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Prolonged use of Furosemide in Pediatrics

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ABSTRACT

One of the main diuretics used in pediatric intensive care units is furosemide, which acts on the loop of Henle, causing an increase in urinary flow and electrolyte excretion. It has multiple uses in the pediatric age, being used in chronic pulmonary, renal, and cardiovascular pathologies, among other uses. However, its prolonged use can cause different effects from electrolyte imbalances such as hypokalemia, hypomagnesemia, hypercalcemia, alterations of the base acid state, and nephrolithiasis to ototoxicity.

Key words: Adverse effects, furosemide, pediatric

INTRODUCTION

Furosemide is the most used diuretic in neonatal and pediatric intensive care,[1-3] belongs to the sulfonamide group, and acts by blocking the Na + −K + −2Cl cotransporter in the ascending branch of the Henle loop increasing the urinary excretion of these electrolytes.[4,5] It is widely used for bronchopulmonary dysplasia, water overload, renal dysfunction, heart failure, and post-operative management of cardiovascular surgery.[6-9]

Its prolonged use is associated with electrolyte abnormalities such as hypocalcemia, hypomagnesemia, metabolic alkalosis, and hypercalcicuria is also described, which increases the risk of developing nephrocalcinosis and renal lithiasis, which has been observed more frequently in low birth weight and premature neonates. They required furosemide.[10]

Other effects described in addition to the time of use and high accumulated doses, especially when administered intravenously is the ototoxicity generally irreversible, causing alterations in hearing such as tinnitus, hearing loss, vertigo, and deafness, increasing the risk when associated with drugs such as aminoglycosides.[6,11,12] In this article, an updated and careful review of the published medical literature is made on the adverse effects and recommendations for the prevention of these.

USE OF FUROSEMIDE

Electrolyte fluid disorders

The mechanism of action of furosemide is to inhibit the Na + / K + / 2 Cl − cotransporter in the ascending branch of the Henle loop increasing the urinary excretion of these electrolytes.[6,5] It causes an increase in the excretion of Na + and Cl −, but also causes an increase in the excretion of calcium and magnesium due to the alteration in the transepithelial potential difference, the mechanism of action in two situations is explained in Figure 1. It can be explained how in excessive amounts of prolonged diuretic use can lead to alterations in the balance and electrolytes with depletion of water, which can be manifested with hypotension due to the depletion of volume of extracellular fluid, hyponatremia, hypomagnesemia, hypercalcemia, and hypokalemia.[5,13,14]

The increase in the release of Na + toward the distal tubule and proximal tubule, triggers an increase in urinary excretion of K + and H +, which produces a metabolic alkalosis and hypokalemia,[8] which causes a pseudo-Bartter syndrome giving hypomagnesemia symptoms, hypocalcemia, and persistent metabolic alkalosis as in the case described.[15]
The exhaustion of magnesium plays a very important role, this is important in the enzymatic reaction, in energy-producing metabolism, and in protein synthesis, and membrane transport. Depletion of magnesium plays a role very important, by the enzymatic reaction in the production of energy metabolism and synthesis and membrane protein transport. The main site of reabsorption of magnesium is a renal level in the loop of Henle in 70-80%, which affects the maintenance of furosemide decreasing intracellular magnesium and excessive loss in the urine to hypomagnesemia causing, for example, the myocardial involvement with arrhythmias such as atrial fibrillation.\textsuperscript{[14,16-19]}

Magnesium and calcium are reabsorbed paracellularly creating tight junctions known as paracelin-1 or claudin1. In the distal tubule, resorption is described by an active mechanism using the TRPM67 magnesium channel, while the active mechanism in the thick loop of Henle and distal tubule is unknown, thought to be driven by the electrochemical gradient of the Na\textsuperscript{+}/K\textsuperscript{+} -ATPase pump when the magnesium reabsorption is inhibited, the potassium channels are reversibly inhibited by altering the NKCC2 cotransporter and in the production of the electric gradient generated with the potassium exit Figure 1b.\textsuperscript{[20]}

