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POSSIBLE ADVERSE SIDE EFFECTS FROM TREATMENT WITH LAETRILE

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ABSTRACT

Individuals who have a diminished capacity ot detoxify cyanide to thiocyanate because of either a genetic predispositio (e.g. as occurs in those with Leber's Optic Atrophy) or a diet low in sulfur containing amino acids are predicted to be at increased risk to developing adverse side effects from laetrile, a cyanide containing substance used in cancer treatment.

Key Words: laetrile, amygdalin, vitamin B_{17}, cancer, cancer treatment, cyanide, Leber's Optic Atrophy

INTRODUCTION

With the exception of the attempt of the United States Food and Drug Administration (FDA) to ban the widespread use of saccharin within American society, no other biomedical issue has recently seemed to cause as much commotion as whether laetrile should be allowed as a possible treatment for cancer patients. Various state legislatures, in fact, have bypassed the authority of the FDA to legalize the usage of laetrile within their jurisdiction. Controversy has engulfed the claims of proponents and opponents concerning the effectiveness of laetrile to the extent that at the Slone-Kettering Institute, where research on laetrile has been proceeding for several years, a group of workers challenging "official" conclusions has issued a series of opposing newsletters entitled "Second Opinion". In light of this present controversy and notoriety, it is quite likely that the use of laetrile, at least over the next several years, will dramatically increase until it rises or falls on its patients' outcomes.

Always an important issue in the treatment of cancer patients is the potential problem of adverse side effects. Yet, this has been one component of the laetrile debate which has been largely ignored. Since the extent and nature of possible side effects can significantly affect the utility of anticancer drugs, it is necessary that investigations into possible side effects be rigorously pursued. The purpose of this paper is to identify biological factors (inherent and acquired) which will predispose individuals to the development

of adverse side effects from laetrile treatment.

Laetrile: backgroung information

According to its proponents, the active ingredient in laetrile is called amygdalin or vitamin B_{17} (1). Natural sources of amygdalin include oil of bitter almonds and apricot and peach pits (1,2). Amygdalin is a glucoside which contains cyanide (2); its chemical structure is represented in figure 1. When amygdalin is acted upon by certain hydrolytic enzymes, hydrogen cyanide may be

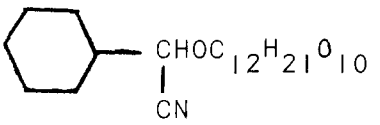

Figure 1. Chemical structure of Amygdalin.

liberated (2,3). According to Richardson (1), amygdalin acts as an anticancer agent via the toxic action of cyanide on the cancerous tissue. Richardson (1) states that the enzyme rhodanese which readily converts cyanide to the relatively non-toxic thiocyanate[a] is not found in cancerous tissue but is generally prevalent elsewhere throughout bodily tissue. More specifically, rhodanese exhibits considerable activity in liver, kidney, thyroid, adrenal and pancreas tissue, but somewhat lower activity in heart, brain, alimentary tract and elsewhere (6). Based on this information it has been suggested that amygdalin destroys cancer cells in a very selective manner, whereas normal tissue is afforded extra protection from cyanide via the detoxifying activity of rhodanese.

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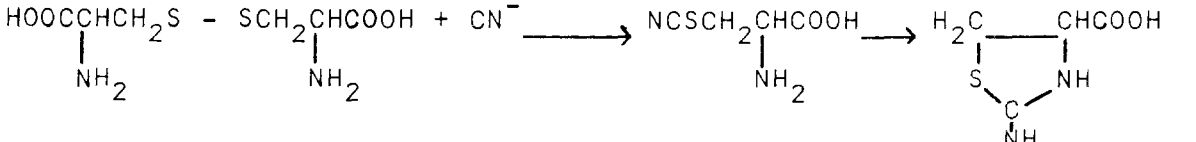
a. According to Williams (4) and Parke (5) the inorganic cyanide ion is conjugated with sulfur to form thiocyanate via the enzyme rhodanese. Thiocyanate conjugation represents a striking detoxification reaction which is accompanied by 200-fold decrease of toxicity.

$$CN^- + S_2O_3^{--} \longrightarrow CNS^- + SO_3^{--}$$

The detoxification of cyanide also occurs via the conjugation of cyanide with cysteine resulting in the formation of 2-iminothiazolidine-4-carboxylic acid.



