submissions

From: Brian Sandle [redacted]
Sent: Tuesday, 10 February 2015 5:49 PM
To: standards management
Subject: Re: Proposal P1016 - Hydrocyanic Acid in Apricot Kernels & other Foods

On 10/02/2015 7:33 p.m., Brian Sandle wrote:
> I wish to make an individual submission on Proposal P1016 -
> Hydrocyanic Acid in Apricot Kernels & other Foods.
>
> My name is: Brian Robert SANDLE
[redacted]
>
>
>
>
>
>

Further point:

If you decide that researchers may buy material under permit, the permit should be at low cost so as not to discourage public good research on a low budget.

If there is worry about the administration costs, according to your proposal there ought to be much saving in money from no longer having to treat so much HCN poisoning, or from delayed cancer treatment. That money could be transferred.

Thanks again from Brian Sandle

This email has been checked for viruses by Avast antivirus software.
http://www.avast.com

submissions

From:	Brian Sandle [redacted]
Sent:	Tuesday, 10 February 2015 5:33 PM
To:	standards management
Subject:	Proposal P1016 - Hydrocyanic Acid in Apricot Kernels & other Foods
Attachments:	00463528e8ed35cf40000000.pdf

I wish to make an individual submission on Proposal P1016 - Hydrocyanic Acid in Apricot Kernels & other Foods.

My name is: Brian Robert SANDLE
[redacted]

[redacted]

email: [redacted]

I have come recently upon this proposal and do not offer a complete grounds for objection, there will likely be others.

The supporting document 2 writes:

FSANZ: "Laetrile, an extract from apricot kernels, was for years promoted as a natural alternative therapy for cancer; yet its efficacy for cancer is unproven with clinical trials in humans failing to find any benefits."

How are benefits to be accounted?

Perhaps FSANZ is relying on older data such as (see my attachment)

http://www.researchgate.net/.../00463528e8ed35cf40000000.pdf which does not say results of treatment which do not involve any by mouth dose. Also it does not seem to accept non-progression of disease as any sort of win in those approx 50% it recounts.

That study used injection of the laetrile and later some eating of the kernels, which my 86-year-old friend does.

FSANZ: "Taking Laetrile, or eating apricot kernels in large amounts, is not only ineffective at treating cancer but could also cause fatal cyanide poisoning"

Eating the kernels in larger amounts or with acid such as vitamin C, or with normal stomach acid would release cyanide. However injection does not bring the laetrile into contact with acid.

FSANZ: "The successes claimed by its supporters are based on individual reports, testimonials, and publicity issued by promoters."

Not true if you consult scholar.google.co.nz amygdalin injected cancer

FSANZ: "Concerns exist about individuals relying on this type of

treatment alone, and avoiding or delaying conventional medical care for cancer This could have serious health consequences."

In my experience people go to it after conventional treatment fails which has a high probability.

There needs to be ways in which researchers may still get substance to test.

I therefore request the proposal be rejected.

Thank you for your attention from Brian Sandle

for example:

"Amygdalin induces apoptosis in human cervical cancer cell line HeLa cells

Febuary 2013, Vol. 35, No. 1 , Pages 43-51
(doi:10.3109/08923973.2012.738688)

PDF (1070 KB)
PDF Plus (1113 KB)

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Amygdalin, a naturally occurring substance, has been suggested to be efficacious as an anticancer substance. The effect of amygdalin on cervical cancer cells has never been studied. In this study, we found that the viability of human cervical cancer HeLa cell line was significantly inhibited by amygdalin. 4,6-Diamino-2-phenyl indole (DAPI) staining showed that amygdalin-treated HeLa cells developed typical apoptotic changes. The development of apoptosis in the amygdalin-treated HeLa cells were confirmed by double staining of amygdalin-treated HeLa cells with annexin V-FITC and propidium iodide (PI) along with increase in caspase-3 activity in these cells. Further studies indicated that antiapoptotic protein Bcl-2 was downregulated whereas proapoptotic Bax protein was upregulated in the amygdalin-treated HeLa cells implying involvement of the intrinsic pathway of apoptosis. In vivo, amygdalin administration inhibited the growth of HeLa cell xenografts through a mechanism of apoptosis. The results in the present study suggest that

amygdalin may offer a new therapeutic option for patients with cervical cancer."

