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PHARMACOKINETICS AND DISPOSITION

# Baclofen overdose treated with continuous venovenous hemofiltration

**Didier Meulendijks · Saheed Khan · Cornelis H. W. Koks · Alwin D. R. Huitema · Jan H. M. Schellens · Jos H. Beijnen**

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**Abstract**
*Purpose* Overdose with baclofen, a derivative of the inhibitory neurotransmitter γ-aminobutyric acid, may lead to severe respiratory and central nervous system depression and can be life-threatening. Prolonged half-lives of baclofen, of up to 34 h, have been reported in patients after overdose. Hemodialysis has proven to be a successful approach to improve clearance of baclofen, but the value of continuous venovenous hemofiltration (CVVH) is unclear. We applied CVVH in a patient with acute baclofen overdose.
*Methods* Pharmacokinetic measurements of baclofen in serum and hemofiltrate were made at six time points after hospital admission. Baclofen concentration-time data were analyzed using non-compartmental methods, and the relative contribution of clearance by hemofiltration to total baclofen clearance was calculated.
*Results* Baclofen concentrations in serum varied between 1.81 and 0.05 mg/L. Concentrations of baclofen in hemofiltrate were within the same range (between 0.74 and 0.05 mg/L), and the elimination half-life during hemofiltration was estimated at 4.8 h. Total clearance and clearance via hemofiltration were estimated at 6.6 and 2.4 L/h, indicating that clearance could be increased by approximately 57 % by applying hemofiltration.
*Conclusions* The presented case demonstrates the usefulness of CVVH in the treatment of baclofen overdose and indicates that CVVH can be used as an alternative to hemodialysis in patients with overdose of baclofen.

**Keywords** Continuous renal replacement therapy · Continuous venovenous hemofiltration · Baclofen · Overdose

D. Meulendijks · J. H. M. Schellens
Division of Clinical Pharmacology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

D. Meulendijks · J. H. M. Schellens
Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

S. Khan
Department of Intensive Care, Slotervaart Hospital, Amsterdam, The Netherlands

C. H. W. Koks · A. D. R. Huitema · J. H. Beijnen (✉)
Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, PO Box 90440, 1006 BK Amsterdam, The Netherlands
e-mail: jos.beijnen@slz.nl

J. H. M. Schellens · J. H. Beijnen
Faculty of Science, Department of Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

## Introduction

Baclofen is a ß-(*p*-chlorophenyl) derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), which is used to treat spasticity in patients with multiple sclerosis or spinal cord injuries. At therapeutic levels of 0.1–0.4 mg/L, baclofen has spasmolytic effects resulting from agonistic activity at presynaptic $GABA_B$ receptors at the level of the spinal cord [1]. A number of cases of life-threatening baclofen overdose have been described in literature, which have occasionally been fatal at serum concentrations of >10 mg/L [2, 3]. Patients with decreased renal function are at risk of accidental overdose [4], since ±80 % of administered baclofen is cleared via glomerular filtration [5–7]. Most other reported cases of overdose were suicide attempts [2]. Supratherapeutic concentrations of baclofen (of >0.4 mg/L) lead to central nervous

system (CNS) and respiratory depression, with hypothermia, flaccid paralysis, and hyporeflexia—resulting from exaggerated $GABA_B$-ergic activity. Autonomic disturbances are also commonly seen but can be inconsistent (e.g., both brady- or tachycardia and hypo- or hypertension can occur) [8]. Patients may have abnormalities on electroencephalogram (EEG) and generalized convulsions, which are thought to result from a net excitatory effect of baclofen in the CNS at above therapeutic concentrations [9].

Treatment of baclofen overdose is symptomatic, with supportive care, and mechanical ventilation if required, as no antidote that reverses the $GABA_B$-ergic effects is available. Under therapeutic conditions, the elimination half-life of baclofen is relatively short: around 3.5 h, with a range of 2.5–6.8 in clinical pharmacological studies [10]. Several reports of baclofen overdose, however, have suggested that at higher doses, the half-life of baclofen might be prolonged, with half-lives of 16 and 34 h reported in two patients after intake of 420 and 450 mg, respectively [11, 12].

