Anaesth Intensive Care 2013; 41: 66-73

Oseltamivir pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation support

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SUMMARY

Extracorporeal membrane oxygenation (ECMO) is known to affect pharmacokinetics and hence optimum dosing. The aim of this open label, prospective study was to investigate the pharmacokinetics of oseltamivir (prodrug) and oseltamivir carboxylate (active metabolite) during ECMO. Fourteen adult patients with suspected or confirmed H1N1 influenza were enrolled in the study. Oseltamivir 75 mg was enterally administered twice daily and blood samples for pharmacokinetic assessment were taken on day 1 and 5. A multi-compartmental model to describe the pharmacokinetics of oseltamivir and oseltamivir carboxylate was developed using a non-linear mixed effects modelling approach.

The median (range) clearance of oseltamivir carboxylate was 15.8 (4.8–36.6) l/hour, lower than the reported mean value of 21.5 l/hour in healthy adults. The median (range) steady state volume of distribution of oseltamivir carboxylate was 179 (61–436) litres, much greater than healthy adults but similar to previous reports in critically ill patients. Substantial 'between subject' variability in systemic exposure to oseltamivir carboxylate was revealed; median (range) area under the curve and C_{max} were 4346 (644–13660) ng/hour/ml and 509 (54–1277) ng/ml, respectively. Both area under the curve and C_{max} were significantly correlated with serum creatinine (r^2=0.37, P=0.02 and r^2=0.29, P=0.02, respectively).

Systemic exposure to oseltamivir carboxylate following the administration of enteral oseltamivir 75 mg twice daily in adult ECMO patients is comparable to those in ambulatory patients and far in excess of concentrations required to maximally inhibit neuraminidase activity of the H1N1 virus. Dosage adjustment for ECMO, per se, appears not to be necessary; however, doses should be reduced in patients with renal dysfunction.

Key Words: H1N1 influenza, ECMO, pharmacokinetics, neuraminidase inhibitors

During the 2009 and 2010 H1N1 influenza pandemic, a significant proportion of patients presented with or developed acute respiratory distress syndrome[1]. In some severe cases, extracorporeal membrane oxygenation (ECMO) was initiated for the treatment of refractory hypoxaemia, hypercapnia or both, which occurred despite mechanical ventilation and implementation of acute respiratory distress syndrome therapies. According to a recently reported cohort study in the United Kingdom[2], ECMO played a key role in the survival of H1N1 influenza-infected, critically ill patients with acute respiratory distress syndrome.

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Accepted for publication on October 24, 2012.

Oseltamivir is an orally active neuraminidase inhibitor prescribed for patients with suspected or confirmed H1N1 infection. It is administered as oseltamivir phosphate (prodrug) which is rapidly hydrolysed by gut and liver esterases, so that following oral dosing the majority of the dose reaches the systemic circulation as oseltamivir carboxylate (active drug). No parenteral formulation of oseltamivir is presently available. In infected patients, oseltamivir carboxylate inhibits neuraminidase, an enzyme that is present on the cell surface of all influenza viruses and which is essential for the release of progeny virions from infected host cells. In this way, oseltamivir carboxylate has been shown to reduce viral replication, viral load and the course of infection in the host[3]. For therapeutic use, oseltamivir is administered twice daily at a standard dose of 75 mg for adults and on the basis of body weight in children.

ECMO is known to affect the pharmacokinetics (PK) of many drugs for multi-factorial reasons, including as a consequence of the expanded circulating volume, altered haemodynamics and interaction of drugs with the polymeric components of

the circuit[4,5]. Hence, doses recommended for the general patient population may not be appropriate to this group of patients. There are two literature reports of oseltamivir PK in ECMO. One report was of seven adult patients, of which three received renal replacement therapy[6]. There is also one report of three children while treated on ECMO[7]. Both studies concluded that ECMO did not appear to influence the PK of oseltamivir carboxylate. However, the limited sample size and the descriptive (non-compartmental modelling) approach to the PK analysis limits the applicability to other ECMO patients.

This study was conducted to investigate the multi-dose PK of oseltamivir and oseltamivir carboxylate in patients undergoing ECMO support and to determine whether target therapeutic concentrations for the treatment of H1N1 infections are being achieved.

