CASE REPORT

An unusual presentation of chronic cyanide toxicity from self-prescribed apricot kernel extract

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SUMMARY

Hypoxia under general anaesthesia is a potentially life-threatening condition. A seemingly well 67-year-old man appeared hypoxic with peripheral pulse oximetric measurement during routine anaesthesia. Postoperatively, the patient admitted to daily self-prescription of apricot kernel extract for a period of 5 years. Apricot kernel is a commonly taken extract used for a range of ailments, and is associated with cyanide toxicity, which was confirmed through blood analysis. Our explanation for the hypoxic measurement was the presence of free cyanide interfering with functioning of the peripheral pulse oximeter. On cessation of the apricot kernel extract, peripheral oxygen saturations returned to normal. Cardiac and respiratory causes together with rare haemoglobinopathies were excluded. This case illustrates how chronic dosing of complementary medicines can result in harmful toxicities, which may carry potential for serious consequences and how these chronic toxicities may present to physicians in atypical ways.

BACKGROUND

Use of complementary medicine is popular with best estimates of 21%–29% of a British population in the 12 months preceding two recent surveys.^{1,2} Many extracts lack quality control in production and are not subject to extensive testing applied to standard medicines; hence efficacy and safety cannot be assured.³ Information on dosing, efficacy, interactions and side effects is often limited. Furthermore, patients may not understand potential toxicities associated with these compounds, and may not readily reveal their use to physicians. Therefore, the management of such patients can be challenging and complex.

Apricot kernel extract (ake) is a popular complementary medicine, and is marketed as a preventative medicine for cancer. Acute life-threatening cyanide toxicity has been described with ake^{4–6} but there have been limited cases in the literature describing asymptomatic presentations of chronic low level toxicity. This case report outlines a presentation of chronic cyanide toxicity, detected as a result of low oxygen saturation readings by peripheral pulse oximetry in a patient presenting for routine anaesthesia.

CASE PRESENTATION

We describe the case of a 67-year-old man who presented for a routine cystoscopy requiring general anaesthesia. His medical history included prostate

cancer in remission, and he denied any symptoms or investigations of cardiovascular disease, anaemia or respiratory disease. He also reported a high level of exercise capacity, cycling over 70 km per week.

Initial pulse oximetry in room air revealed saturations of 89%. As the patient was asymptomatic with no headache or dizziness, with a heart rate of 80/min, blood pressure of 130/70 mm Hg and respiratory rate of 16 breaths/min, the cystoscopy procedure took place. The case took 15 min and it was noted that oxygen levels as measured by pulse oximetry increased slowly to 94%, despite continued administration of 100% oxygen therapy during and after anaesthesia. An arterial blood gas at the time revealed normal arterial oxygen partial pressures and normal carboxyhaemoglobin, methaemoglobin, anion gap and lactate. The patient recovered without incident and then agreed to undergo extensive testing to further investigate the low pulse oximetry oxygen saturation readings.

INVESTIGATIONS

Chest X-ray and lung function testing were normal. Co-oximetric analysis of arterial blood after peripheral capillary oxygen saturation (SpO₂) of 89% in room air revealed an arterial oxygen saturation (SaO₂) of 97, pH of 7.48, pO₂ of 78, pCO₂ of 36, bicarbonate of 24, base excess of +2, carboxyhaemoglobin of 0.7%, methaemoglobin of 0.3%, normal anion gap and lactate of 15 and 1.4 mmol/L. Following 20 min of oxygen with fraction of inspired oxygen of 1.0, a peripheral SpO₂ of 94% was recorded with arterial blood showing an SaO₂ of 100, pH of 7.44, pO₂ of 325 mm Hg, pCO₂ of 39 mm Hg, HCO₃ of 24, base excess of +1, carboxyhaemoglobin of 0.9% and methaemoglobin level of 0.2%. Repeat anion gap and lactate remained normal at 14 and 1.3 mmol/L, respectively.

Transthoracic echocardiographic examination was normal; in particular there were no findings to support intracardiac shunting. Haemoglobin level was 149 g/L, mean corpuscular volume 98 and haemoglobin electrophoresis was normal.

