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Case Report

Malignant Baclofen Induced Coma Reversible by Dialysis in a 67-Year Old Patient with Acute Kidney Injury

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ABSTRACT

Introduction: Baclofen is a commonly used drug for the treatment of muscular spasticity and other conditions such as pain, alcohol withdrawal and myoclonus and is contraindicated in chronic kidney disease. Eliminated predominantly by the kidneys, acute renal insufficiency can lead to acute baclofen overdose with central nervous system affection caused by accumulation. Currently, there is no consensus about the treatment of baclofen intoxication. However, several reports showed that haemodialysis can effectively clear baclofen. We report a 67-year-old patient with baclofen intoxication caused by acute kidney failure presenting in a deeply comatose state that could be completely reversed within hours after one single haemodialysis.

Case report: A 67-year-old woman was admitted with altered mental status and vomiting. Initially she was unresponsive, lethargic, with intermittent ability of nonverbal communication gradually sliding into a comatose state with apneas (Glasgow Coma Scale 5). Initial neurologic and radiologic examinations could exclude a structural lesion of the central nervous system. Laboratory data showed acute renal failure and suspected urinary tract infection with extremely high inflammatory parameters. The patient had a history of multiple sclerosis and received daily oral baclofen (3 × 25 mg daily started with a normal kidney function). Baclofen induced coma secondary to baclofen overdose caused by the renal failure was suspected and haemodialysis started within 24 hours. Cystoscopy and implantation of bilateral JJ stents was necessary because of obstructive nephropathy. During haemodialysis the patient's mental status steadily improved. The patient woke up and was orientated and cooperative. Both clinical and laboratory data widely normalized within days.

Discussion: This report demonstrates rapid and full recovery from deep coma in a patient with baclofen overdose associated with acute renal insufficiency and delayed elimination. We assume that drug elimination was increased with haemodialysis and recovery thus accelerated. Diagnosis of baclofen overdose can be challenging, but adequate supportive therapy including haemodialysis should be considered to reduce time of comatose state and the risk of aspiration pneumonia.

Keywords: Baclofen; Chronic kidney disease; Central nervous system; Haemodialysis; Acute kidney failure

INTRODUCTION

Baclofen is an effective spasmolytic agent [1]. It is given orally or *via* an intrathecal pump. The range between minimal therapeutic and minimal toxic dose is small and it is contraindicated in chronic kidney disease [2]. Its primary site of action is in the spinal cord, where it binds to the inhibitory GABA-B receptor [3]. After rapid absorption from the gastrointestinal tract baclofen has a bioavailability of 70%-80% [2]. Baclofen is predominantly excreted unchanged by passive glomerular filtration with only a small portion being metabolized by the liver. Its serum half-life of 2-6 hours can be

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prolonged in renal insufficiency and when overdosed [1,4]. Continuous absorption from the intestinal tract and redistribution from fatty tissue may further increase its half-life in renal insufficiency [5]. Baclofen overdose can lead to central nervous system toxicity with changes in excitatory and inhibitory neurotransmitters. Baclofen does not readily cross the blood-brain barrier. Hence a relatively high oral dose (60-100 mg/day) or direct intrathecal application is needed to achieve therapeutic effects [6]. When overdosed, patients may present with lethargy, respiratory and cardiac depression, and muscular hypotonia as well as generalized hyporeflexia varying with the degree of intoxication [7]. No threshold dose has been established for the consistent onset of neurologic adverse effects. A specific antagonist does not exist, but flumazenil has been reported to counteract the inhibitory effects of baclofen [8]. Several reports showed that haemodialysis can effectively and rapidly remove baclofen in overdosed patients with renal failure, alleviating overdose symptoms and accelerating recovery time [7]. Nevertheless, no consensus exists on its true benefit [7,9]. We report a 67-year-old patient with baclofen intoxication presenting as coma of unknown origin that originally had a normal renal function that had acutely deteriorated because of urosepsis and was completely reversed by one single haemodialysis.