MATERIALS AND METHODS

This was a single-centre, prospective, open-label, population PK study of oseltamivir prescribed for critically ill adult patients with suspected or confirmed H1N1 influenza infection, receiving ECMO support during the British winter of 2010. The study was conducted following the guidelines of the Declaration of Helsinki. The study was approved by an independent ethics committee (10/H0406/8) and the United Kingdom Medicines and Healthcare Regulatory Agency. Written informed consent was obtained from the relatives or carers of all patients.

The ECMO circuit consisted of polyvinyl chloride tubing (Tekni-Plex Europe), a centrifugal blood pump (Thoratec® Centrimag® [Thoratec Corporation, Huntingdon, Cambridge, UK]) and a polymethylpentene low-resistance oxygenator (Medos® Hilite® [MEDOS Medizintechnik AG, Stolberg, Germany]). There were no modifications to the treatment received by the ECMO patients. The clinical decision to initiate oseltamivir treatment (or continue from the referring hospital) was undertaken by the attending ECMO clinician.

Once cannulated for veno-venous ECMO, patients were prescribed a dose of 75 mg twice daily of enteral oseltamivir. Each dose was prepared for administration using oseltamivir capsules. The capsules were opened and dissolved in water and administered through a nasogastric tube using an enteral dosing syringe. Concomitant medications were recorded throughout the study duration.

A 2 ml blood sample was obtained from the ECMO circuit or via an indwelling central venous catheter pre-dose and at 30 minutes and one, two, three, five, seven, nine and 12 hours post-dose on day 1 and 5 of ECMO. Since this was a population PK design, a sample at each time point was not insisted upon. Samples were taken when possible, normal clinical duties and procedures permitting. Samples were collected in an EDTA (ethylenediaminetetraacetic acid) or sodium fluoride collection tube. The tube was inverted 8–10 times to ensure the anticoagulant was well mixed with the blood. Samples were then centrifuged at 4°C and 1500 g for ten minutes. The supernatant plasma was transferred to a storage tube, before storing at -20°C prior to analysis.

Samples were analysed at PRA International Laboratories in the Netherlands using a highly sensitive and robust LC/MS/MS (liquid chromatography/mass spectrometry and liquid chromatography/tandem mass spectrometry) method that was developed and validated for the routine determination of oseltamivir and oseltamivir carboxylate. The lower limit of quantification was 1.0 ng/ml with a calibration range of 250 ng/ml or less for oseltamivir. The lower limit of quantification was 10.0 ng/ml with a calibration range of 10,000 ng/ml or less for oseltamivir carboxylate.

Pharmacokinetic analysis

A population PK approach was applied to the analysis of the data, wherein all data from different individuals are fitted simultaneously using non-linear, mixed effect models. All model fittings and simulations were performed using NONMEM v7.2 software (Icon Development Solutions, Hanover, Maryland, USA), and the chosen algorithm was first conditional estimation method with interaction. Post processing of NONMEM output was undertaken with the statistical package, R v2.13.0.

Non-linear mixed models take the general form of: $y=f(x;b)=b0+b0*b1*x1+\ldots$, where the x is the vector of independent variables and b is the vector of model parameters. By definition, the model parameters are either fixed (theta [θ]) or random (eta [η] and epsilon [ε]) effects.

Between patient variation

The first random effect component (η) is 'between patient' variation (assumed to be log-normally distributed) and this estimate quantifies the amount of 'biological variation' associated with each of the fixed effect parameters.

Between occasion variation

Since samples were taken on two separate days (day 1 and 5), the variability within one individual between the sampling occasions ('between occasion' variation) was also estimated: $LnCLi=\theta CL+\eta CL+\eta_q CL$, where LnCli is the log-normal clearance in the ith individual, θCL is the population mean, ηCL is the 'between patient' variability and $\eta_q CL$ is the additional 'between occasion' variability.

Within patient variation

The second random component (ε) is 'within patient' variability (assumed to be normally distributed) and this estimate quantifies the amount of residual error or outstanding unexplained statistical 'noise'. The models used here investigated both additive and proportional error structures.

Covariate analysis

The contribution of covariates on the model's ability to describe the observed data was evaluated next. Scatter plots of covariates versus individual Bayesian parameter estimates were examined to detect biologically plausible patient factors that could influence estimation of PK parameters. Continuous (bodyweight, age, serum creatinine and creatinine clearance) and discrete (sex, continuous veno-venous haemofiltration and enteral/parenteral feeding) variables were added to the population PK model as power and linear functions respectively. Subsequent analyses involved backward selection of covariates by removing each in turn from the model and evaluating the influence on the model fit. Only significant covariates were to be retained in the final selected model. For example, with the first conditional estimation method algorithm, the objective function (-2×log likelihood) details the amount of variation explained in the model. If there is an increase of more than 7.88 when two models are compared, then this will be considered to be a statistically significant (P <0.005) and relevant change. However, other selection criteria were also taken into consideration when evaluating models and graphical methods, such as diagnostic goodness-of-fit plots, which might indicate potential biasing problems with particular models.

