Toxicity of threadleaf groundsel (Senecio douglasii var longilobus) to cattle

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SUMMARY

Threadleaf groundsel (Senecio douglasii var longilobus), a common plant on much of the rangeland of southwestern United States, was experimentally fed to 55 cattle by gastric gavage, mixed in alfalfa hay, or pelleted in feed. Since the pyrrolizidine alkaloid (PA) content of threadleaf groundsel fluctuates greatly, dosage was determined by the plant PA content.

Animals that died survived up to 506 days. Whether they were acutely or chronically affected they had typical signs of seneciosis. Major gross and histopathologic changes are reported.

The estimated minimum lethal plant dose by gavage was sufficient to provide 13 mg of PA/kg of calf body weight/day for 15 days or a total of approximately 200 mg of PA/kg in a 15-day period. Cattle that consumed up to 600 mg of PA/kg total in 20- to 100-day periods in hay or pellets were unaffected or minimally affected. These findings emphasize the importance of the time-dose relationship in PA toxicosis in cattle and indicate that there is a threshold level of PA that must be exceeded for the toxicosis to develop.

Threadleaf groundsel is a woody plant (Fig 1) that infests many rangelands of southwestern United States. It is particularly plentiful in western Texas and New Mexico, but its range extends into adjacent northern and western states and into Mexico.

Though other Senecio species on western ranges had been determined to be toxic to horses, threadleaf groundsel was not incriminated as a toxic plant until 1933 when it was found to be lethal to cattle in Utah and Texas. The plant presents no economic problem in Utah, but in Texas, sporadic outbreaks of the toxicosis occur, involving the loss of several thousand cattle sometimes in a single outbreak.

Experimental feedings of threadleaf groundsel to cattle have been few. In the Utah studies, a single dose of green groundsel leaves totaling 1% of a calf's body weight or multiple doses amounting to 52% of a calf's weight fed during a 68-day period were lethal. Some Texas cattle tolerated green plant fed over long periods, but others fed various doses of this groundsel for 8- to 90-day periods died at times ranging from 30 to 90 days. In a study of the diagnosis of Senecio poisoning in cattle, 2 calves fed 10% of their body weight of green threadleaf groundsel in 10 or 20 days died 56 to 75 days later. In another study, calves fed 1% of their body weight of green groundsel each day for 4 days died of acute Senecio poisoning; calves fed a single dose of 0.25% of their body weight of dry threadleaf groundsel died an average of 156 days later, and calves fed 0.75% of their body weight of dry groundsel during a 3-day period died an average of 61 days later.

These studies established that threadleaf groundsel is lethal to cattle whether given in a single large dose or in multiple smaller doses, but provided no information on the plant's toxicity based on its content of pyrrolizidine alkaloids (PA), the compounds responsible for its toxicity. The PA content of threadleaf groundsel can vary 10-fold during its growth cycle, thus, toxicity studies wherein the PA content of the plant is unknown are limited in value.

This work reports the experimental feeding to cattle of a variety of dosages of threadleaf groundsel of known PA content and considers the toxicologic implications relating to PA metabolism.

Materials and Methods

Whole threadleaf groundsel plants were collected from southeastern New Mexico and south central Utah in mid- to late-summer. Plants were air dried and leaves and small twigs were clipped from the dry plants. They were finely ground, bagged in heavy plastic bags, and stored at 5°C until time of use.

Pyrrolizidine alkaloid content of each plant collection was determined by the method of Molyneux et al as percentage by dry weight of the plant and ranged from 0.63% to 2.02% in the experimental plants fed. Dosages to individual calves were based on plant PA content and expressed as milligrams of PA per kilogram of calf body weight per day. Most daily plant dosages were representative of amounts of groundsel that could be easily grazed by calves in a single day.

Experiment 1—Twenty-nine heifer calves, weighing 159 to 288 kg (av 216 kg), were gavaged with threadleaf groundsel in water slurry in amounts and for times indicated in Table 1.

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Calves in both experiments were penned by groups, fed alfalfa hay, and had free access to water. Gavaged groups were given their allotted groundseed in a single morning gavage. Calf groups fed groundseed mixed in chopped hay and those groups fed pellets containing groundseed were fed 2 times a day, morning and late afternoon. Group-fed calves were observed as closely as possible during feeding, and they were weighed each week to determine if there was unequal weight gain.

