Case Report

Treatment of baclofen overdose by haemodialysis: a pharmacokinetic study

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Introduction

Baclofen is currently used in the treatment of muscle spasticity, especially in patients with multiple sclerosis or in patients with spinal or cerebral disorders. Baclofen is eliminated predominantly by the kidneys [1], putting patients with impaired renal function at particular risk for baclofen accumulation. Several investigators have suggested that haemodialysis is effective in the removal of baclofen [2], however the pharmacokinetics of baclofen elimination during haemodialysis remains unclear. We herein report a baclofen-associated encephalopathy, which was resolved by haemodialysis, and pharmacokinetic data is presented. To our knowledge, this is the first reported case of baclofen-related encephalopathy with pharmacokinetic data during haemodialysis treatment.

Case

A 70-year-old woman with end-stage renal disease (ESRD) was treated by haemodialysis regularly for 14 years. She was anuric and received adequate haemodialysis at Kt/V 1.95. She presented with left leg soreness and was given 5 mg of oral baclofen three times daily from the local clinic, receiving a cumulative dose of 45 mg in 3 days. The patient became disoriented, in a state of confusion and was referred to our hospital for evaluation. At admission, she was found drowsy, her blood pressure was 199/60 mmHg and temperature 36.7°C. Laboratory data showed haemoglobin 8.1 g/dl, WBC 4900/mm³, with a normal differential count and platelets 268 000/mm³. Serum sodium was 147.4 mmol/l, potassium 4.42 mmol/l, ammonia < 1 μmol/l, sugar 107 mg/dl, urea 51 mmol/l and creatinine 8.26 mg/dl. The transaminases were normal. A brain CT scan showed cortical atrophy and leukoaraiosis. Under the diagnosis of baclofen intoxication, she received emergency haemodialysis. The dialysate had ethylene vinyl alcohol copolymer resin filters with a surface area of 2.0 m², and the blood flow rate was at a constant 300 ml/h for 4 h without ultrafiltration. There was a complete recovery of consciousness 8 h later. She received another haemodialysis session 30 h after admission. The patient was discharged from the hospital 72 h later in good condition.

Results

Serum baclofen concentrations

Blood samples were collected immediately after arrival, and at 4 (start of first haemodialysis), 5, 6, 7, 8 (end of first haemodialysis), 30 (start of second haemodialysis), 32 and 34 h (the end of second haemodialysis) thereafter. Samples of serum were prepared according to the methods published in previous reports with minor modifications [3]. In brief, serum samples (1 ml) were prepared by adding 200 μl of the internal standard [1 μg/ml of 3-amino-3-(4-chlorophenyl)-propionic acid] and 20 μl of 85% ortho-phosphoric acid and then were loaded into Oasis HLB SPE columns (Waters) for extraction. Gas chromatography/mass spectrometry analysis was performed on an Agilent 5890 gas chromatograph coupled with a 5973 mass selective detector and a 7683 injector. Quantitative analysis was carried out on the Agilent ChemStation. Calibrators were baclofen spiked serum samples at concentrations
Baclofen is a β- (p-chlorophenyl) derivative of the neurotransmitter γ-aminobutyric acid (GABA). This centrally acting GABA agonist is prescribed as therapy for spasticity in the spinal cord region. Ingested baclofen is absorbed rapidly and completely, thereafter 69–85% are excreted without changes in urine and 15% are metabolized by the liver to its inactive deaminated product, β-(p-chlorophenyl)-γ-hydroxybutyric acid [1,5]. The half-life is between 4.5 and 6.8 h in healthy subjects, but increases in ESRD, and an accumulation phenomenon can occur [1]. Baclofen is moderately lipophilic, 30% of the drug is protein bound, and can penetrate the blood–brain barrier, entering the central nervous system after systemic application [6]. Concentrations of baclofen in cerebral spinal fluid (CSF) have been described to be 8.4 times lower than those simultaneously present in plasma [5]. It has a volume of distribution of 0.831/kg in adult [7] and 2.581/kg in children [8].

The therapeutic range of baclofen is ~80–400 ng/ml in normal subjects [9], but the appropriate serum level of baclofen in patients with severely impaired renal function remains unclear. Several authors have suggested that patients with renal failure are more susceptible to baclofen toxicity [2]. This may explain why our patient was comatose, although her plasma baclofen concentrations were all within the therapeutic range of normal subjects.

Several observations of baclofen-associated encephalopathy have been reported in patients with ESRD [10]. Patients with severely impaired renal function generally develop baclofen intoxication soon after the initiation of therapy [2]. Altered consciousness has been the major manifestation in patients with severely impaired renal function. Other symptoms, such as respiratory depression muscular hypotonia and generalized hyporeflexia have been observed in patients of baclofen intoxication with normal renal function [2]. Most ESRD patients experienced marked improvement in clinical toxicity following haemodialysis, compared with patients who did not receive haemodialysis [2]. We measured the changes of baclofen serum concentration during haemodialysis and found that the serum baclofen eliminated up to 79% during the 4 h of the haemodialysis session. Haemodialysis shortened the baclofen half-life from 15.5 to 2.06 h in this patient. Therefore, it is reasonable to suggest that haemodialysis should be used as a treatment modality in cases of baclofen intoxication with renal failure. According to a previous report, patient consciousness improved with several hours time lag after haemodialysis [2]. This delay may be due to the redistribution of baclofen in crossing the blood–brain barrier [2]. This may explain longer central nervous system depression despite reductions in serum drug concentrations to negligible amounts. The consciousness improved after just one session of haemodialysis in this patient, which was different from previous reports where two or more sessions were necessary [2]. Because there were no serum levels and other pharmacokinetic data in previous reports [2], it is difficult to compare the effectiveness of haemodialysis in this report. In our patient, early diagnosis, early start of haemodialysis and lower serum concentrations of baclofen may have resulted in the difference. The larger surface area of our artificial kidney may be another possible cause.

In conclusion, it is necessary to reduce baclofen dosage in patients with renal disease and especially in ESRD patients. Haemodialysis is an appropriate treatment of baclofen intoxication in ESRD patients.
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Conflict of interest statement. None declared.

References


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