TABLE 1
Basic patient demography

Number of patients	14
Age, years (mean±SD)	38.8±7.42
Weight, kg (mean±SD)	97.1±17.0
Sex, male/female	8/6
Serum creatinine, μmol/l (mean±SD)	97.6±64.9
Creatinine clearance, ml/min* (mean±SD)	146±75.0
Number of patients receiving CVVH	4
Number of blood samples (range)	13.3 (6–16)
Early withdrawal, patients	2
Primary reason for withdrawal	Decannulation from ECMO

* Calculated using serum creatinine and the Modified Jelliffe Formula[9]. SD=standard deviation, CVVH=continuous veno-venous haemofiltration, ECMO=extracorporeal membrane oxygenation.

After selection of the most appropriate covariate model, a final assessment of model was undertaken using visual predictive checks (VPC). The VPC is a model diagnostic that allows comparison between alternative models, which can suggest model improvements and support model appropriateness[8]. The VPC is constructed from stochastic simulations from the model and therefore all model components (fixed and random effects) contribute. For this investigation, the final covariate model was used to simulate 2000 times the predicted plasma concentrations of both oseltamivir and oseltamivir carboxylate according to original design of the study. Based on these simulations, percentiles of the simulated and observed plasma concentration data were plotted versus time to aid comparison of predictions with observations.

RESULTS

A total of 14 patients aged from 27–57 years provided blood samples at protocol-specified sampling times following dosing with oseltamivir phosphate 75 mg twice daily (Table 1). All patients were defined as suspected or confirmed H1N1-associated respiratory failure. One patient was 27 weeks pregnant at the time of cannulation, one patient had an emergency caesarean-section just prior to admission to the ECMO unit and one patient had bronchial asthma. The remaining subjects had no known associated risk factors, comorbidities or significant medical histories.

A total of 186 samples were available for evaluation of the PK profiles for oseltamivir and oseltamivir carboxylate on day 1 and 5 of ECMO. The blood samples were obtained from baseline (pre-dose) up

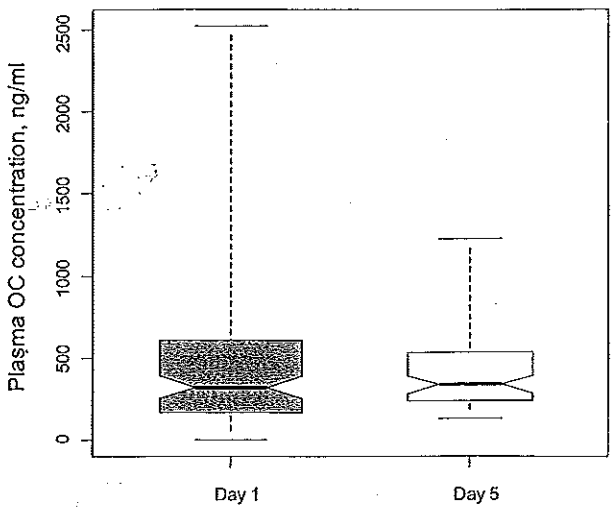

FIGURE 1: Box plot showing distribution of plasma oseltamivir carboxylate (OC) concentrations on day 1 and 5 of extracorporeal membrane oxygenation. The middle black line is the median, the lower and upper bounds of the box are the 25th and 75th percentiles, respectively, and the whiskers cover the range of observed values.

to 13 hours post-dosing. The mean (range) number of samples were 13.3 (6–16). Two subjects provided blood samples on day 1 only, a consequence of early decannulation from ECMO. Figure 1 summarises the oseltamivir carboxylate observations for day 1 and 5 of ECMO.

