

Lack of pharmacokinetic interaction between the oral anti-influenza neuraminidase inhibitor prodrug oseltamivir and antacids

Paul Snell,¹ Charles Oo,² Al Dorr³ & Joanne Barrett¹

¹Department of Research and Development, Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK, ²Hoffmann-La Roche Inc, Nutley, NJ, USA and ³XIQ Coordination Inc., Norman, OK, USA

Aims Oseltamivir is an oral ester prodrug of its active metabolite Ro 64-0802, a potent and selective neuraminidase inhibitor of the influenza virus. The object of this study was to evaluate whether the oral absorption of oseltamivir was reduced in the presence of two main classes of antacid, Maalox[®] suspension (containing magnesium hydroxide and aluminium hydroxide) and Titalac[®] tablets (containing calcium carbonate).

Methods Twelve healthy volunteers completed a randomized, single dose, three-period crossover study. Each volunteer received in a fasted state, 150 mg oseltamivir alone (Treatment A), 150 mg oseltamivir with a 20 ml Maalox[®] suspension (Treatment B), and 150 mg oseltamivir with four Titalac[®] tablets (Treatment C), with 7-10 days washout in between treatments. Plasma and urine concentrations of oseltamivir and Ro 64-0802 were measured using a validated h.p.l.c./MS/MS assay. Pharmacokinetic parameters were calculated for oseltamivir and Ro 64-0802. Since antacids are locally acting drugs and generally not expected to be absorbed substantially into the systemic system, no plasma or urine concentrations of antacids were measured.

Results Bioequivalence was achieved for the primary pharmacokinetic parameters C_{max} and $AUC(0,\infty)$ of Ro 64-0802 following administration of oseltamivir with either Maalox[®] suspension or Titalac[®] tablets *vs* administration of oseltamivir alone. The bioavailability (90% confidence intervals) of Ro 64-0802 following administration of oseltamivir together with Maalox[®] suspension *vs* administration of oseltamivir alone, was 90% (83.6, 96.9%) for C_{max} and 94.1% (91.4, 96.9%) for $AUC(0,\infty)$; similarly, for Titalac[®] tablets, the equivalent values were 95.1% (88.3, 102%) for C_{max} and 94.7% (91.9, 97.5%) for $AUC(0,\infty)$.

Conclusions The coadministration of either Maalox[®] suspension or Titalac[®] tablets with oseltamivir has no effect on the pharmacokinetics of either oseltamivir or Ro 64-0802, and conversely, there is no evidence that coadministration with oseltamivir has an effect on the safety and tolerability of either Maalox[®] suspension or Titalac[®] tablets. There was no pharmacokinetic interaction between oseltamivir with either antacid, demonstrating that the oral absorption of oseltamivir was not impaired in the presence of antacids containing magnesium, aluminium or calcium.

Keywords: antacids, influenza, neuraminidase inhibitor, oseltamivir, pharmacokinetics

Introduction

Oseltamivir (Ro 64-0796) is a highly bioavailable oral ester pro-drug of its active metabolite Ro 64-0802 (oseltamivir carboxylate), a potent and selective inhibitor of

the influenza virus. Oseltamivir has been approved in the United States and in the EU for the treatment (75 mg twice daily) and the prophylaxis (75 mg once daily) of influenza A and B infection in adolescents and adults, and for the treatment of influenza A and B infection in children ≥ 1 years (30 mg, 45 mg and 60 mg twice daily according to body weight).

Oseltamivir is rapidly absorbed from the gastrointestinal tract and undergoes rapid and extensive presystemic conversion via esterase hydrolysis to Ro 64-0802 (Figure 1), by high capacity hepatic carboxylesterases [1, 2]. Nei-

Correspondence: Paul Snell, PhD, Department of Clinical Pharmacology, Roche Products Ltd., 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL73AY, UK. Tel.: 44(0)1707 365766; Fax: 44(0)1707 365887; E-mail: paul.snell@roche.com

Accepted 22 May 2002.