Read More: http://informahealthcare.com/doi/abs/10.3109/08923973.2012.738688

Also:
http://www.cancerjournal.net/article.asp?issn=0973-1482;year=2014;volume=10;issue=5;spage=3;epage=7;aulast=Song

REVIEW ARTICLE
Year : 2014 | Volume : 10 | Issue : 5 | Page : 3-7

Advanced research on anti-tumor effects of amygdalin

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> Abstract

Malignant tumors are the major disease that cause serious damage to human health, and have been listed as the premier diseases which seriously threatened human health by World Health Organization (WHO). In recent years the development of antitumor drugs has been gradually transformed from cytotoxic drugs to improving the selectivity of drugs, overcoming multidrug resistance, development of new targeted drugs and low toxicity with high specificity drugs. Amygdalin is a natural product that owns antitumor activity, less side effects, widely sourced and relatively low priced. All these features make the amygdalin a promising antitumor drugs, if combined with conditional chemotherapy drugs, which can produce synergistic effect. In this paper, we summarized the pharmacological activity, toxicity and antitumor activity of amygdalin, mainly focused on the advanced research of amygdalin on its antitumor effects in recent years, providing new insights for the development of new anticancer drugs, new targets searching and natural antitumor mechanism investigations.

Keywords: Amygdalin, anti-tumor, pharmacological activity, toxicity

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> Introduction Top

Amygdalin is also called bitter apricot, laetrile, almond, it is a cyanogenic compounds and belongs to the aromatic cyanogenic glycoside group. Its molecular formula is: C 20 H 27 NO 11 , the molecular weight is 457.42. The chemical structure is D-mandelonitrile-β-D-glucoside-6-β-glucoside, as shown in [Figure 1]. Amygdalin is widely distributed in plants, especially in the rosaceous plant seed, for example, apricot, peach, cherry, plum etc. [1],[2] It can hydrolyze and generate prunasin and mandelonitrile under the glucosidase action, such as amygdalase and prunase, and ultimately decomposed into benzaldehyde and hydrocyanic acid (HCN). Amygdalin itself is non-toxic, but its production HCN decomposed by some enzymes is poisonous substance. [3] Numerous studies have documented that amygdalin has antitussive and antiasthmatic effects, as well as an effects on the digestive system. Moreover, the pharmacological effects also include antiatherogenic, inhibition of renal interstitial fibrosis, prevention of pulmonary fibrosis, resistance to hyperoxia induced lung injury, immune suppression, immune regulation, antitumor, antiinflammatory and antiulcer. [4],[5],[6],[7] It has been used for the treatment of asthma, bronchitis, emphysema, leprosy, colorectal cancer and vitiligo. [5] Amygdalin were decomposed to hydrocyanic acid, which is an antitumor compound, and benzaldehyde, which can induce an analgesic action, therefore it can be used for the treatment of cancer and relieve pain. [8] Therefore the anti-tumor effect of amygdalin is one of the hots topic in recent years. It has anticancer function by decomposing carcinogenic substances in the body, killing cancer cells, blocking nutrient source of tumor cells, inhibiting cancer cell growth, and could also reduce the incidence of prostate cancer, lung cancer, colon cancer and rectal cancer. [8],[9],[10] It has been manufactured and used to treat cancer in America, Germany, Italy, Japan, Philippines and other 20 countries. It can also ameliorate the symptoms of patients in advanced stage of cancer, and prolong their survival period. In order to provide references for the further investigations of amygdalin and new antitumor drug development, advances in studies of antitumor activities of amygdalin are reviewed in this paper.

Figure 1: Chemical structure of amygdalin

Click here to view

> The pharmacological activity of amygdalin Top

Amygdalin is the effective component of the traditional Chinese medicine (TCM) in bitter almond, which has been studying on for nearly two hundred years. As early as in 1803, Schrader found this substance in the study of bitter almond ingredients. Until 1830, Robiquet separated amygdalin from the bitter almond, which has always been used as auxiliary medicine of cough expectorant agent and cancer therapy. [11],[12]

