Reply to "Letter to the Editor — Consensus document on the management of hyperkalaemia"

Respuesta a «Carta al Director - Documento de consenso sobre el abordaje de la hiperpotasemia»

Dear Editor,

We are grateful for the interest shown by Dr Lorente in the consensus document on the management of hyperkalaemia, which was open for public comment between December 2022 and January 2023.[1] Dr Lorente made a number of comments, which we have summarised and responded to below.[2]

Boxes 1 and 2 refer to the acute treatment of severe hyperkalaemia, not to the mechanism of action of the interventions. In a section on the acute treatment of severe hyperkalaemia, it should be noted that the first measures are still: (1) Antagonise the effects of potassium on the cell membrane: calcium gluconate or calcium chloride; and (2) Introduce potassium into the cells, as shown in Box 1. Avoid giving the impression that the only measure to be applied is to increase digestive elimination. In this regard, ENERGIZE (NCT03337477) was a multicentre, double-blind, placebo-controlled, Phase 2 clinical trial evaluating the efficacy of sodium zirconium cyclosilicate (SZC) in the emergency treatment of hyperkalaemia, added to glucose and insulin, with the primary endpoint being the change in serum potassium.[3] We have not found a similar clinical trial for patiromer (standard measures plus patiromer compared to standard measures plus placebo) with published results,[4] so it was not possible to include patiromer in Boxes 1 and 2. However, the document notes that the PLATINUM study (NCT04443608), a multicentre, randomised, placebo-controlled clinical trial evaluating aspects relating to the use of patiromer in the context of hyperkalaemia in the emergency department, is currently underway. Although we agree with Dr Lorente that it seems reasonable to start chronic treatment as early as possible, Boxes 1 and 2 refer to a specific situation, which is the acute treatment of severe hyperkalaemia.

We also agree with Dr Lorente that the 2022 consensus document, Řëcommendations for the management of hyperkalaemia in the emergency department;̈ of the Spanisch Society of Emergency Medicine and Emergencies (SEMES) [Sociedad Española de Medicina de Urgencias y Emergencias], the Spanish Society of Cardiology (SEC) [Sociedad Española de Cardiología] and the Spanish Society of Nephrology (S.E.N) [Sociedad Española de Nefrología] mentions gastrointestinal cation exchangers in the algorithm for the treatment of hyperkalaemic emergency, without naming any one in particular.[5] Moreover, we also agree that patiromer, SZC and ion exchange resins such as sodium or calcium polystyrene sulfonate are mentioned in the text. However, the text does not present evidence on the use of patiromer or ion exchange resins in this area. The only clinical trial cited in the setting of emergency hyperkalaemia is ENERGIZE,[3] whose authors conclude that SZC with insulin and glucose may provide incremental benefit in the emergency treatment of hyperkalaemia over insulin and glucose alone. Therefore, our interpretation is that although the SEMES-SEC-S.E.N document does not mention any specific gastrointestinal cation exchanger in the algorithm for the treatment of hyperkalaemic emergency, the fact that it only presents evidence for one of them would clarify its position. We would have liked to be able to include patiromer in this area to avoid controversy, but we cannot do this arbitrarily, and we must to base the decision on the available evidence.

We agree with Dr Lorente that the Ëuropean Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstancesïnclude patiromer, SZC and calcium polystyrene sulfonate among the measures to remove potassium from the body in the emergency treatment of hyperkalaemia.[6] The text explains that SZC takes effect within the first hour and lowers blood potassium by 1.1 mmol/l in the first 48 h, while the onset of patiromer action is slower, being evident at 4–7 h and lowering blood potassium by 0.36 mmol/l in 72 h.[6] They consider the above-mentioned studies to be inconclusive.[3,4]

Dr Lorente points out that Box 3 gives a broad description of SZC, but not of patiromer. The extra information is that SZC contributes to the correction of metabolic acidosis. This statement is based on an exploratory analysis of three clinical trials, as reported in the text.[1,7] Dr Lorente points out that patiromer also provides pleiotropic effects, such as lowering phosphorus levels. We agree with Dr Lorente that this may be an advantage for patients with chronic kidney disease (CKD) and hyperphosphataemia.

Unfortunately, the reference he provides is from July 2023,[8] so it is outside the evidence review period. This information will be taken into account in subsequent updates of the document.

Dr Lorente asks on what studies we based the suggestion in the algorithm that SZC should be considered particularly in patients with CKD or metabolic acidosis. The rationale for

DOI of original article:
https://doi.org/10.1016/j.nefro.2023.09.009.

considering SZC in patients with metabolic acidosis, a common and often undiagnosed condition in CKD patients, is that SZC can correct it.[7] Given the high prevalence of undiagnosed metabolic acidosis in CKD, this was expressed as "CKD or metabolic acidosis". However, in an ideal world where the acid-base status of CKD patients is regularly assessed, the term "CKD with metabolic acidosis" could preferably be used in addition to isolated metabolic acidosis.

Dr Lorente points out that in the meta-analysis cited above, there is a higher prevalence of CKD and other comorbidities expressed as a percentage among the 654 participants in the trials testing patiromer than among the 1102 participants in the trials testing SZC.[9] Although this is a minor point, it is worth noting that the total number of patients with CKD and other comorbidities was higher in the trials testing CSZ than in those testing patiromer.

Dr Lorente points out that there is no mention in the consensus document that SZC has a European Medicines Agency (EMA) alert for intestinal perforations.