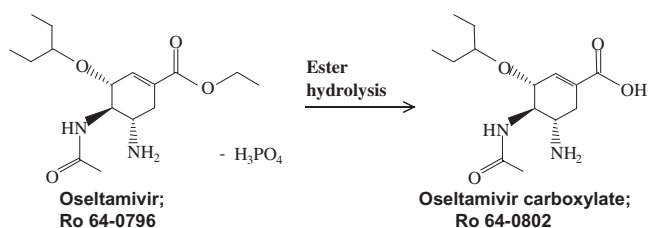


Figure 1 Structures of the prodrug oseltamivir (Ro 64-0796) and its active metabolite Ro 64-0802 (oseltamivir carboxylate).

ther oseltamivir nor Ro 64-0802 undergo further metabolism. Plasma concentrations of Ro 64-0802 reach a maximum 3–4 h post-dose and at that time, substantially exceed oseltamivir concentrations by ≥ 20 fold. After reaching a maximum, plasma concentrations of oseltamivir quickly decline (half-life of 1–3 h), whilst concentrations of Ro 64-0802 decline more slowly (half-life of 6–10 h). Approximately 60–80% of an oral dose of oseltamivir is excreted in the urine as Ro 64-0802. Less than 20% is recovered in the faeces (in equal fractions of oseltamivir and Ro 64-0802) and less than 5% is recovered in the urine as oseltamivir.

Due to the prevalent use of antacid preparations by the general public, drug interactions involving these antacids are plausible, and could lead to therapeutic failure, unrecognized by both the patient and their physician. Drug interactions involving antacids occur in many ways, including effects on gastric emptying, intraluminal binding or chelation, and intraluminal pH or urinary pH [3–8].

The primary objective of this study was to evaluate whether the oral absorption of oseltamivir is decreased in the presence of two main classes of antacid, Maalox® suspension (containing magnesium hydroxide and aluminium hydroxide) and Titrilac® tablets (containing calcium carbonate). The secondary objective was to assess the safety and tolerability of oseltamivir and Ro 64-0802 following coadministration of oseltamivir together with antacid.

Methods

Study design

This was a single centre, open label, randomized, three-way crossover drug interaction study. Twelve eligible subjects were randomly assigned to one of six treatment sequences. The sequence groups (with two subjects each) were ABC, ACB, BCA, BAC, CAB and CBA. Each treatment was separated by a washout period of at least 7 days prior to the next treatment. Each treatment was administered orally, as follows:

Treatment A: Single oral dose of 150 mg oseltamivir, given as two 75 mg capsules taken with 50 ml of water.

Treatment B: Single oral dose of 150 mg oseltamivir, given as two 75 mg capsules taken with 50 ml of water, 1 min after dosing with a single oral dose of 20 ml Maalox® suspension (sugar-free, co-magaldrox containing magnesium hydroxide 195 mg and dried aluminium hydroxide 220 mg per 5 ml, and a low sodium content of less than 1 mmol per 10 ml dose).

Treatment C: Single oral dose of 150 mg oseltamivir, given as two 75 mg capsules taken with 50 ml of water, 5 min after dosing with a single oral dose of four Titrilac® tablets (each tablet containing calcium carbonate 420 mg [168 mg calcium] and glycine 180 mg). Each Titrilac® tablet was chewed for approximately 15 s.

Sample size

Based on previous studies involving a single oral dose of oseltamivir, the intrasubject coefficients of variation (CV) for Ro 64-0802 AUC(0,∞) and C_{\max} (based on natural log transformed data) were estimated to be 6% and 11% [Roche unpublished data]. The primary pharmacokinetic parameters for the assessment of bioequivalence were AUC(0,∞) and C_{\max} of Ro 64-0802, since Ro 64-0802 is the predominant moiety in blood. A CV of 15% with a sample size of 12 provides 80% power for having a confidence interval based on natural log transformed data fall completely between 80% and 125% if the two regimens truly differ by 5% or less.