The structural PK model for oseltamivir and oseltamivir carboxylate was developed as a single integral multi-compartmental model, similar to that reported by Rayner et al in 2008[10]. The parent oseltamivir (prodrug) is rapidly hydrolysed by liver and gut esterases, so that following oral dosing the majority of the dose reaches the systemic circulation as oseltamivir carboxylate (active drug). Thus, the best structural model was one that encompassed first order drug absorption from the dosing compartment with a fraction F absorbed as the parent and a fraction 1-F absorbed as the metabolite. The latter accounted for first pass metabolism of oseltamivir to oseltamivir carboxylate. The oseltamivir profile was described using a two-compartment model with elimination to oseltamivir carboxylate. A metabolism compartment was introduced to account for the delay in the disappearance of oseltamivir and the reappearance of the molecule as oseltamivir carboxylate in the systemic circulation. The disposition of oseltamivir carboxylate was best described using a one-compartment model (Figure 2).

A number of assumptions were made during model development. First, since esterases are ubiquitous in the human body, and in literature reports less than 5% of oseltamivir has been recovered in urine, it was assumed in the model that oseltamivir is fully converted to oseltamivir carboxylate (i.e. no clearance of unchanged drug). Second, since only one parameter

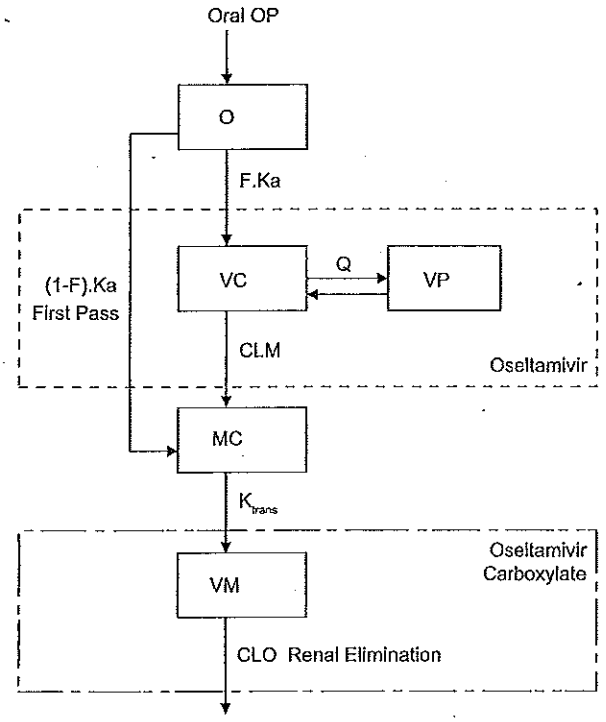

FIGURE 2: Structural pharmacokinetic model. Dose is the oral dose of oseltamivir phosphate (OP) administered. O is the parent drug (oseltamivir) available for absorption in the gut. Ka is the first order absorption rate constant. F is the fraction of parent drug escaping first pass metabolism and hence absorbed into the systemic circulation. 1-F is the fraction of parent drug undergoing first pass metabolism. VC and VP are parameters describing the central and peripheral volume of distribution of oseltamivir while VM is the volume of distribution parameter for oseltamivir carboxylate. CLM is the clearance of oseltamivir to oseltamivir carboxylate. Q is the intercompartmental clearance of oseltamivir. CLO is the renal clearance of oseltamivir carboxylate. MC is the metabolic compartment and Ktrans is the first order rate constant for transit of oseltamivir carboxylate.

