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Route of Oseltamivir Administration Affects Metabolite Concentrations in Critically Ill Children

Sonya C. Tang Girdwood, MD, PhD[a,b,*], **Tomoyuki Mizuno, PhD**[b,d], **Kelli A. Krallman, MS**[c], **Laura A. Benken, MBA**[c], **Erin M. Stoneman**[c], **Toni M. Yunger**[c], **Hector R. Wong, MD**[c,d], **Alexander A. Vinks, PharmD, PhD**[b,d], **Jennifer M. Kaplan, MD, MS**[c,d]

[a]Division of Hospital Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

[b]Division of Clinical Pharmacology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

[c]Division of Critical Care Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

[d]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, United States

Keywords

Oseltamivir; Influenza; Pharmacokinetics; Enteric tube versus oral; Critically Ill

Introduction

Hundreds of influenza-associated pediatric deaths are reported annually, with children under the age of two at the highest risk of mortality [1]. Four medications are approved for influenza treatment but for children under the age of two, oseltamivir is the only approved drug [2]. Oseltamivir is a prodrug of its active form, oseltamivir carboxylate (OC) [3].

Since oseltamivir can only be administered enterally, a nasogastric (NG) tube is used for those unable to take medications orally. Alternatively, it can be delivered through pre-existing enteric tubes in patients with medical complexity, a significant proportion of children hospitalized for influenza [4]. Pharmacokinetic (PK) studies of oseltamivir administered through NG tubes in critically ill children have had varying results; OC exposure has been reported to be higher and lower when compared to previous studies in children who took oseltamivir orally [5, 6]. Since pediatric influenza deaths often occur within 7 days of symptom onset, adequate OC concentrations early in illness are critical [1]. No study has directly compared, in the same cohort of critically ill children, oseltamivir and OC concentrations between oral and enteric tube administration. Therefore, we designed a prospective cohort study to investigate the effects of route administration of oseltamivir on

[*]Address correspondence to Sonya Tang Girdwood, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 9016, Cincinnati, OH 45229 Sonya.Tanggirdwood@cchmc.org.

plasma concentrations in critically ill children with suspected influenza. We hypothesized patients who require oseltamivir administration through an enteric tube would have significantly different concentrations that may be subtherapeutic or potentially toxic.

Materials and Methods

Study Design

We performed a prospective cohort study in critically ill children admitted to the Pediatric Intensive Care Unit (PICU) at Cincinnati Children's Hospital Medical Center (CCHMC). The study was approved by the CCHMC Institutional Review Board and conducted between January 2015 and March 2016 (two influenza seasons). All patients older than 2 weeks of age who were admitted to the PICU and prescribed oseltamivir for suspected or confirmed influenza were eligible for the study, regardless of reason for admission. Legal authorized representatives of patients older were approached for consent (see Text, Supplemental Digital Content 1).

PK Sample Collection

The clinical team determined oseltamivir dosing, treatment length and administration route based on patient clinical status. Clinical dosing was based off the FDA label as follows (Table 1): ages 2 weeks to 1 year: 3 mg/kg twice daily; ages 1 to 12 years: <15 kg or less: 30 mg twice daily; 15.1–23 kg: 45 mg twice daily; 23.1–40 kg: 60 mg twice daily; 40.1 kg or more: 75 mg twice daily; ages > 12 years: 75 mg twice daily. The formulations used were either suspension or capsule. Each subject used the same formulation throughout their treatment duration.

The enteric tube cohort included patients with NG tubes placed during the index hospitalization or pre-existing enteric tubes (e.g. G or GJ tubes). During the first influenza season (January-June 2015), PK samples were collected before and after *the first oseltamivir dose*. Sparse PK sampling was done (see Figure, Supplemental Digital Content 2). Several patients received oseltamivir prior to consent, and therefore samples from early time points were not obtained. Based on missed blood sampling opportunities, we modified the protocol for the second influenza season (January – March 2016) to obtain complete patient PK sampling. For the second season we collected PK samples before and after *the first dose after consent* was obtained (see Figure, Supplemental Digital Content 2).

Measurement of Drug and Metabolite Concentrations

Oseltamivir and OC concentrations were measured using a validated liquid chromatography-tandem mass spectrometry assay by BASi, Inc (West Lafayette, IN). Measured oseltamivir and OC concentrations were compared to PK model-based predictions using the oseltamivir population PK model developed with concentrations in pediatric, adult and geriatric patients by Kamal et al [7].

Clinical Data Collection

Clinical data were collected during the study, including time on supplemental oxygen and number of ventilator days (see Text, Supplemental Digital Content 1).

