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Baclofen Toxicity in Patients with Advanced Nephropathy: Proposal for New Labeling

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Key Words
Baclofen · Toxicity, baclofen · Renal insufficiency

Abstract
Background: Despite several reports in the literature of baclofen toxicity in patients with renal dysfunction, the drug is being used for many patients. ***Methods:*** Herein we report a case of baclofen-induced encephalopathy in a patient with pre-end-stage renal disease and review the literature regarding the magnitude of baclofen toxicity in patients with renal insufficiency. A Medline search for studies in English was performed. Twenty-one case reports involving 41 patients (including our patient) were identified. ***Results:*** The majority of patients were elderly (62.5% above 60 years) males (56.3%) on dialysis (62.9%). Neurotoxicities were almost always present at presentation. Manifestations of baclofen toxicity usually started 2–3 days after starting baclofen; however, periods as long as 16 weeks have been reported. The daily dose of baclofen ranged from 5 to 60 mg with a mean dose of 20 mg. Hemodialysis (HD) was the most common treatment modality used for drug elimination (65.7%). The recovery time ranged from 2 h in patients who received HD, to 8 days with conservative treatment. ***Conclusion:*** The literature does not mention a clear recommendation about baclofen safety and dose adjustment, or a minimum level of kidney function below which the drug should not be used.

Introduction

Baclofen is a γ-aminobutyric acid (GABA) derivative which induces presynaptic motor neuron inhibition and produces a central antispastic response [1]. It is a lipophilic drug that readily penetrates the blood-brain barrier, and although its precise mechanism of action has yet to be elucidated, it appears that in therapeutic doses baclofen acts principally on the $GABA_B$ receptor at the spinal level. Baclofen has been widely used in multiple sclerosis and other spinal lesions that cause skeletal hypertonus and spasticity [2]. Recently, there have been increasing reports that baclofen is also an effective and reliable treatment alternative for hiccups in cancer patients [1, 3].

The elimination half-life of baclofen is 2–6 h for therapeutic oral doses in healthy volunteers and elderly patients [4, 5], but half-life increases with renal insufficiency [6–10]. Baclofen has a limited hepatic metabolism.

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Eighty-five percent of an oral dose is eliminated renally. Its clearance is proportional to creatinine clearance. Therefore, a significant reduction in the daily dose is mandatory in patients with renal insufficiency. Most nephrologists consider baclofen to be a drug that should not be used in patients with end-stage renal disease (ESRD) [7, 8, 11].

Baclofen can be detected in blood by gas chromatography-mass spectrometry and high-performance liquid chromatography, but not by the rapid methods used for toxicology screening tests; therefore, awareness of the problem and a strong index of suspicion are required to consider baclofen toxicity.

Baclofen clearance may be significantly enhanced by hemodialysis (HD) owing to its low volume of distribution and low protein binding. HD appeared to shorten the duration of toxic effects of baclofen in several patients with severely impaired renal function [7, 12]; however, consciousness usually improves only after a delay of several hours after the end of HD. Some authors suggested that HD is not superior to continuous ambulatory peritoneal dialysis (CAPD) for decreasing the recovery time of baclofen-associated neurotoxicity [13].

In the literature, there are several case reports of baclofen toxicity in patients with renal insufficiency. Herein we highlight this serious medical problem in a patient with chronic kidney disease (CKD). To our knowledge, this is the first article that has reviewed all published baclofen toxicity case reports in patients with abnormal kidney function.

Case Report

A 75-year-old African-American male with a past medical history of stage IV CKD had a baseline serum creatinine of 4.3 and blood urea nitrogen of 60 mg/dl, anemia, gout, hypertension, s/p aortic valve repair in 2008 and intractable right knee pain. He had recently been discharged from the hospital after a workup for a right knee injury from a fall related to a syncopal episode. The discharge diagnosis included partial tears of the anterior cruciate ligament and the meniscus of the right knee. He was started on 5 mg oxycodone/325 mg acetaminophen (percocet) 1 tablet every 6 h as needed for pain and baclofen 10 mg 3 times daily and was discharged to a skilled nursing facility for physical therapy. The patient presented 2 days after discharge with altered mental status (AMS). He was noted to be lethargic, responsive only to sternal rub, and to have right-sided rhythmic movements suspicious of a seizure disorder. The patient's vital signs were unremarkable (blood pressure 118/74 mm Hg, pulse 69/min, temperature 37.6°C, and pulse oxygenation >95%). There were no focal neurological deficits. The remainder of the examination was consistent with known problems. Routine laboratory tests showed a serum sodium level of 137 mEq/l, potassium 4.8 mEq/l, chloride 100 mEq/l, bicarbonate 27 mEq/l, blood urea nitrogen 67 mg/dl, creatinine 4.5 mg/dl, glucose 121 mg/dl, white blood cells 9,700/mm^3, hemoglobin 11.2 mg/dl, and platelets 158,000/mm^3. Liver function tests (including transaminases, albumin, bilirubin, and serum ammonia) were normal. Arterial pH was 7.40, PaO_2 99 mm Hg, and $PaCO_2$ 39 mm Hg. Carboxyhemoglobin was not detected. Routine toxicological screens were performed on both blood and urine samples with negative results except for opioids. The patient received 2 doses of 0.4 mg i.v. naloxone without improvement.

