HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2051414 (2 pages)
https://doi.org/10.1080/21645515.2022.2051414

Taylor & Francis
Taylor & Francis Group

LETTER

Reply letter to the editor concerning the article 'Safety of Sars-Cov-2 vaccines administration for adult patients with hereditary fructose intolerance'

Elsa Izquierdo-Garcia, Elena Alba Alvaro Alonso, Berta Montero Pastor, Ana Such Díaz, and Ismael Escobar Rodríguez

Pharmacy Department, Infanta LeonorUniversity Hospital, Madrid, Spain

ABSTRACT

According to the current European medicines legislation, on the labeling is mandatory a warning contraindicating for hereditary fructose intolerance (HFI) patients medicines with oral or parenteral fructose and sorbitol, and oral sucrose, invert sugar, isomaltitol, lactitol and maltitol, but parenteral sucrose is not mentioned. Intravenous administration of sucrose does not increase blood glucose concentrations, because sucrose is poorly oxidized to CO_2 and mainly excreted in the urine as a disaccharide; absence of enzimatic activity outside the gut explains why there is not a warning for parenteral sucrose presentations. For this reason, parenteral drugs with sucrose are allowed in HFI patients. Nevertheless, due to interindividual variability and the fact that not all parenterally administered sucrose is recovered in urine, HFI patients need to be closely monitored after parenteral administration of sucrose-containing drugs, especially when the amount exceeds the maximum permissible thresholds.

ARTICLE HISTORY
Received 7 February 2022
Accepted 7 March 2022

Dear Editor,

We have read with interest the following letters to the editor "**Safety of Sars-Cov-2 vaccines administration for adult patients with hereditary fructose intolerance (HFI)**" by *Silvana A.M. Urru et al.*[1] and its reply letter which analyses the situation in children diagnosed with HFI by *Rebeca Saborido-Fiaño et al.*[2] recently published in Human Vaccines & Immunotherapeutics Journal.

In these articles authors analyzed the amount of sucrose (glucose-fructose disaccharide) in the different presentations of the Sars-Cov-2 vaccines available in Europe: Comirnaty® (BioNTech/Pfizer) with 6 mg sucrose/dose, Spikevax® (Moderna) with 43.5 mg sucrose/dose, Vaxzevria (AstraZeneca) with 30 mg sucrose/dose and Janssen Covid-19 vaccine with no sucrose content. These authors affirmed that these vaccines are safe in HFI adult and children because these vaccines contain less than the threshold limit recommended by *the Istituto Superiore di Sanità of Italy* for vaccines (2.4 mg/kg/dose)[3] with the exception of Spikevax® in children ≤3 years of age. All of them are approved for intramuscular administration.

The use of sucrose or polyols, such as sorbitol, is widely used in protein/peptide drugs (mainly antibodies or vaccines) or other intravenous drugs because of their stabilizing and cryopreserving properties. According to the current European medicines legislation, is mandatory a warning in medicines with oral and parenteral fructose and sorbitol, and oral sucrose, invert sugar, isomaltitol, lactitol and maltitol contraindicating for HFI patients,[4] but parenteral sucrose is not mentioned.

The sucrose metabolism in humans after its parenteral administration has not been extensively studied. There are older studies that indicate that after intravenous administration of sucrose in humans there is no increase in blood glucose concentrations, because sucrose is poorly oxidized to CO_2 and is mainly excreted in the urine as a disaccharide (after iv administration of 10 g of sucrose 6.3 ± 1.3 g of the sucrose was excreted in 24-hour urine sample).[5] Although not all of the sucrose administered is recovered, these data suggest that there is no disaccharidase activity outside the gut, so that parenteral administration of sucrose would not release fructose. Absence of this enzymatic activity outside the gut explains why there is not a warning for parenteral sucrose presentations in the currently legislation.

On the other hand, parenteral administration of fructose or sorbitol is contraindicated in HFI patients, because they pass through directly into the bloodstream. Sorbitol will be converted to fructose almost completely by iditol or sorbitol dehydrogenase and fructose will follow the fructolysis pathway, which is deficient in these patients due to Aldolase B deficiency.[6] Furthermore, European Medicines Agency (EMA) indicates that intravenous medicines with fructose or sorbitol must be contraindicated in babies and young children (below 2 years of age) because they may not yet be diagnosed with HFI. EMA also indicates to review these patients' clinical history regarding the symptoms of HFI in detail prior to being given this medicinal product if there is an overwhelming clinical need and no alternatives are available.[4] For this reason, a warning for HFI patients appears on labeling in parenteral vaccines or other parenteral medicines containing sorbitol but not on those containing sucrose.