We were able to confirm the presence of cyanide in the body in venous blood through a thiocyanate assay, the preferred method of evaluation for cyanide in our institution and by the measurement of whole blood cyanide ion at an external forensic toxicology laboratory involving the same blood sample. Thiocyanate levels were elevated in the setting where our patient was self-prescribing ake, the level being 521 µmol/L (reference interval for non-smokers 20–80 µmol/L). Whole-blood cyanide

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levels during this period were also elevated at 1.6 mg/L (reference interval for non-smokers <0.025 mg/L). DNA sequencing of the patient's alpha and beta haemoglobin genes looking for rare haemoglobin variants, in particular low oxygen affinity variants, was negative.

In summary, clinical findings reflected abnormally high-blood cyanide and thiocyanate levels and low peripheral pulse oximetric oxygen saturations in the setting of self-prescription of ake, suggesting that a modifiable factor linked with ake has interfered with peripheral pulse oximetry readings. Preparations of ake, Novodalin (a proprietary preparation) and a home-made preparation were also brought in and analysed for cyanide content. The patient self-administers three tablets of Novodalin and has two teaspoons of home-made extract per day. Analysis of the Novodalin showed cyanide levels of 220 mg/kg and the home-made extract 1600 mg/kg of cyanide. One tablet of Novodalin weighs about 2 g, while one teaspoon of home-made extract weighs about 5 g, meaning that our patient ingests approximately 17.32 mg of oral cyanide per day.

DIFFERENTIAL DIAGNOSIS

Chronic cyanide poisoning was confirmed through the presence of high venous thiocyanate and whole blood cyanide in the setting of regular ake ingestion, following investigation and exclusion of potential causes of low oxygen saturation measured by peripheral pulse oximetry. These include true causes of low oxygen saturation such as significant lung disease, intracardiac shunting, anaemia, as well as presence of high levels of abnormal haemoglobin species such as methaemoglobin and carboxyhaemoglobin and rare haemoglobinopathies, all of which we were able to exclude through co-oximetry and DNA testing. The next category of differential diagnoses we excluded is a range of other factors that may cause erroneous peripheral pulse oximetry readings such as nail polish, exposure to strong external light source, strong electromagnetic fields, skin pigmentation and irregular signals as may be caused by cardiac arrhythmia.

TREATMENT

Once the diagnosis of low-grade cyanide toxicity was confirmed, and the cyanide identified in the proprietary and home-made ake, the patient ceased ake for 3 days and presented for review where peripheral SpO₂ with pulse oximetry was 97% on room air, arterial SaO₂ 97 and venous thiocyanate level measured at under 80 µmol/L, which is normal.

OUTCOME AND FOLLOW-UP

Our patient remained asymptomatic during the periods with and without ake ingestion following his minor surgery. Despite conveying our concerns regarding the continued ingestion of ake and being satisfied that our viewpoint was understood, the patient elected to continue self-administering ake.

DISCUSSION

We have described a case where self-administration of ake was associated with abnormally high venous blood levels of thiocyanate and cyanide, presenting as low SpO₂ readings with peripheral pulse oximetry. The prevalence of ake use as a complementary medicine is not accurately known. However, international authorities are aware of the risks posed by apricot kernels and apricot kernel derivatives. Food Standards of Australia and New Zealand have issued a consultation impact statement in reference to hydrocyanic acid in apricot kernels and other foods based on existing evidence linking ake to cyanide

poisoning.⁷ The recommendations from this statement include a clear statement outlining maximum quantities of raw apricot kernels considered safe for consumption as a foodstuff (two kernels per day), mandatory labelling to inform consumers of potential risks of health products derived from apricot kernels and prohibition of products derived from apricot kernels being used as foods. Internationally, the UK has issued a statement on safe levels of apricot kernel intake (one to two kernels per day) through the UK Food Safety Authority Committee on Toxicity of Chemicals in Food Consumer Products and the Environment,⁸ while Canada has posted warnings on its advisory and warnings website that apricot kernels should not be consumed for medicinal or natural health purposes.⁹ The US have safe levels for cyanide (25 mg/kg) for foodstuffs and have outlined one form of proprietary apricot kernel extract (laertrile), which is detained under import legislation.⁷

Estimates of cyanide content of apricot kernels range from 0.122 to 4.09 mg/g.¹⁰ Our measurement of cyanide content involved both a commercial preparation, Novodalin showing a level of 220 mg/kg (0.220 mg/g) and a home-made extract of apricot kernel containing 1600 mg/kg of cyanide (1.6 mg/g) after analysis at our institution, both of which are consistent with the estimated range.