Indeed, the EMA states that, "*The risk for intestinal perforation with the use of Lokelma is currently unknown. Since intestinal perforation has been reported with potassium binders including Lokelma, specific attention should be paid to signs and symptoms related to intestinal perforation*".[10] For patiromer, "*Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies. Gastrointestinal ischaemia, necrosis and/or intestinal perforation have been reported with other potassium binders. The benefits and risks of administering patiromer should be carefully evaluated in patients with current or history of severe gastrointestinal disorders, before and during treatment*".[11]

Dr Lorente cites the EMA as stating that SZC should be separated by 2 h from tacrolimus administration because of a possible interaction with tacrolimus; this decision is dated 10 January 2023 and was therefore issued after the evidence review period.[10] In any case, it is correct that the consensus document does not detail the drug-drug interactions of the drugs discussed. It is obvious that every prescribing physician should periodically review the conditions of use of the medicines he or she prescribes. In this regard, the EMA's "summary of product characteristics" for patiromer explains in the "Posology" section that "Administration of Veltassa should be separated by 3 *hours from other oral medicinal products* (see section 4.5, shown in the annex)". Notably, it does not make an exception for tacrolimus, and the EMA does not include *in vivo* studies on patiromer and tacrolimus where the area under the tacrolimus curve is determined, such as the study that motivated the EMA recommendation for SZC, which analysed a dose of SZC (15 g) which is not among the presentations available in Europe (5 and 10 g).[11] The "posology" section of the EMA's "summary of product characteristics" for SZC has no limitations with respect to other drugs.[10] However, in section 4.5, shown in the Annex, it states, "However, sodium zirconium cyclosilicate should be administered at least *2 hours before or 2 hours after oral medicinal products with clinically meaningful gastric pH dependent bioavailability*".

Finally, Dr Lorente suggests that the use of patiromer could be associated with a lower risk of heart failure hospitalisations compared to SZC in real clinical practice. However, the article he cites found no statistically significant differences in heart failure hospitalisations between SZC and patiromer.[12]

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https://doi.org/10.1016/j.nefroe.2023.09.006

Extended online hemodiafiltration associated with single-pass albumin dialysis, a feasible alternative for patients with hepatorenal insufficiency

Hemodiáfiltración en línea extendida asociada a diálisis con albúmina de paso simple, una alternativa factible para pacientes con insuficiencia hepatorenal

Dear Editor,

Liver failure is a severe condition with a high mortality rate resulting from the loss of the liver's capacity for detoxification of endogenous substances (ammonium, bilirubin, glutamine, lactate), regulation and synthesis function (coagulation factors, albumin).[1,2] The consequences are coagulation disorders, circulatory dysfunction, encephalopathy, and multi-organ failure including kidney failure.[2] Treatment of liver failure depends on its cause and reversibility. Liver transplantation is an effective treatment in fulminant failure or progression of chronic liver disease, while in transient situations (viral infections, poisoning) there may be regeneration of the liver parenchyma and functional recovery.[1,2] In these situations (awaiting transplantation or functional improvement), supportive therapies aimed at clearing liver toxins may become necessary, to which dialysis may be added to counteract the accompanying kidney failure.[2] For the treatment of acute liver failure there are five artificial systems in use: molecular adsorbent recirculation system (MARS); single-pass albumin dialysis; fractionated plasma separation and adsorption (Prometheus); selective plasma filtration therapy; and haemodiafiltration.[2–5] Single-pass albumin dialysis was described as an alternative to sophisticated devices (MARS) in the late 1990s. It is the simplest artificial liver device and can be applied in any unit where a standard dialysis monitor is available. No additional adsorbent columns or circuits are required. The patient's blood is dialysed through a high-flux dialyser using an albumin-containing dialysis fluid. After passing through the dialyser, the dialysate is discarded (in contrast to MARS, where albumin dialysate is regenerated), and toxins are thus removed from the system. Considerable amounts of albumin are used, making this treatment potentially costly.[4] We describe here a case of liver failure associated with acute renal failure, in which extended online haemodiafiltration associated with single-pass albumin dialysis was performed.

The patient was a 39-year-old woman diagnosed with adenocarcinoma of the colon with liver metastases in the left lobe. Reversed chemotherapy with adjuvant criteria was chosen as a therapeutic strategy, producing a good response with a reduction in the volume of the primitive tumour and liver metastases, for which reason a coordinated left hepatectomy was performed. At 48 h, the patient showed a progressive increase in bilirubin and transaminases, associated with a severe decrease in prothrombin time and lactic acidosis (Table 1). Clinically she had marked jaundice, hepatic encephalopathy and sustained haemodynamic deterioration with shock. In this context, she also developed anuric acute kidney injury (KDIGO 3). In view of the patient's acute liver failure and anuric acute kidney injury, renal replacement therapy with extended online haemodiafiltration (8 h) was opted for, combined with dialysis with single-pass albumin (treatment of acute liver failure). Haemodiafiltration provides an additional contribution to the clearance of water-soluble residues associated with liver failure. For the procedure we used a Fresenius-4008H® monitor, Fresenius-Acqua1C®multipass osmosis, Fresenius-FX80® high-flux dialysers (2), continuous infusion pump (2) to generate circulation of the albumin

DOI of original article:
https://doi.org/10.1016/j.nefro.2021.09.024.