Antitussive and antiasthmatic effects

After oral administration, amygdalin decomposed into hydrocyanic acid and benzaldehyde; hydrocyanic acid could inhibit the respiratory center to a certain level, which could calm down the respiratory movement and finally achieve the antitussive and antiasthmatic effects. Amygdalin can promote the synthesis of pulmonary surfactant in animal experimental model of respiratory distress syndrome and ameliorate the disease. [13],[14]

The effects on the digestive system

Benzaldehyde is another component that is decomposed by amygdalin through enzyme decomposition. It can inhibit the activity of pepsin and affect the digestive function. Administration of pepsin hydrolysate of almond water-solution at a dose of 500 mg/kg on CCl 4 treated rats, which found that it could inhibit the level of AST, ALT and increase hydroxyproline content, inhibiting the extention of euglobulinlysis time. In pathology, the soluble pepsin hydrolysate of almond water can inhibit the proliferation of connective tissue of rat liver, but could not inhibit D2 D-galactosamine induced the increase of rats' AST, ALT level. In addition, it is reported that amygdalin has a good therapeutic effects on rats with chronic gastritis and chronic atrophic gastritis. [15],[16],[17]

Analgesic effect

The mouse hot plate and acetic acid-induced writhing test confirmed that amygdalin has analgesic effects and no tolerance; mice without tail-erecting response and nalorphine induced jump response after treated with amygdalin. [12],[18] It is demonstrated that amygdalin isolated from Prunus armeniaca can alleviate formalin-induced pain in rats in a dose-dependent manner with dose range less than 1 mg/kg. [19] The mechanism may involve with inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), as well as c-Fos. [19],[20] Moreover, in mouse BV2 microglial cells, amygdalin produced antiinflammatory and analgesic effects probably by inhibiting prostaglandins E2 and nitric oxide synthesis through suppressing lipopolysaccharide (LPS) induced expression of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS) on mRNA levels. [21],[22]

Promoting apoptosis of human renal fibroblast

Amygdalin enhanced the activity of type I collagenase that secreted by the human kidney fibroblasts (KFB) within a certain concentration and action time, inhibiting the expression of type I collagen and KFB cell proliferation, promoting apoptosis of KFB cells. [23]

Improving the immune function of organism

Amygdalin can significantly increase polyhydroxyalkanoates (PHA) induced human peripheral blood T lymphocyte proliferation; and can promote peripheral blood lymphocytes stimulated by PHA secrete IL-2 and IFN-g, and then inhibit the secretion of TGF-β1, therefore enhance immune function. [24] Amygdalin play a positive role in the expression of regulatory T cells in the treatment of atherosclerosis, and can also expand the lumen area, reduce aortic plaque coverage. [25],[26]

Other effects

Amygdalin can specifically inhibit the alloxan induced hyperglycemia, the effective intensity was related to the drug concentration in blood. [27] Research has shown that amygdalin has therapeutic effect on experimental gastric ulcer. Amygdalin inhibits angiogenesis in the cultured endothelial cells of diabetic rats. [6]

The toxicity of amygdalin

The acute toxicity experiments of amygdalin has proved that the toxicity of oral administration route is far greater than the intravenous route. The mean lethal dose (LD50) of amygdalin in rats was reported to be 880 mg/kg body weight (BW) by oral administration. [28],[29] The LD50 of intravenous injection in mice are 25 g/kg, while intraperitoneal injection are 8 g/kg. The maximum tolerance dose of intravenous and intramuscular injection of amygdalin in mice, rabbits, dogs are 3 g/kg, 0.075 g/kg orally respectively; [30],[31] human intravenous injection are 5 g (approximately 0.07 g/kg). Out of 10 mice injected intravenouly with 500 mg/kg eight died and two survived. Research shows that the main reason is that the amygdalin was hydrolyzed by intestinal microbial after oral administration, producing more hydrocyanic acid. [32] In the mice treated by inhibiting the intestinal microbial growth, the stomach administration of 300 mg/kg also has no death phenomenon; while in the untreated mice, the mortality increased by 60% at the same dose. [32],[33],[34],[35],[36] Human can present systemic toxicity after oral administration of amygdalin 4 g per day, lasted for half a month or intravenous injection of a month. Moreover, the digestive system toxicity response is more common, with changes of atrial premature beats and ECG T wave. The toxicity response above can disappear after drug withdrawal. If the dose is reduced to daily oral doses of 0.6 ~ 1g, it can avoid toxicity. [32],[33],[34],[35],[36],[37],[38]

