



Administration of baclofen in end-stage renal disease

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Abstract

Baclofen with chemical name of 4-amino-3-(4-chlorophenyl)-butanoic acid is commonly used to treat dysfunctional voiding, intractable hiccups, palatal myoclonus and for alleviation of signs and symptoms of skeletal muscle spasticity and spasm. It is also currently used to treat trigeminal neuralgia, addiction to opiates, alcohol, or cocaine and for alleviation of pain among patients with multiple sclerosis or in patients with spinal or cerebral disorders. In individuals with disturbed kidney function and particularly in the patients with end-stage renal disease (ESRD), the accumulation of the drug is occurred and the half-life of the drug is prolonged which can lead to significant side effects and complication including neurological deterioration and coma.

Keywords: Baclofen, End-stage renal disease, Coma, Gamma-aminobutyric acid

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Introduction

Baclofen with chemical name of 4-amino-3-(4-chlorophenyl)-butanoic acid is commonly used to treat dysfunctional voiding, intractable hiccups, palatal myoclonus and for alleviation of signs and symptoms of skeletal muscle spasticity and spasm (1). It is also currently used to treat trigeminal neuralgia, addiction to opiates, alcohol, or cocaine and for alleviation of pain among patients with multiple sclerosis or in patients with spinal or cerebral disorders.

The most of the baclofen is eliminated by the kidneys without changes. In individuals with disturbed kidney function and particularly in the patients with end-stage renal disease (ESRD), the accumulation of the drug is occurred and the half-life of the drug is prolonged which can lead to significant side effects and complication including neurological deterioration and coma.

According to rapid increases in the prevalence of chronic kidney disease and due to frequency of musculoskeletal complain among these patients, it is possible that baclofen be used for this purpose. The aim of this review article is to investigate the effects and side effects of baclofen especially among patients with ESRD.

Materials and Methods

For this mini-review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ).

The search was conducted, using combination of the following key words and or their equivalents; acute interstitial nephritis, chronic interstitial nephritis, drug hypersensitivity, interstitial inflammation, chronic kidney disease, acute renal failure, baclofen, end-stage renal disease and interstitial nephritis.

Administration of baclofen in clinical practice

One of the drugs that can affect on the muscles, is baclofen. Gamma-aminobutyric acid (GABA) that has inhibitory neurotransmitter function, is analog of this drug. This drug affects on B type of GABA receptors in nervous cells. Therefore, when these receptors activated by baclofen, conductance of potassium increased into the nervous cells. Then, their GABA receptors activated and become hyperpolarized. Accordingly the activated cells can not release their excitatory neurotransmitter (1). Its relaxant function can inhibit mono and polysynaptic reflexes when baclofen reaches to spinal cord and causes inhibition in releasing of neurotransmitter that has excitatory function in nervous system. In addition, baclofen has sedative action on brain (2). However, in other diseases associated with increase muscularity tone and spasticity like multiple sclerosis, some spinal cord diseases, and some disorders in myelopathies, other drugs like diazepam can be administered too. However, effect of baclofen on muscles spasticity relief in multiple sclerosis is more than diazepam. On the other hand, this drug has no

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■ Implication for health policy/practice/research/medical education