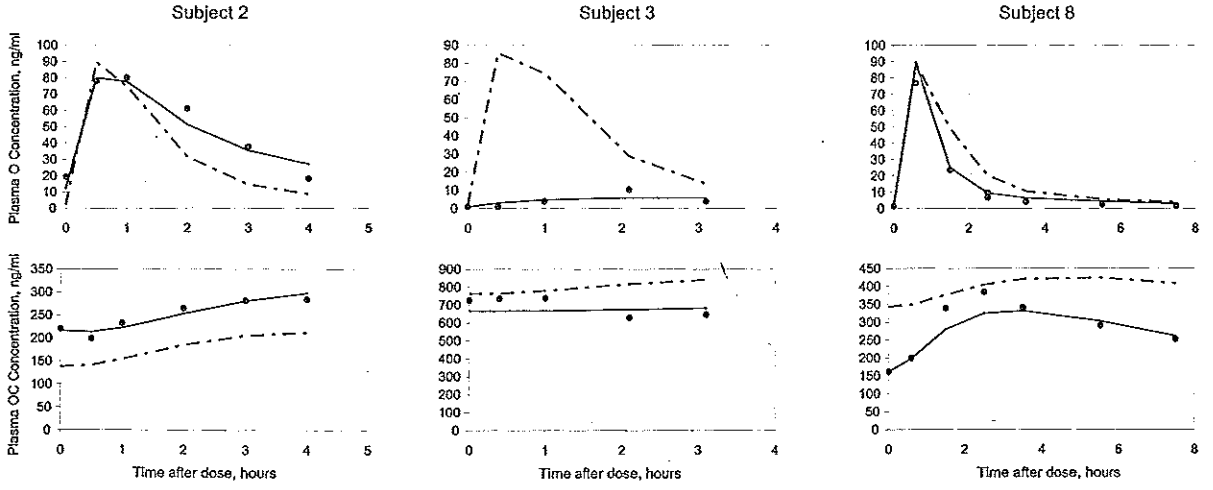

FIGURE 3: Selected individual subject model fits to oseltamivir (upper panel) and oseltamivir carboxylate (lower panel) on day 5 of ECMO. Filled circles are actual observed values, continuous line is the model fit according to the individual subject's empirical Bayes estimates of pharmacokinetic parameters, broken line is the model fit according to the population parameters estimates. OC=oseltamivir carboxylate, O=oseltamivir.

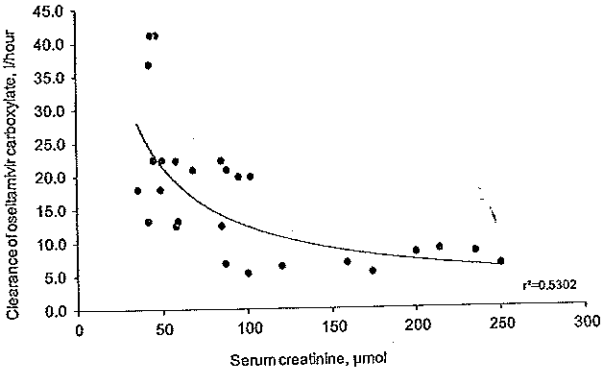

FIGURE 4: Plot to show the relationship between plasma clearance of the active metabolite, oseltamivir carboxylate and serum creatinine.

of either the fraction of parent drug escaping first pass metabolism (F) or central volume of distribution of oseltamivir (VC) / volume of distribution parameter for oseltamivir carboxylate (VM) is identifiable in the model, it was decided to fix F to 0.25 in the model, based on previous literature reports[10,11]. That is to say, the model assumed that 75% of the absorbed dose underwent first pass metabolism to the metabolite (oseltamivir carboxylate) and 25% was absorbed as unchanged drug, oseltamivir[10,11].

The covariate analysis clearly suggested a correlation of metabolite clearance with creatinine clearance and serum creatinine, but correlation with other covariates was not shown. In the final covariate model, serum creatinine was preferred to creatinine clearance since, as well as decreasing the maximum likelihood

TABLE 2

.Population pharmacokinetics parameters from the final covariate model

Population PK parameters (n=14)*	Mean	BSV (%)†	BOV (%)
Oseltamivir			
KA (per h)	1.39 (12.3)	15.6 (195)	
VC (l)	59.7 (7.4)	94.6 (40.6)	88.9 (30.7)
CLM (l/h)	97.5 (4.3)	69.9 (37.4)	
Q (l/h)	42.1 (10.7)	129 (46.1)	
VP (l)	176 (4.7)	64.7 (56.1)	
Bioavailability	0.25 fixed	NE	
Alpha half-life (h)‡	0.19 (0.03–0.49)	NE	
Beta half-life (h)‡	4.27 (1.63–21.2)	NE	
Oseltamivir carboxylate			
VM (l)	350 (3.94)	37.9 (81.9)	117.4 (26.8)
CLO (l/h)**	1274 (12.8) × $SCR^{-1.03}$	34.8 (45.0)	
K_{trans} (metabolic compartment)††,‡‡	0.46 (56.0)	68.4 (106)	
Bioavailability	0.75 fixed	NE	
Half-life (h)‡	7.71 (2.48–53.7)	NE	
Residual error models	Oseltamivir	Oseltamivir Carboxylate	
Additive error (ng/ml)	0.24 (261)	57.6 (40.2)	
Proportional error (% CV)	0.32 (14.7)	0.05 (13.6)	