Calves were observed daily for signs of sepsis. Samples of venous blood were collected 1 or 2 times each week during critical periods of the experiment to follow progress of the toxicoses and to monitor the calves' general condition. Packed cell volume, RBC, WBC, and serum aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) activities were determined by methods previously reported (Table 3).

Calves that became moribund or in an irreversible wasting state were euthanized by electrocution and necropsied. Liver, lung, pancreas, thyroid, adrenal gland, gallbladder, spleen, kidney, and heart tissues were obtained, fixed in 10% buffered formalin, stained with hematoxylin and eosin (H&E), and examined histopathologically.

Calves that survived were retained for observation for at least 6 months and some for as long as 2 years. Some calves were slaughtered after the observation period and liver tissue collected for histopathological examination; liver biopsies were conducted from other calves at appropriate time intervals for histopathological evaluation.

**Results**

Calves in experiment 1 gavaged with groundseed doses containing 5 to 10 mg of PA/kg of body weight/day for 16 to 18 days had a survival rate of 85% (Table 1). Calves gavaged with groundseed to provide 10 mg of PA/kg/day for 20 days had a survival rate of 29%; and calves gavaged with groundseed to provide 13 to 15 mg of PA/kg/day for 14 or 15 days survived at the rate of only 8%. Two calves fed *Senecio* at the high rate of 40 mg of PA/kg/day for 2 days died on the 3rd day.

Survival time of individual calves that died (excluding calves given the 40 mg dosage) ranged from 21 to 506 days. Only 3 of the 17 calves that died survived longer than 81 days and the remaining calves that died survived an average of 49 days.

Most gavaged calves whose serum GGT values increased beyond 6-fold did not survive (Table 3; AST, that is less specific for hepatic damage, was less indicative of lethal insult.

Signs of the *Senecio* toxicoses were similar to those reported previously, but none of the stated signs of roughened coat, dry scaly nose, diarrhea or tenesmus, fixed staring faces, continuous slight staggering walk, and slightly dropped head was constant. Signs varied with the rapidity with which the toxicosis developed. Continuous walking was a sign in the more chronically affected animals. Diarrhea was generally absent probably because of the dry feed the calves were given, and tenesmus seemed to be related to the amount of lower digestive tract edema. The fixed, staring faces, slightly drooped head, and gradually staggering walk were the most constant signs in all but acutely affected calves.

Gross pathologic changes also were variable, with fibrinous liver and large gallbladder the most constant findings (Fig 2 and 3). Liver appearance was extremely

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**Experiment 2**—Twenty-six additional heifer calves, weighing 179 to 239 kg (av 201 kg), were assigned to 6 groups of 3, 4, or 5 calves each and were fed groundseed mixed in their hay ration or in alfalfa pellets in amounts and for times indicated in Table 2. Pellets were 65% alfalfa hay, 20% rolled barley, 5% molasses, and 10% dried threadleaf groundseed.

Studies on some calf groups reported in both experiments herein were not designed as part of detailed studies, so that this study represents a summation of feeding trials from several experiments. This necessitated the use of several collections of threadleaf groundseed of various PA content.

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**Table 1—Mean mortality in calves fed PA (by gastric gavage) in threadleaf groundseed (experiment 1)**

<table>
<thead>
<tr>
<th>Group No.</th>
<th>No. of calves</th>
<th>PA dosage (mg/kg)</th>
<th>Daily</th>
<th>Total</th>
<th>Days fed</th>
<th>Mortality (%)</th>
<th>Mean survival time (days)</th>
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<td>250</td>
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* Interrupted feeding period (fed Senecio 10 days; rested 30 days; fed Senecio 10 days).

**Table 2—Effects of PA on calves consuming threadleaf groundseed mixed in their hay ration (experiment 2)**

<table>
<thead>
<tr>
<th>Group No.</th>
<th>No. of calves</th>
<th>PA dosage (mg/kg)</th>
<th>Daily</th>
<th>Total</th>
<th>Days fed</th>
<th>Toxicologic signs</th>
<th>Serum enzyme activity changes</th>
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<td>None</td>
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<td>3</td>
<td>300</td>
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<td>120</td>
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* AST and GGT. † Repetent of group 5 after 40-day rest. ‡ Pelleted. Not eaten well—calves took 24 hours to consume daily dose.

