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Short Communication

Pharmacokinetics of zanamivir in critically ill patients undergoing continuous venovenous hemofiltration

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Abstract

Background: Limited data exist for dosing of zanamivir in the setting of CVVH in the intensive care unit (ICU). Our objective is to report the pharmacokinetics and sieving coefficient (S_v) of zanamivir in patients receiving continuous venovenous hemofiltration (CVVH).

Methods: In this prospective observational study, patients of ≥18 years admitted to the ICU with a life-threatening Influenza A or B infection, treated with zanamivir i.v. undergoing CVVH were included. Patients received a zanamivir loading dose of 600 mg i.v., 12 h later followed by maintenance dosages two times daily according to the treating physician. Per patient, nine CFT plasma and nine ultrafiltrate samples were drawn on day 2 of treatment and analysed with a validated HPLC-MS/MS method.

Results: Four patients were included in the study. The zanamivir elimination half-life was prolonged with 5.6–9.9 h, compared to patients with normal renal function. A S_v of approximately 1.0 was identified, with unrestricted transport of zanamivir to the ultrafiltrate.

Conclusions: Zanamivir is well cleared by CVVH. In absence of the possibility for therapeutic drug monitoring, the ultrafiltration rate seems as a good surrogate parameter to estimate the CL_{CVVH} and may help guide the dosing of zanamivir.

Keywords

influenza, antiviral therapy, neuraminidase inhibitor, ICU, sieving coefficient, zanamivir, pharmacokinetics, CRRT

Introduction

In the critically ill patients, zanamivir is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months).[1] Little is known about the pharmacokinetics of zanamivir in patients undergoing

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continuous venovenous hemofiltration (CVVH) and the dosage to be used for optimal treatment in these critically ill patients. Alterations in drug disposition and clearance occur commonly in patients undergoing CVVH and therefore dosing regimens often need adjustments.[2,3]

Zanamivir is eliminated unchanged in urine by glomerular filtration with a half-life of 2–3 h. The plasma protein binding of zanamivir is less than 10% and the volume of distribution (V) of zanamivir in adults is approximately 16 L, which approximates the volume of extracellular water.[1] This makes zanamivir available for clearance by extracorporeal devices, and data are needed to guide dosing in renal replacement therapy.

In patients with normal renal function, the advised dosage is i.v. zanamivir 600 mg b.i.d.[1] In patients with renal failure (glomerular filtration rate <80 mL/min/1.73 m^2), the half-life is increased and dose adjustments are necessary (Table 1).[1] In patients dependent on CVVH, the dose has to be adjusted by the clearance of the CVVH (Table 1).[1] However, the Sieving Coefficient (S_v) in order to calculate CL_{CVVH} is not described in the literature.

Till now, no concentration-response relationship has been established for zanamivir.[4] In vitro models suggest different pharmacodynamic targets for optimal treatment of zanamivir, which should be further elucidated.[4,5] When zanamivir is dosed 600 mg twice daily in patients with normal renal function, it has been shown to distribute to the respiratory mucosa and is protective against infection and disease following experimental human Influenza A inoculation in humans.[6] The objective is therefore to generate an isomorphic zanamivir exposure profile for patients dependent on CVVH compared to patients dosed according to their renal function. A zanamivir $AUC_{0-12\ h}$ of 90–217 μg/mL*h is considered as adequate exposure by Marty et al.[7] Another objective of our study is to report the S_v of zanamivir in order to calculate CL_{CVVH}.

Methods

Participants and procedure

All patients of ≥18 years, admitted to the intensive care unit (ICU) of the Isala Hospital from 2014 to 2019, with life-threatening pulmonary complications due to Influenza A or B infection with different stages of renal function (for example anuria (urine output <100 mL per day), oliguria (urine output <0.5 mL/kg/h), or better renal function) and CVVH therapy.[8] Four patients were included in the analysis (Table 2).

All patients were on invasive ventilation due to respiratory failure because of Influenza A (patient 2, 3, 4) or Influenza B (patient 1) infection. Patients 1 and 3 also had an Aspergillus resp. pneumococcal co-infection.

Patients received a zanamivir loading dose of 600 mg intravenously, 12 h later followed by subsequent maintenance dosages two times daily as prescribed by the treating physician, see Table 2. Zanamivir plasma and ultrafiltrate samples were drawn on day 2 before the start of the next dose (t = 0) and 0.5, 1, 2, 3, 4, 6 and 8 h after the start of the same dose and analysed with a validated HPLC-MS/MS method. A Prismaflex ST150 1.5 m^2 membrane filter was used for CVVH with post-dilution replacement of fluid. All patients were at least 48 h on CVVH therapy with stable conditions before sampling started.

