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Pharmacokinetics and delivery of the anti-influenza prodrug oseltamivir to the small intestine and colon using site-specific delivery capsules

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Abstract

This study investigated the site-specific absorption of oseltamivir using targeted delivery and gamma scintigraphy. On four separate occasions, nine healthy male subjects each received a single 150 mg of oseltamivir administered via the Enterion™ capsule to the stomach, proximal small bowel, distal small bowel and the ascending colon. Pharmacokinetic parameters of oseltamivir and its carboxylate metabolite show that absorption was similar in the proximal and distal small bowel compared to stomach delivery, but reduced from the ascending colon, demonstrating that absorption-rate limited disposition occurred only for the ascending colon. The metabolite-to-parent ratios were minimally reduced. The results support the feasibility of modified-release formulation development whilst confirming the high and consistent oral bioavailability of oseltamivir.

Keywords: Oseltamivir; Pharmacokinetics; Prodrug; Absorption; Controlled delivery; Gamma scintigraphy

Oseltamivir is an orally available ester prodrug of oseltamivir carboxylate, and is approved as a 75 mg twice daily regimen for the treatment of influenza A and B. Oseltamivir is metabolized in the liver with a high hepatic extraction ratio, and about 80% of an orally administered dose of oseltamivir reaches the systemic circulation as the active carboxylate metabolite (He et al., 1999). After reaching a maximum, plasma concentrations of the prodrug quickly decline ($t_{1/2}$ of 1–3 h), while levels of carboxylate decline more slowly ($t_{1/2}$ of 6–10 h). Oseltamivir is fairly polar while its carboxylate is highly polar (log *P* of 0.36 and −2.1). Oseltamivir has a high aqueous solubility (>500 mg/ml) and moderately low Caco-2 permeability coefficient ($1.2 \pm 2.2 \times 10^{-5}$ cm/s). Therefore, its absorption could be variable and intestinal site dependent, as a BCS class III drug (Data on file, Hoffmann-La Roche Inc.). The purpose of this study was to investigate the effect of intestinal site on the rate and extent of oseltamivir absorption using

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a site-specific delivery technology, and to consider the feasibility for modified-release (MR) formulation development for a once daily administration.

This study was conducted in nine healthy male subjects aged 19–46 years old, in a randomized 4-period crossover manner with a 7-day washout. The study was approved by an independent ethics committee. Oseltamivir (150 mg) was delivered to four separate specific sites along the gastrointestinal tract: the stomach (reference site), the proximal small bowel or jejunum, the distal small bowel or ileum, and the ascending colon by the remotely activated Enterion™ capsule (Wilding, 2001). Gastrointestinal location of the capsule was monitored in real time by gamma scintigraphy. The subject was dosed with the Enterion™ capsule with 200 ml water, approximately 4 h after a light breakfast. Gamma scintigraphic images were recorded at approximately 10 min intervals until device activation and also for the 4 h period post-activation, and less frequently thereafter. When the capsule reached the activation site, a blood sample for pharmacokinetic assay was taken and immediately afterwards the capsule was activated. Following activation, 6 ml venous blood samples were collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0 and 36.0 h.

Plasma samples were analyzed for oseltamivir and its metabolite by BAS Analytics, Kenilworth, UK, using a previously reported HPLC/MS/MS method (Wiltshire et al., 2000). The limit of quantitation for plasma concentrations of oseltamivir and its carboxylate were 1.0 and 10.0 ng/ml, respectively. WinNonlin® was used to calculate the non-compartmental pharmacokinetic parameters and perform analysis of variance. C_{max} and T_{max} were estimated directly from raw data, and the area under the drug plasma concentration–time curve (AUC) was obtained using the linear trapezoidal rule. The metabolite-to-parent ratio was computed by dividing $AUC_{0-\infty}$ of the metabolite by $AUC_{0-\infty}$ of the parent, adjusted for molecular weight difference.

Table 2
In vivo activation time (post-dose) and anatomical location for the site-specific delivery capsule (Mean ± S.D. in hours)

Target activation site	Activation time	Activation site
Stomach	0.11 ± 0.07	100% stomach
Proximal small bowel	2.27 ± 1.46	100% jejenum
Distal small bowel	2.66 ± 0.63	100% terminal ileum
Ascending colon	6.08 ± 1.58	100% ascending colon

One subject withdrew from the study by failing to return following the first dosing. All treatments of oseltamivir were well tolerated by the subjects. The transit times of the Enterion™ capsules at specific gastro-intestinal sites and the total transit prior to recovery are provided in Table 1. In vivo activation times of the Enterion™ capsules and the anatomical location for the confirmation of the release are listed in Table 2. In general, pharmacokinetics of oseltamivir and its carboxylate were similar for the proximal and distal small bowel, compared to those for the stomach, while the parameters for the ascending colon were reduced (Table 3). $AUC_{0-\infty}$ of oseltamivir and C_{max} and $AUC_{0-\infty}$ of the carboxylate following delivery to the proximal small bowel and to the distal small bowel were bioequivalent to delivery to the stomach, since the 90% confidence intervals of the ratio of natural log transformed least square means (from 71.0 to 121.0) fall within ±30%.

