

Severe hypokalaemia following misuse of a food supplement containing liquorice and rhubarb

ANSES received a report of a severe adverse effect (Level 3 severity with life-threatening prognosis) likely to be associated with misuse (intentional overdose) of the Rhubarbe® food supplement marketed by Juvamine. Causality was deemed to be likely in this case. Given the severity of the adverse effect described, ANSES felt it necessary to bring this case to the attention of the general public and health professionals, with a view to improving protection of consumer health.



As part of its nutrivigilance scheme created in 2009, ANSES received a report of severe¹ hypokalaemia² likely to be associated with misuse (intentional overdose) of the Rhubarbe® food supplement marketed by the company Juvamine. This product contains rhubarb root, liquorice, marshmallow and artichoke bract extracts aiming to facilitate intestinal transit.

Case description

The subject was a fifty-six-year-old woman suffering from depression, anxiety, migraines and chronic constipation with use of laxatives. In 2012, she experienced a first episode of hypokalaemia in an unspecified context.

In autumn 2017, she began taking Juvamine's Rhubarbe® food supplement with the stated aim being weight loss. The maximum dosage recommended by the manufacturer is one capsule three times a day, for 10 days. She began with the recommended dosage and then gradually increased it.

In mid-August 2018, she went to the emergency department for muscle pain. Biological testing found hypokalaemia with serum potassium levels of 1.43 mmol/l (normal: 3.50-5.10 mmol/l), rhabdomyolysis (destruction of striated muscle tis-

sue) and mild kidney failure. When this hypokalaemia episode occurred, she said she had been taking "three handfuls of tablets per day" for several months, i.e. around 30 capsules per day. She stopped taking the food supplement that day and potassium supplementation was initiated.

Blood tests were conducted to check if there was hyperaldosteronism³ a frequent cause of hypokalaemia. The results did not provide conclusive evidence of this diagnosis.

Six days after her arrival at the emergency department, her potassium levels returned to normal and she was in good general condition despite the persistence of some muscle pain. She was discharged from the hospital after 10 days.

Nutrivigilance intrinsic causality score⁴

The food supplement's causality in the occurrence of hypokalaemia was estimated by applying the method defined in the ANSES Opinion of 11 May 2011 on the development of a method for determining causality in reports of adverse reactions in nutrivigilance [1].

1. Level 3 severity with life-threatening prognosis on a scale of 4

2. Hypokalaemia is a low blood potassium level mainly associated with serious cardiac disorders potentially leading to death. It is particularly serious because there are no warning signs. Only a potassium blood test and/or an electrocardiogram can diagnose it before it is too late. That is why all substances that reduce blood potassium should be administered with caution

3. This syndrome is characterised in particular by sodium retention in the kidneys, arterial hypertension, hypokalaemia due to renal leakage, and low plasma renin activity

4. The intrinsic score ranges from 10 (excluded) to 14 (very likely).

The time to onset of the adverse effect was found to be “compatible”. Since the effect abated after discontinuation of the product and after emergency treatment, the progression was described as “suggestive” of an association. Moreover, in this case, only one other cause of the hypokalaemia was investigated and ruled out. The responsibility of the food supplement in the occurrence of the hypokalaemia was therefore considered likely.

Literature data

In this case, the literature search focused on the relationship between the consumption of rhubarb, liquorice, marshmallow or artichoke and the onset of hypokalaemia.

Pour la guimauve et l’artichaut, à ce jour, aucune étude disponible dans la littérature n’a mis en évidence l’existence d’hypokaliémies causées par la consommation de ces ingrédients.

For marshmallow and artichoke, to date, no studies available in the literature have shown the existence of hypokalaemia caused by the consumption of these ingredients.

For rhubarb, to date, no studies available in the literature have shown the existence of direct hypokalaemia caused by its consumption. However, through its laxative properties, rhubarb can indirectly cause potassium loss from the digestive tract and modify serum potassium concentrations [2].