Subjects/Ethics

Healthy male and female subjects were enrolled into the study. No concomitant medication was permitted except for oral contraceptives and hormonal replacement therapy, and medication to treat adverse effects. Mineral and calcium supplements and dairy products were avoided for 72 h prior to administration of all three treatments. This study was approved by the Roche Welwyn Clinical Pharmacology Unit Ethics Committee and was conducted in full compliance with the principles of the 'Declaration of Helsinki' and 'Good Clinical Practice' guideline. Written informed consent was obtained from each subject prior to enrolment in the study.

Study procedures

Medical history, a comprehensive physical examination, a random drugs of abuse urine screen, blood and urine clinical laboratory safety tests (serum chemistry and haematology), serum creatinine (required to be normal), vital signs (blood pressure, pulse rate) and 12 lead ECG were performed at screen. Pregnancy tests were per-

formed at screen, pre-dose for each treatment period, and at follow-up. Subjects fasted from midnight on the evening prior to each treatment. Water was allowed *ad libitum* except for 1 h prior to dosing and up to 2 h after dosing. Adverse events were monitored throughout the study. A 5 ml blood sample was collected from each subject into a Monovette (containing EDTA as an anticoagulant) immediately before dosing, and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post-dose. Urine samples were collected within 30 min pre-dose, and 0–4, 4–8, 8–12 and 12–24 h after drug administration. A follow-up medical examination, including a comprehensive physical examination, 12 lead ECG, vital signs (blood pressure, pulse rate) and blood and urine clinical laboratory safety tests were performed (4–10 days after completing the study).

Sample analysis

Plasma and urine concentrations of oseltamivir and Ro 64–0802, were determined by BAS Analytical Systems Inc., Kenilworth, Surrey, UK (plasma) and West Lafayette, Indiana, USA (urine) using a specific h.p.l.c./MS/MS method [9]. The limits of quantification for plasma concentrations of oseltamivir and Ro 64–0802 were 1.0 and 10.0 ng ml⁻¹, respectively. The limits of quantification for urine concentrations of oseltamivir and Ro 64–0802 were 5.0 and 30.0 ng ml⁻¹, respectively. The assay for plasma and urine concentrations of oseltamivir and Ro 64–0802 has been reported previously [9], and the coefficients of variation were ≤10%. Because antacids are locally acting drugs and generally not expected to be absorbed substantially into the systemic system, no plasma or urine concentrations of Maalox[®] suspension or Titalac[®] tablets were measured.

Data analysis

Pharmacokinetic parameters were derived from the resulting plasma and urine concentration–time data using noncompartmental methods. The following parameters were calculated from the reported concentration–time data for oseltamivir and Ro 64–0802: C_{\max} (maximum observed plasma concentration), t_{\max} (time to maximum observed plasma concentration), t_{lag} (the observed time before a measurable plasma concentration), $\text{AUC}(0, \text{last})$ (AUC from 0 to the time at which the last measurable concentration was observed (t_{last}), computed using linear trapezoidal summation), $\text{AUC}(0, \infty)$ (AUC extrapolated to infinity, computed as $\text{AUC}(0, \text{last}) + C_{\text{last}}/K_{\text{el}}$, where C_{last} is the last measurable concentration, and K_{el} is as defined below), CL/F (oral clearance, computed as $\text{Dose}/\text{AUC}(0, \infty)$); and for Ro 64–0802 corrected for the chemical form for the analyte content in the dose by express-

