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Cyanide intoxication by apricot kernel ingestion as complimentary cancer therapy

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Dear editor,

Complementary and alternative medicine (CAM) is frequently used in patients with cancer, up to 90% within one year for at least part of their therapy.[1,2] Both beneficial and adverse effects of such therapy remain controversial, and CAM has even been associated with shorter overall survival.[3]

The use of amygdalin, usually in the form of laetrile, has been one of the most popular alternative 'cancer cures' in the past 40 years.[4] Importantly, laetrile and amygdalin are pharmacologically distinct compounds and their names are often used interchangeably. Amygdalin is a cyanogenetic glycoside compound[5] found in the pits of many fruits and can be applied, e.g. via ingestion of apricot kernels. Laetrile is an acronym from laevorotatory and mandelonitrile, used to describe a purified form of amygdalin.

Briefly, the working mechanism of amygdalin has been proposed to rely on the specific vulnerability of malignant cells to cyanogenic glycosides because of 1) a higher level of beta-glucosidases and beta-glucuronidase as compared with normal cells, leading to a more rapid intracellular release of cyanide from amygdalin and 2) a deficiency in rhodanese, an enzyme that converts cyanide into the harmless compound thiocyanate.

There is circumstantial evidence that amygdalin is a potential anti-cancer drug, mostly based on *in vitro* experimental studies,[6,7] although no clinical evidence supporting these findings has emerged over the past decades.[8] Moreover, it was even associated with toxic blood cyanide levels and reduced overall survival when used in the form of laetrile as described.[9] Despite this, use of amygdalin is recently increasingly advocated as an anticancer therapy.[8] It can be applied by intravenous administration, tablet or apricot kernel ingestion.[9]

In the present case report we describe the occurrence of elevated liver chemistry tests in correlation with chronic cyanide intoxication after apricot kernel ingestion as CAM in a patient suffering from metastatic colon carcinoma.

Case

A 58-year-old man receiving palliative chemotherapy (capecitabine, oxaliplatin, and bevacizumab) because of metastatic colon carcinoma visited our outpatient clinic before the start of the sixth cycle of chemotherapy. He did not report any symptoms. However, peripheral blood analysis revealed abnormal liver chemistry tests (*figure 1*). Progression of liver metastases was ruled out as an ongoing tumour response was observed on computed tomography. He was not on any relevant concomitant medication.

The patient then mentioned the use of 70 apricot kernels per day, which he chopped thoroughly. He had taken them for 45 days in a row up to a week before the outpatient visit. He discontinued the use as it was too much work to chop them.

He was evaluated for cyanide intoxication at the emergency department but fortunately no lactic acidosis was detected. The level of thiocyanate, the hepatic cyanide metabolite, became available a few days later and showed a high level within the toxic range. Serial measurements of thiocyanate levels are shown in the perspective of the liver chemistry demonstrating a time-dependent correlation (*figure 2*).

We measured a thiocyanate concentration of 71 mg/l a week after the last intake of kernels. Assuming first-order kinetics and a calculated elimination half-life of 9.5 days, thiocyanate concentration on the last day of intake would have been a toxic 118 mg/l.

DISCUSSION

In the present case report, we demonstrate, for the first time, elevated liver chemistry tests as a result of chronic cyanide intoxication after apricot kernel ingestion. Thus far, elevated liver chemistry tests have not been reported as an effect of cyanide intoxication. In our patient there is a clear time-dependent relationship between the levels of

the toxic cyanide metabolite and the liver chemistry tests after apricot kernel ingestion.

To our knowledge, therapeutic use of amygdalin has only been associated with liver failure in one case concerning cirrhotic liver disease.[10] Elevated liver chemistry tests are not a common adverse effect of cyanide intoxication in humans, although chronic cyanide ingestion was reported to cause degenerative changes in the liver of rabbits and pigs.[11,12]

Most common reported side effects of amygdalin use in humans are nausea, vomiting, hyperpnoea, headache, palpitation, cyanosis and obtundation.[9,13] None of these effects were reported by our patient.

In our patient liver chemistry tests were normal before he started using apricot kernels. In this perspective, the disturbed liver chemistry tests during follow-up strongly suggest a correlation with the apricot kernel ingestion. Liver chemistry abnormalities do not affect amygdalin pharmacology or metabolism.[13] Two drugs from the chemotherapy regimen that our patient received rarely cause disturbed liver chemistry tests, and in our patient it is unlikely that this would have been the cause as the prior four cycles were administered without this adverse effect. Additionally, he was re-exposed to oxaliplatin and capecitabin without detrimental effects to the liver chemistry.