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**Figure 1**—Threadleaf groundseed (*Senecio douglasii* var. longilobus), sometimes called woody groundseed due to its color (gray).
Table 3—Mean serum enzyme activities in groups of calves gavaged with PA in threadleaf groundsel.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>No. of calves</th>
<th>PA dosage (mg/kg)</th>
<th>Serum ALT activity (Reitman-Frankel Unit)</th>
<th>Change (X)</th>
<th>Peak (day)</th>
<th>Range</th>
<th>Change (X)</th>
<th>Peak (day)</th>
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<td>14</td>
<td>16-179</td>
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<td>12.3</td>
<td>2</td>
<td>14-205</td>
<td>14.8</td>
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Fig 2—Cut section of liver from calf affected with seneciosis, showing generalized fibrosis.

Fig 3—Liver and gallbladder of calf affected with seneciosis, showing an extremely large gallbladder.

Fig 4—Severe edema of abomasal folds (A) and large intestine (ansa spiralis); (B) in calf fed threadleaf groundsel (experiment 1, group 6).

variable and, as might be expected, was related to speed with which the toxicosis developed. Livers of acutely affected calves were swollen and often hemorrhagic. Liver discoloration was related to the degree of icterus, hemorrhage, and fibrosis. Edema, when present, was pronounced in the abomasum (Fig 4), gallbladder wall, and large intestinal folds (Fig 4). Ascites sometimes occurred in variable quantities, occasionally exceeding 10 liters. Kidney changes reported by others were not noted.

Results of histopathologic examination of tissues revealed that the principal lesion was in the liver. Changes were similar to those reported by others and consisted mainly of hepatocyte swelling and necrosis, fibrosis, and biliary hyperplasia to the extent that the integrity of the liver was often totally disrupted (Fig 5 and 6).

Groundsel mixed in the hay ration and fed to calves...
Senecio species vary in their toxicity to cattle and other animals according to the following factors: (1) the individual PA composition of the plant species; (2) the total PA content of plants within the species; (3) the ability of the mixed function oxidases in the liver of the animal that eats the plant to convert the nontoxic plant PA to their corresponding toxic pyrroles; and (4) the relative toxicity of these formed pyrroles. Threadleaf groundsel contains 4 PA: senecionine, seneciphylline, retrorsine, and riddelliine.7 The toxicity of their corresponding pyrrole metabolites has not been studied in livestock.

Until recently, researchers often lacked the methods and procedures to assay PA. Thus, methods to test PA content of Senecio plants were developed recently, as this method was found sufficient to cause toxicity signs or death.1-3,5 This method was acceptable for plants that maintained a relatively constant toxin content, but was of little value for plants with high PA content. The PA content of threadleaf groundsel may vary from <1% by dry weight to as high as 8%, with the variation not only within the plant's yearly growth cycle, but also from year to year and according to location.4 In the studies reported herein, several plant collections were fed that varied 3-fold in PA content. Thus, calves fed 5 mg of PA/kg (plant dry weight PA concentration of 0.75%) to receive comparable PA would have had to consume 457 g of that green plant per day, whereas those calves fed 2 times as much PA (10 mg/kg) from another collection at a plant PA concentration of 2.02% would have had to eat only 340 g/day; those that were fed 19 mg of PA/kg (plant PA concentration 0.63%) would have had to eat 2,068 g of green plant/day to receive comparable PA, whereas those that were fed 40 mg at 1.88% PA concentration would have had to eat only 1,460 g/day. Thus, it is apparent that animal feeding trials of threadleaf groundsel without knowledge of the PA content of the plants fed would not be adequate to determine the toxic potential of the PA content of plants fed.

Discussion

Each toxic Senecio species contains a characteristic set of PA that may vary in number from 1 to 6.4 Thus...
plant are of little value if comparisons to other feeding trials and to field intoxications are to be made.