ing the oseltamivir dose as Ro 64–0802 equivalents, i.e., as equivalent to the dose of oseltamivir multiplied by the ratio of molecular weight for Ro 64–0802 [284] to that of oseltamivir [312]), $\text{CL}_{\text{R}}(0, 24 \text{ h})$ (renal clearance over 24 h, computed as the ratio of the amount of drug excreted into urine to the equivalent plasma AUC), K_{el} (elimination rate, computed as the magnitude of the slope from the terminal linear portion of the log-linear regression of the plasma concentration curve), $t_{1/2}$ (terminal elimination half-life, computed as $\ln 2/K_{\text{el}}$), and $U_{\text{cum}}(0, 24 \text{ h})$ (percent of drug excreted into the urine over 24 h, computed by summing the products of urine volumes and drug urine concentrations and dividing by the administered dose for Ro 64–0802, correcting for the chemical form for the analyte content in the dose, as described previously]).

An analysis of variance appropriate for this study design was performed including terms for sequence, subject within sequence, period and regimen. The analysis was performed on the natural logarithm transformed scale for $\text{AUC}(0, \infty)$ and C_{\max} of oseltamivir and Ro 64–0802, and untransformed t_{\max} of Ro 64–0802. Confidence intervals (90%) for the difference in computed parameter least square means were calculated and expressed as a percentage of the reference (Treatment A, oseltamivir alone). Confidence intervals were calculated for Treatment B *vs* Treatment A, and for Treatment C *vs* Treatment A. WinNonlin[®] (version 3.1) (Pharsight Corporation, Mountain View, CA, USA) was used to perform pharmacokinetic analysis and the analysis of the variance. The primary pharmacokinetic parameters for the assessment of bioequivalence were $\text{AUC}(0, \infty)$ and C_{\max} of Ro 64–0802.

Results

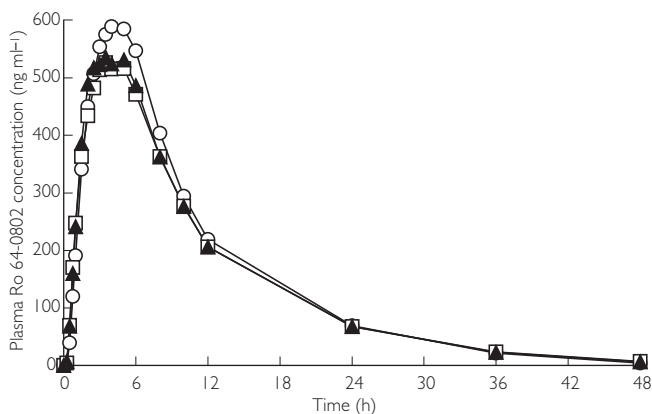
Thirteen healthy subjects (all Caucasians, six males, seven females) aged 30–61 years old (mean 47 ± 12 years) with a body mass index of 18–30 participated in the study. One subject withdrew prematurely from the study and was replaced. Only the 12 subjects who received all three study treatments (A, B and C) were included in the pharmacokinetic analysis population. All 13 subjects who were enrolled in the study and received at least one dose of study medication were included in the safety population.

All three treatments were well tolerated, and the incidences of adverse events were mild and resolved prior to the end of the study. The overall pattern of adverse events was comparable following administration of all three treatments, with the most frequent one being headache, which was reported by two subjects, and bruising at the venepuncture site, which was reported by three subjects. There were no clinically relevant changes in vital signs.

Table 1 Mean (CV%) values and 90% confidence intervals (CI) for Ro 64–0802 pharmacokinetic parameters following administration of oseltamivir alone (Treatment A), oseltamivir with Maalox® (Treatment B) and oseltamivir with Titalac® (Treatment C).