Figure 2. *Level of thiocyanate (left Y-axis), the measurable metabolite of cyanide as a result of amygdalin metabolisation, compared with ASAT and ALAT values (right Y-axis). Values above a thiocyanate concentration of 60 mg/l are within the toxic range. Time in months. The first data point represents the values at initial presentation with abnormal liver chemistry tests*

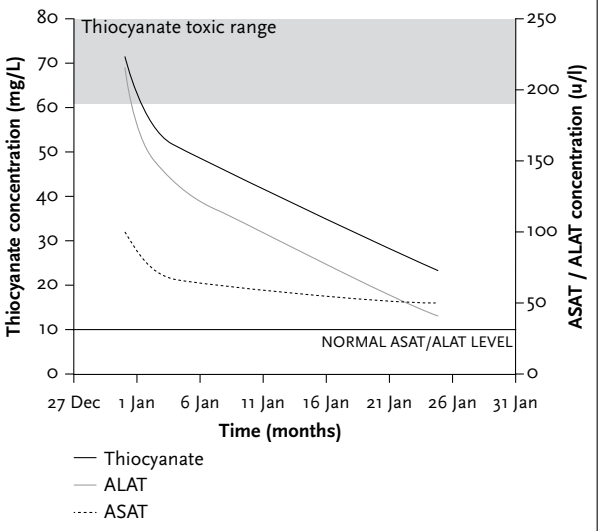
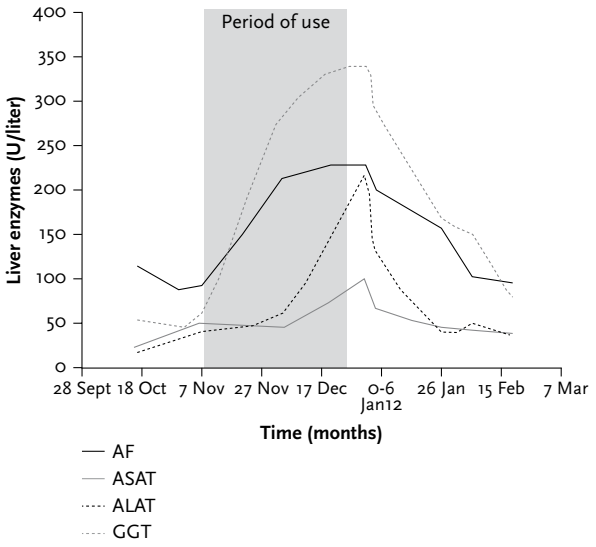


Figure 1. *Level of the four different liver enzymes (U/litre) over time (in months). The grey area indicates the period of use of apricot kernels. Throughout this period there is an increase of the four liver enzyme values, whereas these values rapidly decrease when the use of apricot kernels is discontinued*



Despite the fact that the apricot kernel ingestion had already been halted for one week, there were still toxic levels of thiocyanate, however not resulting in lactic acidosis.

It is striking that with the large number of apricot kernels ingested per day, our patient did not present with an acute cyanide intoxication but a chronic intoxication. In theory, cyanide binds to the ferric ion of mitochondrial cytochrome oxidase, which causes an almost total inhibition of cytochrome oxidase activity, leading to anaerobic metabolism and subsequent lactic acidosis, the hallmark of acute cyanide intoxication. The latter was absent in our patient and we do not have a proper explanation for this fact. Nevertheless, we demonstrate a clear time-dependent relationship in the levels of the cyanide metabolite and the liver chemistry tests.

With an estimated daily intake of 1.4-2 g of amygdalin, based on an amygdalin content of 4.5-6.5% on dry weight,[14] maximal daily cyanide exposure in our patient would be 0.12 g, assuming all the cyanide is released from amygdalin. This would lead to a near-lethal plasma cyanide concentration of 3 mg/l (distribution volume of 0.41 l/kg, lethal concentration >3 mg/l).[15] In practice the degree of cyanide release is much lower and depends on the intensity of grinding of the kernels.

In conclusion, this case report illustrates for the first time that a daily intake of 70 apricot kernels during more than six weeks induces abnormal liver chemistry tests without other toxicity signs. As a remark, this case report stresses the importance of physicians being aware of the use of complementary and alternative medicine when commencing anti-cancer therapy and indicates that unexplained abnormalities in the follow-up of cancer patients should prompt the question about the use of complementary medicine.

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