

Original Article

The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis

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Abstract

Background. Oseltamivir dose reduction is recommended for patients with end-stage renal disease (ESRD). However, dosing recommendations are not available for treatment or prophylaxis of influenza in these patients. This study assessed the pharmacokinetics and tolerability of oseltamivir in ESRD patients undergoing maintenance haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD).

Methods. In this open-label, multiple-dose study, patients received 30 mg oral oseltamivir suspension over 6.5 weeks. This dose was predicted to be suitable for ESRD patients based on a 2-compartment model. HD patients received 9 doses given 1 h after the completion of alternate HD sessions (three times a week). CAPD patients received 6 doses given once weekly after a dialysate exchange. The primary parameters were peak plasma concentration (C_{max}) and the area under the curve (AUC) for oseltamivir and oseltamivir carboxylate.

Results. In HD patients, the C_{max} for oseltamivir carboxylate after single and repeated dosing were 943 and 1120 ng/ml, respectively. The mean AUC_{0-42} was 31 600 ng h/ml for days 1–5 and 38 200 ng h/ml for days 38–43. Similarly, in CAPD patients, mean C_{max} after the first and sixth doses were 885 and 849 ng/ml, respectively. The mean AUC_{0-48} values for days 1–6 and days 36–43 were 33 400 and 32 400 ng h/ml, respectively. Oseltamivir was well-tolerated in both the patient groups.

Conclusions. A 30 mg dose of oseltamivir given once weekly in CAPD or after alternate sessions in HD patients provides sufficient exposure to oseltamivir carboxylate to allow safe and effective anti-influenza treatment and prophylaxis.

Keywords: dialysis; dosing recommendations; ESRD; oseltamivir; pharmacokinetics; safety

Introduction

Oseltamivir (Tamiflu[®]) is the prodrug of oseltamivir carboxylate, a potent inhibitor of influenza virus neuraminidase. It is effective and well-tolerated when used for the treatment or prophylaxis of influenza A and B in adults and children alike [1–8] as well as in high-risk populations such as the elderly, who are more susceptible to influenza-associated complications and can experience significant morbidity and mortality [5, 9, 10].

Patients with renal dysfunction are also more susceptible to influenza virus infections, and are at an increased risk of complications from influenza [11]. As the excretion of oseltamivir carboxylate is primarily via the kidneys, patients with impaired renal function experience decreased renal clearance and increased systemic exposure to oseltamivir carboxylate as the severity of their renal impairment increases [12]. Thus, oseltamivir dose reduction is recommended [13] for patients with a creatinine clearance (CL_{cr}) between 10 and 30 ml/min [pre-end-stage renal disease (ESRD)]. However, dosing recommendations are not available for either the treatment or prophylaxis of influenza for ESRD patients on maintenance dialysis treatment.

The purpose of this study was to determine a dosing strategy for oseltamivir in patients with ESRD, undergoing dialysis, and to investigate the safety of the proposed dosing regimen.

Patients and methods

This was an open-label, multiple-dose study of the pharmacokinetics and tolerability of oseltamivir oral suspension (30 mg dose) at repeated dosing intervals to ESRD patients on maintenance haemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). The study was conducted at a single centre in New Zealand, approved by The Canterbury Ethics Committee and in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice. All patients provided written informed consent.

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Patients

Male and female patients with ESRD on CAPD or HD were eligible for this study if they were aged ≥ 18 years, had a body mass index (BMI) of 18–34 kg/m² and a stable CL_{cr} of <10 ml/min. Subjects were excluded if they had severe and/or unstable comorbidity, known HIV or hepatitis virus infection, a history of hypersensitivity to oseltamivir or related compounds, a history of drug or alcohol abuse within the previous year, were pregnant or lactating, or were currently participating or had recently participated in another investigational study.

