Chronic Cassava Toxicity

Proceedings of an interdisciplinary workshop

Editors: Barry Nestel and Reginald MacIntyre
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Chronic Cyanide Toxicity in Domestic Animals

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Abstract Cases of acute cyanide poisoning are well-authenticated in animals grazing on cyanogenic forages, but chronic toxicity from continuous intake of low levels of cyanogenic plant material, including cassava, has not been clearly identified. Although chronic hydrogen-cyanide toxicity may be influenced by concomitant nutritional deficiencies, such toxicity does not appear as a serious practical problem in the utilization of cassava or cassava products by domestic animals. There is evidence that ataxic neuropathy in humans is associated with high cassava consumption, and that continuous low-level dosage of rats with potassium cyanide will produce lesions in the central nervous system. Such observations have a parallel in the toxic effect of lathrogens and other neurotoxins contained in plants. Some goiters in humans have been attributed to cassava consumption, and experiments with animals strongly suggest that thiocyanate formed during the detoxication of ingested cyanide interferes with the utilization of iodine for thyroxin production. There are interesting similarities between cyanogenic glucosides found in cassava and other plants and the glucosinolates found in Brassica species. The latter are, however, the more complex compounds and can yield a greater variety of hydrolytic products.

Résumé Les cas d’empoisonnement aigu par le cyanure sont bien prouvés chez les animaux broutant des fourrages qui contiennent du cyanogène, mais la toxicité chronique de matériel végétal à faible teneur en cyanogène, y compris le manioc, ingéré de façon continue, n’a pas encore été clairement identifiée. Quoique la toxicité chronique de l’acide cyanhydrique puisse être affectée par des déficiences alimentaires concomitantes, elle ne semble pas, dans la pratique, causer de problèmes sérieux dans l’utilisation du manioc ou de ses produits par les animaux domestiques. On a des indications que la neuropathie ataxique chez les humains est liée à une forte consommation de manioc. On sait de plus que les rats soumis à des dosages continus d’une faible quantité de cyanure de potassium développent des lésions au système nerveux central. Ces observations ont leur parallèle dans l’effet toxique des lathrogènes et autres neurotoxines contenues dans les plantes. Certaines formes de goitre chez les humains sont attribuables à la consommation de manioc, et des essais sur des animaux suggèrent fortement que le thyocyanate formé au cours du processus de désintoxication du cyanure ingéré entrave l’action de l’iode dans la production de thyroxine. Il existe des ressemblances intéressantes entre les glucosides cyanogènes du manioc et autres plantes et les glucosinolates présents chez les espèces du genre Brassica. Ces derniers sont toutefois des composés plus complexes qui donnent, à l’hydrolyse, une plus grande variété de produits.

There are no reviews dealing specifically with cyanide toxicity in domestic animals. However, there are several reviews which relate to the basic role of hydrocyanic acid (HCN) in nutrition, particularly those of Montgomery (1965, 1969) and Oke (1969).

Many species of plants contain HCN, usually in the form of cyanogenic glycosides which release
HCN on hydrolysis. At least 300 species of plants tested yield HCN with 52 species in the family Leguminosae and 25 in Gramineae (Quisimbing 1947). The following major species have been associated with HCN poisoning of animals: millet (Sorghum vulgare), sudan grass (Sorghum sudanense), Johnson grass (Sorghum halepense), star grass (Cynodon plectostrachyum), arrow grass (Triglochin maritima), lucerne (Medicago sativa), white clover (Trifolium repens), blue couch grass (Cynodon incompletus), sedge (Carex rulpina), linseed (Linum usitalissimum), reed sweet grass (Glyceria spectabilis), common vetch (Vicia sativa), lima bean (Phaseolus lunatus), and cassava (Manihot esculenta).

The amount of HCN which can be released from a given species is influenced by many factors. Apart from the fact that some varieties of a species characteristically yield little or no HCN, conditions of drought or wilting, stage of growth, and soil fertility may affect the toxicity (Winks 1940; Anonymous 1934; Lahke 1955; Acharya 1933; Favero 1953; Guisti 1935). Subsequent treatment of the crop may affect the amount of HCN. For example, Sorghum vulgare grown under drought conditions may contain dangerous levels of HCN but drying for several days, or ensiling, will reduce the HCN to zero (Kehar and Talapatra 1947). Also, there is evidence for a diurnal variation in the HCN content of plants. Taranenko (1958) and Wolf and Washko (1967) found that HCN concentration reached a peak at midday or early afternoon when photosynthesis was at a maximum.

