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Colchicine Poisoning after Mix-up of Ramsons (*Allium ursinum* L.) and Meadow Saffron (*Colchicum autumnale* L.)

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Abstract

Ramsons (*Allium ursinum* L.) is a popular spice and vegetable. When not in flower, it may be confused with Meadow Saffron (*Colchicum autumnale* L.), a toxic plant containing colchicine. Several accidental poisonings with Meadow Saffron mistaken for Ramsons have been described in literature. The case presented here is another accidental colchicine poisoning after mix-up of these two plants. The patient had typical symptoms of colchicine poisoning such as vomiting and abdominal pain. Plasma and urine samples of the patient and left-over plant material were analyzed by gas chromatography-mass spectrometry leading to detection of colchicine in the plant material, but not in plasma and urine. Liquid chromatographic-mass spectrometric analysis of the plasma sample led to identification of colchicine. Semi-quantitative determination yielded a colchicine plasma concentration of 19 µg/L which is in the toxic range.

Introduction

Ramsons, *Allium ursinum* L., has become a very popular spice and vegetable, in part probably due to the back-to-nature movement. From a toxicological point of view, consumption of Ramsons itself is no cause for concern. However, upon the first look, the leaves of Ramsons are somewhat similar to the leaves of Meadow Saffron, *Colchicum autumnale* L., as can be seen in Figure 1, which shows a picture of Ramsons on the left and one of Meadow Saffron on the right. Meadow Saffron is a highly toxic plant because of its colchicine content. For these reasons, it is not surprising that several accidental poisonings with Meadow Saffron mistaken for Ramsons have been described in recent years, some of them with lethal outcome [1-4]. In the following, another case of colchicine poisoning caused by confusion of non-toxic Ramsons with toxic Meadow Saffron will be described.

Figure 1: Pictures of Ramsons, *Allium ursinum* L. (left) and Meadow Saffron, *Colchicum autumnale* L. (right).

Case details

A 66-year-old man had gathered what he supposed to be Ramsons in the nearby countryside. From about 30 g of the collected plants he prepared himself a salad, which he ate for lunch around noontime. In the following hours, he developed symptoms like nausea, vomiting, abdominal pain and severe diarrhea. Around midnight he was admitted to hospital, where blood and urine samples were collected. The patient was treated with activated charcoal and replacement of fluids and electrolytes. Vomiting, diarrhea and abdominal pain persisted for the next two days. Serum glutamic oxaloacetic transaminase (SGOT) activity increased from 91 U/L on admission to 194 U/L on day 3 (reference range 10-50 U/L). In the same time frame, creatinine kinase (CK) activity increased from 312 U/L to 1346 U/L (reference range <174 U/L). Lactat dehydrogenase (LDH) activity increased from 574 U/L on admission to 1258 U/L on day 2 and then decreased again to 783 U/L on day 3 (reference range 135-225 U/L). On the morning of the fourth day, the blood and urine samples collected on admission as well as left-over plant material were submitted to the authors' laboratory for toxicological analysis.

Analytical methods

Blood plasma and urine samples were analyzed according to the authors' standard systematic toxicological analysis procedure (STA) [5-7]. Screening in urine was performed using full-scan gas chromatography-mass spectrometry (GC-MS) after acid hydrolysis, liquid-liquid extraction, and acetylation. The plasma sample was extracted at native pH and at alkaline pH after addition of the routine internal standard trimipramine-d_3. The combined extracts were analyzed also by full-scan GC-MS. Identification and quantification of colchicine in plasma was performed by liquid chromatography-mass spectrometry (LC-MS) using this routine plasma extract with chromatrographic conditions and interface settings as described previously [8, 9]. For identification of colchicine, the LC-MS was operated in the full-scan mode as described in references [8, 9]. For semi-quantitative determination of colchicine, the LC-MS was operated in the selected ion monitoring (SIM) mode with the ions *m/z* 384, 386, and 400 (target ion) for colchicine and *m/z* 298 for the internal standard. Quantification was performed by comparing the peak area ratio (colchicine vs. internal standard) from the plasma sample to that of a spiked calibrator containing 20 µg/L of colchicine.