Considering the life-threatening consequences of prolonged exposure to high concentrations of baclofen, hemodialysis has been applied in an attempt to facilitate more rapid clearance [12–15]. Pharmacokinetic studies in patients after overdose have confirmed that the clearance of baclofen can be substantially increased by applying hemodialysis, with half-lives of several hours reported in patients with renal insufficiency [14, 15]. In contrast to hemodialysis, so far, no studies have evaluated the usefulness of continuous venovenous hemofiltration (CVVH; also known as continuous hemofiltration or continuous renal replacement therapy) in the treatment of baclofen overdose. CVVH is based on the principle of convection, i.e., plasma solutes are carried through a semipermeable hemofilter along with water as a result of a transmembrane pressure gradient, thereby removing all solutes smaller than the pore size of the hemofilter. Replacement fluid is administered concurrently to maintain blood volume and provide electrolytes. Given that baclofen is primarily cleared unchanged renally (80 %), has relatively low plasma protein binding (30 %), a low molecular weight (213.7 g/mol), and an intermediate volume of distribution (0.7 L/kg [1]), CVVH could potentially be effective at increasing clearance of baclofen and, therefore, useful in the treatment of patients after overdose. We applied CVVH in a patient after ingestion of 340 mg baclofen and performed pharmacokinetic measurements of baclofen in serum and hemofiltrate to investigate its effectiveness.

## Case description

A 57-year-old man known with type 2 diabetes mellitus, hypertension, and hypercholesterolemia had been suffering from severe back pain symptoms for several years prior to admission. He was prescribed different drugs in an attempt to control his pain, however, without relevant symptom relief. In a desperate attempt to control his pain, he had purchased baclofen tablets via an online pharmacy after having read reports of it being effective as an antinociceptive drug for back pains. At the evening of his admission, he had decided to try baclofen in the presence of a friend, under whose supervision he had taken a large amount of tablets (34 tablets of 10 mg in total). Within 2 h, he became increasingly drowsy and eventually lost consciousness, at which point he was rushed to the hospital. At presentation in the emergency room, he was completely unconscious and reacted only to painful stimuli (Glasgow coma scale, GCS, E1M4V1). His blood pressure was 166/99 mmHg, heart rate 58 bpm, temperature 35.6 °C, oxygen saturation 99 %, and his breathing was moderately slow (10/min). He was known to use the following medications: diazepam, metformin, diclofenac, amlodipine, losartan, pantoprazole, alprazolam, mirtazapine, calciumcarbonate/vitamin $D_3$, and rosuvastatin.

The patient was intubated under succinylcholine and etomidate. Because he was also known to have used high doses of opioids in the past, he was challenged with two doses of naloxone (0.4 mg IV) to which he showed no significant response. A CT scan of the brain was made, which showed no abnormalities. Intravenous N-acetylcysteine was started, prophylactically, in case a large dose of acetaminophen had also been ingested. Serum measurements of acetaminophen and ethanol were ordered. Laboratory tests showed slightly reduced hemoglobin (7.9 mmol/L) and increased leukocytes ($10.7 \times 10^9$/L), but otherwise normal hematology. Chemistry was unremarkable except slightly reduced sodium (133 mmol/L) and increased glucose (9.6 mmol/L). The calculated glomerular filtration rate was in the normal range (>60 mL/min).

It was decided to initiate CVVH, via the right internal jugular vein, with bicarbonate-buffered substitution fluid given in predilution mode with a substitution dose of 4.8 L/h. A multiFiltrate® CVVH machine (Fresenius SE & Co. KGaA, Germany) was used with an Ultraflux® AV 600 S hemofilter with Polysulfone® membrane (1.4 $m^2$ surface area, Fresenius). Rate of blood flow was set at 200 mL/min (12 L/h). Nadroparin was initiated for anticoagulation and potassium chloride to compensate for potassium loss during CVVH.

An EEG was then made, which showed slow frontal lobe activity with sharp waves and no peaks or spike-wave complexes; there was no epileptiform activity. There was no reaction on EEG in response to pain stimuli. Thirty-five hours after admission GCS was E2M5Vt (while being intubated). The toxicological screens for acetaminophen and ethanol were reported to be negative. At 40-h past admission, the patient started to wake up and showed severe restlessness, probably due to preexistent back pains, for which fentanyl was initiated. When the patient became fully conscious on the third day after admission, CVVH was stopped; and on the fourth day, he left the intensive care unit.

## Methods

Baclofen was measured in serum and hemofiltrate at the following time points after hospital admission: 1.5, 3, 6.5, 7, 11, 22, and 36 h (serum) and 4, 8, 11, 22, and 36 h (hemofiltrate). Serum samples were centrifuged and serum stored at −70 °C until analysis, hemofiltrate samples were frozen directly and stored at −70 °C until analysis. Hemofiltrate was sampled from the effluent collection reservoir. Therefore, the measured concentrations reflected concentrations of baclofen in hemofiltrate in the preceding time interval, rather than the concentration at the exact time of sampling. Concentrations of (total) baclofen in serum and in hemofiltrate were measured using a validated LC-MS/MS method (details on bioanalytical methods available upon request).

