ANSES Opinion
Request No 2018-SA-0209

The Director General

Maisons-Alfort, 15 January 2019

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on a case of severe hypokalaemia following misuse of the food supplement Rhubarbe® containing liquorice

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity, the French language text, dated 15 January 2019, shall prevail.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Under the nutrivigilance scheme it set up in 2009, ANSES received a report of a severe adverse effect (Level 3 severity with life-threatening prognosis, on a scale of 4) likely to be associated with misuse (intentional overdose) of the Rhubarbe® food supplement marketed by Juvamine. Causality in this case, registered in the nutrivigilance database under number 2018-448, was found to be likely.

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.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

ANSES entrusted the expert appraisal to two external rapporteurs and to the Working Group (WG) on "Nutrivigilance". This opinion was discussed on 11 September 2018 and adopted on 13 November 2018 by the "Nutrivigilance" WG, and then presented to the CES on "Human Nutrition" on 5 December 2018, the date on which the document was validated.

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES

As part of its nutrivigilance scheme, ANSES received a report of severe hypokalaemia likely to be associated with an intentional overdose of the food supplement Rhubarbe® marketed by the company Juvamine. This case was registered under the number 2018-448.

3.1. Product composition

One Rhubarbe® tablet contains 222 mg of rhubarb (root), as well as liquorice (root), marshmallow (root) and artichoke (bract).

3.2. Case description

This involved a 56-year-old woman with a BMI of 19.8, suffering from depression, anxiety and migraines. She had also had high blood pressure for more than 10 years, which was untreated following several treatment attempts resulting in adverse effects of an unspecified nature. In 2012, she had an episode of hypokalaemia. She was being treated with Tercian® and Effexor®.

In autumn 2017, she began taking Juvamine's Rhubarbe® food supplement (transit aid) 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. When the adverse effect occurred, she reported having taken "three handfuls of tablets a day" for several months. This daily intake was estimated at about 30 capsules a day.

In mid-August 2018, she went to the emergency department for myalgia. Biological testing found hypokalaemia with serum potassium levels of 1.43 mmol/L (normal: 3.50-5.10 mmol/L), rhabdomyolysis with CPK levels of 8349 IU/L (normal: 30-135 IU/L) and mild kidney failure with CKD-EPI at 55 mL/min/1.73m^2 (normal: >60 mL/min/1.73m^2). She stopped taking the food supplement that day.

Potassium supplementation was introduced (precise date unknown).

Three days later, an aldosterone and renin test was performed. Serum potassium levels had not returned to normal (2.5 mmol/L). The results did not provide conclusive evidence of hyperaldosteronism.

The following day, serum potassium levels were 2.81 mmol/L and CPK levels were 20,138 IU/L.

Six days after her arrival at the emergency department, she was in good general condition despite the persistence of some myalgia. Cardiopulmonary auscultation was normal and blood pressure fluctuated from 134/75 to 154/88. Serum potassium was normal (4.3 mmol/L) and CPK levels were 10,190 IU/L.

Ten days after her arrival at the emergency department, the clinical picture had returned to normal. Serum potassium levels were 5.14 mmol/L and CPK levels were 1239 IU/L. She was discharged from hospital on this day.

This clinical picture equates to Level 3 severity with a life-threatening prognosis on the Nutrivigilance[1] scale.

[1] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).

3.3. Causality

The food supplement's causality in the occurrence of hypokalaemia was analysed 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 (ANSES 2011). It was established by the Working Group (WG) on "Nutrivigilance".

3.3.1.Intrinsic score

The chronological score refers to the time taken for the adverse effect to appear, its progression and its recurrence when the products are reintroduced. In this case, the onset time for the 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". The food supplement was not reintroduced. Based on this information, the chronological score is C3[2].

The semiological score is determined after establishing a differential diagnosis for the observed effect. In this case, there was no mention of any search for certain aetiologies that may have been responsible for the major hypokalaemia. The semiological score is therefore S2[3].

The intrinsic score, which results from the combination of the chronological score and the semiological score, is therefore I3, meaning that the food supplement was likely responsible for the occurrence of hypokalaemia[4].

3.3.2.Extrinsic score

3.3.2.1. Bibliographical score

The bibliographical score reflects the scientific knowledge available at the time of the search for the adverse effects reported for a product and/or its components. In this case, the literature search focused on the relationship between the consumption of rhubarb, liquorice, marshmallow or artichoke and the onset of hypokalaemia.

- **Marshmallow, artichoke**

To date, no studies available in the literature have shown the existence of hypokalaemia caused by the consumption of marshmallow or artichoke. The bibliographical score for these components is therefore B0[5].