Nephrolithiasis also this diuretic use is related to the formation of nephrolithiasis is urolithiasis or nephrocalcinosis, secondary to given hypercalciuria cations Ca\textsuperscript{2+} is reabsorbed in the loop of Henle by passive mechanisms of transport of chloride sodium. Nephrocalcinosis refers to calcium deposits in the kidney tissue, can be spinal cord, cortical or diffuse, and histologically intratubular and interstitial, and was described for the 1st time in 1982 in premature patients with prolonged use of furosemide; the rate of prevalence ranges between 7 and 64% in premature with low weight for gestational age.\textsuperscript{[21-23]} He is explained by their renal immaturity that facilitates the retention of the crystal and its low rate of glomerular filtration. In premature patients who used cumulative dose of furosemide 10 mg/kg may increase the risk of nephrocalcinosis up to 48 times more, and in some studies, this is considered the factor with greater risk for nephrocalcinosis.\textsuperscript{[21,24-26]}

Andrioli et al. conducted a retrospective study of patients under 1 year of age with renal lithiasis and nephrocalcinosis, where they evaluated their follow-up, 44% of these patients had received furosemide, 22% corresponded to nephrocalcinosis, and found that 37% of these cases diagnosed patients presented renal lithiasis in their evolution.\textsuperscript{[27]} Other studies of nephrocalcinosis follow-up in children have shown a spontaneous resolution, establishing that around 57.1% of patients with premature nephrocalcinosis at 1 year had spontaneous resolution.\textsuperscript{[24,25]}

Ototoxicity and drug interactions
Furosemide is part of the most common drugs that produce ototoxicity; this occurs because the transporter Na\textsuperscript{+} K\textsuperscript{2}Cl\textsuperscript{2}, also present in marginal cells and stria vascularis, leads to inhibition of potassium reabsorption and decreased endocochlear potential, and usually, its affectation is bilateral and usually reversible, although permanent damage has been described. High doses of furosemide, prolonged treatment, and intravenous administration increase this risk, it has also been described that when it is administered with drugs such as aminoglycoside-type antibiotics the toxicity synergy increases.\textsuperscript{[28-31]}

Prevention of alterations due to prolonged use of furosemide
For its prevention of these effects with the use of furosemide, it has been described that low initial dose should be used until
achieving an adequate fluid balance and urine production between 1 and 3 ml/kg/h, and not to exceed cumulative dose of 10 mg/kg.\textsuperscript{[32,33]}

Gulbis and Spencer conducted a systematic review, evaluating the efficacy of continuous intravenous furosemide, and found that this form of administration maintained a sustained diuresis unlike intravenous furosemide administered intermittently after cardiovascular surgery.\textsuperscript{[34]} Other studies also support use in cardiovascular pathologies, the use of furosemide infusion continues on intermittent use, as advantage shown diuresis steadily but described side effects as the disorder of the electrolytes and long-term deterioration of renal function; so it is recommended for use only in unstable patients to maintain a restricted use.\textsuperscript{[35-40]}

In our case, we can observe that I present as adverse effects to this loop diuretic, electrolyte disorders, which could be due to the initiation of continuous intravenous furosemide in its postsurgical or prolonged use of it later, requiring corrections in electrolytes daily in your stay at pediatric intensive care; it is common that these electrolyte disorders lead us to other pathologies and especially in our pediatric population to pathologies of genetic origin such as Bartter syndrome, which is why it is important to know about the adverse effects of drugs used, for their prevention and proper use.

**CONCLUSIONS**

Compression toxicities and electrolyte disturbances secondary to loop diuretics like furosemide are a neglected subject, by which you want to show because the prolonged use of this medication must be especially careful, you should create awareness that the use of diuretics requires a careful use, take into account time of use, dosage, avoiding high doses, to reduce doses toxic and high concentrations in addition to take into account that the therapy long-term power all adverse effects.

**REFERENCES**

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