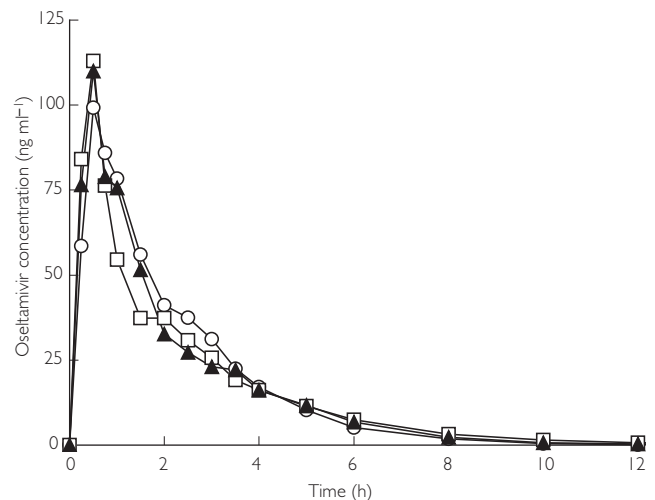
Ro 64–0802 Parameter	Treatment A (n = 12) Mean (CV%)	Treatment B (n = 12) Mean (CV%)	Treatment C (n = 12) Mean (CV%)	Ratio LSM Treatment B/A (90% CI)	Ratio LSM Treatment C/A (90% CI)
C_{max} (ng ml ⁻¹)	615 (20.9)	561 (27.5)	599 (32.4)	90.0 (83.6, 96.9)*	95.1 (88.3, 102)*
AUC(0,∞) (ng ml ⁻¹ h)	7310 (16.9)	6890 (17.4)	6940 (18.9)	94.1 (91.4, 96.9)*	94.7 (91.9, 97.5)*
AUC(0,last) (ng ml ⁻¹ h)	7110 (16.6)	6680 (17.8)	6740 (19.1)	93.7 (90.7, 96.8)*	94.5 (91.4, 97.7)*
t_{max} (h)	4.13 (24.9)	4.13 (37.6)	3.96 (35.5)	100 (82.4, 118)**	96.0 (78.4, 114)**
t_{lag} (h)	0.33 (86.6)	0.23 (72.9)	0.25 (112.8)	N/A	N/A
$t_{1/2}$ (h)	7.12 (25.8)	7.71 (20.3)	7.27 (23.3)	N/A	N/A
CL/F (ml min ⁻¹)	320 (15.7)	340 (16.7)	339 (17.0)	N/A	N/A
U _{cum} (0,24 h) (%)	64.0 (12.6)	57.9 (14.2)	61.7 (8.58)	N/A	N/A
CL _R (0,24 h) (ml min ⁻¹)	228 (17.5)	221 (13.8)	236 (17.8)	N/A	N/A

Treatment A = 150 mg oseltamivir alone, treatment B = 150 mg oseltamivir plus 20 ml Maalox® suspension, treatment C = 150 mg oseltamivir plus four Titalac® tablets, LSM = Least Square Means, * = 90% CI of the ratio of LSM falls within the ± 20% bioequivalence interval (80–125%), ** = 90% CIs of the ratio of untransformed LSM falls within the ± 30% bioequivalence interval (70–143%). N/A = not applicable.

**Figure 2** Mean plasma concentration *vs* time profiles of Ro 64–0802 following administration of oseltamivir alone (Treatment A, ○), oseltamivir together with Maalox® suspension (Treatment B, □) and oseltamivir together with Titalac® tablets (Treatment C, ▲).

Mean plasma concentration–time profiles for Ro 64–0802 and for oseltamivir following administration of oseltamivir alone (Treatment A), oseltamivir together with Maalox® suspension (Treatment B), and oseltamivir together with Titalac® tablets (Treatment C) are shown in Figures 2 and 3, respectively. Means and coefficients of variation (CV), and ratios of least square means (LSM) and 90% confidence intervals (CI) for Ro 64–0802 and oseltamivir are presented in Table 1 and Table 2, respectively.

