



Trastornos electrolíticos inducidos por diuréticos de asa en los adultos mayores. Revisión sistemática

Loop diuretic-induced electrolyte disorders in older adults. a systematic review

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Palabras claves:

Electrólitos,
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mayores,
hiponatremia,
reacciones adversas.

Keywords:

Electrolytes,
diuretics, older
adults,
hyponatremia,
adverse reactions.

Resumen

Introducción: el uso crónico de medicamentos diuréticos de asa, desencadenan trastornos electrolíticos como parte de sus reacciones adversas (RAMS). Se ha observado que los adultos mayores tienden a desarrollar este tipo de RAMS, debido a los cambios en la función renal al envejecer. **Objetivo:** analizar los trastornos electrolíticos que provocan los diuréticos de asa en la población adulta mayor, según la evidencia científica publicada durante el periodo 2018-2023. **Metodología:** revisión sistemática documental, usando el método Prisma; se recopiló información de diferentes estudios retrospectivos, observacionales y transversales. **Resultados:** se observó una prevalencia significativa de hiponatremia, hipomagnesemia e hipocloremia por el uso crónico de diuréticos de asa, la edad de los pacientes fue de 60 años en adelante, con respecto al potasio, no queda claro si la hipo o hiperpotasemia es más frecuente, ya que los estudios sugieren una prevalencia similar de ambas condiciones. **Conclusiones:** por otro lado, los electrolitos menos alterados fueron el calcio y el fósforo. La buena alimentación durante el uso de diuréticos de asa contribuye al equilibrio de varios electrolitos. **Área de estudio general:** Bioquímica y Farmacia. **Área de estudio:** Farmacología Clínica. **Tipo de estudio:** Artículo de revisión sistemática.

Abstract

The chronic use of loop diuretic medications triggers electrolyte disturbances as part of their adverse drug reactions (ADRs). It has been observed that older adults tend to develop this type of ADR due to changes in renal function as they age. This research aimed to analyze the electrolyte disturbances caused by loop diuretics in the older adult population, according to the scientific evidence published from 2018-2023. The methodology applied was a systematic documentary review using the PRISMA method. Information was collected from different retrospective, observational, and cross-sectional studies. There was a significant prevalence of hyponatremia, hypomagnesemia, and hypochloremia due to chronic use of loop diuretics. The patients were 60 years and older. Concerning potassium, it is unclear whether hypo- or

hyperkalemia is more common since studies suggest a similar prevalence of both conditions. On the other hand, the least altered electrolytes were calcium and phosphorus. Good nutrition while using loop diuretics contributes to the balance of various electrolytes. General area of study: Biochemistry and Pharmacy. Area of study: Clinical Pharmacology. Type of study: Systematic review article.

Introduction

Most people as they age tend to have a higher risk of chronic diseases, including congestive heart failure (CHF), edema, high blood pressure, nephrotic syndrome, and acute kidney failure, which are the most common in older adults. The causes can vary. The most commonly used medications for this type of disease are loop diuretics, which continuously improve symptoms or complications. However, the chronic use of loop diuretics causes different homeostatic imbalances.(1, 2).

The diuretic effect depends on the amount of medication present in the tubular lumen and the degree of renal function. Electrolyte disorders are recurrent as a consequence of polypharmacy, as happens in older adults and in patients with comorbidities. According to statistical data, 24% of the adult population over 65 years of age and 31.4% of patients aged 85 years suffer from four or more chronic conditions, because the immune system becomes more susceptible to diseases with age.(3, 4, 5).

The incidence of electrolyte disorders varies according to the electrolyte that is altered, as do the clinical manifestations, which in turn are associated with the magnitude of the imbalance, and can range from asymptomatic to severe alterations. Hyponatremia is one of the most frequent electrolyte disorders due to the prolonged use of furosemide, according to the data analyzed in this research.(6, 7).