Plasma samples were collected from an indwelling arterial catheter and placed in tubes containing EDTA. Ultrafiltrate samples were collected postfilter. The tubes were stored in the refrigerator, gently mixed and centrifuged for 15 min at 1500 *g* within 30 min of sample collection to obtain plasma and remove cells from the ultrafiltrate. The plasma and ultrafiltrate were transferred to a polypropylene tube, frozen at −80°C and shipped in dry ice to the laboratory of the Erasmus Medical Centre, for analysis.

Plasma zanamivir concentrations were measured after filtration by high-performance liquid chromatography with tandem mass spectrometry, using penciclovir as an internal standard (UPLC-MS/MS Thermo TSQ vantage). The standard curve was linear from 1 to 8 μg/mL, and inter- and intraassay accuracy RSD was <15% with precision coefficient of variation of <15%. Independent quality control samples were used within every run. Concentrations greater than 8 μg/mL were diluted according to defined volumes to obtain values within the linear range. Blood concentrations were then calculated according to the percentage of volume dilution.

Statistical analysis

The AUC, V and half-live value ($T_{1/2}$) were estimated with non-compartmental analysis using PK Solver software, a validated platform for non-compartimental analysis.[9] Total clearance (CL_{total}) was calculated using the ratio of zanamivir maintenance dose/plasma $AUC_{0-12\ h}$. The S_v was calculated in the time paired samples as the ratio of ultrafiltration concentration/plasma concentration. Per patient, the average S_v was calculated for all time paired ratio's. The overall S_v was calculated as the average of the sum of the S_v per patient. The CL_{CVVH} was calculated as the sieving coefficient × ultrafiltration flow rate.[10]

Results

Drug concentrations according to time and pharmacokinetic parameters are graphically displayed in Figure 1. All grouped samples were drawn within 6 min of the first collected sample in the time group. Except for the plasma

Table 1. Initial and maintenance dose regimens for adults according to their renal function according the summary of product characteristics of zanamivir.

CL_{CVVH} (mL/min) or CL_{CR} (mL/min/1.73 m^2)	Initial dose (MG)	Maintenance dose (mg twice DAILY)
>80	600	600
50 to <80	600	400
30 to <50	600	250
15 to <30	600	150
<15	600	60

CL, clearance; CVVH, Continuous venovenous hemofiltration; CR, creatinine.

Table 2. Patient characteristics and pharmacokinetics of zanamivir on day 2 of zanamivir treatment.

	Patient ID			
	1	2	3	4
Sex	M	M	M	F
Age (years)	60	57	48	51
Height (cm)	185	174	174	164
Weight (kg)	87	75	86	68
BMI (kg/m^2)	25.4	24.8	28.5	25.3
APACHE IV	80	134	89	57
SOFA	4	15	9	11
SAPS II	57	75	50	31
ECLS	–	+	+	+
Patient survival	+	+	–	–
Maintenance zanamivir dose (mg twice daily)	600	150	250	400
Urine production (mL/h)	5	44	2	0.5
Urine production (mL/kg/h)	0.05	0.59	0.02	0.01
Ultrafiltrate flow Cvvh (mL/min)	67	50	33	50
Bloodflow CVVH (mL/min)	200	180	160	180
Replacement filter in use CVVH (days)	2	2	2	2
Zanamivir plasma C_{max} (ug/mL)	36	10	25	28
Zanamivir plasma C_{trough} (ug/mL)	5.9	2.4	6.7	7.8
Zanamivir plasma $AUC_{0\text{-}12h}$ (ug/mL*h)	155	52	140	162
Zanamivir dialysate $Auc_{0\text{-}12\ h}$ (ug/mL*h)	149	60	133	177
Cl_{total} (mL/min)	64	48	30	41
CL_{CVVH} (mL/min)	64	53	30	45
V (L)	24	22	14	19
$T_{½}$ (H)	5.6	9.5	8.9	9.9
S_v (C_{uf}/C_p)	1.0	1.1	1.0	1.1

BMI, Body Mass Index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score; ECLS, Extra Corporeal Life Support; CVVH, Continuous venovenous hemofiltration; AUC, Area under the curve; CL, clearance; V, Volume of distribution; T1/2, half-life; Sv, Sieving coefficient; Cuf, Concentration ultrafiltrate; Cp, Concentration plasma.