Chronic ingestion of liquorice induces a syndrome similar to that of primary hyperaldosteronism. Hypokalaemia is caused by the inhibition of an enzyme by a compound resulting from the metabolism of glycyrrhizin (found in liquorice), preventing cortisol from being converted to cortisone in the renal tissue. The cortisol then activates the aldosterone receptor, leading to renal losses of potassium [3, 4].

More than 10 cases of severe hypokalaemia (serum potassium levels between 1.3 and 2.8 mmol/l) associated with consumption of liquorice (as root, tea, flavouring or traditional medication) have been reported in the literature. The consumption periods ranged from two weeks to several months or even several years. The doses of liquorice involved, when mentioned, ranged from 5 to 200 grams per day.

Conclusion and recommendations

This was the first case of hypokalaemia associated with the consumption of a food supplement containing rhubarb, liquorice, marshmallow or artichoke reported to ANSES’s nutrivigilance scheme.

Cases of hypokalaemia related to the consumption of liquorice are well known and documented in the medical literature. Due to its laxative properties inducing potassium loss in stool, rhubarb can also indirectly lead to hypokalaemia.

The severity of the adverse effect observed in this report can be attributed to the combination of these two plants, consumed in excess.

In the Ministerial Order of 24 June 2014⁵ intended for manufacturers of food supplements, the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) stipulates for liquorice that the “*recommended daily amount should not lead to an intake of glycyrrhizic acid exceeding 100 mg. The label should include a warning that reads as follows: ‘Do not use for more than six weeks without medical advice’. The label should include a warning advising against use by children*”. For rhubarb, “*the label should include a warning advising against use by children under 12 years of age and by pregnant and breastfeeding women, and a statement advising against use for long periods*”. This order mentions no restrictions on use for marshmallow or artichoke.

Therefore, ANSES advises consumers to:

- Notify a healthcare professional of any adverse effect occurring after consumption of a food supplement;
- Comply with the conditions of use specified by the manufacturer;
- Avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional (doctor, dietician, pharmacist, etc.);
- Exercise extreme caution with weight-loss products;
- Exercise great vigilance regarding the purchase of products sold through alternative channels (Internet, gyms, etc.) and without personalised advice from a healthcare professional.

ANSES reminds healthcare professionals of the importance of their participation in reporting cases of adverse effects they suspect of being associated with the consumption of food supplements, and invites them to report these to the nutrivigilance scheme.

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5. Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions for their use. <https://www.legifrance.gouv.fr/affichTexte.docidTexte=JORFTEXT000029254516&categorieLien=id>

References :

- [1]. ANSES. 2011. "Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the development of a method for determining causality in reports of adverse reactions in nutriviigilance. (Request No 2010-SA-0195)". Maisons-Alfort, Fr: Anses. 8 p. (In French)
- [2]. Singh, N. P., et A. Prakash. 2011. "Nephrotoxic potential of herbal drugs." *Journal International Medical Sciences Academy* 24 (2):79-81.
- [3]. Omar, H. R., I. Komarova, H. D. Abdelmalak, M. R. Yerramadha, Y. Ali, M. Ghonemi, R. Rashad, A. Fathy, E. Helal, et E. M. Camporesi. 2012. "Licorice abuse: Time to send a warning message." *Therapeutic Advances in Endocrinology and Metabolism* 3 (4):125-138. doi: 10.1177/2042018812454322.
- [4]. Nazari, S., M. Rameshrad, et H. Hosseinzadeh. 2017. "Toxicological Effects of Glycyrrhiza glabra (Licorice): A Review." *Phytotherapy Research* 31 (11):1635-1650. doi: 10.1002/ptr.5893.

POUR EN SAVOIR PLUS, VOUS POUVEZ CONSULTER:

[ANSES Opinion on a case of severe hypokalaemia following misuse of the food supplement Rhubarbe[®] containing liquorice](#) (In French)

Where should reports be made?

Adverse effects can be reported on the [Adverse Health Event Reporting Portal](#) of the Ministry of Social Affairs and Health or directly by completing [the online reporting form](#).