Methodology

A bibliographic review of references based on research articles related to electrolyte disorders induced by the chronic use of loop diuretics in the elderly was conducted. Information was collected through a search in databasesdatabase that includes recognized and high-impact indexed journals such as: PubMed, SciELO, Springer, Medline, Taylor & Francis, Google Scholar, and the Virtual Library of the Catholic University of Cuenca. In addition, articles in English and Spanish published from six years ago to 2023 were included.

Eligibility criteria

- Randomized clinical trials
- Cohort studies
- Observational studies
- Review studies of the pharmacodynamics of loop diuretics.
- Clinical perspectives

Inclusion criteria

- Articles published during the period 2018-2023.
- Original articles in English and Spanish.
- Original national and international articles.
- Articles that address people over 50 years of age.

Exclusion criteria

- Restricted access articles
- Literature review articles

For the search for information, keywords were used and Boolean operators were included that allow us to logically connect the main variable in this case: Electrolytes AND loop diuretics/ furosemide NOT thiazide diuretics/ "Characteristics" PRE/4 "loop diuretics"/ electrolytes AND imbalance/ loop diuretics AND Older adults NOT young people / Adverse reactions AND loop diuretics / Hyponatremia "OR" Hypernatremia AND loop diuretics / mechanism of action AND furosemide / Chronic "OR" furosemide / electrolyte disorders NEAR/3 Heart failure / Hyperkalemia "OR" Hyperchloremia AND older adults / Mortality AND older adults AND electrolyte disorders.

These parameters were used to improve specificity in the search, to unite variables that may have the same meaning and thus avoid confusion when searching the different databases already mentioned. For inclusion and exclusion, the studies were evaluated using the PRISMA method, a flow chart that included the identification, screening, eligibility, and selection of each study.

The data collected were presented in a narrative table prepared based on systematic information from the literature obtained from the different articles. Finally, a comparative analysis was developed where the most important aspects of this research were detailed.