Study design

Rationale for dosage selection. In a previous study, a single oral dose of 75 mg oseltamivir in ESRD patients on HD and CAPD produced plasma levels of oseltamivir carboxylate ~10 times higher than those associated with clinical efficacy [14]. Based on these data, a single dose of 75 mg oseltamivir should deliver effective neuraminidase inhibition adequate for the treatment of influenza illness in ESRD patients who receive routine HD or CAPD. No dose recommendation could be made for prophylaxis of influenza in these patients as repeat dose exposures were not explored. A 2-compartment model was used to predict repeat dose regimens which could be suitable for either treatment or prophylaxis of influenza in these patients. The model predicted that a 30 mg dose given weekly to patients undergoing CAPD, or after alternate HD treatments in patients undergoing HD three times a week, would deliver effective neuraminidase inhibition for the short-term (5 day) treatment of influenza and the prophylaxis of influenza over a 6 week influenza season. These dose regimens were chosen for this study.

As the study was also intended to provide information regarding suitable doses for the prophylaxis of influenza, the total dosing period in both the groups was 6.5 weeks. All HD patients had 19 HD sessions [three times a week (Monday, Wednesday and Friday) for 5 h each] during the 6.5 week study period. HD patients received 30 mg of oseltamivir oral suspension (12 mg/ml) given 1 h after the completion of alternate HD sessions (9 doses in total). The following HD sessions occurred between 42 and 47 h post-dose. CAPD patients also received 30 mg of oseltamivir oral suspension, but on a once a week schedule (Monday), immediately after a dialysate exchange. All CAPD patients received usual CAPD treatment (four exchanges per 24 h) during the 6.5 week study period and received 6 doses in total.

All the patients consumed a standard meal 30 min before each oseltamivir dose. Giving oseltamivir with food has been shown to minimize the frequency of gastrointestinal (GI) adverse effects [15].

Assessments

Pharmacokinetic parameters. The primary study parameters were peak plasma concentration (C_{max}) and the area under the plasma concentration–time curve (AUC) for oseltamivir and oseltamivir carboxylate. Other computed parameters were considered secondary.

The following pharmacokinetic parameters were calculated: C_{max}; terminal elimination half-life (t_{1/2})

computed as natural logarithm 2 = 0.693147181/elimination rate constant (K_{el}); AUC extrapolated to infinity, calculated as AUC_{last} + C_{LQCT}/K_{el}, where C_{LQCT} is the last measurable concentration; dialysis clearance (CL_d); renal clearance (CL_r) and oral plasma clearance (CL/F; where F is the bioavailability).

For HD patients, CL_d = Qb (C_{in} - C_{out})/C_{in}; where C_{in} = dialyser plasma concentration before dialyser from a 5 h arterial sample, C_{out} = filter plasma concentration after dialyser from 5 h venous sample and Qb = blood flow rate through HD filter. For CAPD patients, CL_d = amount of drug recovered in dialysis fluid divided by the AUC during dialysis procedure. CL_r was computed as the ratio of the amount of drug excreted over a given time interval to the AUC over the same time interval.

Schedule of assessments. Evaluations were performed at screening (2–28 days prior to the first dose) and post-study (7–14 days after the final pharmacokinetic assessment). Evaluation of vital signs, ECG, laboratory safety tests and pregnancy testing were performed at screening, pre-dose (day 1) and at follow-up.

HD patients

Serial blood sampling for pharmacokinetic analysis was conducted after the first and the 17th HD sessions (days 1 and 38) immediately before dosing, then at 1, 2, 4, 8, 12, 20, 32 and 42 h after dosing. HD patients were hospitalized for the whole of the pharmacokinetic assessment period. Arterial and venous dialyser blood samples were collected during the 2nd and 18th HD sessions at 1, 2, 4 and 5 h after the start of HD. Two additional blood samples were collected 1 and 2 h after the completion of the 2nd and 18th HD sessions (~48 and 49 h post-dose) and one additional blood sample just before the initiation of the 3rd and the 19th HD sessions. Blood samples for urea reduction rate (URR) were collected immediately before and 30 min after the 2nd and 18th HD sessions. Blood samples for the determination of trough oseltamivir carboxylate concentrations were collected within 1 h of the completion of the 5th, 9th and 13th HD sessions but before drug dosing. Urine samples were collected over the following periods: 0–12, 12–24 and 24–42 h after the first dose.