Feeding Experiments with Cyanogenic Species

It is necessary to distinguish between chronic and an acute condition of poisoning which is usually fatal.

Acute poisoning from the consumption of cyanogenic plants has been the subject of many reports and is a well-established phenomenon. Many plants, since they serve as forages, or are contaminatees of forages, are more of a risk to grazing animals than to poultry and swine which are, to a large degree, fed formulated diets. Surprisingly, there are some known carriers of cyanogenic glycosides which rarely seem to produce acute toxic reactions. A striking example is linseed meal. This protein supplement is fed widely to ruminants and pigs at quite high levels but there are very few reports of toxic reactions in these animals. However, chicks and poults consistently show depressed growth and increased mortality when they are fed linseed meal but these effects can be prevented if the meal is let stand in water at 28–37°C before feeding (MacGregor and McGinnis 1948; Kratzer 1949). It is not known if the toxic factor thus removed or inactivated is HCN arising from linamarin, although HCN may well be involved. Probably during the processing of flax seed to linseed meal there is sufficient heat application to destroy the linamarase thus preventing, in most samples, the subsequent release of significant amounts of HCN.

In contrast to acute poisoning, chronic toxicity, which could be the more serious problem, is largely unresolved. It might be assumed that when fatal toxicity has occurred in certain individuals in a herd or group many others may be affected less obviously. However, controlled feeding experiments are necessary to detect effects which may be exhibited superficially only by somewhat reduced weight gains and feed efficiency.

Feeding trials with cattle and sheep using a variety of plants with cyanogenic potential have, in general, failed to clearly indicate chronic toxicity. Cassava fed in various forms to cattle and sheep, including tapioca meal and chopped-up roots, has not produced obvious ill effects (Brouwer 1932; Anonymous 1937; Assis et al. 1962; Mathur et al. 1969).

Flux et al. (1956) and Butler et al. (1957) found that feeding white clover containing cyanogenic glycosides equivalent to 129 mg of cyanide per 100 g of dry matter to sheep produced no deleterious effect on weight gains, but raised the level of thiocyanate in the plasma, evidence for a metabolic effect from the toxic principle. No strong evidence of a goitrogenic effect was obtained in these studies.

Results with swine are more variable. There are a number of reports in which large amounts of cassava in various forms have been fed to swine with satisfactory results and no evidence of HCN toxicity (Anonymous 1920; Mondenedo and Bayan 1927; Mondenedo 1928; Mondenedo and Alonte 1931; Woodman et al. 1931; Alba 1937). On the other hand, Peixoto (1965) and Velloso et al. (1965–66) found reduced gains as the level of cassava in the swine diet was increased.

Workers at the Centre for Tropical Agriculture, Colombia (Maner and Buitrago 1964; Maner and...
Jiménez 1967; Maner et al. 1967, 1970; Maner 1971) have investigated the use of fresh, dried and finely ground and ensiled cassava roots for growing and finishing swine and for gestation and lactation.

In general, cassava was a satisfactory replacement for corn in practical diets. A possible exception was the dried and finely ground cassava which gave a decrease in weight gains proportional to the level of cassava used, with the maximum depression being about 10% when a diet containing 60–70% level of cassava was compared to the control diet. The reason for the growth depression was not clear, but in this experiment, and in others conducted by the Colombian workers, there was no evidence that cassava was contributing a toxic level of HCN to the diets.

There are several publications which indicate that levels of cassava meal over 10–15% in the diet of chicks will reduce gains (Vogt and Penner 1963; Vogt and Stute 1964; Yoshida et al. 1966; Rendon et al. 1969), but adult hens seem to be quite tolerant and maintain egg production even when fed tapioca leaves with a high HCN content (Jalaludin and Yin 1972; Hamid and Jalaludin 1972). The effect of linseed meal in poultry diets and the effect of soaking with water have already been mentioned. The soaking procedure is of considerable interest since Yoshida et al. (1966) found that soaking cassava meal in water overnight reduced its growth-retarding effect on chicks, a result which they attributed to a lessening of HCN toxicity.

