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TOXIC PLANTS II

PYRROLIZIDINE ALKALOIDS

The pyrrolizidine alkaloids (PA's) are a group of naturally occurring chemicals synthesized by many plant species. The ingestion of PA's in plant material has produced widespread toxicity problems in both humans and food producing animals. The PA's occur in plants that are eaten by livestock and occasionally used by humans as herbal remedies. Pyrrolizidine alkaloids usually produce a chronic delayed toxicity, thus the signs and symptoms of PA toxicity are not seen until a long time after ingestion has occurred. Because of this long delay between ingestion and the appearance of toxic symptoms, in many instances it is very difficult to diagnose PA intoxication. Currently there is no known remedy to counteract the toxic effects of the PA, thus preventing intoxication is the best method to control the problem.

Pyrrolizidine alkaloid poisoning has been reported in all parts of the world. Poisoning of livestock was first reported in South Africa in the early 1900's. In California, PA poisoning of livestock may be the most important plant related veterinary problem at this time. Pyrrolizidine alkaloid poisoning is not limited to veterinary species however. Recent outbreaks in 1976 of human poisoning in Afghanistan and in India serve as dramatic examples. In both instances food grain had become contaminated with weed seeds that contained PA's. In India 67 cases were reported with a mortality rate of 42%. In Afghanistan more than 1600 cases were reported.

Human exposure to pyrrolizidine alkaloids has also occurred in the United States. Two recent cases were diagnosed in Mexican-American children who had been given herbal teas made from PA containing plants.

Some of the species of plants that are of greatest concern to residents of California, Oregon and Washington are:

Common Name	**Scientific Name**
Fiddleneck	Amsinckia intermedia
Common groundsel	Senecio vulgaris
Threadleaf groundsel	Senecio longilobus (or douglasii)
Tansy ragwort	Senecio jacobea

In California the most prominent plants involved are fiddleneck, tansy ragwort and common groundsel. Pyrrolizidine alkaloid content of

these plants ranges from less than 0.5% up to 1.2% dry weight. Comfrey, which is used as an animal feed and human herbal remedy, also contains small quantities of PA's. Plant parts ranked in decreasing concentration of PA's are: flowers and seeds > leaves > stems > roots. The plants contain PA's at all stages of growth. The PA's are resistant to heat, and also maintain their toxicity in dried plant material and hay.

The PA's toxic action is principally exerted on the liver, and depending on the animal species, the kidney and lungs may also be affected but to a lesser extent than the liver. Pyrrolizidine alkaloids are activated by liver metabolism to toxic pyrrole metabolites which have been shown to be carcinogenic, mutagenic, and embryotoxic. Most of the toxic effects of the PA's can be traced to their destructive effect on liver cells, and thus the clinical signs and symptoms of PA intoxication are those of progressive liver failure.

Pyrrolizidine alkaloids produce very characteristic pathological changes in the structure of the liver. The characteristic hepatic lesion of PA toxicity is hemmorhagic centrilobular necrosis without inflammation, occlusion of the central veins, sinusoid distension, and megalocytosis (enlarged cells). The severity of the changes reflect the degree of damage. Extensive fibrosis (cirrhosis) may be seen in the liver of patients that recover from acute PA poisoning and patients that have had chronic exposure to PA's. In humans this disease has been called venoocclusive disease (VOC) and no other known toxin produces this histopathological picture.

Pyrrolizidine Alkaloid Poisoning of Animals

Cattle and horses are the most sensitive species to the toxic effects of PA's, pigs and chickens are less sensitive, and sheep, goats and turkeys are the least sensitive. The young of all species are more sensitive than are adults. Numerous feeding trials have been conducted using cattle, sheep, goats and horses, and the results of these trials, although somewhat confusing, indicate that the PA's produce a classical time-dose-response toxicity picture. Thus high doses of PA's fed over a period of a few days will produce toxicity in a short period of time whereas low doses fed over a longer period will produce a very similar but much delayed toxicity. There is presumably a no effect level for PA plants and it is probably less than 5% of the total ration. One of the more resistant species, the goat, has to consume a quantity of tansy ragwort at least equal to its body weight in order to be poisoned.

The clinical signs of PA poisoning in animals vary from species to species. In cattle, common signs are: dull haircoat, dry muzzle, lack of conditioning, photosensitization, diarrhea with tenesmus (straining), rectal prolapse, depression and death. In horses the neurological signs predominate, and they gradually lose condition, become anorexic, depressed, and wander aimlessly (Walk-about Disease). In sheep, acute deaths are rare but the liver damage produced by the PAs often predispose sheep to copper toxicity. In goats the clinical picture is similar to that seen in cattle. The amount of plant material that must be ingested in order to produce serious toxicity is dependent on the species, the period of consumption and the alkaloid content of the plants. Estimates range from 5-10% of body weight for cattle and horses to more than 100% for sheep and goats. Smaller amounts may depress production without producing observable signs.

The degree of liver damage produced by the PAs can be assessed by measuring certain serum enzyme activities. Some of the enzymes which have been useful in predicting the degree of PA induced liver damage are: glutamate dehydrogenase, alkaline phosphatase, sorbitol dehydrogenase, gama-glutamyl transpeptidase, and lactate dehydrogenase. These enzymes are released when the liver cells are damaged and increased enzymatic activity in blood serum is indicative of cellular damage. A recent study at the Veterinary Medical Teaching Hospital at the University of California at Davis looked at the effects of PAs on plasma amino acid patterns in the horse. The ratios of various amino acids were followed during PA intoxication in horses.