CAPD patients

In CAPD patients, two series of blood samples for pharmacokinetic analysis were collected before and after the 1st and 6th study doses (days 1 and 36) immediately before dosing, then at 1, 2, 4, 8, 12, 24, 48, 72, 120 and 168 h after dosing. In addition, three trough blood samples were collected just before the 3rd, 4th and 5th study doses. Urine samples were collected over the following periods: 0–12, 12–24 and 24–48 h after the first dose. Dialysate bag volumes (by weight) and samples were collected at 0–4, 4–8, 8–12, 12–24, 24–28, 28–32, 32–36 and 36–48 h after the first study dose. The dialysate was changed four times every 24 h.

Sample collection and storage. Venous blood samples for drug assay (4 ml) were collected into monovettes or vacutainers containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Each blood sample was kept frozen after collection. Plasma was separated by

centrifugation within 30 min of collection if collected in the unit, and within 90 min if collected at the patient's home. Plasma samples were analysed for oseltamivir and oseltamivir carboxylate by BAS Analytics, Kenilworth, UK.

Urine was collected and stored at $\sim 4^{\circ}\text{C}$ until the end of the collection interval; the pH and volume of all specimens were measured. Approximately 10 ml of each sample was transferred to polyethylene tubes for analysis. The dialysate bag for CAPD patients was well-shaken before the collection of the dialysate pharmacokinetic samples (10 ml). The syringe was filled and emptied twice with the dialysate from the dialysate bag before drawing up the actual sample for analysis. Plasma, urine and dialysate samples were stored as soon as possible after the collection at $\sim -20^{\circ}\text{C}$ until analysis.

Safety assessments. Adverse events were monitored throughout the study period. Vital signs (blood pressure and pulse rate) were monitored pre-dose and 8 h post-dose on the serial sampling days. Venous blood samples (10 ml) were collected for haematology and biochemistry analysis, and urine samples for urinalysis, at screening, pre-dose, after the last pharmacokinetic sample had been taken and at follow-up. Three venous blood samples (5 ml) were collected from HD patients for biochemistry tests within 1 h of completion of the 5th, 9th and 13th HD sessions.

Statistical analyses

Oseltamivir and oseltamivir carboxylate plasma concentrations and computed pharmacokinetic parameters were listed and summarized by treatment regimens (mean, SD, coefficient of variation, geometric means, median, minimum, maximum and number of observations). Individual and mean plasma concentrations were plotted against time. All the patients who received at least one dose of study drug and a safety follow-up were included in the safety analysis.

Results

Patient

A total of 24 patients with ESRD (HD, $n = 12$; CAPD, $n = 12$) took part in this study. One patient was switched from HD to CAPD in mid-study at his own request. Thus, his data were only included in the first dose analysis of the HD group (days 1–5) and excluded from the second dose analysis (days 38–43). All screened patients were assigned to and completed treatment, and all of their pharmacokinetic and safety data were analysed. No patients were prematurely withdrawn from the study.

The demographic data and baseline characteristics of the HD and CAPD study populations are shown in Table 1. HD and CAPD groups differed with regard to sex and race.

Pharmacokinetic results

HD patients. The mean plasma concentration–time profiles for oseltamivir carboxylate on days 1–5 and 38–43 are shown in Figure 1.

Table 1. Demographic data and baseline characteristics of HD and CAPD patients

Parameter	HD ($n = 12$)	CAPD ($n = 12$)
Sex		
Male, n (%)	11 (92)	5 (42)
Female, n (%)	1 (8)	7 (58)
Race		
Caucasian, n (%)	8 (67)	11 (92)
Other, n (%)	4 (33)	1 (8)
Age, mean (SD) (years)	48.0 (13.23)	54.4 (14.30)
Height, mean (SD) (cm)	171.3 (7.7)	169.1 (8.1)
Body mass index, mean (SD) (kg/m^2)	25.39 (4.48)	25.71 (4.76)