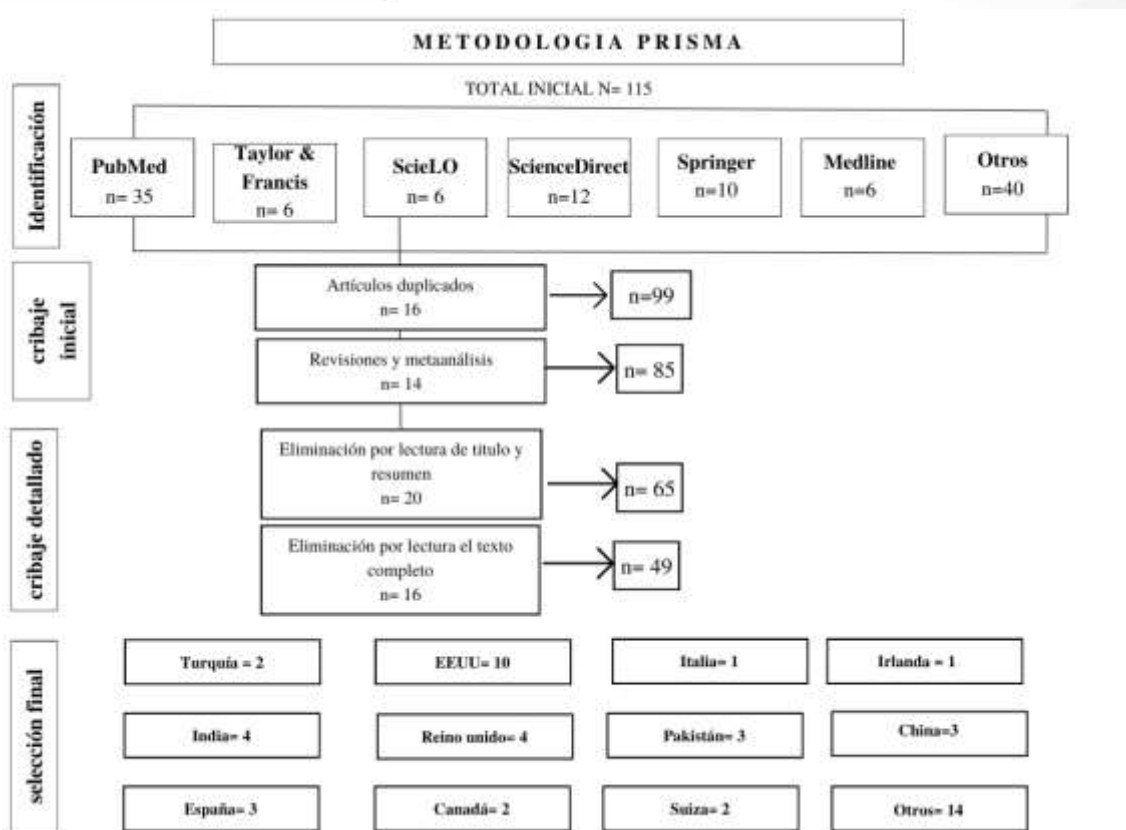


Figure 1. Flowchart of the raw methodology

Note: Data taken from different search engines for scientific articles and attached publications

Results

Scientific evidence shows that loop diuretics, by frequently acting on the inhibition of sodium, potassium and chloride cotransporters, located in the cells of the thick ascending limb of the loop of Henle in the nephron, cause an increased excretion of water and electrolytes in the urine. The alteration of sodium, potassium, calcium, phosphorus, magnesium and chloride is highlighted in some studies, according to the type of alteration one of the prefixes "hypo" and "hyper" is added followed by the altered electrolyte and the ending "emia"(8).

The following table presents observational, cross-sectional and retrospective studies that have been conducted over the past 6 years regarding the prevalence of electrolyte disturbances due to the frequent use of loop diuretics.

Table 1. Analysis of altered electrolytes

Author	Year	Sample	altered electrolytes	Main results
Trelles Torres Anabelle Mariuxi.	2019	165 older adults between the ages of 65 and 74	Sodium	Hyponatremia was manifested in 55% of cases with chronic use of furosemide. It was observed that this drug is mostly prescribed for diabetes mellitus and arterial hypertension.(9).
Heybeli et al.	2022	464 elderly people, the average age was 72 to 83 years	Sodium, potassium, calcium, phosphorus, magnesium	Hyponatremia (11.2%), hypomagnesemia (9.1%) and hypermagnesemia (8.8%) were relevant. In contrast, hypokalemia was frequent (0.7%), as was hyperkalemia (6.7%), hypernatremia (1.7%), hypocalcemia (4.7%), hypercalcemia (2.6%); hypophosphatemia (5.0%) and hyperphosphatemia (2.6%). 1.5% had 2 or more electrolyte imbalances at the same time.(10).
Ravioli et. al.	2022	376 adult patients admitted to the emergency department.	Sodium	0.7% had a serum sodium level greater than 145 mmol/L on admission. Of this percentage, 0.2%, corresponding to 109 patients, had clinically relevant hypernatremia greater than 147 mmol/L. Recent falls were present in 17%, symptoms of drowsiness in 42% and disorientation in 30%.(11).
Real et al.	2020	198 patients, mean age was 55 years.	Magnesium	Hypomagnesemia was manifested in 31% of the 198 elderly adults analyzed due to the use of furosemide, anxiety symptoms were identified in 9.09%, muscle spasms in 8.08% and headache in 31.31%(12).

Table 1.Analysis of altered electrolytes (continued)

Author	Year	Sample	altered	Main results
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			electrolytes	
Cuthbert et. al.	2018	5,613 patients with low serum chloride.	Chloride	Prevalence of 10.7% of hypochloremia in patients with heart failure. Patients with hyperchloremia had a lower rate of prescription of furosemide compared to patients with hypochloremia. Sudden death was more frequent among patients with hypochloremia.(13).
Patel et. at.	2022	177 patients diagnosed with high blood pressure.	Potassium, sodium, chloride	33 adults aged 61 years were treated with loop diuretics, hyponatremia (33.8%), hypokalemia (19%) and hyperkalemia (7%) were identified, there was no significant percentage of chloride. Women tended to present more hyponatremia than men.(14).
Rivera-Juarez et al.	2020	603 adults with severe dyskalemia.	Potassium	240 adults presented hyperkalemia and 363 hypokalemia, in total 178 adults used loop diuretics, hypokalemia was associated in 28%, in older adults (55 to 81 years), hyperkalemia instead occurred in 34% in ages between 57 and 81 years(15).