- **Rhubarb**

To date, no studies available in the literature have shown the existence of direct hypokalaemia caused by rhubarb consumption. However, through its laxative properties, rhubarb can indirectly modify serum potassium concentration (Singh and Prakash 2011). The bibliographical score for this component is therefore B1[6].

- **Liquorice**

Chronic ingestion of liquorice induces a syndrome similar to that of primary hyperaldosteronism. This syndrome is characterised by sodium retention, hypertension, hypokalaemia, metabolic

[2] The chronological score ranges from C0 (zero) to C4 (high).

[3] The semiological score ranges from S0 (other aetiology proven/very probable) to S3 (no other aetiology).

[4] The intrinsic score ranges from I0 (excluded) to I4 (very likely).

[5] The bibliographical score ranges from B0 to B3. A B0 score corresponds to an effect that has never been reported.

[6] A B1 score corresponds to an effect reported in very few scientific publications.

alkalosis and low plasma renin activity. Hypokalaemia is caused by the inhibition of 11β-hydroxysteroid-dehydrogenase-2 by a compound resulting from the metabolism of glycyrrhizin, which is found in liquorice. This inhibition prevents cortisol from being converted to cortisone in kidney tissue. The cortisol then activates the aldosterone receptor, leading to renal losses of potassium (Omar *et al.* 2012, Nazari, Rameshrad, and Hosseinzadeh 2017).

More than ten 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. The glycyrrhizin doses are rarely specified (van den Bosch *et al.* 2005, Yasue *et al.* 2007, Mumoli and Cei 2008, Francini-Pesenti *et al.* 2008, Meltem *et al.* 2009, Delacour *et al.* 2011, Omar *et al.* 2012, Panduranga and Al-Rawahi 2013). Bernardi *et al.* (1994) studied the effects on serum potassium concentration of prolonged ingestion of incremental doses of liquorice in healthy volunteers (six subjects per group). A significant decrease in serum potassium concentration from 4.3 ± 0.2 to 3.5 ± 0.5 mmol/L (p=0.014) was observed at the 800 mg daily dose.

The bibliographical score for this component is B3[7].

3.3.2.2. Other cases recorded in the nutrivigilance database

To date, no other cases of hypokalaemia likely to be associated with the consumption of other food supplements containing in particular the ingredients rhubarb, liquorice, marshmallow or artichoke have been reported to the nutrivigilance scheme.

3.4. Conclusions of the WG and the CES

ANSES received a report of severe hypokalaemia of Level 3 severity with life-threatening prognosis involving an overdose of the food supplement Rhubarbe®. This adverse effect is likely due to chronic poisoning by the product in question. Without ruling out an effect due to the other substances contained in this product, liquorice and rhubarb may respectively cause a loss of potassium by the body through direct and indirect mechanisms.

4. CONCLUSION OF THE AGENCY

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) adopts the conclusions of the Working Group on "Nutrivigilance" and the Expert Committee on “Human Nutrition”.

The Agency received a report of severe hypokalaemia of Level 3 severity with life-threatening prognosis involving an evident overdose through misuse of the food supplement Rhubarbe®, containing liquorice and rhubarb. The causality of this food supplement in the occurrence of the adverse effect is considered likely. Cases of hypokalaemia have been reported in the literature following the consumption of liquorice. Due to its laxative properties, 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.

[7] A B3 score corresponds to a notable effect.

The food supplement involved in this report was taken with the stated aim of weight loss. On the basis of its expert appraisal published in 2010, the Agency reiterates that seeking to lose weight without a formal medical indication involves risks and requires support from a health professional (ANSES 2010).

In general, the Agency 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, etc.);
- exercise great vigilance with regard to products targeting weight loss and, more generally, with regard to any improper claims;
- exercise great vigilance regarding the purchase of products sold through alternative channels (internet, gyms, etc.) and without personalised advice.

The Agency 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.

Dr Roger Genet

KEYWORDS

Complément alimentaire, hypokaliémie, réglisse, *Glycyrrhiza glabra* L., rhubarbe, *Rheum* spp.
Food supplement, hypokalaemia, liquorice, *Glycyrrhiza glabra* L., rhubarb, *Rheum* spp.