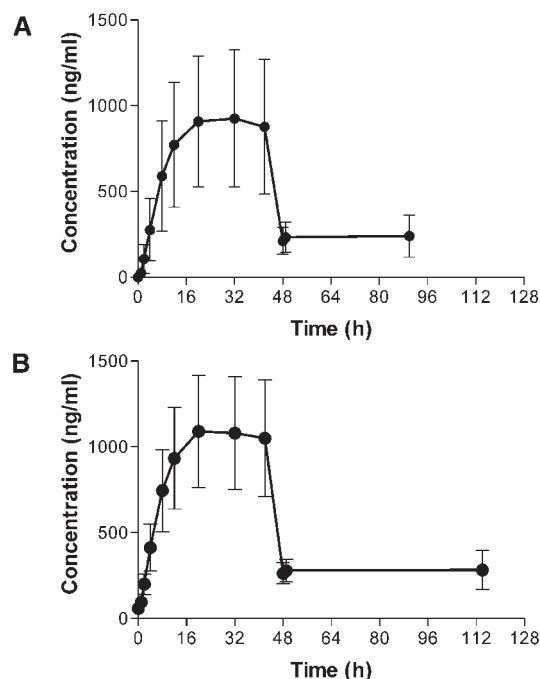


Fig. 1. Mean (\pm SD) plasma concentration–time profile for oseltamivir carboxylate on days 1–5 (A) and 38–43 (B) in HD patients.

Mean values of the main pharmacokinetic parameters for oseltamivir and oseltamivir carboxylate in HD patients are summarized in Table 2. The C_{max} for oseltamivir was reached within 1–2 h in most patients, and plasma concentration declined rapidly thereafter due to the metabolism to the carboxylate; in most patients, the trough plasma concentrations of oseltamivir occurred at 8 h and concentrations were below the lower quantification limit at 12 h. Peak concentrations of oseltamivir carboxylate are substantially delayed in HD patients following single and repeated dosing [time to C_{max} (T_{max}) of 29.7 and 29.2 h, respectively]. Plasma concentrations of oseltamivir carboxylate were higher after repeated dosing than after the first dose, as shown by increases in C_{max} , AUC and AUC_{last}. HD contributed substantially to the total body clearance; as expected with these type of patients, renal clearance was negligible (Table 2).

Table 2. Mean values (SD) of the main pharmacokinetic variables for oseltamivir and oseltamivir carboxylate in HD patients

Parameter	Oseltamivir		Oseltamivir carboxylate	
	Days 1–5	Days 38–43	Days 1–5	Days 38–43
C_{max} (ng/ml)	20.2 (12.3)	22.6 (9.69)	943 (393)	1120 (320)
T_{max} (h)	1.75 (1.14)	1.18 (0.40)	29.7 (8.0)	29.2 (9.61)
AUC ^a (ng h/ml)	63.9 (24.6)	68.5 (19.5)	31 600 (14 100)	38 200 (11 500)
AUC _{last} (ng h/ml)	62.1 (26.8)	65.6 (20.1)	44 400 (19 000)	60 400 (16 700)
CL/F ^a (l/h)	677 (727)	474 (141)	1.20 (1.05)	0.779 (0.239)
CL _d (l/h)	NC	NC	7.42 (0.45)	8.43 (3.02)
CL _r ^a (l/h)	0.0521 (0.133)	NA	0.0203 (0.057)	NA
Drug excreted (%)	0.00982 (0.022)	NA	1.86 (4.660)	NA

^aAUC, CL/F and CL_r are for the intervals 0–12 h for oseltamivir and 0–42 h for oseltamivir carboxylate. C_{max} , peak plasma concentration; T_{max} , time to C_{max} ; AUC, area under the plasma concentration–time curve; CL/F, oral plasma clearance; CL_d, dialysis clearance; CL_r, renal clearance; NA, not applicable; NC, not calculated.

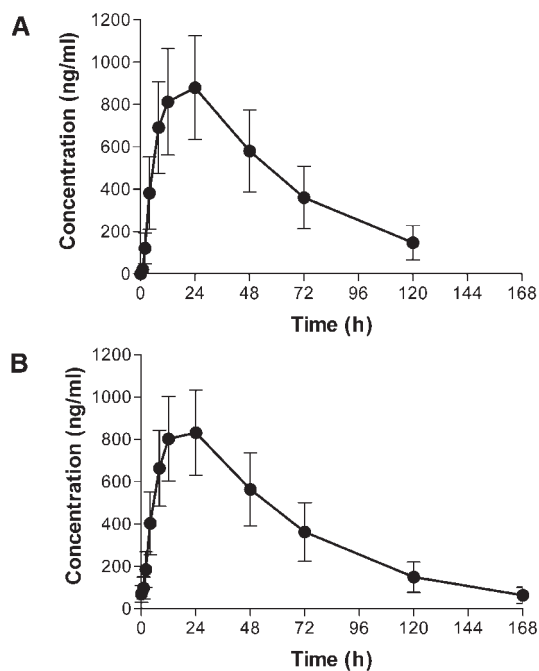
Table 3. Mean plasma concentrations (SD) of oseltamivir carboxylate during the 5 h HD session from 42–47 h for dialyser inflow ('arterial') and outflow ('venous') on days 3 and 40