Serum baclofen concentration-time data were analyzed using non-compartmental methods [16]. Clearance via hemofiltration ($CL_{HF}$, in L/h) was calculated as the hemofiltration rate ($Q_{HF}$, in L/h) times the sieving coefficient (SC), and further multiplied by the dilution factor (DF)—since CVVH was applied in predilution mode (Eq. 1 [17]).

$$CL_{HF} = Q_{HF} \times SC \times DF \quad (1)$$

The SC is defined as the concentration of baclofen in hemofiltrate $C_{HF}$ divided by the concentration in serum $C_{SERUM}$. Since approximately 30 % of baclofen is plasma protein bound, the theoretical value for SC is 0.70. This value was used in subsequent calculations, since the actual measured concentrations in hemofiltrate were collected from the reservoir as stated earlier.

The dilution factor DF was calculated using Eq. 2 [17], where $Q_{BF}$ is the blood flow in liters per hour (12 L/h in our patient) and $Q_{SF}$ is the flow of the substitution fluid (4.8 L/h in our patient, i.e., equal to the rate of filtration).

$$DF = \frac{Q_{BF}}{Q_{BF} + Q_{SF}} \quad (2)$$

The total clearance during hemofiltration, $CL_{TOTAL}$, was calculated using the formula $CL_{TOTAL} = k_e \times V_d$. Since $V_d$ could not be calculated reliably from the data and because there is very little variation among patients with regard to $V_d$ of baclofen, we used an average value from literature (0.70 L/kg) [1]. During hemofiltration, $CL_{TOTAL}$ equals the physiological—renal + nonrenal—clearance $CL_{R+NR}$ plus the clearance via hemofiltration $CL_H$. The relative contribution of hemofiltration to total clearance was estimated by calculating the fraction of clearance via hemofiltration relative to total clearance, $CL_H$ divided by $CL_{TOTAL}$.

## Results

The concentration-time curves for baclofen in serum and in hemofiltrate are shown in Fig. 1. The first plasma concentration was measured around 3 h after ingestion. The elimination half-life before hemofiltration was approximated at 1.13 h ($k_e$ =0.613) based on the first two concentration-time points, which is most likely an underestimation of the terminal half-life of baclofen since these concentrations were measured during the distribution phase. The elimination half-life during hemofiltration was estimated from the last three serum concentrations at 4.75 h ($k_e$=0.146). The estimated $V_d$ of our patient (64 kg) was 45 L. $CL_{TOTAL}$, therefore, was estimated at 6.6 L/h. Clearance via hemofiltration ($CL_{HF}$) was estimated at 2.4 L/h. Consequently, the fraction of clearance via hemofiltration relative to total clearance was 0.36. $CL_{R+NR}$ equaled the remaining fraction of 0.64, which corresponds to 4.2 L/h, which translates to a theoretical half-life of baclofen of 7.4 h in absence of hemofiltration. By applying hemofiltration, the clearance of baclofen during the terminal phase could be increased by approximately 57 %.

## Discussion

We report for the first time the use of CVVH in a patient treated for baclofen overdose with pharmacokinetic measurements of baclofen in hemofiltrate. There is one other report that mentions the use of continuous venovenous hemodiafiltration, but no pharmacokinetic measurements in hemofiltrate were presented [18]. As expected from the pharmacokinetic properties of baclofen, CVVH was effective at increasing clearance of baclofen, which was confirmed by our pharmacokinetic measurements. The fraction of clearance via hemofiltration relative to total clearance indicated that CVVH increased clearance of baclofen in our patient to a relevant

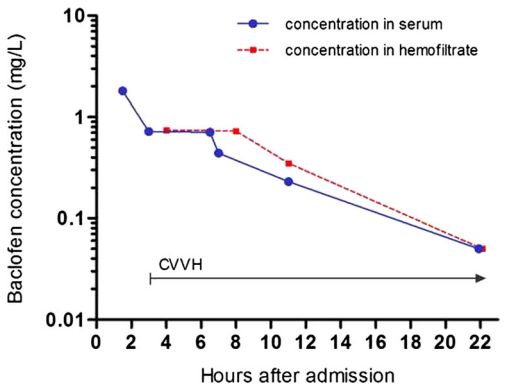


**Fig. 1** Concentrations of baclofen in serum and in hemofiltrate during CVVH

extent and, although the SC could not directly be calculated, the measurements in hemofiltrate indicate that substantial amounts of baclofen were eliminated using CVVH.

We observed a very short half-life of baclofen before hemofiltration, of 1.13 h, which is much lower than previously reported (mean 3.5 h). This is most probably caused by the fact that the first samples were collected during the distribution phase of baclofen (reported distribution half-life 0.54 h, $T_{max}$ around 3 h [6]).