* All figures in parentheses are parameter precision and are expressed as percent relative standard error (100% × standard error / parameter estimate), † BSV / BOV = variance^{½} × 100%, ‡ Derived from each individual's empirical Bayes estimates of model parameters, ** serum creatinine (µmol/l), †† First order rate constants for transit from metabolic compartment, ‡‡ Mean transit times (h) = (n+1) / K_{trans} = 4.3 h. PK=pharmacokinetics, BSV=between subject variability, BOV=between occasion variability, KA=first order absorption rate constant, h=hours, VC=central volume of distribution of oseltamivir, l=litres, CLM=clearance of oseltamivir to oseltamivir carboxylate, Q=intercompartmental clearance of oseltamivir, VP=peripheral volume of distribution of oseltamivir, NE=not estimated, VM=volume of distribution parameter for oseltamivir carboxylate, CLO=clearance of oseltamivir carboxylate, SCR=serum creatinine, K_{trans}=first order rate constant for transit from metabolic comparment, CV=coefficient of variation.

objective function value (>7.88 [P <0.005)]), the model converged without difficulties and parameter estimates were precise (i.e. 95% confidence intervals did not include zero). The goodness-of-fit diagnostic plots for the final covariate model showed no apparent bias, suggesting that the model was adequate in describing parent and metabolite plasma profiles in the study population. Selected individual subject fits are shown in Figure 3. The population predictions of both oseltamivir and oseltamivir carboxylate plasma concentrations (derived from the population parameter estimates) are not always good and reflect large unaccounted variability. Figure 4 shows that the plasma clearance of oseltamivir carboxylate decreases by >50% when serum creatinine increases to >150 μmol/l. The PK parameter estimates from the final selected PK model are summarised in Table 2.

The VPC plots for oseltamivir and oseltamivir carboxylate (Figure 5) show that overall, the predicted median, 5th and 95th percentiles 'capture and envelope' the observed data for both analytes reasonably well, suggesting model appropriateness.

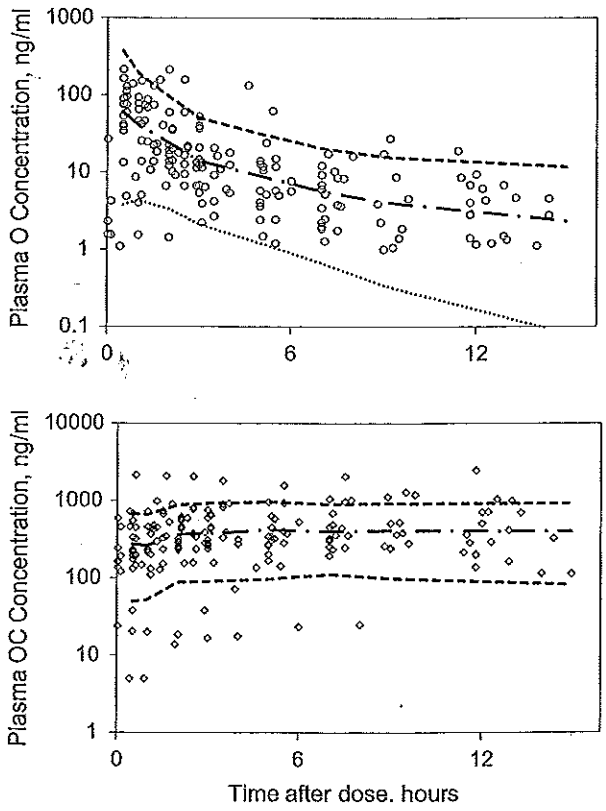

FIGURE 5: Visual predictive plots of the final covariate model describing the structure and variability of the pharmacokinetics of oseltamivir (upper panel) and oseltamivir carboxylate (lower panel) on day 5 of ECMO. The median, 5th and 95th percentile of the predictions from 2000 simulations are overlaid on the actual observed values (open circles and diamonds). OC=oseltamivir carboxylate, O=oseltamivir.

However, very high plasma oseltamivir carboxylate concentrations were observed with one subject on day 1 of ECMO, which appears to be an outlier and is not explained by the model. This subject had 48 hours pre-ECMO exposure to oseltamivir and was admitted with severe renal dysfunction. Data on renal function prior to ECMO was not available and therefore the estimate of variability of oseltamivir carboxylate PK parameters during ECMO may be underestimated and imprecise.