CASE REPORT

A 67-year-old woman was admitted to the neurological emergency unit of the Medical University of Graz with altered mental status and vomiting, progressing to a comatose state (GCS 5). Relatives reported normal communication and the absence of any symptoms the day before admission with progressive unresponsiveness and dizziness within twelve hours. Upon arrival the patient showed body temperature 35.9°C, blood pressure 110/60 mmHg, tachycardia 105 bpm and eupnoea. The patient was unconscious but did initially react to commands nonverbally, but within minutes only to deep pain stimuli (Glasgow Coma Scale score of 5). Flumazenil and naloxone did not have any effect. Her medical history comprised longstanding multiple sclerosis with impaired mobility (wheelchair bound), breast cancer and osteoporosis. The patient had been on oral baclofen therapy in a high dose for years (75 mg per day). Laboratory data revealed leukocytosis (white blood cell count 25 10^9/L, 86% neutrophiles), acute renal insufficiency (creatinine 3.0 mg/dL, three weeks before: 1.0 mg/dl), increased C-reactive protein 369 mg/L and procalcitonin 4.1 ng/mL in Table 1. An initial arterial blood gas analysis showed no relevant pathology. Electrocardiography showed sinus tachycardia. Neurologic examination revealed mydriatic pupils with direct and consensual pupillary light reflexes, muscular hypotension with no spontaneous movement and absent plantar reflexes but no meningeal signs. Urinary analysis was suspicious for urinary tract infection. A cerebral computed tomography scan excluded bleeding and infarct demarcation. The synopsis of clinical findings and laboratory data initially suggested septic shock of urogenital origin with acute on chronic renal insufficiency. Empiric antibiotic treatment with piperacillin/tazobactam and intravenous fluids was introduced. Regarding oral baclofen therapy with a relatively high daily dose, a toxic encephalopathy secondary to baclofen overdose due to renal failure was suspected. After consultation with the poison center haemodialysis was considered as a therapeutic option, as baclofen is an easily removable substance by dialysis and there are other case reports in the literature showing recovery of consciousness in patients with baclofen overdose due to renal failure [7,10]. Haemodialysis started, but had to be interrupted after 30 minutes for cystoscopy and implantation of ureteral stents during the night due to obstructive nephropathy. During this painful intervention, her neurologic status remained deeply comatose (GCS 3), and the patient did not need any analgesic or sedative medication. A second haemodialysis treatment over 5 hours was necessary the following day. During this second haemodialysis, the patient's mental status steadily improved. The patient woke up and was completely orientated and cooperative. The fast recovery of consciousness is in line with other case reports that also described the rapid effect of haemodialysis in patients with baclofen overdose and renal failure [7,10,11]. Results of a blood culture revealed *Pseudomonas aeruginosa* infection. Subsequently, both clinical and laboratory data including renal function widely normalized, and communication was possible without any restriction.

Laboratory analysis	
White blood cell count	25 10^9/L
Neutrophiles	86%
Creatinine	3.0 mg/dL
C-reactive protein	369 mg/L
procalcitonin	4.1 ng/mL

Table 1: Laboratory analysis of baclofen therapy.

RESULTS AND DISCUSSION

This report demonstrates rapid and full neurological recovery in a patient with previously normal kidney function presenting with relative baclofen overdose using a high but approved daily dose of 75 mg caused by acute renal insufficiency associated with obstructive nephropathy and urosepsis.

First, we would like to prompt clinicians to consider baclofen as an important and reversible cause of unexplained coma in patients with acute deterioration of renal function. This is currently rarely considered, especially when baclofen is applied *via* an intrathecal pump.

Second, we suggest empiric use of haemodialysis in similar situations although currently there is no consensus about the indication of haemodialysis in patients with baclofen intoxication. We postulate that in our case delayed elimination of baclofen due to acute renal insufficiency was the main reason for the comatose state of the patient. Because no specific therapy of baclofen overdose exists, supportive therapy is usually recommended preventing complications of central nervous system, muscle spasticity and fluctuations of blood pressure. Baclofen is ideal for removal by haemodialysis because of low

protein binding and small molecular weight allowing for improved drug elimination and shortened half-life. In animal models, the half-life is reduced from 5 to 1.5 hours in the first two hours of haemodialysis [11]. In our case, the comatose state improved already within the first hours of haemodialysis, which is in line with similar reports in literature [7,9,12]. We would like to point out that diagnosis of baclofen overdose can be challenging, but adequate supportive therapy as well as haemodialysis can lead to excellent prognosis, reduce time of comatose state and related risks such as aspiration pneumonia.

CONCLUSION

Neurotoxicity of baclofen can occur at approved oral doses when renal elimination is decreased. We suggest evaluating the risk-benefit ratio of baclofen treatment in aging patients with impaired renal function and observe them closely for toxicity. Baclofen can cause nervous system depression due to accumulation following renal failure resulting in a clinical picture of deep comatose state. Haemodialysis may be an efficient and rapid method in treating patients with baclofen overdose.

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