The anti-tumor effect of amygdalin

Amygdalin is one of the most commonly used alternative drug in the treatment of tumor in the last 40 years. Amygdalin has many nicknames, including: vitamin B17, nitriloside, mandelonitrile, laetrile, etc. [39] Although laetrile and amygdalin can both represent amygdalin, they are different substances. Natural amygdalin exists as a right-handed structure (R-amygdalin), which is the active form. Laetrile is the acronym of laevorotatory and mandelonitrile. [39],[40] Amygdalin which has been applied for a USP (United States patent) is the semi synthetic derivatives, the structure is D-mandelonitrile-β-glucose, however it is different with Mexico made amygdalin (D-mandelonitrile-β-gentiobioside) in structure. [11],[41]

Amygdalin was separated and purified first in 1837 by two chemists-Robiquet and Boutron, and was named as emulsion by Liebig. [42],[43] A Russian doctor first tried it in the treatment of cancer in 1845. In America, amygdalin was first used to treat cancer during 1820s. In 1850s, innocuous intravenous amygdalin, called Laetrile, was registered as a patent. USA National Cancer Institute (NCI) analysis shows that, Mexico produced oral and intravenous forms of amygdalin do not conform to the American drug production standards, and other components were detected. [44] In spite of this, many American are still using amygdalin produced in Mexico. In view of this situation, USA NCI conducted clinical studies on its effectiveness. In 22 cases of drug treated patients, only 6 cases had good effects against cancer, it does not good enough to support the antitumor effects of amygdalin. [45]

American food and drug administration (FDA) prescribed amygdalin (Laetrile) products as toxic in 1979, which cannot be used as drug. Amygdalin was banned in America. [46],[47] In 1980, 23 states of USA restored application of amygdalin in the treatment of advanced cancer patients. [48] Unfortunately, American FDA approved NCI two clinical trials of amygdalin, the results could not confirmed the effectiveness of amygdalin. In 1987, the imports of amygdalin were banned in USA, afterwards amygdalin was banned in USA and Europe. [48] In the UK, the drug can produce cyanide and has been listed as a prescription drug, which can be used under the supervision of a doctor. [49] Thus, as an antitumor drug, of the mass production and application of amygdalin is mainly in Mexico. [50]

Amygdalin is mainly as an alternative therapy for traditional cancer treatment, or combined with other nonconventional treatments, such as metabolic therapy, urine therapy, dietotherapy, intake of fruit seeds, intravenous injection of β-glucosidases and so on. [51],[52],[53] β-glucosidases enzyme was found from the intestinal bacteria, [32] it also can be found in edible plants, with function of decomposing amygdalin into benzaldehyde, glucose and hydrocyanic acid. [54] Amygdalin exists in the related products of amygdalin and Laetrile, is the active component of drugs. [55]

Many experiment results supported that, amygdalin has antitumor activity. [39],[56],[57] Amygdalin and other cyanogenic sugar, are also considered to be a potential alternative antitumor drug. [57],[58]

Recently, some advances had been made on the antitumor mechanism of amygdalin. Kwon et al., confirmed that amygdalin can induce apoptosis in human promyelocytic leukemia (HL-60) cells; [59] Park et al., have shown that amygdalin inhibited the proliferation of human colon cancer SNU-C4 cell, and the mechanism is the inhibition of expression of cell cycle related genes; [9] Chang et al., identified that amygdalin can induce apoptosis in prostate cancer DU145 and LNCaP cells by regulating the expression of Bax and of Bcl-2. [8],[11],[60] Chen, Y. et al., [10] found that amygdalin can inhibit the survival rate of HeLa cells, in a concentration dependent manner. Amygdalin can induce apoptosis of HeLa cells mediated by endogenous mitochondrial pathway. Amygdalin could also inhibit the growth of HeLa cell in nude mice bearing tumors through inducting tumor cell apoptosis. The detection results of human whole genome U133 microarray showed that 573 genes of HeLa cells had differential expression in the amygdalin treated group, compared with the control group, JNK/c-Jun pathway is involved in the process of amygdalin induced apoptosis in HeLa cells. Nevertheless, the antitumor mechanism of amygdalin is not completely clear. Clinical trials and large retrospective studies showed that bitter almond had no stable antitumor effect, most importantly is the existence of some adverse reactions after large dose application, such as gastrointestinal tract reaction and headache. [61],[62],[63],[64],[65],[66],[67] But in view of the quantity and quality of clinical data are limited, so far clinical studies have no paired and reliable design, so it is necessary to conduct more carefully designed controlled clinical trials for bitter almond, and prove its effect in vivo. [60]