Pharmacokinetic Modeling to Estimate PK parameters

PK analysis was performed with MWPharm (Mediware, Prague, Czech Republic) [8] using an oseltamivir population PK model [7] and Bayesian estimation for patients with complete PK sampling. Maximum concentration (C_{max}) and area under the concentration-time curve for 12 hours post-dose ($AUC_{0–12hr}$) were estimated and compared for patients who took oseltamivir by mouth (PO) versus by enteric tube.

Results

During the first influenza season, six patients were enrolled (see Figure, Supplemental Digital Content 3), of whom only 3 had complete PK sampling (see Figure, Supplemental Digital Content 2). Under the revised protocol in the second season, five subjects had PK sampling obtained. For patients who remained in the PICU on day 4, PK samples were obtained around dose seven. In total, 11 subjects had PK sampling. None of the subjects received oseltamivir prior to hospitalization.

Four and seven patients were in the PO cohort and tube cohort, respectively. The median age of the entire cohort was 7 years (range 0.7–19 years) and 45% of subjects were male (see Table, Supplemental Digital Content 4). There were no group differences in baseline characteristics. Both cohorts had comparable illness severity at time of PICU admission, as demonstrated by pediatric risk of mortality (PRISM) III (6 [0–8] vs. 0 [0–4.5], tube vs. PO, $p = 0.41$) and pediatric logistic organ dysfunction (PELOD) scores (13.3 ± 3.5 vs. 14.3 ± 10, tube vs. PO, $p = 0.82$). No patient had hepatic dysfunction that would affect metabolism of oseltamivir to OC, but one patient (subject 3) did have acute kidney injury (AKI).

Concentrations of Oseltamivir and Metabolite

Dosing route and regimens were determined by clinical teams based on influenza testing results and clinical status (Table 1). For patients who tested negative for influenza, oseltamivir was appropriately discontinued. The measured oseltamivir and OC concentrations obtained on treatment days 1 and 2 were compared with published PK model-based predictions [7] (Fig. 1A). Within the PO group, 91% (10/11) of measurable oseltamivir concentrations were within the 90% prediction interval of the model. In contrast, only 47% (9/19) of oseltamivir concentrations measured in enteric tube patients were within this range, with 42% (8/19) of oseltamivir concentrations falling below the predicted 5^{th} percentile. For the metabolite, 92% (12/13) of measured OC concentrations were within the 90% prediction interval in the PO group compared to 47% (8/17) in the enteric tube group. The one measured OC concentration above the 95^{th} percentile is from subject 3 in the PO group who had AKI. No measured OC concentration in the PO group was below the predicted 5^{th} percentile compared to 53% (9/17) of OC concentrations in the tube group.

Pharmacokinetic Analysis

When comparing the PO and enteric tube patients who had sufficient samples for PK modeling, and thus did not include the patient with AKI, there were no significant differences in oseltamivir C_{max} or $AUC_{0–12hr}$ despite differences in concentrations as described above. On days 1 and 2, the C_{max} and $AUC_{0–12hr}$ estimates of OC were

significantly lower in the enteric tube group (109±80 ng/mL and 1,036±824 hr*ng/ml, respectively) compared with the PO group (360±92 ng/mL and 3,122±523 hr*ng/ml, $p<0.05$) (Fig. 1B). The OC $AUC_{0–12hr}$ for the enteric tube group was below the suggested target range of 2,000–8,000 hr*ng/mL, defined by previous pediatric studies [9]. By day 4, OC C_{max} and $AUC_{0–12hr}$ in the enteric tube group increased significantly (448±144 ng/mL and 4,501±1,393 hr*ng/ml) and were comparable with those in the PO group on days 1–2.

Clinical Outcomes

Enteric tube patients required supplemental oxygen for statistically significant longer time compared to PO patients (median 190 hr [range 92–1524] versus 33 hr [range 6.5–105]). There was a higher percentage of patients who required mechanical ventilation or non-invasive positive pressure ventilation in the enteric tube group versus PO group (86% vs 25%, $p=0.09$).

Discussion

This is the first study, to our knowledge, directly comparing the two routes of oseltamivir administration prospectively in critically ill pediatric patients. Within our cohort, we found that oseltamivir delivered by enteric tube resulted in lower concentrations and exposure ($AUC_{0–12hr}$) to the active metabolite OC in the first two treatment days. Previously published oseltamivir PK data in critically ill children on extracorporeal membrane oxygenation (ECMO) support requiring enteric tube administration have reported lower than expected metabolite concentrations as well [6]. The authors concluded that ECMO does not appear to affect oseltamivir PK but instead NG administration and gastric dysmotility may have significant influence on OC concentrations. Among critically ill children with influenza, treatment with a neuraminidase inhibitor within 48 hours of illness onset is significantly associated with survival [10]. If patients receiving oseltamivir by enteric tube are not achieving metabolite concentrations as expected in the first 48 hours, they may be at risk of higher mortality.