Time (h)	Day 3 (<i>n</i> = 12)		Day 40 (<i>n</i> = 12)	
	Arterial blood (ng/ml)	Venous blood (ng/ml)	Arterial blood (ng/ml)	Venous blood (ng/ml)
1	570 (229)	284 (121)	666 (179)	317 (103)
2	412 (157)	202 (74.4)	496 (125)	229 (69.6)
4	227 (82.2)	127 (69.1)	281 (58.8)	128 (37.3)
5	171 (61.8)	84.3 (29.6)	218 (45.6)	95.4 (27.7)

Plasma concentrations of oseltamivir carboxylate decreased by ~70% (to 171 ng/ml) during the 5 h dialysis session on day 3 (Table 3; Figure 1) but rebounded to 240 ng/ml at 90 h post-dose. Similarly on day 40, oseltamivir carboxylate concentrations decreased by 67% (to 218 ng/ml) but then rebounded to 283 ng/ml at 114 h post-dose. The minimum mean plasma concentrations of oseltamivir carboxylate were 240 ng/ml on day 5 and 283 ng/ml on day 43.

CAPD patients. The mean plasma concentration–time profiles of oseltamivir carboxylate on days 1–6 and 36–43 are shown in Figure 2.

Mean values of the main pharmacokinetic parameters for oseltamivir and oseltamivir carboxylate in CAPD patients are summarized in Table 4. The pharmacokinetic profile for oseltamivir carboxylate in CAPD patients was similar to that in HD patients. Following dosing on day 1 and day 36, the C_{max} of oseltamivir occurred within 1–2 h in most CAPD patients, followed by a rapid decline because of metabolism to the active moiety. Trough plasma concentrations of oseltamivir occurred at 8 h in most patients and were below the lower quantification limit at 12 h. The mean AUC_{0–48} of oseltamivir carboxylate on days 1–6 in CAPD patients was similar to the mean AUC_{0–42} in HD patients (31 600 ng h/ml); doses given on days 36 or 38 produced an AUC_{0–42} of 38 200 ng h/ml in HD patients compared with an AUC_{0–48} of 32 400 ng h/ml in CAPD patients. Mean C_{max} values in CAPD patients after the first and the

**Fig. 2.** Mean (\pm SD) plasma concentration–time profile for oseltamivir carboxylate on days 1–6 (A) and 36–43 (B) in CAPD patients.

sixth doses were similar to those in HD patients. Mean T_{max} was achieved earlier in CAPD than in HD patients because of the continuous dialysis. CAPD constituted 32.6% of the total body clearance of

Table 4. Mean values (SD) of the main pharmacokinetic variables for oseltamivir and oseltamivir carboxylate in CAPD patients

Parameter	Oseltamivir		Oseltamivir carboxylate	
	Days 1–6	Days 36–43	Days 1–6	Days 36–43
C _{max} (ng/ml)	32.0 (20.4)	27.7 (15.9)	885 (244)	849 (200)
T _{max} (h)	1.50 (0.52)	1.28 (0.05)	20.00 (5.91)	19.00 (6.18)
K _{el} (1/h)	NC	NC	0.0211 (0.006)	0.0200 (0.005)
t _{1/2} (h)	NC	NC	34.8 (8.4)	36.3 (7.5)
AUC ^a (ng h/ml)	85.6 (40.7)	72.4 (28.3)	33 400 (9700)	32 400 (8210)
AUC _{last} (ng h/ml)	78.5 (41.8)	67.7 (27.7)	56 800 (18 300)	60 800 (18 800)
CL/F ^a (l/h)	424 (183)	485 (215)	0.882 (0.250)	0.898 (0.246)
CL _d (l/h)	–	NA	0.425 (0.046)	NA
CL _r ^a (l/h)	0.146 (0.250)	NA	0.0665 (0.114)	NA
Drug excreted renally (%)	0.0290 (0.049)	NA	6.44 (10.80)	NA
Drug eliminated by dialysis (%)	0.0037 (0.013)	NA	32.6 (8.8)	NA