> Conclusion Top

There has been done a lot of work in the analysis of amygdalin, the

analysis and detection methods of amygdalin were more perfect and mature; and a large number of studies have shown that amygdalin plays a supporting role in the treatment of cancer, diabetes, atherosclerosis, immune suppression, leprosy and other diseases. This paper reviews recent progression of amygdalin in cancer research. Amygdalin has a clear pharmacological activity, but there are still little in-depth research on the pharmacological mechanism of the compound, so it has an important application value to systematically investigate the mechanism of amygdalin pharmacological activity and develop antitumor drugs.

> Acknowledgements Top

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Life-Threatening Interaction Between Complementary Medicines: Cyanide Toxicity Following Ingestion of Amygdalin and Vitamin C

Jonathan Bromley, Brett GM Hughes, David CS Leong, and Nicholas A Buckley

OBJECTIVE: To describe a case of severe accidental cyanide poisoning following a single ingestion of amygdalin with therapeutic intent.

CASE SUMMARY: A 68-year-old patient with cancer presented to the emergency department shortly after her first dose (3 g) of amygdalin with a reduced Glasgow Coma Score, seizures, and severe lactic acidosis requiring intubation and ventilation. The patient also ingested 4800 mg of vitamin C per day. She responded rapidly to hydroxocobalamin treatment. The adverse drug reaction was rated probable on the Naranjo probability scale.

DISCUSSION: Amygdalin and laetrile (a synthetic form of amygdalin) are commonly used as complementary or alternative medicine (CAM) for the treatment of cancer. Vitamin C is known to increase the in vitro conversion of amygdalin to cyanide and reduce body stores of cysteine, which is used to detoxify cyanide. Amygdalin has been used for decades by patients with cancer who are seeking alternative therapies, and severe reactions have not been reported with this dose. An interaction with vitamin C is a plausible explanation for this life-threatening response.

CONCLUSIONS: This case highlights the fact that CAMs can produce life-threatening toxicity. This case also adds a further note of caution, namely, the potential for serious interactions between CAMs, particularly where there is no tradition of concomitant use.

KEY WORDS: amygdalin, cyanide, laetrile, vitamin C.

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Complementary and alternative medicines (CAMs) are commonly used among patients with cancer in addition to or instead of conventional medical therapies.

We describe a case of a patient who developed severe toxicity after starting amygdalin while using a number of other CAM therapies. This case serves to highlight the potential dangers and interactions between these CAM therapies. We also review the history of amygdalin use and the evidence on its safety and efficacy in oncology.

Case Report

A 68-year-old female presented to the emergency department complaining of dizziness and feeling unwell. She had taken her first dose (six 500-mg tablets) of amygdalin approximately 2½ hours earlier that evening with a dinner consisting of fish and vegetables. These tablets had been obtained from the UK over the Internet; however, the tablets themselves were produced in Mexico (Figure 1). She began to feel ill within about 30 minutes after taking amygdalin.

Author information provided at the end of the text.

The patient had recently been diagnosed with locally advanced (stage T4N0M0) urothelial carcinoma of the bladder. This was initially managed with chemotherapy consisting of intravenous cisplatin and gemcitabine. As a result of prolonged myelosuppression after receiving her first cycle, clinicians decided to discontinue chemotherapy and manage the cancer with palliative radiotherapy. The woman's medical history otherwise consisted of hypercholesterolemia, osteoporosis, and a recent deep venous thrombosis of the left leg.