It is not possible in most of the publications referred to above to relate the effect of the plant material on weight gains to the intake of cyanogenic glycosides or HCN. HCN was present in the diet in some experiments but in most this information was not obtained or recorded. A number of investigators who recorded good production with potentially cyanogenic material reported an absence of gross pathological evidence for HCN. With the exception of the reports by Flux et al. (1956) and Butler et al. (1957) none of the feeding experiments with domestic animals reviewed here evaluated the effect on thyroid tissue or reported metabolic effects which might be related to HCN ingestion.

When plant material is evaluated for its toxic potential, careful attention must be given to the diet composition. It is obvious that inferior gains given by diets high in potentially cyanogenic plant material cannot necessarily be attributed to HCN ingestion. For example, Maust et al. (1969) found that poor gains and parakeratosis in pigs fed a diet containing 36% cassava meal was corrected when extra zinc was added to the diet, even though the level of zinc and its proportion to calcium in the unsupplemented diet were adequate on the basis of accepted standards. Choo and Hutagalung (1972) found that swine diets containing 20% cassava leaf meal, which is relatively high in fibre, were greatly improved by increasing the energy level of the diet and adding methionine. Chick diets high in cassava meal have been improved to the level of a corn control by the addition of methionine (Olson et al. 1969), and those high in cassava leaf meal by increasing the metabolizable energy content as well as the methionine (Ross and Enriquez 1969).

A generalization is that diets containing a high level of cassava are likely to be deficient in methionine and cystine. These amino acids are proportionately low in cassava and, furthermore, it is a reasonable suggestion that cyanogens in the diet might increase the need for sulfur amino acids owing to a generally recognized need for cystine to participate in the detoxication of HCN.

The question remains: does chronic HCN toxicity from the ingestion of cyanogenic plants occur in domestic animals and, if so, what is the nature of the effect? Better controlled experiments than those cited above are needed to satisfactorily resolve this question.

Neuropathic Role of Cyanide in Animals

Studies on the etiology of human ataxic neuropathy in Nigeria (Osuntokun et al. 1969) and in Tanzania (Makene and Wilson 1972) have led to the hypothesis that this condition is caused by chronic exposure to cyanide or cyanogens ingested in cassava. Whether a parallel situation might exist with domestic animals is not known. Experimental evidence from feeding trials designed to study neuropathological effects from cyanide is only available for rats and dogs. Martino (1935) reported that rats fed cassava roots developed neuromuscular symptoms. Lumsden (1950), Rose et al. (1954), Ibrahim et al. (1963), and Smith et al. (1963) subjected rats, and in one case dogs, to repeated sublethal doses of potassium cyanide and found lesions in the central nervous system but, in all cases, only in a small proportion of the animals.
treated. Only for the experiments of Smith et al. in which very frequent small doses of potassium cyanide were used, can results be reasonably attributed to chronic rather than acute anoxic effects of cyanide. In a later study, Smith and Duckett (1965) following a similar low-level dosing procedure found an increased level of thiocyanate in the serum and confirmed their previous observations of degeneration of myelin in the central nervous system.

Certain similarities of ataxic neuropathy to neurolathyrism has led to interest in a possible relationship of chronic HCN toxicity to that given by the lathyrogens and neurotoxins, in general. The subject of lathyrism has been recently reviewed by Rao et al. (1969).

Lathyrism in animals is commonly considered to be of the osteo type. However, animals are susceptible to various neurotoxins contained in plants. An example is Vicia sativa which contains both a cyanogenic glycoside and the nitrile, β-cyanoalanine, and can produce neurotoxic symptoms in rats (Ressler 1962). Howell (1970) described other neurotoxins which can affect the nervous system of farm animals.

While the relationship among cyanogenic glycosides, HCN, and other cyano compounds in pathological effects in animals and humans may be coincidental, the subject deserves more study.