^aAUC, CL/F and CL_r are for the intervals 0–12 h for oseltamivir and 0–48 h for oseltamivir carboxylate. C_{max}, peak plasma concentration; T_{max}, time to C_{max}; K_{el}, elimination rate constant; t_{1/2}, terminal elimination half-life; AUC, area under the plasma concentration–time curve; CL/F, oral plasma clearance; CL_d, dialysis clearance; CL_r, renal clearance; NA, not applicable; NC, not calculated.

oseltamivir carboxylate as CL_r was low or negligible in these patients (Table 4). At the time of the last two sample collections at 120 and 168 h, plasma concentrations of oseltamivir carboxylate were 147 and 63 ng/ml, respectively.

Safety analysis

Oseltamivir was generally well-tolerated in this study, adverse events reported being generally minor. In the HD group, eight of the 12 patients experienced 22 adverse events and in the CAPD group, 10 of 12 patients experienced 39 adverse events. GI events, including nausea and vomiting were reported by 50% (*n*=6) of the HD patients and 50% (*n*=6) of the CAPD patients. There was a low frequency of GI events occurring on day 1 of dosing (*n*=1, HD group). In two patients in the HD group, the adverse events were judged by the investigator to be probably related to treatment (diarrhoea and mouth ulceration) and in four patients, remotely related. In the CAPD group, none of the adverse events were probably related to treatment, one was possibly related and 11 in six patients were remotely related. Serious adverse events occurred in three patients (HD group: *n*=1 unstable angina; CAPD group: *n*=1 peritonitis, *n*=1 coccydynia and pericarditis), none of which were considered to be treatment related and all recovered without sequelae. No deaths or withdrawals due to adverse events were reported. There were no apparent effects of any dosing regimen on the clinical laboratory parameters or vital signs.

Discussion

This study shows that Tamiflu® (30 mg oral suspension), in ESRD patients who are undergoing HD or CAPD, provides an exposure to oseltamivir carboxylate that has been shown to be clinically effective in other patient groups.

Previous treatment studies in subjects with normal renal function showed that oseltamivir dosages of 75 mg twice daily result in oseltamivir carboxylate plasma levels sufficient to inhibit neuraminidase enzyme activity from all the tested influenza virus strains [12]. Other studies have shown that oseltamivir 75 mg, given once daily for prophylaxis, effectively prevents influenza illness [1,5,6,8]. However, exposure to oseltamivir carboxylate increases with decreasing renal function, and dose reduction is recommended for patients with severe renal impairment (CL_{cr} of >10 and ≤30 ml/min). Furthermore, single doses of 75 mg oseltamivir produce a C_{max} substantively above that observed in subjects with normal renal function; although these have not been associated with adverse events, the number of subjects studied is small [12].

The pharmacokinetics of oseltamivir carboxylate in HD and CAPD patients observed in the present study differ from those of patients with normal renal function (CL_{cr} of >90 ml/min), given single or repeated doses of 75 mg oseltamivir [16]. T_{max} was longer in ESRD patients than in patients with normal renal function (3 h at a steady state) [16], as expected, given the reduced excretory capacity in dialysis patients. C_{max} was approximately four times higher in ESRD patients after a single 30 mg dose of oseltamivir than in patients with normal renal function after a single 75 mg dose (225 ng/ml) [16]. C_{max} values after repeated dosing in ESRD patients were also higher than in patients with normal renal function (348 ng/ml) [16]. The AUC_{0–last} of oseltamivir carboxylate in HD and CAPD patients after repeated 30 mg doses was approximately three times higher than the AUC_{0–last} at steady state in patients with normal renal function, receiving repeated doses of 75 mg twice daily (21 752 ng h/ml) [16]. In addition, a high degree of inter-individual variability was noted in all the pharmacokinetic parameters of oseltamivir carboxylate taken from both HD and CAPD patients, the variability exceeding that observed in healthy