There are several potential reasons for the pharmacokinetic differences between the two groups in our study. We initially hypothesized that patients who receive enteric tube administration would have higher acuity of critical illness. If patients with enteric tubes were more severely ill, they may have decreased absorption or poor motility from gastroparesis leading to delayed absorption. We found no statistically significant difference between illness severity scores in our groups in contrast to our hypothesis. Our inability to show statistical significance in severity scores may reflect the small study sample size.

We found no difference in the C_{max} and $AUC_{0–12hr}$ of the prodrug, oseltamivir, but lower exposures to the metabolite, suggesting differences in drug metabolism. Oseltamivir is hydrolyzed by carboxylesterases into OC. It is known that proinflammatory cytokines, such as interleukin-6, reduce expression and activity of carboxylesterases [11]. Patients in the tube group may have higher inflammatory mediators leading to reduced metabolite conversion, and thus lower plasma OC concentrations. However, this was not evaluated in the current study.

The drug could have adsorbed to the enteric tubes, which were made of different materials (silicone for G/J tubes, polyurethane for NG tubes). However, with a low $P_{octanol/water}$ [12], oseltamivir is not highly lipophilic and would not be expected to adsorb to enteric tubes in significant quantities.

There are several limitations of this study. First, we grouped patients with NG tubes newly placed during the hospitalization of interest and those with pre-existing G-tubes into the same cohort. Patients with G-tubes likely have chronic medical conditions that could contribute to delayed motility or altered drug absorption. In addition, different formulations of oseltamivir were used. All enteric tube patients received oseltamivir as a suspension, but half of PO patients received oseltamivir as an intact capsule. Finally, the small number of patients enrolled in this study is an additional limitation.

Understanding the mechanisms causing the differences in pharmacokinetics between the oral and enteric tube cohorts is critical. Further studies are warranted to validate these findings in a larger cohort of patients, especially to distinguish possible differences between delivery through a newly placed NG tube or through a pre-existing enteric tube. Clinicians should be aware of possible under-dosing of oseltamivir in critically ill children when an enteric tube is used.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Sources of support:

Dr. Kaplan reports financial support to the institution (Cincinnati Children's Hospital Medical Center [CCHMC]) for work on a DSMB of a clinical trial (Eli Lilly) not related in any way to the work in the manuscript. Dr. Wong and the institution, CCHMC, hold patents for sepsis-related biomarkers. All remaining authors report no conflict of interest.

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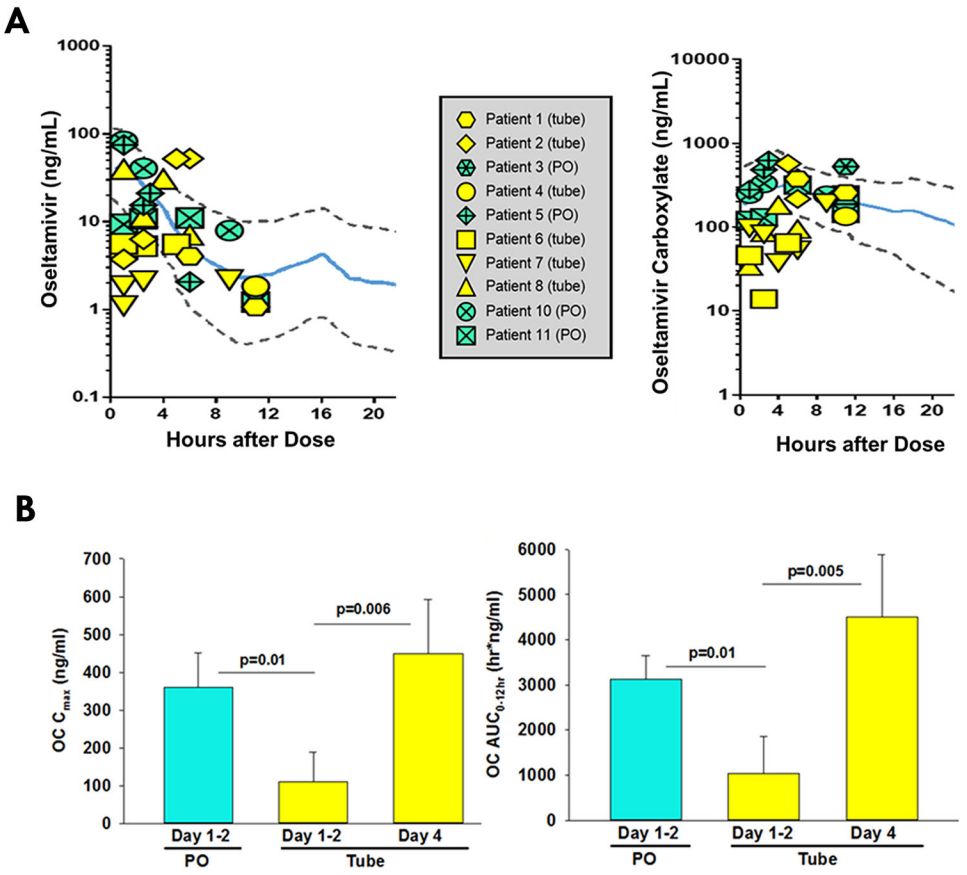