Compared to $AUC_{0-\infty}$, C_{max} had higher variability, and the corresponding oseltamivir and the carboxylate C_{max} values were reduced by 54 and 60%, respectively, following delivery to the ascending colon. T_{max} for oseltamivir and its carboxylate of sites other than the stomach were delayed. Elimination $t_{1/2}$ of oseltamivir and its carboxylate were similar when oseltamivir was released in the stomach, the proximal

Table 1
Gastrointestinal transit data for the site-specific drug delivery capsule (Mean ± S.D. in hours)

Activation site	Gastric emptying	Small bowel transit	Colon arrival	Total transit
Stomach	1.79 ± 1.12	4.00 ± 1.89	5.80 ± 2.08	23.98 ± 6.84
Proximal small bowel	1.91 ± 1.39	4.44 ± 1.54	6.36 ± 1.87	23.13 ± 8.67
Distal small bowel	0.96 ± 0.64	4.81 ± 1.38	5.77 ± 1.35	26.61 ± 9.04
Ascending colon	1.30 ± 1.69	4.24 ± 1.94	5.46 ± 1.63	25.35 ± 13.68

Table 3
Oseltamivir and carboxylate pharmacokinetic parameters (mean; CV%) after 150 mg oseltamivir released in the proximal small bowel, distal small bowel and ascending colon compared with release in the stomach

Parameter	Stomach	Proximal small bowel	Distal small bowel	Ascending colon
Oseltamivir				
C_{max} (ng/ml)	99.5 (21.8)	104 (41.7)	132 (42.1)	48.6 (65.5)
$AUC_{0-\infty}$ (ng h/ml)	189 (23.1)	176 (23.4)	178 (36.0)	157 (33.8)
T_{max} (h)	0.50 (0.0)	0.61 (36.1)	0.56 (30.0)	0.84 (51.9)
$t_{1/2}$ (h)	1.6 (41.8)	1.3 (13.5)	1.4 (24.3)	6.6 (82.8)
Carboxylate				
C_{max} (ng/ml)	487 (19.9)	463 (19.6)	442 (38.7)	197 (39.2)
$AUC_{0-\infty}$ (ng h/ml)	5660 (19.4)	5660 (18.8)	5040 (25.1)	3830 (23.4)
T_{max} (h)	2.9 (20.8)	3.9 (23.9)	3.2 (13.7)	5.9 (36.5)
$t_{1/2}$ (h)	6.5 (19.2)	6.8 (14.8)	6.6 (15.0)	9.8 (30.9)
Metabolite-to-parent ratio	34.0 (23.6%)	36.5 (24.3%)	33.0 (23.7%)	29.5 (34.1%)

and distal small bowels, but were noticeably longer when oseltamivir was released in the ascending colon. The longer $t_{1/2}$ of oseltamivir (6.6 h) and carboxylate (9.8 h) could be explained by the delayed absorption rate in the colon, therefore, $t_{1/2}$ values reported here were associated with the slower absorption rate rather than the real elimination rate (flip-flop phenomenon); while additional $t_{1/2}$ of the carboxylate (more polar and hence less permeable versus the parent) could be explained by slow sequestering from the liver following formation. The metabolite-to-parent ratios were similar for those for the stomach and the small intestine, and only slightly lower for the colon, which were compatible with the splanchnic and hepatic blood flow to the liver; thus release in the distal small bowel, and to a greater extent in the colon, minimally avoids the liver on first pass and thereby the rate of metabolism of oseltamivir to the active metabolite is intact.

Therefore, the selection of delivery systems that release oseltamivir in any region of the small intestine will have minimal effect on absorption and metabolism of oseltamivir, while colonic delivery may result in reduced absorption. However, the residual colonic absorption is nevertheless substantial, and could supplement small bowel absorption.

Oseltamivir is a reasonably polar drug, which suggests the potential for paracellular absorption to play a significant role in drug uptake. However, previous studies have shown reduced colonic absorption for polar drugs due to the low porosity of the tight junctions in the large bowel (Rigby et al., 1985). The good absorption of oseltamivir in the colon therefore suggests a mixed absorption mechanism with significant opportunity for transcellular uptake despite the relatively polar properties of the prodrug.

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