She had begun taking a number of complementary preparations in addition to her conventional treatment. Her total daily intake of vitamin C was 4800 mg. Medications included:

1. vitamin C 1000 mg 4 times daily;
2. Executive B (vitamin B supplement that also contains 250 mg of vitamin C per tablet);
3. vitamin B_6 25 mg/zinc 25 mg/magnesium 50 mg;
4. Bio Ace 1 tablet daily (vitamin C 550 mg, beta-carotene 3 mg, vitamin E 75 IU, thiamine 10 mg, calcium pantothenate 55 mg, pyridoxine 25 mg, zinc amino acid chelate 25 mg);
5. Co Q Max 150 mg (naturally occurring human protein also known as ubiquinone);
6. Flor/essence 30 mL twice daily (unquantified amounts of burdock, sheep sorrel, slippery elm, blessed thistle, brown algae, watercress, red clover, Turkish rhubarb);
7. shark fin 500 mg/day (shark cartilage extract); and
8. warfarin 5 mg/day.

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On arrival at the hospital, the patient's Glasgow Coma Score (GCS) was 13 and her heart rate was 136 beats/min and regular. Soon after arrival, she had 2 generalized tonic–clonic seizures, with a postictal GCS of 5. She was intubated and mechanically ventilated with 100% oxygen. Her blood cell count, electrolyte levels, and renal function tests were unremarkable aside from a white blood cell count of $5.7 \times 10^3/mm^3$. The presentation was recognized as consistent with cyanide toxicity secondary to amygdalin (Table 1).[1] Serial arterial blood gases after intubation are shown in Table 2. Plasma lactate concentrations are probably the best indicator of the severity of cyanide poisoning and the response to treatment in this case,[2] as no cyanide levels were available.

Activated charcoal was administered orally, and the cyanide antidote hydroxocobalamin 5 g was infused intravenously over 30 minutes. The patient made a satisfactory neurologic recovery over the course of the night and was extubated the following morning. She was discharged 2 days later with no residual sequelae. The laboratory effects of cyanide toxicity are shown in Table 2. The amygdalin preparation was sent to the Therapeutic Goods Administration for analysis; the tablets contained the claimed 500 mg of amygdalin per tablet. On the Naranjo probability scale, the adverse drug reaction was rated probable.[3]

Discussion

MECHANISM OF TOXICITY OF AMYGDALIN AND THE INTERACTION WITH VITAMIN C

Amygdalin causes toxic effects by producing cyanide. Cyanide inhibits mitochondrial cytochrome oxidase and, therefore, oxidative phosphorylation.[4] As a consequence, anaerobic metabolism is increased and lactic acid is produced. Notably, our patient had severe lactic acidosis on presentation. There were no other likely explanations for this acidosis, which resolved rapidly with hydroxocobalamin, a specific antidote for cyanide poisoning.

Figure 1. The amygdalin container prepared in Mexico: note lack of prescription, dosing instructions, and warning labels.

Hydrolysis of the amygdalin molecule yields up to 6% (w/w) hydrogen cyanide (HCN), benzaldehyde, and glucose.[5] Thus, this dose (3000 mg) of amygdalin could theoretically produce as much as 180 mg of cyanide, well above the estimated potentially lethal dose of 50–100 mg.[4] Hydrolysis after absorption is very low, and parenteral administration of amygdalin rarely causes toxicity.[4,6] Hydrolysis may occur in the gut and is promoted by β-glucosidases (present in almonds and apricot kernels and produced by some gut bacteria), heat, mineral acids, and high doses of ascorbic acid.[5] β-Glucosidases are not normally abundant in the upper gastrointestinal tract.

The dose used by our patient was slightly higher than that administered in formal studies of amygdalin (usually 1.5–2 g/day).[7,8] At these doses, long-term use did not appear to ever cause severe cyanide toxicity. However, doses as high as 9 g/day are recommended on some Web sites,[9,10] and, as of July 1, 2005, there have been no reports of serious cyanide toxicity with oral doses <6 g.[4] We believe the best explanation for her severe reaction is that "mega-doses" of vitamin C (>3 g) not only might increase hydrolysis by the above mechanism, but also markedly decrease the body stores of cysteine, a sulfur-containing amino acid that facilitates the detoxification of cyanide.[11] Cyanide is largely metabolized by the abundant mitochondrial enzyme rhodenase,[4] and the rate-limiting step in detoxification is the availability of intracellular cystine and cysteine.[4,12] Animal studies have confirmed the greater toxicity of amygdalin given with high doses of vitamin C.[13]

HISTORY OF AMYGDALIN USE FOR CANCER

Amygdalin is a substance found in the kernels of apricots and other stone fruits. It was first isolated in 1830 by French chemists. The suggested mechanism of amygdalin's anticancer action has changed over the years, but probably the most widely stated claim is that neoplastic cells are rich in an enzyme that causes amygdalin to release cyanide that kills the neoplastic cells. Non-neoplastic cells are protected from this process by another enzyme that renders the cyanide harmless.[14] There is no convincing evidence for a selective effect on neoplastic cells.