Figure 1:

(A) Comparison of measured oseltamivir (left) and metabolite (right) concentrations to the oseltamivir PK prediction model by Kamal et al. [7]. Measured concentrations of oseltamivir and its active metabolite, oseltamivir carboxylate, for our study population were superimposed onto the median (solid blue lines) and 90% prediction interval (area between dashed lines) of an oseltamivir pharmacokinetic model based on data from pediatric, adult and geriatric patients. (Amended with permission from American Society for Microbiology)

(B) Comparison of estimated mean C_{max} and $AUC_{0–12hr}$ of OC metabolite between PO and tube groups. (Left) C_{max} of OC and (right) $AUC_{0–12hr}$ of OC. The p values compare the means between the two groups. PO = oral administration. Tube = enteric tube administration. C_{max} = estimated maximum concentration. AUC = estimated Area Under the Curve. Statistical significance defined as $p \leq 0.05$ using student's t-test.

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Table 1:

Dosing information and diagnoses for enrolled subjects.

PO = oral administration. Tube = enteric tube administration.

NG = nasogastric; G = gastric; GJ = gastrojejunal; RSV = respiratory syncytial virus

Patient and Dosing Characteristics										
Subject # (based on enrollment order)	**Age (yrs)**	**Weight (kg)**	**Reason for PICU admission**	**Influenza Testing result/ Other infectious diagnosis**	**Route (Tube [NG, G,GJ]/PO)**	**Formulation**	**Day of Oseltamivir when PK sampling done**	**Dosing #**	**Dosage[a] (mg)**	**Food within 2 hours of oseltamivir doses?**
Subjects administered oseltamivir orally (PO)										
3	6	19.5	Uncompensated septic shock	Influenza A	PO	Suspension	1	1	45	No
5	7	25	Respiratory failure[b]	Influenza B	PO	Capsule	1	1	60	No
10	5	15.2	Status asthmaticus	Influenza A	PO	Suspension	2	3	45	No
11	11	64.8	Septic shock, respiratory distress	Negative/Rhinovirus	PO	Capsule	1	2	75	Yes
Subjects administered oseltamivir by enteric tube										
1	6	22	Respiratory failure	Negative/RSV	Tube (GJ)	Suspension	1	1	45	No
2	2	9	Respiratory failure	Negative/RSV	Tube (NG)	Suspension	1	1	30	No
4	8	18.9	Septic shock, hypoxia	Influenza B	Tube (G)	Suspension	1	1	45	No
6	15	46.7	Septic shock, respiratory failure	Influenza B/Haemophilus influenzae, Streptococcus pneumoniae	Tube (G)	Suspension	1	1	78[c]	Yes
							4	7		
7	0.67	9.7	Respiratory failure	Influenza A/RSV	Tube (NG)	Suspension	1	2	30	Yes
							4	8		
8	13	32	Respiratory failure	Influenza A	Tube (G)	Suspension	1	1	60	Yes
							4	7		
9	19	64.5	Septic shock, hemorrhage, respiratory failure	Influenza B/Pseudomonas aeruginosa, Stenotrophomonas, Candida	Tube (NG)	Suspension	4	7	78	No

[a]Dosage recommendations (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf):

Ages 2 weeks – 1 year: 3 mg/kg twice daily

Ages 1–12 years: <15 kg or less: 30 mg twice daily; 15.1–23 kg: 45 mg twice daily; 23.1–40 kg: 60 mg twice daily; 40.1 kg or more: 75 mg twice daily

Ages > 12 years: 75 mg twice daily

[b] Defined as requiring positive pressure ventilation or intubation

[c] Higher dose given due to rounding of volume of suspension