Changes in the amino acid pattern have been used in human medicine as markers of hepatic damage and it has been proposed that these changes in amino acid ratios in the serum may be responsible for some of the toxic effects seen in hepatic failure. A more recent experimental approach to the treatment of hepatic failure involves restoration of normal amino acid balance in the plasma. Because serum enzyme levels and amino acid levels are non-specific markers of hepatic damage, definitive diagnosis of PA intoxication requires microscopic examination of biopsy or necropsy material. At necropsy, the liver is small, pale, firm and may have a nutmeg appearance. The gall bladder is almost always full and very distended. Edema of the gastrointestinal tract (especially the abomasum) may also be seen. Jaundice, ascites and petechial (paintbrush) hemorrhages are more variable findings. The discovery of the characteristic histopathological changes in liver structure produced by the PAs can be used to make a definitive diagnosis.

Treatment of PA induced liver damage is supportive because there are currently no specific antidotes. In many cases diagnosis of PA intoxication occurs post mortem, but if the diagnosis is made in time and feeding of PAs is discontinued, the animals may recover due to the liver's reserve capacity and ability to regenerate.

Human Poisoning by Pyrrolizidine Alkaloids

Pyrrolizidine alkaloid intoxication has recently been documented in two Hispanic children in Arizona given teas prepared from plants which contained PAs. In both instances the herb was referred to as gordolobo and was purchased by the parents at a local drugstore, made into tea, and given to the children for medicinal purposes. The gordolobo herb was identified as threadleaf groundsel and the presence of PAs in the plant material was established. Both infants were admitted to the hospital with signs of severe hepatic failure, and one subsequently died. In children, signs of PA intoxication start with mild signs of irritability, lethargy, colic and vomiting. More severe cases may present with abdominal distension (ascites), jaundice and central nervous system signs of hepatic failure. Histopathological examination of liver biopsies obtained from the two children revealed characteristic lesions of PA intoxication.

At least two species of plants are sold under the name of gordolobo. The Gnaphalium species is a non-toxic herbal remedy, whereas the Senecio species, (S. longilobus) which is similar in appearance to the Gnaphalium, contains PAs. The extent of use of gordolobo tea and the identification of the actual plant material in gordolobo teas, has not been established in the U.S. There is evidence to suggest that these herbal remedies are used mainly by people with Hispanic heritage. Another herbal remedy called Matarique (Cacalia decomposita) has recently been found to contain PA's too. The ingestion of teas prepared from PA containing plants represents a potential public health problem in California. Because of the long lag time between the ingestion of PA and the appearance of clinical signs, it is very difficult to make the association between the disease and the exposure. Thus, an herbal remedy containing PAs may be ingested for a period of weeks to months without producing any adverse effects. When clinical signs do appear, they may not be related to the ingestion of the plant material because it has been ingested "safely" for such a long period of time. The definitive diagnosis of PA intoxication in humans usually requires the examination of liver biopsy samples.

Treatment of human cases of PA ingestion first involves discontinuance of ingestion, although hepatic damage may continue to progress for a period of time. Non-specific supportive therapy for liver failure is also required. Complete or partial recovery may occur depending upon the stage at which the illness is first recognized. Because of the liver's remarkable reserve capacity, clinical signs may not be seen until liver damage is quite extensive. As with other species, young children are much more susceptible than adults.

Summary

Prevention is the best "cure" for PA intoxication. In veterinary species, preventing exposure to PA containing plants often means preventing the growth of the plants in forage. Because fiddleneck and groundsel are principally spring seasonal plants, most problems are associated with first cut hay. Most animals find PA plants unpalatable and will not eat them if better forage is available, but they will ingest toxic amounts of PA plants if they have nothing better. Animals can't select PA plants out of cubes or pellets and last year, hay containing PA plants was made into a pelleted feed which was responsible for losses in a feed lot in southern California. In Oregon, ranchers have used sheep to clear the Tansy ragwort from their pastures. Apparently there were no problems in these sheep however in feeding trials, liver damage in sheep was often not seen until after 2 seasons of exposure.

Because the chemical analysis of PA's in plant material is difficult and expensive, the procedure is not readily available for checking samples. In the past, primary prevention of human exposure to PAs involved minimizing seed contamination of grain products. Occasional low level exposure would not present the hazard to health that continuous usage would. Some people believe that the human cases that have been seen represent the "tip of the iceberg". Ingestion of these alkaloids should certainly be kept at a minimum in humans and livestock. If PAs are fed to lactating animals low levels of PAs do get into milk, however, the health implications of milk contamination by PA's is unknown.

If you are involved in any cases that are confirmed PA intoxications (based on liver histopathology) I would like to know about it. The overall incidence of PA problems in livestock in California has yet to be established.

Update 2,4-D - The presence of dioxins in 2,4-D continues to be a hot topic, even though "THE" dioxin (2,3,7,8-TCDD) has not been detected in any 2,4-D samples tested. Repeat teratogenicity, mutagenicity and oncogenicity study results will not be in for some time.

Threshold for Oncogenesis: A Society of Toxicology Task Force recently reanalyzed the National Cancer Institute "Mega-mouse" study which examined tumor induction due to low level exposure to a known genotoxic carcinogen. Genotoxic carcinogens theoretically might exhibit a linear dose-response interaction (no-threshold). Their analysis stated that the results did not fit a linear model, and that in the lower dose region of the dose response curve, they found a slope of zero (indicative of a threshold). The threshold-no-threshold dose debate will probably be with us for some time yet.

Announcement:

"Toxicology: The Science of Poisons", Leaflet number 21221 is now available for distribution from the Agricultural Sciences Publications office in Richmond. I would appreciate feedback from you about it,

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