The median (range) terminal half-life of the parent oseltamivir and metabolite oseltamivir carboxylate displayed substantial 'between subject' variability, 4.3 (1.6–21.2) and 7.7 (2.5–53.7) hours respectively (Table 2). Systemic exposure to oseltamivir carboxylate also reveals substantial variability; median (range) area under the curve (AUC), C_{max} and C_{min} on day 5 of ECMO were 4346 (644–13660) ng/hour/ml, 509 (54–1277) and 322 (146–1230) ng/ml, respectively. Both AUC and C_{max} were significantly correlated with serum creatinine (r^2=0.37, P=0.02 and 0.29, P=0.02, respectively) and is explained by the effect of renal function on metabolite clearance in the model, as identified during the covariate analysis.

DISCUSSION

Oseltamivir is the only enterally active treatment against influenza and it is strongly recommended by the World Health Organinization for cases of suspected or confirmed H1N1 infection[12]. The licensed dose of 75 mg twice daily has been shown to achieve plasma concentrations that exceed the 50% maximal inhibitory concentration (IC_{50}) greater than 50-fold for all influenza strains and to be effective in treating uncomplicated acute H1N1 influenza in adults[11,13]. However, the efficacy and safety of this dose has not been evaluated in critically ill patients on ECMO support. It has previously been reported that ECMO can alter PK as a consequence of altered circulation and sequestration of drugs by circuit tubing and the oxygenator[4,5]. The situation is hugely complex with the interplay of many physiological and physico-chemical factors. Hence, to properly understand the disposition of a given drug during ECMO and the clinical factors that influence key parameters, such as clearance, requires PK investigations.

In this study, plasma concentration time profile data for oseltamivir and oseltamivir carboxylate was collected from 14 ECMO adult patients revealing considerable variability in systemic exposure. The median T_{max} for oseltamivir carboxylate on day 5 of ECMO was 4.5 hours, not too dissimilar to that

TABLE 3
Comparison of systemic oseltamivir carboxylate exposure following twice daily dosing

	Ambulatory adults*		ECMO (median values)		
Dose	Day 7 C_{max} (ng/ml)	Day 7 AUC (ng/h/ml)	Day 5 C_{min} (ng/ml)	Day 5 C_{max} (ng/ml)	Day 5 AUC (ng/h/ml)
75 mg†	335	2976	322	509	4346
150 mg‡	786	6229			

* Similar active metabolite profiles have been observed following administration of oral oseltamivir in healthy volunteers and patients with experimentally induced or naturally acquired influenza[11]. † Midpoint of mean exposure following 50 and 100 mg dose[11]. ‡ Midpoint of mean exposure following 100 and 200 mg dose[11]. ECMO=extracorporeal membrane oxygenation, AUC=area under the curve.

reported in healthy volunteers following multiple oral doses (2.7–3.9 hours)[11]. However, a wide range was observed in this study (2.5–9 hours) suggesting delayed oseltamivir absorption following nasogastric administration in some subjects.

Renal function was found to significantly influence the elimination clearance of the active metabolite, oseltamivir carboxylate. This is not surprising since oseltamivir carboxylate is not further metabolised but eliminated entirely by renal excretion[3,11]. The population mean clearance of oseltamivir carboxylate for a patient with a normal serum creatinine of 88 μmol/l was 15.8 l/hour, lower than the previously reported value of 21.5 l/hour in healthy adult subjects[10]. Irrespective, both these values exceed glomerular filtration rate (7.5 l/hour), indicating that tubular secretion occurs in addition to glomerular filtration.

The median steady state volume of distribution of oseltamivir carboxylate was significantly greater than previously reported following intravenous administration in healthy adult volunteers (179 vs 26 litres)[11]. Lemaitre et al reported a mean volume of distribution in seven ECMO patients as 72 litres[6]. Similar to the present study, Ariano et al estimated the median volume of distribution of oseltamivir carboxylate in critically ill adult patients with normal renal function to be 148 litres[14].

The substantial variability in clearance and volume of distribution for both parent drug and metabolite largely reflect the underlying variability in oral bioavailability in this population. Impaired drug absorption in critically ill and septic shock patients as a consequence of decreased gut motility, impaired gut perfusion and oedema of the bowel wall has previously been reported[15]. In addition, the considerably larger estimated steady state volume of distribution in this study population may also be a reflection of their critically ill nature. Critical illness has previously been shown to inflate the volume of distribution of antibiotics as a consequence of oedema, capillary leak syndrome and third spacing[16,17]. Furthermore, the ECMO circuit will necessarily expand the circulating volume.