Acute intoxication with apricot kernels has been described. One clinical scenario initially describes suspected ingestion of 20–30 apricot kernels with no symptoms 40 min after ingestion, with development of symptoms 70 min after ingestion of tachycardia, hypotension, tachypnoea, with a peripheral SpO₂ reading of 93% with 3 L/min of supplemental oxygen, metabolic acidosis of 7.20 and an anion gap of 23.⁴ Another scenario describes a life-threatening presentation of metabolic acidosis causing weakness and dyspnoea progressing rapidly to coma.¹¹ Both scenarios required administration of sodium thiosulfate,^{4 11} while in the first scenario the patient also received amyl nitrate and hydroxycobalamin.⁴

Our case study investigates the effect of ake and peripheral pulse oximetry. The peripheral pulse oximeter is a non-invasive device used to estimate oxygen saturation in arterial blood. It works via a mechanism based on Beer-Lambert's law.

Low oxygen saturation from peripheral pulse oximetry may arise from environmental factors interfering with red and infrared light transmission or as a result of interference or replacement of oxyhaemoglobin as a result of high levels of variant haemoglobin species. Measurable modified haemoglobin species include methaemoglobin and carboxyhaemoglobin, and their presence in higher than normal concentrations can produce low oxygen saturation readings that may not be an accurate reflection of the true oxygen saturation. Blood gas analysers use a co-oximeter module which uses spectrophotometry at several different wavelengths to peripheral pulse oximetry, allowing the measurement of haemoglobin derivatives such as carboxyhaemoglobin and methaemoglobin, taking these into account when reporting the fractional SaO₂.

We measured abnormally high levels of both cyanide and thiocyanate with this measurement reflecting that our patient had been exposed to high levels of cyanide. Cyanide is rapidly detoxified by mitochondrial thiosulfate sulfurtransferase, rhodanese¹² and at any given time exists as both cyanide and thiosulfate.

Prior to the action of rhodanese, cyanide can exist in the body in plasma and in erythrocytes.¹³ Erythrocyte cyanide is bound to methaemoglobin as cyanomethaemoglobin.¹³ Similar to methaemoglobin, cyanomethaemoglobin is not able to bind oxygen and its presence may interfere with the estimation of oxygen saturation with peripheral pulse oximetry through similar mechanisms

to methaemoglobin, although this has not been reported. Unlike methaemoglobin, blood gas co-oximetry does not report cyanomethaemoglobin. In addition, the distinctive absorbance peak for methaemoglobin at around 630 nm, is abolished by binding of cyanide ion.¹⁴ Presence of cyanomethaemoglobin levels may not be measured by co-oximetry but may interfere with absorption spectra involving peripheral oximetry in some yet to be explained way, as revealed by our observations.

A recent reported case of apricot kernel toxicity showed the presence of high levels of methaemoglobin (10%) with an associated SpO₂ of 93% with supplemental oxygen.⁴ This was however, following treatment with amyl nitrate, a generator of methaemoglobin used to induce the formation of the cyanomethaemoglobin, through sequestration of cyanide ions, minimising the toxic effect of free cyanide on cytochrome oxidase. In this situation, there are high methaemoglobin and cyanomethaemoglobin levels, whereas our situation may only have involved high cyanomethaemoglobin in the setting of normal methaemoglobin as we did not identify an increase in methaemoglobin (0.3%) in our patient when cyanide levels proved to be elevated.

It is also feasible that haemoglobinopathies involving low oxygen affinity variants involving both alpha and beta chains detectable by DNA testing may account for a low SpO₂ in the setting of normal SaO₂.^{15 16} We were able to exclude this cause through DNA analysis of alpha and beta haemoglobin.

Our case has demonstrated that chronic subacute cyanide toxicity may manifest as low SpO₂ reading by peripheral pulse oximetry in the setting of no other possible causes and normal levels of methaemoglobin. Physicians should be aware that self-prescription with complementary medicines can result in

potentially harmful toxicities, and may be more common than currently understood.

Contributors AK initially managed and consented the patient. MSK investigated the biomedical equipment. AK, MSK, AB and JS conducted and interpreted further testing with patient and helped prepare the manuscript.

Competing interests None declared.

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Learning points

- Complementary medications appear prevalent and their use is difficult to regulate and measure accurately.
- Clinicians will not often consider taking a history of complementary medication use in their patients.
- Apricot kernel extract contains high levels of cyanide and has scientifically unproven but publicised efficacy as a cancer preventative.
- Low-level cyanide toxicity may be common and can present only as low oxygen saturation measured by peripheral pulse oximetry.

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