The initial phase of rapid clearance was followed by apparent lack of clearance, as serum concentrations between 3 and 6.5 h after admission did not lower to a relevant extent, even though the patient was on CVVH, and renal function and urine production were normal. Previous reports have described "rebound" kinetics of baclofen after overdose [2, 19, 20]. Table 1 summarizes the studies that have reported pharmacokinetics after overdose of baclofen. Three of these reports describe secondary increases in plasma concentration of baclofen (at around 3–5 days) after ingestion of very large doses of baclofen. All of these reports also describe half-lives of baclofen that are much longer than under therapeutic conditions, in contrast to several other reports in which no prolonged half-life was observed after a high dose. Baclofen is cleared primarily via glomerular filtration, and renal clearance of baclofen has been found to equal creatinine clearance in humans [7] (although up to 15 % has been reported to be cleared hepatically). Tubular secretion might play a role in the clearance of baclofen, but this is thought to contribute only marginally compared to glomerular filtration [21]. Since glomerular filtration is the primary clearance mechanism, it is not likely that saturation of clearance will occur at higher doses of baclofen. For this reason, reduced renal or nonrenal clearance is unlikely to explain prolonged half-life of baclofen, as in our patient and as reported previously [2, 19, 20]. More likely is that the observed slow (apparent) clearance (between 3 and 6.5 h after admission) is the result of redistribution of baclofen from a tissue compartment into the circulation. This may also explain the increases in half-life that have been reported, as suggested previously [2, 20].

Of note, our patient experienced CNS depression much longer than would be expected based on the serum concentrations of baclofen that are observed in retrospect. In fact, it took 40 h before our patient started waking up, while serum concentrations were undetectable past 22 h. Our patient was known to use diazepam and alprazolam, two benzodiazepines with long half-lives. However, based on the information provided by the relatives, there were no indications for overdose with these drugs. Notwithstanding, since no toxicological screening was performed, this does provide an alternative explanation for the prolonged CNS depression which we cannot rule out. Similarly, massive overdose with opioids could also explain the clinical course, but considering the available information this was also considered unlikely. Perry and colleagues made a similar observation of discrepancy between baclofen plasma concentrations and clinical status and described three young patients who remained intoxicated and required mechanical ventilation while having subtherapeutic baclofen concentrations in serum [8]. Wu et al. reports a similar observation of a patient that remained unconscious while baclofen levels had dropped to within the therapeutic range [15]. Interestingly, preclinical (animal) studies have shown that CNS levels of baclofen take longer to develop and longer to drop compared with serum levels [5], which might be an explanation for these observations.

A remark should be made about the CVVH settings. We applied CVVH in predilution mode, pragmatically, since our

**Table 1** Summary of studies reporting pharmacokinetic measurements after baclofen overdose

| Estimated dose of baclofen (mg) | Renal function of patient | Estimated half-life of baclofen in absence of hemodialysis (h) | Estimated half-life of baclofen during hemodialysis (h) | Rebound levels of baclofen? | Reference |
|---|---|---|---|---|---|
| 340 | Normal | 7.4[a] | 4.7 (CVVH) | Yes, between 3 and 6 h | Current study |
| 60–600 | Normal | – | – | No | Perry et al. [8] |
| 1000 | Normal | 4.6 | – | No | Anderson et al. [22] |
| 2000 | Normal | 8.6 | – | No | Gerkin et al. [23] |
| 420 mg | Normal | 15.7 | 3.1 | No | Hsieh et al. [12] |
| 450 | Normal | 34.5 | – | Yes (day 3), rebound at ±0.1 mg/L | Ghose et al. [19] |
| 1520 mg | Normal | 24 | – | Yes (day 5), rebound at ±0.1 mg/L | Lipscomb et al. [20] |
| 2000 | Normal | 25 | – | Yes (day 4), rebound at ±0.2 mg/L | Weißhaar et al. [2] |
| Unknown | End-stage renal disease | 15.5 | 2.1 | No | Wu et al. [15] |
| 25 | Acute renal failure | 12.6 | 3.7 | No | Brvar et al. [14] |

experience is that clotting of the hemofilter is much more frequent with postdilution than with predilution. From a pharmacokinetic perspective, however, postdilution would be preferable, since this allows for more efficient clearance of drugs (approximately 30 % higher clearance could potentially be achieved).

## Conclusion

Baclofen intoxication can lead to prolonged respiratory and CNS depression and can be life-threatening. Previous reports have demonstrated that hemodialysis can effectively increase baclofen clearance both in patients with renal dysfunction and in patients with normal renal function. The present case demonstrates the usefulness of CVVH in the treatment of baclofen overdose, and our results suggest that CVVH can be used as an alternative to hemodialysis in patients after overdose of baclofen.

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