A head computerized tomography scan without contrast did not reveal any acute findings. He was placed on seizure prophylaxis medication and transferred to MICU for monitoring via video capture electroencephalography (EEG). The EEG results revealed no evidence of epileptogenic movements and pointed to possible toxic/metabolic encephalopathy.

Baclofen was discontinued and 5 h of HD was performed specifically to enhance elimination of baclofen. The patient's baclofen serum levels dropped from 400 to 100 ng/ml after his first HD treatment. The patient also received another HD on the 2nd day of admission. The patient's AMS began to resolve during the 4th h of the first HD treatment and EEG normalized. He was discharged without any residual neurologic deficits.

Discussion

In open-label studies on the oral administration of baclofen, the drug was demonstrated to improve spasticity in 70–87% of patients with improvement in spasms reported in 75–96% of patients [14]. Additionally, its uses as an anti-hiccup agent in cancer patients [1, 3], a surreptitious intoxicant [15], and a recreational drug [16] have been reported.

The therapeutic dosage range of baclofen is between 15 and 80 mg/day, and the therapeutic blood level is considered to be 80–400 ng/ml. When baclofen is administered in therapeutic doses, spinal effects predominate, while neurotoxicity becomes increasingly evident as the dosage is increased. Baclofen is primarily excreted by glomerular filtration, with a clearance proportional to creatinine clearance. Thus, baclofen accumulation and neurotoxicity may occur when normal doses are administered to patients with impaired renal function. Several reports have also suggested that baclofen neurotoxicity may be increased in the elderly or in patients with cerebral lesions [17]. Our patient's baseline renal compromise had never been suspected for this acute onset AMS. Furthermore, his mental status did not improve after 2 doses of naloxone, leading us to suspect baclofen as the cause of AMS in spite of a serum baclofen level that was near the upper therapeutic limit. We believed this to be baclofen toxicity because he was elderly and probably

Table 1. Clinical characteristics of baclofen-induced toxicity in patients with renal failure

Study	Patients n	Degree of renal insufficiency	Age, years	Sex M/F	Onset of symptoms days	Baclofen dose mg/day	Treatment modality	Time to recovery h
Seyfert et al. [26], 1981	3	1 CKD stage III	46	F	1	30	supportive	?
		2 ESRD on HD	29/48	F/F	5/4	10	HD	
Dahlin and George [27], 1984	1	AKI	64	M	2.3	60	supportive	96
White [16], 1985	1	CKD stage III	74	F	4	45	supportive	36
Mery and Kenouch [28], 1987	1	CKD stage IV	85	M	3	30	HD	?
Himmelsbach et al. [29], 1992	2	1st: kidney transplant with AKI	36	F	7–10	15	HD	?
		2nd: CKD stage III	57	M	1	40	HD	48
Lee et al. [30], 1992	1	ESRD on HD	64	M	3	37.5	HD	4
Aisen et al. [6], 1994	1	CKD stage III	39	F	112	?	supportive	?
Chen et al. [7], 1997	9	2 pre-ESRD 7 ESRD	72/66	F/F	1.6/1	20/20	HD/supportive	6/192
		1 on CAPD	63	F	2	20	HD	120
		6 on HD	65/55/39/39/66/47	M/M/F/M/F/F	1/3/2.5/1/3.3/1	30/15/15/15/5/20	HD	10–12
Peces et al. [9], 1998	2	ESRD on HD	69/71	M	1.5/4	15/30	HD	4
Bassilios et al. [8], 2000	1	ESRD on HD	65	M	4	5	HD	4
Choo et al. [31], 2000	1	ESRD on CAPD	72	M	1	10	CAPD	?
Hadjiyannacos et al. [24], 2001	1	ESRD on HD	75	?	7	10	HD	72
Krozac and Rakus [32], 2001	1	ESRD on HD	12	F	?	20	HD	2
Chen et al. [12], 2003	3	ESRD on CAPD	50/58/76	M	4.5/1.5/1.5	20/15/30	CAPD	48/72/48
Sanjay et al. [25], 2003	4	ESRD on HD	?	?	0.5–1	2.5	HD	?
Wu et al. [11], 2005	1	ESRD on HD	70	F	3	45	HD	8
Lois et al. [10], 2006	1	ESRD on CAPD	75	M	7	5	CAPD	120
Chou et al. [33], 2006	2	1st: CKD stage IV	68	M	4	15	supportive	72
		2nd: CKD stage V	73	F	2	10	HD	4
Brvar et al. [34], 2007	1	AKI	60	M	6	50	HD	4
Su et al. [35], 2009	4	1st: ESRD on HD	61	F	0.5	15	HD	48
		2nd: ESRD on PD	82	?	1	20	CAPD	120
		3rd: ESRD on HD	64	?	0.5	20	HD	24
		4th: AKI	47	?	0.5	40	HD	48
Our case	1	CKD stage IV	75	M	2	30	HD	4