The plant material was first studied concerning its morphological features. Subsequently, approximately 1 g of leaf material was chopped up and extracted with 1 mL of ethyl acetate. After centrifugation (5000*g*, 3 min), the organic phase was transferred to an autosampler vial and 2 µL were analyzed by GC-MS using the same conditions as for analysis of the urine sample.

Results

The plant was identified as Meadow Saffron (*Colchicum autumnale* L.) via characteristic morphological features. In the picture of Meadow Saffron shown in Figure 2, the characteristic seed pods can be clearly seen. These were also present in the plant material sent to the authors' laboratory, although they were more unripe and, therefore, much smaller.

The morphological determination of the plant was confirmed by the results of GC-MS analysis of the plant material in which colchicine was unambiguously identified by library search as demonstrated in Figure 3, which shows the mass spectrum found in the plant extract (upper spectrum), the reference spectrum, (lower spectrum), the hit list from computer library search, and the molecular structure of colchicine. GC-MS analysis of plasma and urine samples led to detection of lidocaine and diphenhydramine metabolites, but colchicine could not be detected.

However, Colchicine was identified in the plasma sample by LC-MS in the full-scan mode. Its subsequent semi-quantitative determination in the SIM mode yielded a colchicine plasma concentration of approximately 19 µg/L.

Figure 2: Picture of Meadow Saffron, *Colchicum autumnale* L., with its characteristic seed pods.

Discussion

In the presented case, the patient had intended to gather non-toxic Ramsons plants for preparation of a salad. However, as the analytical results show he mistakenly gathered toxic Meadow Saffron. The reason for this mix-up was the similarity of Ramsons and Meadow Saffron when not in flower, as already described above and shown in Figure 1. Ramsons is in flower from March to May and Meadow Saffron from August to October, so in April, when the presented case took place, Meadow Saffron might easily be mistaken for Ramsons.

The toxicity of Meadow Saffron is due to its content of colchicine. The mechanism of action of colchicine is its binding to tubulin leading to depolymerisation of microtubules in the cell [10-12]. This in turn interferes with cell motility; e.g. of neutrophils, and can lead to arrest of cell division. Colchicine is therapeutically used in the treatment of gout, but may lead to (severe) side effects such as nausea, vomiting, abdominal pain, and severe diarrhea, possibly associated with gastrointestinal haemorrhage [10-12]. These are also the most common symptoms in overdose and poisoning cases.

However, more serious complications such as seizures and acute insufficiency of kidney and liver may occur in cases of severe colchicine poisoning and quite a number with lethal outcome have been described [2, 4, 13-21]. There is no specific antidote for colchicine poisoning, so primary detoxication and supportive measures are the only treatment options. In the presented case, the typical gastrointestinal symptoms were observed. Furthermore, the elevated activities of SGOT, CK, and LDH were probably an indication of a certain extent of cell damage. Nevertheless, the outcome was favorable and the patient felt much better on day 4.

The authors' standard screening procedures for systematic toxicological analysis of plasma and urine samples did not lead to detection of colchicine. The negative finding in plasma is most probably due to the low plasma concentrations of colchicine even in poisoning cases as the one described here.