In contrast with many CAM therapies, there is no history of traditional ethnic use of amygdalin for cancer. The history is dominated by quackery—extravagant and unsupported claims based on pseudo-scientific theories and attempts to bypass regulation by those with questionable

Table 1. Clinical Effects of Cyanide Toxicity[1]

Mild:	headache, tachycardia, confusion, weakness
Moderate:	cyanosis, coma, convulsions, cardiac arrhythmias
Severe:	circulatory and ventilatory failure, cardiac arrest, death

qualifications. In 1950, 2 Americans, Ernest T Krebs Sr. MD, and his son, Ernest Jr., began using a "purified" version of the drug, which they patented as laetrile for "disorders of intestinal fermentation." However, their main promotion of laetrile was as an anticancer drug.[14,15] Krebs Sr. worked as a pharmacist before he received his medical degree in San Francisco 50 years earlier. His son referred to himself as Dr. Krebs, but had failed medical school. He was awarded an honorary "doctor of science" degree by the American Christian College in Oklahoma after delivering a lecture on laetrile; interestingly, the college had no science department. In 1970, in an attempt to circumvent Food and Drug Administration regulations, Krebs claimed that laetrile was in fact a vitamin (B_{17}), as vitamins are not subject to the same safety and efficacy requirements as drugs.[14,15]

The ensuing years have seen the battle for laetrile play out in food and drug regulation, the courts, and the newspapers. It is effectively banned in the US, but available in special clinics in Mexico, the original source of our patient's medication. While there is no evidence of the use of laetrile in Australia in Krebs' era, the increased availability of pharmaceuticals through the Internet seems to have given it greater accessibility in our region.

Despite an absence of scientific evidence, it has been apparently easy to raise some public support for laetrile among cancer support groups. Support is fueled by anecdotal cases of miraculous results from the drug that do not hold up to scrutiny. For example, a woman set up the International Association of Cancer Victims and Friends in 1963 to support its use, convinced that it had saved her life. She had undergone a radical mastectomy for early breast cancer and also had received treatment with laetrile. The fate of actor Steve McQueen, also a strong advocate of the drug, is perhaps more telling. He travelled to Mexico to undergo treatment with laetrile at a clinic in 1980 and died within a few weeks of commencing treatment.[14]

LACK OF EVIDENCE FOR EFFICACY OF AMYGDALIN

There has never been any scientific support for amygdalin, but studies have been performed on a number of occasions largely in response to its use. In 1962, the Californian Cancer Advisory Council reviewed 100 case histories and decided that none showed any evidence that laetrile was beneficial against cancer. They recommended that regulations be issued to ban the use of laetrile and similar agents for the treatment of cancer.[14]

In 1982, the National Cancer Institute undertook a Phase II clinical trial using patients taking amygdalin.[7] Most of the patients had breast, colon, or lung cancer. Amygdalin was administered by injection for 21 days, followed by oral maintenance therapy. Vitamins and pancreatic enzymes were also given, and dietary changes were instituted. During treatment, cancer progressed in 54% of the patients, and only one partial response was seen among 175 patients who were evaluated for tumor response. Furthermore, several patients were found to have symptoms suggestive of mild cyanide toxicity, significant blood levels of cyanide, or both.

WIDESPREAD USE OF CAM THERAPIES

The use of CAM therapies in addition to or instead of conventional therapies has continued to rise. Large numbers of patients are taking one or more nonprescribed medications, and many are not reporting these at consultation with healthcare providers. In the US, 34% of survey respondents admitted using alternative therapies in 1990, with this figure rising to 42% in 1997.[16] In addition, it was found that disclosure of these medications to physicians was only 38% and 40%, respectively. Previous reviews have highlighted the issue of interactions betweens drugs and CAM therapies,[17] but the issue of interactions between CAM therapies has received little attention.