The 90% confidence intervals of the ratio of the least square means for C_{max} and AUC(0,∞) of Ro 64–0802

**Figure 3** Mean plasma concentration *vs* time profiles of oseltamivir following administration of oseltamivir alone (Treatment A, ○), oseltamivir together with Maalox® suspension (Treatment B, □) and oseltamivir together with Titalac® tablets (Treatment C, ▲).

following administration of oseltamivir with either Maalox® suspension or Titalac® tablets relative to oseltamivir alone were within the ± 20% bioequivalence range, while the values for t_{max} were within the ± 30% bioequivalence range. Similarly, for oseltamivir, the 90% confidence intervals of the ratio of the least square means of AUC(0,∞), were within the ± 20% bioequivalence range, while the values for C_{max} , were within the ± 30% bioequivalence range.

Table 2 Mean (CV%) values and 90% confidence intervals (CI) for oseltamivir pharmacokinetic parameters following administration of oseltamivir alone (Treatment A), oseltamivir with Maalox[®] (Treatment B) and oseltamivir with Titalac[®] (Treatment C).

Oseltamivir Parameter	Treatment A (n = 12)	Treatment B (n = 12)	Treatment C (n = 12)	Ratio LSM Treatment	Ratio LSM Treatment
	Mean (CV%)	Mean (CV%)	Mean (CV%)	B/A (90% CI)	C/A (90% CI)
C_{max} (ng ml ⁻¹)	158 (40.6%)	158 (46.9%)	149 (38.2%)	98.5 (72.8–133)**	94.8 (70.1–128)**
AUC(0,∞) (ng ml ⁻¹ h)	223 (19.1%)	213 (27.5%)	216 (17.1%)	93.9 (83.9–105)*	96.9 (86.7–108)*
AUC(0, last) (ng ml ⁻¹ h)	219 (20.1%)	208 (27.8%)	212 (17.2%)	93.7 (83.4–105)*	97.1 (86.5–109)*
t_{max} (h)	0.81 (47.5%)	0.48 (34.9%)	0.60 (64.7%)	N/A	N/A
t_{lag} (h)	0.02 (346.4%)	0.02 (346.4%)	0.08 (147.7%)	N/A	N/A
$t_{1/2}$ (h)	1.43 (37.9%)	2.05 (31.2%)	1.52 (34.1%)	N/A	N/A
CL/F (ml min ⁻¹)	11600 (19.7%)	12500 (25.1%)	12000 (19.6%)	N/A	N/A
U_{cum} (0,24 h) (%)	3.22 (20.2%)	2.90 (42.1%)	3.39 (16.0%)	N/A	N/A
CL _R (0,24 h) (ml min ⁻¹)	371 (21.0%)	336 (32.9%)	400 (16.9%)	N/A	N/A

Treatment A = 150 mg oseltamivir alone, Treatment B = 150 mg oseltamivir plus 20 ml Maalox[®] suspension, Treatment C = 150 mg oseltamivir plus four Titalac[®] tablets. LSM = Least Square Means. * = 90% CI of the ratio of LSM falls within the \pm 20% bioequivalence interval (80–125%), ** = 90% CI of the ratio of LSM falls within the \pm 30% bioequivalence interval (70–143%).

N/A = not applicable.

Discussion

The results of this study support a general finding that (with a few exceptions) antacids have relatively limited interaction with other medications [10]. Based on the primary pharmacokinetic parameters, AUC(0,∞) and C_{max} of Ro 64–0802, there is no pharmacokinetic interaction between this drug and either Maalox[®] suspension or Titalac[®] tablets, since the values were within the \pm 20% bioequivalence interval. AUC(0,last) for Ro 64–0802 was also within the \pm 20% bioequivalence interval. In addition, the 90% confidence intervals of the ratio of the least square means for t_{max} of Ro 64–0802 and for the AUC(0,∞), AUC(0,last) and the C_{max} values for oseltamivir were within the \pm 30% bioequivalence interval, which further support the absence of an interaction between oseltamivir and the antacids. There was a statistically significant period effect for the C_{max} of Ro 64–0802, which was probably a chance event.