Discussion

Of all the studies analyzed, regarding the alteration of sodium due to frequent use of loop diuretics, a total of 263 adults out of 769 presented relevant hyponatremia or hypernatremia. Of these, 143 adults were between 65 and 93 years old. Trelle T. in his study indicates that hyponatremia (low sodium levels) is observed in 55% of a total of 165 older adults between the ages of 65 and 74 years, similarly hyponatremia was prevalent in 11.2% in the study by Heybeli et al. where 195 adults between the ages of 72 and 93 years were analyzed.(8, 9, 10, 13).

In a third study, hyponatremia was also present in 33.8% of 33 older adults, who were 61 years of age or older. Hypernatremia (high sodium levels) was present in 0.2% of 195 adults who were admitted to the emergency room and were using loop diuretics as treatment, with significant symptoms of drowsiness, disorientation and falls.(6,

7) Hyponatremia affects most of the elderly population due to the chronic use of furosemide (loop diuretic). (10, 13).

Approximately 20 to 40% of older adults commonly use furosemide in the treatment of edema related to high blood pressure, heart failure, acute renal failure, among other diseases. Unlike other loop diuretics, this one has a potent and rapid diuretic action, which is why it is called high ceiling. (16, 17). Eating salty, canned foods, broths or soups can help balance sodium. (18, 19).

Regarding potassium disorders, 406 older adults with dyskalemia were analyzed in total, of which 6.7% showed hyperkalemia (high potassium levels), as opposed to hypokalemia (low potassium levels), which occurred in 0.7%. In a second study, the prevalence of hypokalemia was shown in 19%, while hyperkalemia occurred in 7%. On the other hand, in a third study, a percentage of 28% of 178 older adults was found to have hypokalemia, as opposed to 34% of hyperkalemia. (10, 14, 15).

Therefore, hyperkalemia was more frequent when using loop diuretics chronically according to the three articles analyzed. However, Yaqoot et al. indicated in their study that hypokalemia is more prevalent in patients with heart failure who are treated with diuretics, this disorder was associated with higher mortality and morbidity, since it increases heart rate. (20) Similarly, another study indicated that hypokalemia tends to occur largely due to the use of loop diuretics (21.74%), osmotic laxatives (6.8%), catecholamines (21.74%) and thiazide diuretics (8.69%). (20, 21).

The combination of loop diuretics with potassium supplements is one of the options used to counteract the loss of potassium caused by loop diuretics. These supplements have different forms of presentation, which in addition to increasing potassium levels, help balance fluids in the body. (23). Mansoor et al. in their article published in September 2021, describe that potassium levels are higher in patients with hemorrhagic stroke, any alteration of this electrolyte in the body can cause a decline in the neurological conditions of these patients. (23, 24).

Thiazide diuretics and potassium binders such as sodium cyclosilicate and patiromer can be combined with torasemide and furosemide to control potassium levels. Sodium zirconium cyclosilicate reduces potassium levels, patiromer facilitates the use of loop diuretics in patients with renal failure and heart failure. (27, 28).

Magnesium levels were also altered in the study by Heybeli et al. Hypomagnesemia (low magnesium levels) occurred in 9.1% and 32% of a total of 195 and 198 older adults analyzed, and they also presented symptoms of anxiety, muscle spasms and headache due to this disorder. Raju et al. indicated that Uncontrolled hypomagnesemia can cause muscle

weakness and respiratory failure, while hypermagnesemia (high levels of magnesium) is associated with neuromuscular blockade and therefore muscle paralysis.(10,29).

Hypomagnesemia is very common in older adults, compared to hypermagnesemia. In a study conducted by Gautam and Khapunj, 42.8% of women between the ages of 60 and 70 presented severe hypomagnesemia. Although men are generally the most affected by this condition, it may be due to the use of medications, more frequent alcohol consumption than women, and gastrointestinal diseases.(30).

