average from 0.82 το 1.31 h. One subject exhibited extended gastric residence times of 19.08 h and 43.34 h for regimens B and

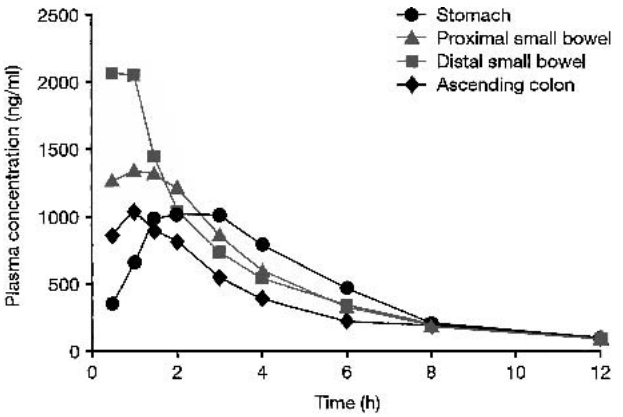

Fig. 1. Mean plasma concentrations of lumiracoxib following regional delivery in the GI tract during 12 h.

Table II. Key Pharmacokinetic Parameters Following Regional Delivery of Lumiracoxib in the Gastrointestinal Tract

	Mean ± SD			Median (range)
Site of activation	$AUC_{0-\infty}$ (ng·h/ml)	AUC_{0-t} (ng·h/ml)	C_{max} (ng/ml)	T_{max} (h)
Stomach	6146 ± 944	6011 ± 940	1390 ± 513	2.0 (1.0–6.0)
Proximal small bowel	6603 ± 2186	6355 ± 2321	1628 ± 663	1.0 (0.5–2.0)
Distal small bowel	6842 ± 1473	6691 ± 1525	2413 ± 996*	1.0 (0.5–1.0)
Ascending colon	4983 ± 1145	4736 ± 1144	1109 ± 612	1.0 (0.5–2.0)

* Statistically significant vs. the reference site (stomach).

C, respectively. Capsule activation in the stomach, proximal small bowel, distal small bowel, and ascending colon occurred at mean times of 0.22, 1.52, 3.43, and 11.46 h post dose, respectively (Table I). Drug release was rapid, occurring 0.08–0.13 h after activation. Mean small intestine transit times ranged from 4.45 to 4.89 h.

Pharmacokinetic Profile of Lumiracoxib

Plasma concentration vs. time (post-dose) profiles for each of the targeted sites of capsule activation are shown in Fig. 1. In general, plasma concentrations of lumiracoxib were quantifiable up to 24 h post dose. Following release of lumiracoxib in the stomach, a mean C_{max} of 1390 ng/ml was achieved 2 h post dose (Table II). Mean AUC_{0-t} and $AUC_{0-\infty}$ following release of lumiracoxib in the proximal or distal small bowel were similar to that observed following release in the stomach, although in both cases C_{max} was higher (Table II). Release of lumiracoxib in the ascending colon resulted in only a slightly lower AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} than in the other three regions. Median T_{max} following capsule release in the stomach was longer than that seen for capsules released in the small bowel or colon.

Statistical comparisons of AUC parameters showed only slightly decreased bioavailability following drug release in the ascending colon relative to that following drug release in the stomach. Bioavailability of lumiracoxib following capsule activation in the stomach and small bowel were similar. C_{max} appeared to be approximately 1.5 times higher in the distal small bowel than in the stomach, and T_{max} occurred approximately 1.5 h later in the stomach than in the small bowel and ascending colon.

Safety and Tolerability

Study treatments and procedures were well tolerated. The subject discontinuation was not due to AE incidence. Six of the 11 subjects reported a total of 14 AEs, mostly of mild-to-moderate intensity and not judged to be drug related. No clinically significant or drug-related changes were seen in vital signs, ECG, hematology, clinical biochemistry, or urinalysis findings.

DISCUSSION

Using a novel site-specific capsule delivery technique, we have shown that bioavailability of lumiracoxib from the GI tract does not appear to be site-specific. Lumiracoxib was well absorbed from the proximal and distal small bowel, resulting in AUCs directly comparable with those achieved following stomach delivery (Table II). The significant reduction in colonic surface area often leads to decreased C_{max} following specific delivery in the large bowel (1). Despite this, excellent bioavailability was also observed from the ascending colon, with mean AUC_{0-t} and $AUC_{0-\infty}$ ratios of 0.82 and 0.85, respectively, in comparison with those observed in the stomach.

In contrast with other COX-2 selective inhibitors, lumiracoxib is a weak acid (pK_a, 4.7), which results in limited solubility in the stomach fluids (<0.01 mg/ml at pH 1.2 stimulated gastric fluid and 0.25 mg/ml at pH 6.8 stimulated intestinal fluid). The drug was dosed as a PEG 4000 solution, and it is possible that following release in the stomach, the drug became less soluble and came out of solution in the gastric contents due to the low aqueous solubility at acidic pH. However, on gastric emptying the drug was able to redissolve quickly due to the enhanced pH properties of the jejunum. This may explain the longer T_{max} observed for lumiracoxib released in the stomach compared with the small bowel and ascending colon (Table II). These findings suggest that lumiracoxib more rapidly dissolves in the basic environment of intestines leading to an increased absorption rate as demonstrated by the improvement in C_{max}. However, it is interesting to speculate on the differences in C_{max} between PSB and DSB delivery for lumiracoxib. There are subtle but significant differences in the pH of these intestinal sites; PSB (jejunum) is likely to have a pH of circa 6.5 whereas the DSB (terminal ileum) is about one pH unit higher at 7.5 (13). The solubility of lumiracoxib at the pH of the DSB is approximately 8 times greater than in the PSB and presumably minimizes the possibility of any crystallization following delivery into the latter regions of the small bowel which enhances the C_{max}. However, importantly, clinical studies with conventional IR capsules indicate that concentrations of lumiracoxib almost 10-times higher that the EC_{50} required to inhibit COX-2 are still achieved in plasma 30 min after administration of the drug within the clinical dose range (10).

Overall, our results indicate that lumiracoxib is rapidly and efficiently absorbed by the GI tract and has no specific window for absorption. This provides an opportunity for rational development of IR formulations as well as alternative dosage forms.

ACKNOWLEDGMENTS

This study was supported by a grant from Novartis Pharma AG.

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