Table 3 shows a comparison of the AUC and C_{max} values of the active metabolite observed in phase III influenza field trials and healthy volunteers with those observed in ECMO adult subjects. The IC_{50} of oseltamivir carboxylate for the pandemic H1N1 viruses has been reported by laboratories within the range 0.09–0.19 ng/ml[14,18].

The minimum oseltamivir carboxylate plasma concentrations estimated in this study population are 1000 to 4000-fold higher than the IC_{50} for H1N1. In addition, a dose of 75 mg twice daily results in mean systemic exposures on day 5 of ECMO that are in excess of non-ECMO patients and healthy volunteers. This is as a consequence of reduced renal elimination of the active metabolite in ECMO patients as discussed above and therefore suggests that a dose of 75 mg twice daily provides therapeutic levels. However, it should be noted that there is considerable unaccounted 'between subject' variability in both the AUC and C_{max} in critically ill ECMO patients. It may be prudent to increase the dose in subjects where enteral absorption maybe sub-optimal.

In conclusion, mean systemic exposure of oseltamivir carboxylate following the oral administration of 75 mg twice daily in ECMO adult patients is comparable to that of ambulatory patients and is far in excess of the concentrations required to maximally inhibit neuraminidase activity of the H1N1 virus. Therefore, dosage adjustment for ECMO, per se, is not necessary, although it may be necessary to increase doses in individuals with impaired enteral absorption. Finally, as revealed in other patient populations, doses ought to be reduced in those patients with renal dysfunction.

AKNOWLEDGEMENTS

We acknowledge the help of all ECMO nurses and specialists who helped in the collection of pharmacokinetic blood samples for this study.

FINANCIAL SUPPORT

This work was supported, in part, by Roche (bioanalysis and other laboratory costs). Roche had no role in the design, data collection, analysis or reporting of this study. No other specific funding was received to support this study.

REFERENCES

1. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest 2012; 122:2731-2740.
2. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). JAMA 2011; 306:1659-1668.
3. Davies BE. Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations. J Antimicrob Chemother 2010; 65:ii5-ii10.
4. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care 2012; 27:741.e9-741.e18.
5. Mulla H, Lawson G, Firmin RK, Upton DR. Drug disposition during extracorporeal membrane oxygenation (ECMO). Paediatr Perinat Drug Ther 2001; 4:109-120.
6. Lemaitre F, Luyt CE, Roullet-Renoleau F, Nieszkowska A, Zahr N, Corvol E et al. Impact of extracorporeal membrane oxygenation and continuous venovenous hemodiafiltration on the pharmacokinetics of oseltamivir carboxylate in critically ill patients with pandemic (H1N1) influenza. Ther Drug Monit 2012; 34:171-175.
7. Wildschut ED, de Hoog M, Ahsman MJ, Tibboel D, Osterhaus AD, Fraaij PL. Plasma concentrations of oseltamivir and oseltamivir carboxylate in critically ill children on extracorporeal membrane oxygenation support. PLoS One 2010; 5:e10938.
8. Karlsson MO, Holford N. A tutorial on visual predictive checks. PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe 2008; 17:1434. From www.page-meeting.org/?abstract=1434.
9. Bouchard J, Macedo E, Soroko S, Chertow GM, Himmelfarb J, Ikizler TA et al. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. Nephrol Dial Transplant 2010; 25:102-107.
10. Rayner CR, Chanu P, Gieschke R, Boak LM, Jonsson EN. Population pharmacokinetics of oseltamivir when coadministered with probenecid. J Clin Pharmacol 2008; 48:935-947.
11. 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.
12. WHO guidelines for pharmacologic management of pandemic (H1N1) 2009 influenza and other influenza viruses. World Health Organization 2009. From www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en.
13. Dutkowski R. Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients. J Antimicrob Chemother 2010; 65:ii11-ii24.
14. Ariano RE, Sitar DS, Zelenitsky SA, Zarychanski R, Pisipati A, Ahern S et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 2010; 182:357-363.
15. Power BM, Forbes AM, van Heerden PV, Ilett KF. Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet 1998; 34:25-56.
16. Mehrotra R, De Gaudio R, Palazzo M. Antibiotic pharmacokinetic and pharmacodynamic considerations in critical illness. Intensive Care Med 2004; 30:2145-5216.
17. Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 2011; 15:R206.
18. Hall RJ, Peacey MP, Ralston JC, Bocacao J, Ziki M, Gunn W et al. Pandemic influenza A (H1N1)v viruses currently circulating in New Zealand are sensitive to oseltamivir. Euro Surveill 2009; 14:19282.