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Acute Renal Failure Induced by Madder

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Abstract

Madder or *Rubia tinctorum* called in Morocco ELFOUA is a plant belonging to the *Rubiaceae* family. Used in Morocco for its cosmetic food and therapeutic properties in particularly anemia and all blood diseases. It can be toxic if it is incorrectly dosed. We report 3 cases of nephrotoxicity collected in the nephrology and hemodialysis service of the IBNROCHD university hospital center in Casablanca: 3 women aged 15, 39 and 47 years, following the ingestion of infusion of this plant at doses indeterminate, presented with acute tubule-interstitial nephritis. These new cases of nephrotoxicity at *Rubia tinctorum* must challenge the need to know how to evoke the diagnosis, to inform, to fight against the trivialization of its consumption, to encourage research on the traditional pharmacopoeia allowing to identify their therapeutic properties in order to formalize, rationalize and codify their prescriptions.

Introduction

Rubia tinctorum (El FOUA) is a plant widely used for thousands of years as a source of red color with its variants for dyeing textiles (Figure 1, 2), in cosmetology, in food as an additive but also as a drug with many therapeutic properties. It is very widespread in the world and particularly in Europe, Asia and North Africa.

In Morocco and in the Mediterranean basin, it is a ubiquitous plant. It is used for dyeing purposes by obtaining a red dye intended for dyeing, painting and even food. Added to this is its medicinal use in many fields. Indeed it is very popular with Moroccan women, as a purgative, after childbirth. A decoction of the whole plant is prescribed in anemia and all diseases of the blood. Its daily intake is recommended to increase blood volume and improve the complexion.

However, *Rubia tinctorum* is very rich in anthraquinone derivatives. It is considered according to the World Health Organization (WHO) and some other health and food organizations (such as Health Canada or the French Ministry of Agriculture) as involving risks for the consumer. Recent studies have shown a certain toxicity especially on the kidney with a mutagenic or even carcinogenic power of certain anthraquinone derivatives [1].

Patients and Methods

We report 3 cases of nephrotoxicity collected in the nephrology and hemodialysis service of the IBNROCHD hospital center in Casablanca: Women aged 15 39 years and 47 years following the ingestion of infusion of this plant in undetermined doses to treat anemia.

Results

Observation 1

HE aged 15, with no particular pathological history, admitted to the nephrology department for a glomerular syndrome with renal insufficiency at 66 mg/L of plasma creatinine and 24-h proteinuria at 1 g/24 h and aseptic leukocyturia after taking *Rubia tinctorum* for ten days, infused several times a day for iron deficiency anemia.

On examination, the patient is apyretic, normo tensioned to 130/70 mmHg, presence of a protein cross with urinary strips without traces of blood, diuresis is calculated at 300 ml per day.

The assessment revealed an acute renal failure at 66 mg/L of creatinine, 24-h proteinuria at 1 g/24 h without impact on the protidogram, sterile ECBU with leukocyturia at 200,000 e/ml. Kidney ultrasound showed good kidneys, well differentiated without dilation of the excretory tract.

Observation 2

LN aged 39, with no pathological history, hospitalized in the nephrology department for glomerular syndrome with 24-h proteinuria at 2 g/24 with severe acute renal failure at 90 mg/l

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Figure 1: Plant and madder leaf [13].

Figure 2: Dyeing of cotton threads and fabrics [13].

Figure 3: Madder Root [13].

of plasma creatinine and aseptic leukocyturia without hematuria or hypertension in the context of incoercible vomiting following the taking of "elfoua" for 5 days taken in front of a skin-mucous pallor.

On examination, the patient is non-pyretic, normo-tensioned at 120/70 mmHg, diuresis is calculated at 500 ml per day, with two urine strips of protein without hematuria on the urine strip. mg/L creatinine, 24-h protein at 2 g/24 h without impact on the protidogram, ECBU sterile with leukocyturia at 120,000 e/ml. The renal ultrasound was without abnormality.

Observation 3

AH aged 47, hospitalized in nephrology for acute renal failure at 73 mg/l of plasma creatinine incidental discovery during a CPA assessment for cholecystectomy with the notion of taking "ELFOUA" a week before admission.

On examination, the patient is apyretic, normo-tense, diuresis is kept at 1000 ml per day, with urine strip a protein cross without hematuria. The assessment revealed an acute renal failure at 73 mg/L of creatinine, 24 h protein at 1 g/24 h without impact on the protidogram, ECBU sterile with leukocyturia at 100 000 e/ml. The renal ultrasound was without abnormality, patients underwent renal biopsy punctures which showed acute tubulointerstitial nephritis. Therapeutically all our patients were put on corticosteroid therapy with a good improvement in creatinine.