sample in patient 3 at t = 4, where no plasma sample was obtained. The residual urine output was small in all patients. Three patients were anuric. Patient 2 had the highest severity of illness scores (APACHE IV, SOFA, SAPS II) and had an urine output better than oliguria (0.59 mL/kg/h). The ultrafiltrate rates differed between patients from 33 to 67 mL/min. The filters were functioning for 2 days when the measurements took place, indicating good permeability of the AN69 filter. The non-compartmental analysis revealed that the $AUC_{0–12\ h}$ of patient 2 with 52 μg/mL*h was low. The other patients had a zanamivir $AUC_{0–12\ h}$ between 14 and 162 μg/mL*h. The overall S_v from all four patients was 1.0. The median zanamivir clearance [interquartile range] for the CL_{CVVH} and CL_{total} was

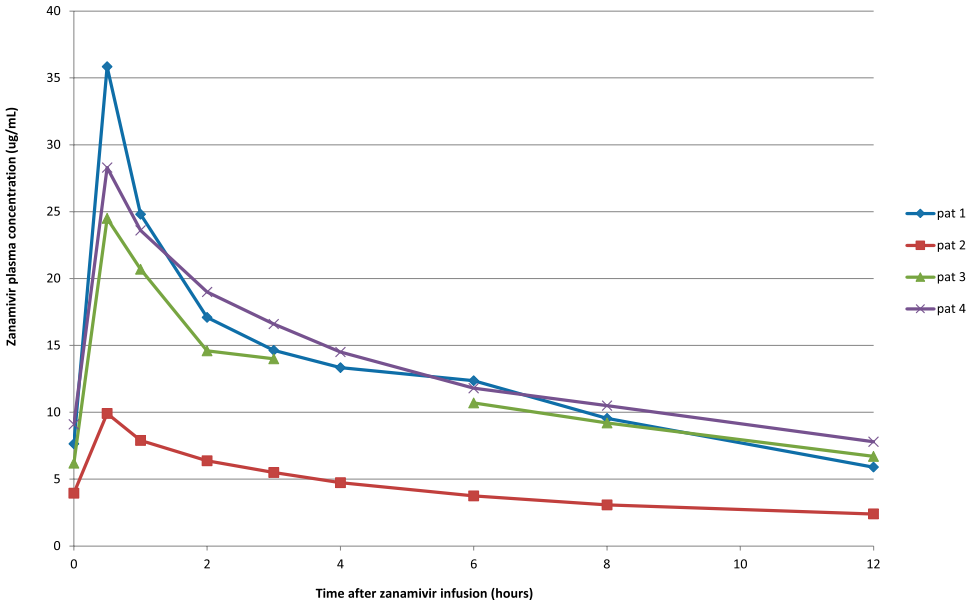

Figure 1. Concentration time curve of zanamivir on day 2 of zanamivir treatment in patients undergoing CVVH.

49 [41–55] mL/min resp. 45 [38–52] mL/min. The zanamivir half-life ranged from 5.6 to 9.9 h.

Discussion

To our knowledge, this is the first study describing pharmacokinetic data on the dosing of zanamivir in critically ill patients on CVVH. The prescribed maintenance dosages of zanamivir were variable probably because of sparse information about the CL_{CVVH} of zanamivir. Our study shows the S_v is 1.0, with unrestricted transport of zanamivir to the ultrafiltrate. Three patients had a small residual renal function ($CL_{renal} \sim 0$ mL/min). Patient 2 had an urinary output better than oliguria, but compared with the CL_{CVVH} the contribution of the CL_{renal} component in the CL_{total} is also small. Therefore, the contribution of the CL_{CVVH} is almost 100% of the CL_{total} in our patients indicating that the ultrafiltrate rate seems as a good estimate parameter to calculate the CL_{CVVH} in patients with small residual renal function. In patients with better residual renal function, the CL_{renal} can have significant impact on the elimination of zanamivir. Subsequently, zanamivir can be dosed with the CL_{CVVH} plus CL_{renal} according to the SPC of zanamivir.[1]

In some patients, higher ultrafiltrate concentrations were measured then blood values. We speculate this is the result of ultrafiltrate samples being drawn structurally as a first sample with further elimination of zanamivir before blood samples were drawn. Also, variation in the analysis of zanamivir values can be an explanation.