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similar strength as carbamazepine in neuralgia treatment. Moreover baclofen is one of the choosing drugs for treatment of neuralgia, while this drug has weaker effect on muscular spasticity (3). Other prescriptions of baclofen except muscular spasticity, is in bladder spasticity, external urinary sphincter hypertonicity, dyssynergia in detrusor external sphincter, trigeminal neuralgia, cerebral palsy, chronic hiccup, some abuses like cocaine, alcohol, tobacco, and Huntington's chorea (4-6). Adverse effects of baclofen are sedation, dizziness, insomnia, slurred speech, pruritus and skin rash, but between the adverse effects of this drug, sedation is very frequent; but decrease in blood pressure and confusion is less prevalent among adverse effects of baclofen. In cases of baclofen overdoses status, respiratory depression, loss of brain stem reflexes, seizure and coma may happen. When other drugs that have CNS depressants activity like alcohol or azelastine, prescribed with baclofen, their depressant activity of these drugs increases depression of CNS and it has been recommended that avoided to administer such these drugs together (7). Beside these adverse interactions of baclofen, in some diseases like ESRD, administration of baclofen should be with caution, while baclofen has slight solubility in water. In fact, baclofen is one of the drugs that is in lipophilic category and has low volume distribution and protein binding. This drug can cross brain-blood-barrier, in patients that have poor renal function or have to use hemodialysis treatment. Baclofen can stay long time in body fluid and accumulate in it and therefore cause malfunction and negative changes in brain activities and its function. Therefore, it has been recommended to administer the dosage of baclofen lower than normal situations. One of the points that we have to consider it in using of anti-spasticity indication of baclofen, is the need to increase the drug dosage when more time elapsed since onset of muscle spasticity. This need to increase dosage, is also in old patients. Other sides that be recommended it is that when there is sudden withdrawal in baclofen dose, some complications like tachycardia, anxiety and sometimes visual hallucination can be occurred (8). Half-life of this drug in normal situation and orally is about 2 to 6 hours in healthy persons, but in those who have renal insufficiency, this half-life become longer and in addition rate of entering of baclofen into brain and central nervous system become more. This function causes some negative effects on central nervous system like depression, syncope and some disturbances human psychology. Furthermore the other effects of baclofen except in central nervous system, have been seen in other

body systems, for example, changing in respiratory rate and cardiovascular system also be seen in those who using baclofen. In patients that are under hemodialysis treatment, baclofen dose in such patients is significantly decreased. Hence, side effects of baclofen in patients that have poor renal function but use hemodialysis, can clear out from the body rapidly compared to patients that are not under hemodialysis, and have lesser baclofen toxicity (9,10).

It has been tested adverse and negative effects of baclofen that has inhibitory function on brain cells activity and nervous cells in central nervous system, can have influence on sides effects of this drug. For example, some adverse effects of baclofen when be used in normal dose like drowsiness, lethargy, orthostasis and nausea has been seen, but on the other hand when we used baclofen in larger dose, other adverse effects of baclofen on central nervous system cells and other cells that have been affected by this drug like depression in respiratory system, delirium, sedation, hallucinations, paraphasia can be seen (11). Among these negative effects of baclofen in situations that high dose of baclofen be used, preservative behaviors and delirium have lesser prevalence. It is interesting to note that inhibitory function of baclofen on nervous cells in central nervous system, can worse activity of seizure in patients that have history of seizure. It is assumed that inhibitory effects of baclofen, decrease threshold of nervous cells activity and thus increase seizure in such patients. In acute over dose of baclofen that its dose is more than 80 mg, can cause other side effects of this drug like areflexia, muscular hypotonia and change in respiratory function like depression besides nervous side effects of baclofen. In some situations, intoxication of baclofen can result to prolonged coma, absence in some brain stem reflexes, and even brain death in such patients have been seen (8,12). For treatment of these patients, it has been advised that enough time be given to these patients to baclofen clear from body. The risk of baclofen in patients who have poor renal activity and ESRD, is elevated. Baclofen clearance happens in kidney and when this renal clearance of baclofen from body decreased by poor renal function in such patients, intoxication and adverse effects of baclofen is very likely to be occurred. In some case reports, even using small dose of baclofen can alter mental activity. It is better to note that rate of baclofen intoxication in research conducted by El-Husseini et al, was higher as stage of chronic kidney disease was elevated (13).

Management of these patients that have baclofen intoxication is also very important. First step in management of baclofen intoxication, it has been recommended that we rely on supportive care. In addition because of possibility of respiratory depression in these patients, careful monitoring of respiratory system should be done. When renal function is normal or is in mild range, supportive care and patient monitoring can be enough but in patients that have poor renal function like ESRD or high ESRD, in such patients that drug intoxicating like mental alteration, myoclonus, seizure and respiratory

depression may likely occur, it is better we instantly use hemodialysis to clear baclofen from body rapidly (13). We have to consider some situations in management of these patients, for example, neurogenic adverse effects of baclofen in ESRD can have delay in return into normal situation even after high dose of baclofen clear out from body and reach to lower dose after using such treatment like hemodialysis. In addition, other factors like duration and frequency of dialysis and management of supportive care have to be regarded (14).

Authors' contribution

All authors contributed to the paper equally.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

The authors of this manuscript declare that they all have followed the ethical requirements for this communication. Also, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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