Eating legumes, nuts and grains can help in the correct balance of magnesium, there are also oral magnesium supplements, which can be taken in the form of magnesium gluconate.(31, 32)For mild hypomagnesemic state, sodium restriction and diuretics should be considered.(33,34)In an emergency intervention, parenteral administration of magnesium is effective.(35).

Hypochloremia, i.e. low chloride levels, occurred in 59% of 246 elderly patients with heart failure analyzed; furosemide was found in the treatment regimen of the patients. However, in a second study, a significant percentage was not observed due to the chronic use of loop diuretics.(13,14)Zhang et al. indicated that older adults are more likely to die from hypochloremia, regardless of gender.(21).

Hypochloremia is considered an independent marker of short- and long-term mortality among patients with heart failure (CHF) and predicts a decreased response to diuretics.(36, 37). While hyperchloremia (high chloride levels) is common due to the indiscriminate use of intravenous solutions with a high chloride content and patients with septic shock or sepsis. In another study, significant hypochloremia was observed due to the high dose and constant use of furosemide.(38, 39).

Loop diuretics may contribute to metabolic alkalosis by reducing extracellular fluid volume in older adults with heart failure, even hypochloremia may occur with hyponatremia, saline may help the administration of intravenous furosemide in those patients who are in intensive care units(39, 40).

In relation to calcium and phosphorus, these electrolytes showed a lower incidence in the majority of studies analyzed. Hypocalcemia (low calcium levels) was present in 4.7% of the 195 older adults analyzed, while hypercalcemia (high calcium levels) was seen in 2.6%. Regarding phosphorus disorders, hypophosphatemia (low phosphorus levels) was observed in 5.0% and hyperphosphatemia (high phosphorus levels) in 2.6%.Shrimanker et al. in July 2022, clarifies that hypocalcemia can cause muscle cramps and spasms, paresthesias, tetany or seizures(10, 41)Hypercalcemia, on the other hand, can cause general malaise, weakness, depression, apathy and inability to concentrate.(42,43).

In a study carried out by Bonanad C. et al. in Spain in 2021, it was analyzed hypocalcemia in patients with severe clinical forms, indicates that the risk is significantly increased by age, gastrointestinal losses and inflammatory status, the results suggest that surveillance is necessary in patients with severe disease. For calcium balance, it is necessary to consume dairy products, tofu and fortified products.(43,44,45).

Phosphorus disturbances can contribute to the development of kidney damage and also contribute to mortality in critically ill elderly patients, so constant monitoring and early detection are necessary to balance phosphorus levels appropriately.(42,47).

In general, a balanced diet is necessary, since studies show that it can significantly control disorders and electrolytes that may appear during the use of loop diuretics. Since they provide the body with essential nutrients to function optimally and prevent nutritional deficiencies(48, 49).

Conclusions

- Electrolyte disorders in older adults were analyzed in different studies, considering the eligibility, inclusion and exclusion criteria. The information collected suggests that electrolyte disorders contribute to mortality in these patients, due to decreased renal function. Hyponatremia was found to be more frequent than hypernatremia due to prolonged use of loop diuretics, with each percentage being relevant.
- On the other hand, the presence of both hypokalemia and hyperkalemia was observed; since, according to this research, they have a similar prevalence. Hypomagnesemia and hypochloremia showed a lower incidence compared to the other alterations, however, the presence of these two conditions can cause damage to the muscles and heart. Regarding the alteration of calcium and phosphorus, they do not usually occur frequently.
- Furosemide was the most commonly used loop diuretic by older adults with heart failure, high blood pressure, and other conditions. Several studies have indicated that good nutrition while using loop diuretics, as well as the combination with certain supplements, chelators, or other diuretics, significantly influence the balance of various electrolytes.

Conflict of interest

There is no conflict of interest.

Authors' contribution statement

Judith Guevara Sarmiento: Responsible for the complete execution of this document, including planning, research, writing and general organization of the content.

Dr. Maritza del Rosario Martínez León, Mgt: Responsible for the critical review, correction and academic guidance of this document.

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