Cysteine

2-Iminothiazolidine-4- carboxylic acid

Laetrile treatment: possible side effects

The question now arises as to what happens to individuals who are receiving amygdalin treatment and who also may experience a decreased capacity to convert cyanide to thiocyanate. What is the likelihood of such an occurrence and what would be the toxic effects if any? There are several conditions which may exacerbate the toxicity of cyanide: (a) the genetic (or developmental) trait called Leber's Optic Atrophy, and (b) diets low in sulfur-containing amino acids and vitamin B_{17}.

Leber (7) noted a genetic disorder which resulted in visual failure either subacutely or insidiously. This condition, Leber's Optic Atrophy, is characterized by severe bilateral central scotomata and pallor of the optic discs. Wilson (8) stated that this disease is usually first noted in males in late teenage years or early twenties. In western cultures, 85% of those afflicted with this condition are males. As a result of both the hereditary nature and clinical phenomena of Leber's Optic Atrophy, Wilson (8) concluded that the disease results from an inborn metabolic disorder whose clinical expression is significantly affected by exogenous influences such as smoking. The relationship of smoking with Leber's Optic Atrophy is based on (a) the well known occurrence of several neurotoxic substances in cigarette smoke such as cyanide and (b) experimental data indicating that repeated exposure of animals to cyanide has resulted in neurological effects very comparable to Leber's Optic Atrophy. Furthermore, individuals with Leber's Optic Atrophy who smoke exhibited significantly lower levels of thiocyanate in the plasma and urine than appropriately matched controls. Such evidence led Wilson (8) to suggest that patients with Leber's Optic Atrophy have reduced genetic capacity to detoxify cyanide.

Although the above evidence suggests that those with Leber's Optic Atrophy may be at increased risk to cyanide containing substances (e.g. cigarette smoke) the results are only of a preliminary nature and need further replication. However, the implication is clear that individuals with this syndrome are predisposed to experiencing toxic side effects if treated with laetrile or any other cyanide containing substance. Certainly more information is needed concerning the precise nature of the metabolic disorder and the frequency of this condition in the population.

Dietary factors affecting cyanide toxicity

The occurrence of cyanogenetic glucosides has been reported in a number of common plants including lima beans, cassava, sweet potato, maize, and sorghum. In fact, numerous cases of human poisoning have been reported following consumption of cassava and lima beans (3,9).

Furthermore, importation of lima beans to the United States is limited to those varieties with less than 20 mg HCN/100 g of seeds (3).

Osuntokun has reported a rather widespread "tropical neuropathy" highly comparable to Leber's Optic Atrophy in association with the consumption of cassava, a tuber whose outer integument has high levels of the cyanogenetic glycoside, linamarin (10). Those affected with the "tropical neuropathy" as previously described by Osuntokun had diets low in cysteine and other sulfur containing amino acids (see footnote a). It was thought that the synergistic interaction of low dietary levels of these amino acids and their increased use for the detoxification of cyanide may have resulted in extremely depleted levels of plasma cysteine and methionine in these patients (9). However, the precise mode of action by which toxic symptoms result remains to be determined, although it has been suggested as resulting from direct intra-neuronal enzymatic inhibition by cyanide or by the inactivation of vitamin B_{12} (8).

CONCLUSION

Patients receiving laetrile treatment should be closely examined for the occurrence of adverse side effects resulting from the cyanide toxicity. Individuals with reduced metabolic capacity to detoxify cyanide to thiocyanate as a result of genetic and/or diet factors would be at increased risk to the development of such side effects.

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