**Goitrogenic Role of Cyanide in Animals**

Ekpechi et al. (1966) suggested that the incidence of human goitre in Nigeria is related to a chronic intake of HCN from cassava. Goitrogenic substances are present in many plants but have not generally been identified with cyanogenic glycosides. However, linseed meal which contains varying amounts of the cyanogenic glycoside, linamarin, gives goitrous lambs if fed to pregnant ewes (Care 1954). Also reported (Courrier and Cologne 1960) are lesions in the thyroids of rats fed linseed meal. Flux et al. (1956) and Butler et al. (1957) found no clear evidence of a goitrogenic effect from feeding white clover containing cyanogenic glycosides to sheep. However, in later studies, Flux et al. (1960, 1963) reported that lambs from ewes grazed on pastures containing cyanogenic clover, and in some cases the ewes, exhibited enlarged thyroids. The production of frank thyroid enlargement seemed to depend on the level of iodine intake relative to the HCN intake, not appearing if iodine intake was comparatively high. No deleterious effect on weight gains or lambing performance was observed in any of the sheep in these experiments.

It is possible that goitrogenic activity could arise from thiocyanate formed during detoxication of the HCN. Shiombing et al. (1971) found that administering thiocyanate to pigs decreased growth and produced enlarged thyroids. Langer (1966) found a similar effect with rats. Blakely and Coop (1949) administered potassium cyanide to sheep by rumen fistula and found a marked rise of thiocyanate in the serum and urine. It has already been noted that Flux et al. (1956) and Butler et al. (1957) observed increased plasma thiocyanate levels in sheep grazing on cyanogenic white clover.

Where goitrogenic effects can be attributed to thiocyanate or HCN acting directly on the thyroid gland or from some other compound, perhaps formed from thiocyanate or HCN, is not known. A number of plant substances can cause thyroid enlargement in animals, and it is of interest that where information is available such substances have in common cyanide or closely related groupings. Rapeseed, especially the species Brassica napus, is a potent carrier of antithyroid compounds. The potentially goitrogenic compounds in the seed are glucosinolates (thioglucosides). These are carried over into the meal by-product from oil extraction, and can cause problems when the meal is used as a feed for livestock (Bowland et al. 1965). Analogous to the cyanogenic glycoside the glucosinolates must be hydrolyzed to release the toxic products and this occurs in the ground seed or meal if suitable enzymes are active. Several biologically active hydrolytic products may result depending, among other factors, on temperature, pH, age of seed, and also on the chemical nature of the aglycone moiety of the glucosinolates (van Etten et al. 1969). The best recognized products are thiocyanates, isothiocyanates and cyclized isothiocyanate, goitrin (5-vinyl-oxazolidine-2-thione). Figure 1 shows hydrolytic products of linamarin and typical products of the glucosinolates of rapeseed. The thiocyanates and particularly goitrin are goitrogenic. The activity of the former can be alleviated by supplementation of the diet with iodine, but the latter acts by direct interference with organification of the iodine (Lo and Hill 1971).
Saturated and unsaturated nitriles in which the cyanide grouping is not directly linked to sulfur can also result from the hydrolysis of rapeseed glucosinolates (Lo and Hill 1972a) and these substances, while rather unstable, are very toxic with an LD50 for rats of about one-eighth of that of goitrin. The severe growth depression exhibited by pigs, chicks, and rats consuming raw ground rapeseed could be attributed to nitriles rather than the known goitrogens. Heat-treated rapeseed is much less toxic and exhibits a much reduced goitrogenic action presumably because, like the cyanogenic plants, destruction of the hydrolyzing enzyme in the seed prevents, to a larger degree, subsequent release of the toxins. It is not known if the nitriles can in themselves act as goitrogens either directly or as intermediates in the synthesis of goitrogenic substances. The fate of ingested unhydrolyzed glucosinolates is not known but some hydrolysis of ingested glucosinolates can occur in the rat since Lo and Hill (1972a) found both nitriles and goitrin in the urine of rats which had been dosed with rapeseed meal prepared from enzyme-inactivated seed.

The less complicated chemical structure of the cyanogenic glycosides, as compared to the glucosinolates, probably precludes an equivalent complexity of hydrolysis products. However, the possibility of the formation of similar products during metabolism or of the occurrence of a yet unrecognized potentially toxic substance in cassava and plant materials in general should not be ignored. Recently, chlorogenic acid, a potent trypsin inhibitor (as judged by in-vitro tests), has been identified in the polyphenolic fraction of rapeseed (Lo and Hill 1972b).

References