Conclusions

We postulate that our patient inadvertently increased her risk of cyanide toxicity by coingestion of amygdalin with megadoses of vitamin C. This case also highlights the fact that CAM therapies can have serious and life-threatening toxicities and further refutes the commonly held myth that they are universally safe. Clinicians should be aware of the potential for serious interactions between different CAM therapies, particularly where there is no long tradition of safe concomitant use.

Table 2. Serial Blood Gas Analysis on Presentation to the Emergency Department

Parameter (reference range)	Immediately After Intubation	10 min After Start of Hydroxocobalamin	Hydroxocobalamin Infusion Complete
pH (7.34–7.44)	7.22	7.09	7.38
PCO_2 (35–45 mm Hg)	31	37	32
HCO_3 (22–26 mEq/L)	12.4	11.0	18.3
Base excess (–2.4 to 2.4 mEq/L)	–15.3	–18.7	–6.9
Lactate (4.5–18 mg/dL)	118	99.7	35.9

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EXTRACTO

OBJETIVO: La amigdalina y el laetrilo (una forma sintética de amigdalina) se usan comúnmente como medicina complementaria o alternativa en la terapia contra el cáncer. Describimos un caso de envenenamiento accidental severo por cianuro tras la ingesta de amigdalina para propósitos terapéuticos.

RESUMEN DEL CASO: Una paciente de cáncer de 68 años de edad se presentó a la sala de emergencias tras la primera dosis de amigdalina complementaria con una puntuación reducida en la escala de coma de Glasgow, convulsiones, y acidosis láctica severa, requiriendo intubación y ventilación. La paciente también consumía 4800 mg de vitamina C diariamente. Ella respondió rápidamente a tratamiento con hydroxicobalamina. La reacción adversa fue catalogada como "probable" en la escala de probabilidad de Naranjo.

DISCUSIÓN: Es sabido que la vitamina C aumenta la conversión invitro de amigdalina a cianuro y reduce el almacenaje corpóreo de cisteína, la cual se utiliza para detoxificar el cianuro. La amigdalina ha sido utilizada por décadas por pacientes de cáncer buscando terapias alternas sin que se haya reportado reacciones severas con esta dosis. Una interacción con la vitamina C es una explicación razonable para esta respuesta amenazante a la vida.

CONCLUSIONES: Este caso ilustra que la terapia complementaria puede tener efectos serios y toxicidad potencialmente amenazante a la vida. Este caso añade otra nota de precaución, específicamente, el potencial para interacciones entre medicamentos complementarios distintos, particularmente si no existe una tradición de uso concomitante.

Mitchell Nazario

RÉSUMÉ

OBJECTIF: L'amygdaline et le laetrile (forme synthétique d'amygdaline) sont couramment utilisés comme compléments ou alternatives santé dans le traitement du cancer. Nous décrivons ici un cas d'intoxication sévère au cyanure suite à une ingestion unique d'amygdaline à des fins thérapeutiques.

RÉSUMÉ DU CAS: Une patiente cancéreuse de 68 ans s'est présentée aux urgences peu après sa première prise du complément santé amygdaline avec un score de Glasgow diminué, des convulsions, et une acidose lactique sévère ayant nécessité intubation et ventilation. La patiente prenait aussi 4800 mg par jour de vitamine C. Elle a rapidement répondu au traitement par hydroxocobalamine. L'effet indésirable a été coté comme probable sur l'échelle d'imputabilité de Naranjo.

DISCUSSION: La vitamine C est connue pour augmenter in vitro la transformation d'amygdaline en cyanure et pour diminuer les réserves corporelles en cystéine, qui intervient dans la détoxification du cyanure. L'amygdaline a été utilisée pendant des décennies par les patients cancéreux à la recherche de traitements alternatifs et il n'avait pas été signalé de réactions sévères à cette dose. Une interaction avec la vitamine C est une explication plausible de cette réaction mettant en jeu le pronostic vital.

CONCLUSIONS: Ce cas illustre le fait que les compléments santé peuvent présenter des toxicités sévères et mettre en jeu le pronostic vital. Ce cas apporte un nouvel élément de précaution, à savoir le risque potentiel d'interactions graves entre différents compléments santé, notamment lorsqu'il n'existe pas d'expérience de leur co-utilisation.

Michel Le Duff