Based on our previous experience with Senecio jacobaea (tansy ragwort), we have found that a 15- to 20-day feeding period by gavage is the optimum time for causing maximum signs of seneciosis and probably more closely approximates field grazing situations.12 Feeding beyond this time, or after the calf has already been lethally insulted may have little additional effect if hepatocytes have been injured so that they can no longer produce the mixed function oxidases necessary to convert PA to their toxic pyrroles.13 Thus, longer feeding may only lead to difficulty in interpreting results. In experimental feeding of Senecios, as well as in evaluating suspected field intoxications, the most difficult part is determining when lethal insult has occurred. Liver biopsy may provide this information in some experimental situations, but is not practicable to do in most field occurrences. Similarly, serum enzyme analysis of suspects also may be helpful in some field situations, but again, practicable application is limited,14,15 especially in cattle in the free ranging areas of the Southwest where threadleaf groundsel occurs.

These studies indicate that gavaged doses of threadleaf groundsel PA of < 10 mg/kg/day for 16 to 18 days were not lethal to most calves and that 5 mg/day caused few changes. As the PA dosage approached 10 mg/kg/day and time of feeding reached 20 days, lethality increased. Doses of threadleaf groundsel PA of from 10 to 13 mg/kg/day for 15 to 20 days were lethal to most calves. When the dosage was increased, time of feeding to produce maximum toxicologic effects was reduced as indicated by the fact that 15, 19 mg of PA/kg/day for only 14 or 15 days severely insulted the calves (Tables 1 and 3) and their survival time was short. Furthermore, 40 mg of PA/ day for only 2 days was acutely lethal to 2 calves in only 3 days.

For these dosages to exert their maximum effect, however, they must be taken in rapidly. Few or no effects were observed in calves fed 20 and 30 mg of PA/kg/day in their hay and consumed over the full 24-hour day. By gavage, these dosages would have been highly lethal. These animals were observed for many months after groundsel feeding was discontinued and no serum enzyme changes or loss in animal condition were noted.

Furthermore, the cumulative effects observed by others6 of multiple small PA doses in laboratory rodent studies were not seen in these studies on cattle. Considering the relationship of total PA dosage to feeding time, we note in group 9, Table 1, that 80 mg of PA fed in 2 days was acutely lethal, whereas the same total PA fed group 1 calves in 16 days caused no effects. Also in groups 4 through 8, total PA of 195 to 284 mg/kg fed during 14 to 20 days caused marked serum enzyme changes (Table 3) and 81% mortality (Table 1), yet, in calves fed totals of 200 to 600 mg/kg in hay during a 100-day period (groups 1, 2, and 3, Table 2), few or no effects were noted. These results seem to indicate that in cattle there is either a threshold of tolerance by the liver that must be exceeded for hepatic damage to occur or there is a gastrointestinal PA level or some other preabsorbance influence that must be exceeded or overridden for PA to be absorbed in toxic amounts.

Regardless of the reason for some degree of tolerance to PA in calves, it is obvious from this study that the time-dose relationship in PA toxicity to cattle is all-important. Cattle may graze large amounts of threadleaf groundsel that has a high PA content and die within a few days; they may consume moderate amounts over a 2- to 3-week period, be lethally insulted, and die many months later. If the plant PA content is sufficiently high, or, if the plant PA content is low, they may graze small amounts of the groundsel for long periods without ill effects.

In our experience from experimentally feeding threadleaf groundsel and tansy ragwort, we know that cattle do not readily eat harvested and dried PA-containing plants. Others have made similar observations.9 Personal field observations and discussion with livestockmen indicate that the live plant also is unpalatable. However, as with other poisonous plants, livestock do eat PA-containing plants when food selection is poor and under field conditions that are not understood. Occasionally, reports are received that indicate livestock may actually prefer PA-containing plants at certain times.

Our knowledge of PA toxicity in cattle remains sketchy, for much of it is extrapolated from the numerous rat studies that have been done. Reactions relating to PA metabolism in rat livers are likely to be similar to those that occur in livers of ruminant animals and thus extrapolation may be somewhat justified. However, whatever similarity exists between rat and ruminant ends at this point and the multitude of differences in their digestive tracts must then be considered. Possibilities for oxidation or reduction of the PA molecule are great in the rumen; solubility differences due to pH differences in rat and ruminant stomachs also may influence absorption or excretion rates of the PA; and possible influences of the multitude of microorganisms in the rumen are numerous. Thus, extrapolation from rodent to ruminant may be more akin to speculation, and a definitive answer to questions regarding reactions that influence PA toxicity in ruminants must await further experimentation in that class of animal.

References