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ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP

Chair

Mr Pascal CRENN – University Professor – Hospital Practitioner (Raymond Poincaré Hospital) – Speciality: hepato-gastroenterology

Members

Ms Catherine ATLAN – University Lecturer – Hospital Practitioner (Luxembourg Hospital Centre) – Specialities: metabolic diseases, nutrition and endocrinology

Mr Alain BOISSONNAS – Retired, University Professor – Hospital Practitioner (University Hospital Paris-Sud) – Speciality: general medicine

Ms Patricia BOLTZ – Hospital Practitioner (Poison Control and Monitoring Centre of Nancy University Hospital) – Speciality: clinical toxicology, toxicovigilance

Mr Nicolas DANEL BUHL – Medical Nutritionist (Artois Regional Hospital Grouping, GHT) – Speciality: nutrition

Mr Michel GERSON – Practitioner – Speciality: endocrinology, nutrition

Mr Raymond JIAN – Retired, University Professor – Hospital Practitioner (Georges Pompidou European Hospital) – Speciality: hepato-gastroenterology

Mr Pascal PLAN – Substitute Doctor – Speciality: general medicine, geriatrics, palliative care

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Speciality: allergology

Mr Philippe SCHERER – Retired – Speciality: allergology, occupational medicine

Mr Claude SICHEL – Retired, General Practitioner – Speciality: general medicine

Mr Jean-Fabien ZAZZO – Hospital Practitioner, retired (Antoine Béclère Hospital – AP-HP) – Specialities: anaesthesia and resuscitation, nutrition

EXPERT COMMITTEE

The work that is the subject of this report was monitored and adopted by the following Expert Committee:

- CES on "Human Nutrition" – 2018-2021

Chair

Mr François MARIOTTI – Professor (AgroParisTech) – Specialities: metabolism of proteins, amino acids, nutritional requirements and recommendations, postprandial metabolism, cardiometabolic risk

Members

Mr Frédérick BARREAU – Research Manager (Inserm / UMR 1220 / Digestive Health Research Institute, Toulouse Purpan Hospital) – Specialities: chronic inflammatory diseases of the intestine, intestinal mucosa

Ms Charlotte BEAUDART – Post-doctoral researcher (University of Liège) – Specialities: sarcopaenia, epidemiology

Ms Catherine BENNETAU-PELISSERO – Professor (Bordeaux Sciences Agro) – Specialities: phyto-oestrogens, isoflavones, endocrine disruptors, bone health

Ms Clara BENZI-SCHMID – Researcher (Federal Food Safety and Veterinary Office, Switzerland) – Specialities: legal bases of foodstuffs, health claims, food supplements

Ms Marie-Christine BOUTRON-RUAULT – Research Director (CESP Inserm) – Specialities: nutritional epidemiology and cancer, digestive system

Ms Blandine DE LAUZON-GUILLAIN – Research Director (INRA, CRESS, Sorbonne Paris Cité) – Specialities: epidemiology, infant nutrition, nutrition of pregnant and breastfeeding women, public health

Ms Amandine DIVARET-CHAUVEAU – University Hospital Practitioner (Nancy Regional University Hospital) – Specialities: infant nutrition, breastfeeding, food diversification, allergy, epidemiology

Ms Christine FEILLET-COUDRAY – Research Manager (INRA Montpellier) – Specialities: mineral metabolism, metabolic disorders and obesity, polyphenols

Ms Amandine GAUTIER-STEIN – Research Manager (INRA / Inserm U1213, Lyon Est) – Specialities: carbohydrate metabolism, food intake, energy expenditure, nutrition and cognition, metabolic disorders of the liver

Mr Jacques GROBER – University Lecturer (Inserm U1231 / University of Burgundy / Agrosup Dijon) – Specialities: nutrition, lipids, lipid transfer proteins, lipoprotein metabolism

Mr Jean-François HUNEAU – Professor (INRA/AgroParisTech) – Speciality: human nutrition

Ms Emmanuelle KESSE-GUYOT – Research Director (INRA, UMR Inserm U1153/INRA U1125/CNAM/University of Paris 13) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health

Ms Corinne MALPUECH-BRUGERE – Professor (University of Clermont Auvergne) – Specialities: nutrition of pathologies, metabolism of macro- and micronutrients

Ms Christine MORAND – Research Director (INRA Clermont-Ferrand) – Specialities: plant bioactive compounds, vascular dysfunctions

Ms Béatrice MORIO-LIONDORE – Research Director (INRA Lyon) – Specialities: human nutrition, energy metabolism, obesity, physical activity

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Nice Sophia Antipolis) – Specialities: nutrition and physical activity, bioavailability, oxidative stress

Mr Stéphane WALRAND – Research Director (INRA Clermont-Ferrand/Theix) – Specialities: pathophysiology, protein metabolism and amino acids

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Scientific contribution

Ms Gwenn VO VAN-REGNAULT – Nutrivigilance Project Officer – Risk Assessment Department

Ms Irène MARGARITIS – Head of the Nutritional Risk Assessment Unit – Seconded University Professor (University of Nice Sophia Antipolis) – Risk Assessment Department

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