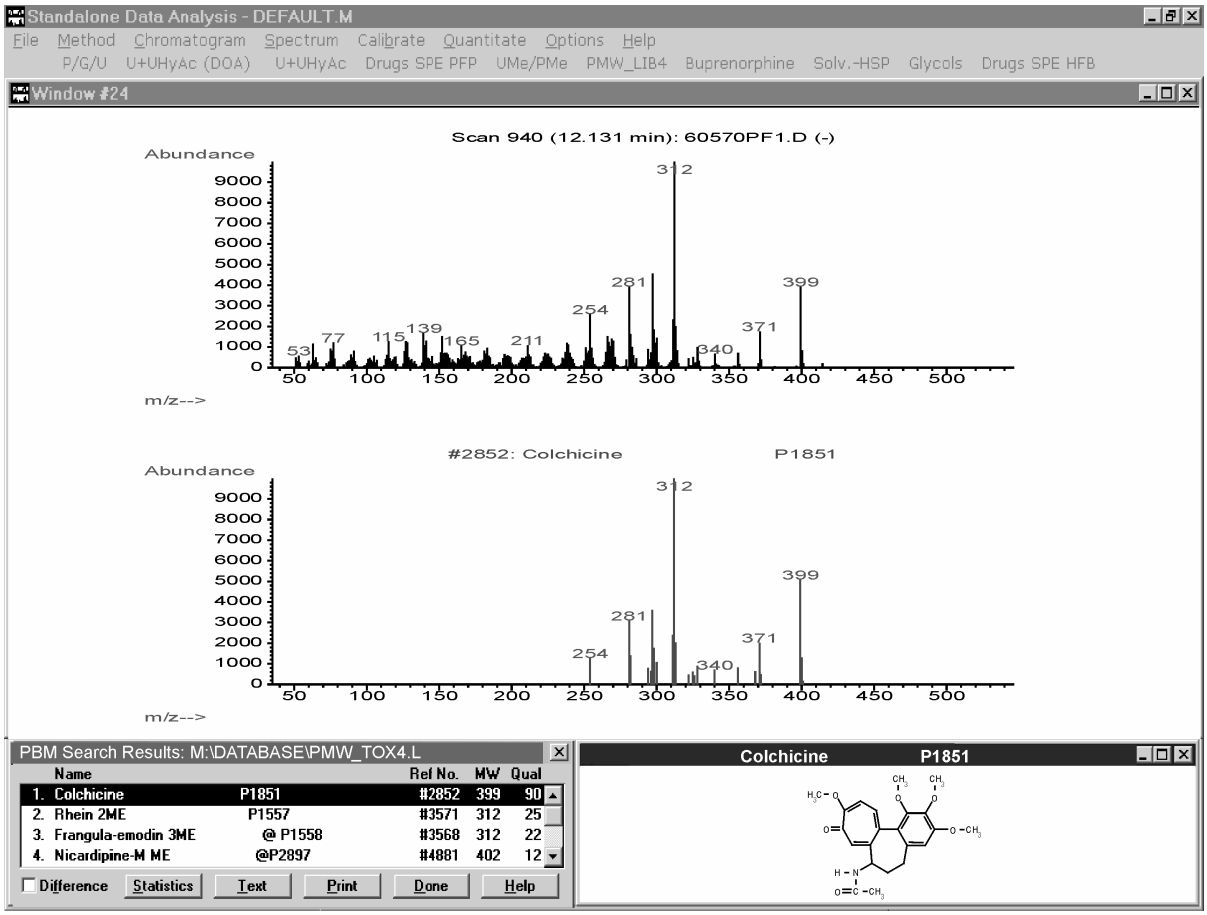

Figure 3: Mass spectrum found in the plant extract (upper spectrum), reference spectrum, (lower spectrum), hit list found by computer library search, and molecular structure of colchicines.

The negative finding in urine is probably at least in part due to fact that colchicine is mainly excreted via the bile. Only 10-30% are excreted in urine mostly in form of metabolites. Fortunately, in the presented case, left-over plant material was also sent for analysis. The sample preparation of this material was a simple extraction step with ethyl acetate. A basic pH value, which is required for liquid-liquid extraction of most alkaloids, was not required for extraction of colchicine, because in contrast to most other alkaloids, it contains an amide instead of an amine moiety. After the plant material had been identified as Meadow Saffron via morphological determination and via its content of colchicine, it was very likely that the patient suffered from colchicine poisoni

ng, even though no colchicine had been found in plasma and urine by GC-MS. Therefore, the plasma sample was analyzed by LC-MS, a technique which had already been applied successfully to analysis of colchicine by other authors [14, 15, 22]. It allowed identification of colchicine in the full-scan mode and its semi-quantitative determination in the SIM mode, which yielded a plasma concentration of 19 µg/L. This is far above the therapeutic concentration range of colchicine in treatment of gout (0.3 to 2.4 µg/L) [23], and therefore in line with the patient's symptoms of colchicine poisoning. Hence, the presented case was indeed an accidental colchicine poisoning after mix-up of Ramsons and Meadow Saffron.

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