volunteers with normal renal function following oral dosing with oseltamivir [12]. Possible reasons for this disparity include either more variable absorption of the drug or altered protein binding of the drug. However, this needs to be studied further. Nevertheless, the increased pharmacokinetic variability observed will have little clinical impact on these populations. Oseltamivir carboxylate has been shown to be well-tolerated at levels above the extremes of C_{max} and AUC observed in the present study [12]. Furthermore, the minimum oseltamivir carboxylate concentrations measured in the present study are still sufficient to inhibit replication of different influenza virus subtypes [17]. Thus, the current dosing regimen in dialysis patients can be considered to be effective and well-tolerated.

Oseltamivir is not currently recommended for use by patients with ESRD (CL_{cr} of ≤ 10 ml/min) because a suitable dose regimen has not been established [18,19]. As subjects with ESRD are at a particular risk of influenza complications [11], most authorities recommend pre-season vaccination [11,20]. However, in circumstances where vaccination is likely to be ineffective (seasons in which the vaccine is a poor match to the circulating strain) or in the early stage of a pandemic, before vaccination is possible, there may be a need for chemoprophylaxis in this high-risk patient group. Model predictions suggested that 30 mg oseltamivir, given weekly to CAPD patients, or following alternate HD cycles in patients undergoing HD three times a week, would deliver anti-viral drug levels suitable for effective prophylaxis of influenza over a 6 week influenza season [14]. Additionally, the model predicted that the plasma concentrations would be above the minimum inhibitory concentration known to be associated with effective treatment of influenza over the first 5 days of use. In the current study, the regimens employed produced plasma concentrations of oseltamivir carboxylate that were greater than the concentration required for 50% inhibition values (i.e. drug concentration reducing viral activity by 50%) for oseltamivir carboxylate reported for various influenza A and B laboratory and clinical isolates [8,21]. The data from this study, therefore, provide useful information from which to provide guidance for the use of oseltamivir in patients with ESRD receiving CAPD or HD for either the treatment, or prophylaxis, of influenza in situations where vaccination is not effective.

As expected, treatment with oseltamivir over a 6.5 week period did not lead to increases in adverse event rates or abnormal laboratory findings in the ESRD patient population, compared with the data reported from studies in the otherwise healthy patients [18]. The present study was conducted over 6.5 weeks, and intermittent episodes of nausea and vomiting are not unusual even in a healthy population over that time period [1]. Nausea and vomiting have previously been reported to occur more often when oseltamivir was administered in a fasting state and at doses of 200 mg once or twice daily [2]. In the present

study, oseltamivir was administered 30 min after a standard meal, and this may account for the low frequency of GI events occurring on day 1. No drug-related serious effects were observed in this study.

The results of the present study suggest that 30 mg oseltamivir in suspension can be given weekly (to CAPD patients) or after alternate HDs (to HD patients), to provide effective treatment for, or prophylaxis against, influenza illness. HD patients should take 30 mg after alternate HD sessions over a 5 day period. For prophylaxis, our results indicate that administration of 30 mg oseltamivir once a week after CAPD and 30 mg after each alternate HD session are well-tolerated when administered over a 6 week period, and further dose reductions need not be made in either of these patient populations. Administration over a 6 week period would normally be sufficient to provide protection for the duration of a local influenza outbreak.

In conclusion, novel dosing regimens of 30 mg oseltamivir, once a week in CAPD or after alternate sessions in patients undergoing HD, provide sufficient exposure to the active metabolite to allow well-tolerated and effective anti-influenza treatment and prophylaxis in patients with ESRD undergoing CAPD or HD. These findings warrant the studies of the efficacy of this dose regimen against influenza in a clinical scenario, such as during an influenza outbreak in a renal unit.

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Conflict of interest statement. R.R. has received funding from various pharmaceutical companies for attending meetings, advisory work and research. M.B. and P.W. are currently employed by Roche Products Ltd. K.L. and A.B. have no conflict of interest.

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