Our objective was to generate an isomorphic zanamivir exposure profile for patients on CVVH compared to patients according to renal function. When examining the zanamivir dosing according to the SPC (Table 1) and the ultrafiltrate rate as marker for CL_{CVVH}, patient 1 was prescribed 600 mg b.i.d. instead of 400 mg b.i.d., but the $AUC_{0–12\ h}$ of 155 μg/mL*h was in the range of $AUC_{0–12\ h}$ of 90–217 μg/mL*h as reported by Marty et al., but we speculate that also the lower dose would adequate. Patient 2 was prescribed 150 mg b.i.d instead of 400 mg b.i.d. and may be underdosed with an $AUC_{0–12\ h}$ of 52 μg/mL*h. Patients 3 and 4 were dosed correctly and the $AUC_{0–12\ h}$ was within range.

The estimated plasma half-life of zanamivir we found varied between 5.6 and 9.9 h, which was higher than that reported in patients with normal renal function: 2–3 h.[1] No (common) side effects like hepatotoxicity or rash were seen in the patients.

Our study has some limitations. We studied a small cohort of heterogenous patients, with differences in disease severity, residual renal function, CRRT settings and zanamivir dosages administered to patients. Also, the results have to be used with caution in other forms of continuous renal replacement therapy (e.g. haemodialysis or hemodiafiltration).

Therapeutic drug monitoring (TDM) of zanamivir's AUC may optimise therapy in critically ill patients treated with CVVH in whom pharmacokinetics are highly variable and unpredictable, as illustrated by these four cases. Our study shows a S_v of 1.0 for zanamivir. In absence of the possibility for TDM, the ultrafiltration rate seems as a good surrogate parameter to estimate the CL_{CVVH} and may help guide dosing. Further research is mandatory for optimal

treatment of the critically ill treated with CVVH and zanamivir.

Author contributions

All authors have participated in the conception, design, execution, and/or writing of the manuscript. BCPK and JJH share co-last authorship for supervising the study.

Declaration of conflicting interests

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Ethical approval

Ethical approval was waived for this study from the Research Ethics Committee of the Isala Hospital, Zwolle, the Netherlands, because of the small number and volume of extra bloodsamples, taken from an existing indwelling arterial catheter with no additional risk for the patient.

Informed consent

Informed consent was signed by the first degree family of the patients.

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References

1. GlaxoSmithKline Trading Services Limited. *Summary of product characteristics: zanamivir 200 mg*, https://www.ema.europa.eu/en/documents/product-information/dectova-epar-product-information_en.pdf/2021 (2019, accessed 21 January 2021).
2. Reetze-Bonorden P, Bohler J, Keller E. Drug dosage in patients during continuous renal replacement therapy. Pharmacokinetic and therapeutic considerations. *Clin Pharmacokinet* 1993; **24**(5): 362–379.
3. Joy MS, Matzke GR, Armstrong DK, *et al.* A primer on continuous renal replacement therapy for critically ill patients. *Ann Pharmacother* 1998; **32**(3): 362–375.
4. Zuo P, Collins J, Okour M, *et al.* Population pharmacokinetic/pharmacodynamic analysis of intravenous zanamivir in healthy adults and hospitalized adult and pediatric subjects with influenza. *Clin Transl Sci* 2020; **13**(1): 157–168.
5. Brown AN, Jurgen B., McSharry JJ, *et al.* Effect of half-life on the pharmacodynamic index of zanamivir against influenza virus delineated by a mathematical model. *Antimicrob Agents Chemother* 2011; **55**(4): 1747–1753.
6. Calfee DP, Peng AW, Cass LM, *et al.* Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 1999; **43**(7): 1616–1620.
7. Marty FM, Man CY, Van der Horst C, *et al.* Safety and pharmacokinetics of intravenous zanamivir treatment in hospitalised adults with influenza: an open-label, multicenter, single-arm, phase II study. *J Infect Dis* 2014; **15209**(4): 542–550.
8. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care* 2013; **17**: 204.
9. Zhang Y, Huo M, Zhou J, *et al.* PK solver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in microsoft excel. *Comput Methods Programs Biomed* 2010; **99**(3): 306–312.
10. Scheetz MH, Scarsi KK, Ghossein C, *et al.* Adjustment of antimicrobial dosages for continuous venovenous hemofiltration based on patient-specific information. *Clin Infect Dis* 2006; **142**(3): 436–437.