Discussion

Despite progress in pharmacology, the therapeutic use of plants is very present in certain countries of the world, especially those developing notwithstanding a medical system modern. Morocco by the richness and diversity of its flora constitutes a true phytogenetic reservoir with around 4500 plant species and subspecies, including *Rubia Tinctorum* (Figure 1) [1]. In the literature, the data concerning intoxication in madder are rare and few documented. Use for food, curative or aesthetic purposes of certain plants possibly toxic, or at least a part (seed, stem, etc.), can induce serious poisoning, even fatal. These poisoning is a frequent accident in most regions of the world [2].

Rubia Tinctorum has been used for thousands of years. The properties most cited in the literature for this plant are [3,4]: Its diuretic activity and especially as a hypotensive, its emmenagogue activity, its activity in obstructions of the spleen, its purgative/laxative activity and its activity cholagogue.

The study of the chemical composition of the roots of Rubia tinctorum has shown its richness in anthraquinones in its two free and combined forms [5]. Free anthraquinone forms have no marked pharmacological activity. These free genins present in the drug or formed by the beginning of gastric hydrolysis and which reach the intestine are absorbed at the level of the small intestine, are glucurono-conjugated at the hepatic level and largely eliminated by the urinary route. We also note the existence of an enterohepatic cycle.

The combined forms are neither absorbed nor hydrolyzed in the small intestine. When they reach the colon, they are hydrolyzed by β-glucosidases from the intestinal flora and the anthraquinones released are reduced and will act on intestinal motility [6]. Action on the Na-K-ATPase pump in the cell membrane of enterocytes: By inhibiting the pump, sodium in the colon cells is increased, which leads to a decrease in the reabsorption of water and sodium. This explains the laxative effect. The excessive use of anthraquinones can lead to recto-colic melanoses [7], by a cytotoxic effect [6].

As part of the assessment of the madder root safety (Figure 3), used as food coloring, toxicity tests were carried out on mice. An acute toxicity test was carried out by administration for 14 madder root days at doses of 0, 500, 2000, 3500, and 5000 mg/kg of body weight. A male mouse receiving 5000 mg/kg body weight died before the end of the study, indicating that the maximum tolerated dose of GR was between 3500 and 5000 mg/kg body weight. A subacute GR toxicity test was also carried out with 62 mice of each sex, with a diet containing madder root at concentrations of 0.3; 0.6; 1.25; 2.5 and 5% for 90

days. All mice tolerated these doses. None of the mice treated with RG showed clinical signs of toxicity. Histopathological examination showed retention cysts in the kidneys and vaginal epidermal cysts in some of the treated or control mice. No hyperplastic, pre-neoplastic and neoplastic lesions and no pathological signs of toxicity were found. These results suggest that dietary exposure to GR at these doses has no acute or subacute toxic effects on mice [8].

Another study of chronic toxicity and carcinogenicity was carried out. For 90 days repeated doses of 0; 0.6; 1.2; 2.5 and 5.0% of the test substance. The results demonstrate toxic effects of madder root on the liver, kidneys and on the hematopoietic system [9].

Histopathological changes were mainly observed in the proximal renal tubules, such as vacuolar microvesicular degeneration in the cortex and caryomegaly in the external medulla, the lesions being evident even with 0.6%. In the external medulla, the increase in cell proliferation activity, appreciated by the proliferation of nuclear antigen cells, has been observed. The Severity of focal hepatocyte necrosis increased only in females, to 5.0%, while the increase in the relative weight of the liver but also that of conjugated bilirubin was evident in both sexes, at the dose 1.2% [10].

A more recent study of the carcinogenicity was conducted to elucidate the long-term effects of *Rubia tinctorum* and its target organs. Histologically, the frequency of caryomegaly and atypical hyperplasia of the tubules, as well as adenomas and carcinomas in the renal cells, increased significantly in the groups treated in both sexes. These results show that RG exerts an unequivocal carcinogenic power on the cells of the renal tubules and hepatocytes in rats [11].

Regarding toxicity in humans, an analysis of 11 studies treating colorectal cancers and the use of laxatives has shown that the use of laxatives has increased risk of colorectal cancer [5].

Other studies have mentioned anthraquinones specifically in evaluating the use of laxatives as a risk factor for cancer. Melanosis coli (discoloration of cells in the colon corresponding to cell death if it is due to excessive use of anthraquinones). In short, anthraquinones should not be used long term and improperly because of the risk of melanosis coli [12].

Conclusion

In the literature, renal toxicity linked to the consumption of elfoua has not been described in humans, but studies done in rats have shown that the administration of this plant can cause tubular necrosis, with nephritis interstitial. These effects have been observed following chronic ingestion of large doses. Cases have been declared and registered according to the pharmacovigilance center of Morocco.

The association of histological lesions and the taking of elfoua in this patient evokes its toxic effect on the kidney that constitutes a limit to the use of this plant despite its therapeutic qualities.

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