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Clearance of Lormetazepam, Midazolam, and Their Conjugated Metabolites by Continuous Venovenous Hemofiltration During Prolonged Sedation in Critically Ill Patients With COVID-19-Associated Acute Respiratory Distress Syndrome

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Dear Editor,

Owing to the shortage of sedatives for patients critically ill with coronavirus disease 2019 (COVID-19), we decided to explore the effects of concomitant administration of enteral lormetazepam in addition to midazolam. However, prolonged sedation during renal failure and renal replacement therapy may lead to the accumulation of conjugated metabolites of lormetazepam and midazolam, and these metabolites may have substantial pharmacological activity.[1,2] Therefore, a first step towards developing an individualized dosing algorithm during renal replacement therapy is to explore the impact of continuous venovenous hemofiltration on lormetazepam and midazolam pharmacokinetics (PK).[2–4]

First, following ethical approval, we selected three critically ill patients with COVID-19-associated acute respiratory distress syndrome (ARDS) and receiving renal replacement therapy and the sedatives lormetazepam and midazolam.

Next, we conducted a PK study and calculated the extracorporeal removal of lormetazepam and midazolam, the pharmacologically active metabolite 1-hydroxy-midazolam, and lormetazepam and midazolam glucuronides.

Two milligrams of lormetazepam was administered twice daily via a nasogastric tube. The dosage of intravenous midazolam ranged from 2 to 15 mg/h. For renal replacement therapy, we performed post-dilution continuous venovenous hemofiltration with regional citrate anticoagulation (RCA-CVVH).[5] Blood flow was 180 mL/min and the net ultrafiltrate rate was 50 mL/min. Prismocitrate 18/0 at 1920 mL/h and Phoxilium at 1600 mL/h were infused as pre-filter and post-filter dilutions.[5] The measured effluent volume was 3578 mL/h. Pre/post-filter and ultra-filtrate samples were collected.[5]

Plasma concentrations of lormetazepam, midazolam, 1-hydroxy-midazolam, and glucuronides were analyzed in leftover samples using validated ultra-performance liquid chromatography–tandem mass spectrometry. MwPharm (version 3.58; Mediware, Groningen, The Netherlands) was used for PK analysis. Sieving coefficients were calculated and are given as the means of four values.[5]

The elimination half-life of lormetazepam and midazolam were 10.6, 10.7, and 10.6 hours and 0.8, 0.65, and 0.75 hours, respectively (Table 1). Lormetazepam and midazolam total body clearances (CL_{TOTALs}) were 12.8, 21.0, and 16.5 L/h and 24.5, 20.3, and 13.3 L/h, respectively. The sieving coefficients of lormetazepam, midazolam, and 1-OH-midazolam were low (<0.09), whereas the sieving coefficient of glucuronide metabolites, including glucuronidated 1-OH-midazolam, ranged from 0.25 to 0.62 (Table 1). Clearance by RCA-CVVH of lormetazepam and midazolam was approximately 0.004% and 0.006% of CL_{TOTAL}.

The hemofilter convection efficacies for lormetazepam, midazolam, and 1-OH-midazolam

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Table 1. Summary of Demographics, Severity of Illness (Apache IV), Laboratory Results, and Clearance Properties of Lormetazepam, Midazolam, and Their Metabolites During Continuous Venovenous Hemofiltration With Regional Citrate Anticoagulation in Mechanically Ventilated Coronavirus Disease 2019 Patients With Acute Respiratory Distress Syndrome and Acute Anuric Renal Failure

	Patient A	Patient B	Patient C
Demographics			
Age (years)/sex	73/M	59/M	50/M
Body mass index (kg/m^2)	26.2	29.8	27.8
Apache IV	66	50	60
Laboratory results			
Hemoglobin (mmol/L)	7.2	5.1	6.1
Hematocrit	0.35	0.26	0.30
Albumin (g/L)	16	14	13
Bilirubin (μmol/L)	9	18	12
PK analysis: lormetazepam			
C_{TROUGH} concentration (μg/L)	7.1	3.6	4.4
Half-life (hours)	10.6	10.7	10.6
Vd[a] (L)	197	323	253
CL_{TOTAL}[b] (L/h)	12.8	21.0	16.5
CL_{CVVH}[b] (L/h)	0.26	0.24	0.40
SC[d]	0.04	0.06	0.09
Lormetazepam glucuronide			
C_{TROUGH} (μg/L)	63	200	91
SC[d]	0.25	0.36	0.31
PK analysis: midazolam			
C_{SS}[e] range (μg/L)	43–667	15–917	530–847
Half-life (hours)	0.80	0.65	0.75
Vd[a] (L)	102	97	188
CL_{TOTAL}[b] (L/h)	24.5	20.3	13.3
CL_{CVVH}[c] (L/h)	0.08	0.08	0.09
SC[d]	0.02	0.02	0.02
Midazolam glucuronide			
C_{SS}[e] range (μg/L)	204–1579	66–2745	808–2633
CL_{CVVH}[c] (L/h)	1.23	2.30	2.08
SC[d]	0.30	0.60	0.50
1-OH-midazolam			
C_{SS}[e] range (μg/L)	20–325	6–90	86–399
CL_{CVVH}[c] (L/h)	0.22	0.28	0.26
SC[d]	0.05	0.07	0.07
1-OH-midazolam-glucuronide			
C_{SS}[e] range (μg/L)	1844–4031	76–3098	259–973
CL_{CVVH}[c] (L/h)	1.85	2.04	1.86
SC[d]	0.62	0.58	0.49

CVVH, continuous venovenous hemofiltration; PK, pharmacokinetics. Lormetazepam was administered by nasogastric tube (2 mg twice daily) and midazolam was administered by continuous infusion (2 to 15 mg/h).

[a] Volume of distribution.

[b] Total body clearance.

[c] Clearance by CVVH.

[d] Sieving coefficient (displayed as mean).

[e] Plasma concentration at steady state.

were low. However, the glucuronide derivatives were eliminated. Although low-molecular-weight substances (eg, lormetazepam and midazolam at <500 kD) are suitable for convectional removal during hemofiltration, the high protein-binding actions and distribution volumes of lormetazepam and midazolam hampered extracorporeal removal by RCA-CVVH. This may explain the sieving coefficient differences. The water solubility of glucuronide derivatives resulted in an increased removal percentage by RCA-CVVH. This indicates that the ultrafiltration rate and sieving coefficient may have decreased influence on the fractions removed but are still factors that contribute to the removal, along with the extent of metabolism into glucuronides.[2,4]

Our results support the development and evaluation of practice guidelines addressing sedation in patients critically ill with COVID-19 undergoing CVVH treatment. Our unique data on the clearance and sieving coefficients of the glucuronide metabolites of

lormetazepam and midazolam can help practitioners to develop robust dosing guidelines.

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Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

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