? = Information not mentioned in the studies. AKI = Acute kidney injury; PD = peritoneal dialysis.

had changes in body compartments which would influence distribution volume as opposed to younger patients, and also because the therapeutic blood level has never been validated in patients with severe renal insufficiency. In addition, we report that baclofen 'toxicity' is a relative term in patients with impaired renal function. We speculate that additive or synergistic variables such as patient's age and concomitant use of a CNS depressant (narcotic) may affect the concentration at which baclofen may become toxic in patients with renal insufficiency.

The limited data on baclofen toxicity in patients with renal disease suggest that administration of the drug in these persons may carry a high risk. Clinicians should be ever vigilant of patients with suboptimal kidney function who may have therapeutic misadventures with this medication.

Baclofen-associated encephalopathy has been reported in patients with varying degrees of renal insufficiency. There is a case report of a patient who developed baclofen-associated encephalopathy with an estimated glomerular filtration rate (eGFR) of 55–60 ml/min and creatinine of 0.8 mg/dl [6]; however, it has been reported mostly in patients with ESRD on renal replacement therapy.

Therefore, the degree of renal insufficiency that would warrant avoidance of baclofen is an elusive and probably multi-factorial variable that cannot be determined without more robust studies. Although the number of reported cases in the literature is limited, the consensus is that baclofen should be avoided in patients with renal insufficiency. In the event of toxicity, HD has repeatedly been shown to resolve the toxic effects. The American College of Physicians' guidance on prescribing in renal failure contains no information on baclofen [18]. Also, no spe-

cific guideline has been established for baclofen dose adjustment in patients with renal impairment in UpToDate [19]. None of the widely used references provide a clear recommendation about safety in people with a low GFR, nor do they state a level of kidney function below which the drug should not be given.

To date, there are 41 reported cases of baclofen-induced neurotoxicity in patients with renal failure, including ours (table 1). The majority of patients were elderly (62.5% above 60 years), males (56.3%) with ESRD (62.9%). 68.2% of the ESRD patients were on HD while 31.8% were on CAPD. Neurotoxicities were almost always present at presentation and usually manifested by AMS. Manifestations of baclofen toxicity usually start early after starting the drug (2–4 days) but a period of up to 16 weeks has been described. The daily dose of baclofen ranged from 5 to 60 mg with a mean dose of 20 mg. HD was the most common treatment modality used for drug elimination (65.7%). The recovery time ranged from 2 h in patients who received HD to 8 days in patients who were treated conservatively or using CAPD. Our case highlights the importance of considering kidney function when prescribing baclofen. Patients treated with baclofen for spasticity may also have a neurogenic bladder, a risk of low kidney function, or low muscle mass that leads to serum creatinine concentrations being overestimates of kidney function.

Baclofen has been used for treatment of intractable hiccups in patients with uremia since the 1980s and 1990s [20–22]. Krahn and Penner [23] considered baclofen as one of the agents of choice in such conditions based on knowing its safety and efficacy at that time. Hadjiyannacos et al. [24] reported that using a small dose of baclofen (2.5 mg twice daily) was not associated with side effects in 2 patients on HD but using larger doses (5 mg twice daily) was associated with neurotoxicity. So they concluded that it is safe to use small baclofen doses in patients with ESRD. However, reviewing the literature showed that baclofen-induced neurotoxicity can also happen with such small doses in patients with ESRD [7, 8, 10, 21].

There are methodological limitations to the published data due to small samples, inadequate or no control groups, and dis-homogeneity of the cases reported. In light of the shortcomings of the existing literature, a more in-depth review of those publications was beyond the scope of this concise report.

We do not recommend using baclofen in patients with an eGFR of <30 ml/min/1.73 m^2. In patients with eGFRs between 30 and 60 ml/min/1.73 m^2 (stage 3 CKD), we recommend starting with very low doses at long intervals and titrating to effect. Patients taking baclofen must be monitored closely for toxicity when declining renal function is present. HD is useful in managing symptoms of people with baclofen intoxication from any cause, but may need to be repeated. We think that it is imperative to include such guidelines in the product monograph and the commonly available drug references.

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