Statistical analysis was not performed on the mean times to maximum plasma concentrations (t_{max}) for oseltamivir due to limited sampling times below 1 h. However, t_{max} for oseltamivir when administered alone, with Maalox[®] suspension, and with Titalac[®] tablets were similar, (0.8, 0.5 and 0.6 h, respectively), suggesting that neither Maalox[®] suspension, nor Titalac[®] tablets have any significant effect on the absorption of oseltamivir. The mean time to maximum plasma concentrations (t_{max}) of Ro 64–0802 was approximately 4 h for all three treatments, confirming that the antacids used in this study also had no effect on the rate at which maximal concentrations of Ro 64–0802 appeared in the plasma. These

results confirm the findings of an earlier study, which showed that increased gastric pH, as induced by cimetidine, did not affect the absorption of oseltamivir [1].

The mean lag time (t_{lag}) for oseltamivir and Ro 64–0802 was similar for all three treatments (approximately 0.02–0.08 h and 0.2–0.3 h, respectively), suggesting that both Maalox[®] suspension and Titalac[®] tablets have no effect on the rate at which measurable concentrations of oseltamivir and Ro 64–0802 appear in the plasma. The mean terminal elimination half-life ($t_{1/2}$) for oseltamivir and Ro 64–0802 was also similar for all three treatments (approximately 1.4–2.1 h and 7.1–7.7 h, respectively). For both oseltamivir and Ro 64–0802, the oral clearance (CL/F), renal clearance over 24 h (CL_R(0,24 h)) and the percent of drug excreted in the urine over 24 h (U_{cum} (0,24 h)), were comparable in the presence and absence of both antacids.

In summary, the results demonstrated that the co-administration of either Maalox[®] suspension or Titalac[®] tablets with oseltamivir has no effect on the pharmacokinetics of either oseltamivir or Ro 64–0802, and that conversely, there was no evidence that co-administration with oseltamivir has an effect on the safety and tolerability of either Maalox[®] suspension or Titalac[®] tablets. There was no pharmacokinetic interaction between oseltamivir and either antacid, demonstrating that the oral absorption of oseltamivir was not impaired in the presence of antacids containing magnesium, aluminium or calcium.

We would like to thank the staff of the Roche Welwyn Clinical Pharmacology Unit for their contribution to this study.

References

- 1 He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet* 1999; **37**: 471–484.
- 2 Oo C, Barrett J, Hill G, *et al.* Clinical pharmacokinetics and dose recommendation of oseltamivir suspension for the treatment of influenza in children. *Paediatr Drugs* 2001; **3**: 229–236.
- 3 Maton PN, Burton ME. Antacids revisited. a review of their clinical pharmacology and recommended therapeutic use. *Drugs* 1999; **57**: 855–870.
- 4 Welling PG. Interactions affecting drug absorption. *Clin Pharmacokinet* 1984; **9**: 404–434.
- 5 Hurwitz A. Antacid therapy and drug kinetics. *Clin Pharmacokinet* 1977; **2**: 269–280.
- 6 Reynolds JC. The clinical importance of drug interactions with anti-ulcer therapy. *J Clin Gastroenterol* 1990; **12**(Suppl 2): S54–S63.
- 7 Gugler AH. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18**: 210–219.
- 8 Lomaestro BM, Bailie GR. Absorption interactions with fluoroquinolones. *Drug Safety* 1995; **12**: 314–333.
- 9 Wiltshire H, Wiltshire B, Citron A, *et al.* Development of a high-performance liquid chromatographic mass spectrometric assay for the specific and sensitive quantification of Ro 64-0802, an anti-influenza drug, and its pro-drug, oseltamivir, in human and animal plasma and urine. *J Chromatogr B* 2000; **745**: 373–388.
- 10 D'Arcy PF, McElnay JC. Drug-antacid interactions: assessment of clinical importance. *Drug Intell Clin Pharm* 1987; **21**: 607–617.