It is important to keep in mind that some vaccines are administered orally, and in these cases the amount of sucrose

CONTACT Elsa Izquierdo-Garcia elsa.izquierdo@salud.madrid.org Pharmacy Department, Infanta Leonor University Hospital, Av. Gran Vía del Este, 80, Madrid 28031, Spain

administered should not exceed the safety recommended threshold of fructose intake (below 40 mg/kg/day),[7] for example the antirotavirus vaccine (Rotarix® - oral suspension) that contain sucrose above 1000 mg per dose.[8]

Indeed, one of the most frequently expressed needs of HFI patients is more knowledge from healthcare professionals about suitable and unsuitable medicines and clear and accessible information on permitted and non-permitted excipients,[9] avoiding the non-prescription of treatments due to doubts about their tolerance.

In conclusion, parenteral vaccines and other parenteral drugs with sucrose are allowed in HFI patients because parenteral sucrose is not metabolized and it is mainly excreted unchanged in the urine. Nevertheless, due to inter-individual variability and the fact that not all parenterally administered sucrose is recovered in urine, HFI patients need to be closely monitored after parenteral administration of sucrose-containing drugs, especially when the amount of sucrose exceeds the maximum permissible thresholds.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Elsa Izquierdo-Garcia http://orcid.org/0000-0002-2173-1027
Elena Alba Alvaro Alonso http://orcid.org/0000-0001-7873-8054
Berta Montero Pastor http://orcid.org/0000-0003-3024-7314
Ana Such Díaz http://orcid.org/0000-0003-3025-3191
Ismael Escobar Rodríguez http://orcid.org/0000-0003-4188-7624

References

1. Urru SAM, Maines E, Campomori A, Soffiati M. Safety of Sars-Cov-2 vaccines administration for adult patients with hereditary fructose intolerance. Hum Vaccines Immunother. 2021;17:4112–14. doi:10.1080/21645515.2021.1943992.
2. Saborido-Fiaño R, Martinón-Torres N, Crujeiras-Martinez V, Couce ML, Leis R. Reply letter to 'safety of SARS-Cov-2 vaccines administration for adult patients with hereditary fructose intolerance'. Hum Vaccines Immunother. 2021;17:4115–16. doi:10.1080/21645515.2021.1959149.
3. Gallo G; Mel R; Ros E and Filia A, editors. 2019. Guida alle controindicazioni alle vaccinazioni (aggiornamento 2018). Roma (Italy): Istituto Superiore di Sanità. (Rapporti ISTISAN 19/3).
4. Excipients in the labelling and package leaflet of medicinal products for human use. Annex to the European Commission guideline. EMA/CHMP/302620/2017. [accessed 2022 Feb 01]. https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en.pdf.
5. Weser E, Sleisenger MH. Metabolism of circulating disaccharides in man and the rat. J Clin Invest. 1967;46:499–505. doi:10.1172/JCI105552.
6. Izquierdo-García E, Moreno-Villares JM, León-Sanz M. Sweeteners in hereditary fructose intolerance patients. Acta Pediátrica Esp. 2014;72:15–23.
7. Ali M, Rellos P, Cox TM. Hereditary fructose intolerance. J Med Genet. 1998;35:353. doi:10.1136/jmg.35.5.353.
8. Maiorana A, Sabia A, Corsetti T, Dionisi-Vici C. Safety of vaccines administration in hereditary fructose intolerance. Orphanet J Rare Dis. 2020;15:274. doi:10.1186/s13023-020-01552-z.
9. Izquierdo-García E, Escobar-Rodríguez I, Moreno-Villares JM, Iglesias-Peinado I. Social and health care needs in patients with hereditary fructose intolerance in Spain. Endocrinol Diabetes Nutr (Engl Ed). 2020;67:253–62. doi:10.1016/j.endinu.2019.06.005.