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Carcinogenicity of bracken fern (Pteridium esculentum) in New Zealand

B. L. Smith*, P. P. Embling*, M. P. Agnew*, D. R. Lauren* and P. T. Holland*


ABSTRACT

Bracken fern (Pteridium esculentum) was harvested from two sites LB and TB one of which (TB) was on a central North Island New Zealand farm where bovine enzootic haematuria (BEH) was known to occur. The fern was dried, ground and incorporated (25% w/w) into a pelleted diet and fed to female rats for a total of 162 days. Fifteen weeks later when the rats were autopsied it was found that numerous tumours, mainly of the ileum and urinary bladder were present in the animals fed the bracken fern from the TB site. Neoplasms were found in 85% of rats from the TB group compared with 11% in the LB group while only a single tumour (a haemangioma of the uterus) was observed in the controls. In all, there were neoplasms in 42, 5 and 1 organ/s from the TB, LB and control rat groups respectively (p<0.001).

Analysis of the fern and pellets for ptaquiloside, the carcinogen in bracken fern, showed much higher levels present in the material from the TB site. There was 26 and 2270 μg ptaquiloside/g of dried fern and, for the pellets from the same fern, 6.5 and 355 μg ptaquiloside/g of pellets, for one collection from the LB and TB sources respectively.

INTRODUCTION

The ubiquitous pteridophyte, bracken fern (Pteridium spp.) is implicated in several animal health problems throughout the world. It causes an acute haemorrhagic syndrome of sheep and cattle(2)(4) associated with leucopenia and thrombocytopenia, "blindness" of sheep associated with retinal degeneration,(1)(4)(5) polioencephalomalacia of sheep and cattle associated with the high levels of thiaminase I in bracken,(11) a thiamine deficiency in horses(12) and a syndrome of multiple urinary bladder tumours of ruminants known as bovine enzootic haematuria (BEH).

BEH which in some places occurs in association with neoplasia of the alimentary tract, has been shown unequivocally to be due to ingestion of bracken fern. Neoplasia of the alimentary tract of cattle is believed to be caused by an interaction of the bracken carcinogen with the bovine papilloma virus.(7) The disease occurs worldwide and has been recorded at several discrete locations within New Zealand (NZ).(8)(12)(13) The reasons for the localised occurrence of BEH in NZ when bracken fern distribution is widespread are not known but local animal management practices, the use of animals to control bracken fern and the possibility of differences in bracken strains have all been considered.

Recently the structure of the carcinogen of bracken fern has been elucidated by independent investigators(6)(9) using different techniques to trace the carcinogen in fractions of bracken fern. The substance, ptaquiloside (PT), (also described as aquilide A)(9) is water soluble and it has been postulated(10) that under alkaline conditions, such as occur in the urinary bladders of herbivores and certain parts of the alimentary tract, it is converted into an active aglycone. The discovery of PT opened the possibility of an analytical method for its detection. This and the continued occurrence of BEH on certain farms prompted a renewed interest in the disease in NZ.

This paper records the results of feeding rats with diets containing bracken fern from two different locations in the North Island of New Zealand and compares the resulting rates of neoplasia with the concentration of PT in the fern from the two localities.

MATERIALS AND METHODS

Unfurling fronds and "fiddle heads" of bracken fern (Pteridium esculentum) were collected during November 1984 and April 1985 from two sites in the North Island of NZ.

Local bracken fern (LB) was collected from roadside sites, mainly on Kaipaki loamy peat within a 15 km west radius of Hamilton. Taumarunui bracken (TB) was collected from a farm 20 km west of Taumarunui where BEH occurs. This bracken was from a roadside site on the Tarangamotu series of composite yellow-brown pumice soil or yellow-brown loam. Collections were made from both sites a few days apart in each of the above two dates.

The collected fern was dried in a hot-air oven at 80 °C for approximately 48 hours and then chopped and ground in a hammer mill to pass a 3 mm screen. The processed fern was added to a commercial rodent diet together with a small amount of molasses. The mix was (w/w):70:5/92 diet; 25% dried ground bracken; 5% powdered molasses. The control diet consisted of commercially prepared 59/2 diet. The pellets made from the November 1984 bracken collection were fed in the first feeding period and those from April 1985 fed during the second feeding period (Fig. 1). Bracken from the farm site (TB) had been subjected to grazing while most from the roadside site had been subjected to mowing.

Fifty-nine female 120 g Sprague Dawley rats were divided into three groups (18 controls, 20 local bracken, 21 Taumarunui bracken) and caged in plastic-based cages with stainless steel wire tops and feed hoppers with ad lib water supply. Initially the experimental feeds were offered ad lib but feed was subsequently rationed in order to avoid wastage. The rats were weighed at two-weekly intervals. Five weeks after the commencement of feeding the LB and TB groups were noticed to be losing weight. Both groups were transferred to the control diet for 14 days after which thiamine (5 μg/l) was added to their water supply and they were returned to their original diets. This corrected the decline in weight and the rats steadily gained weight thereafter.

After 60 days of feeding one of the groups finished the prepared pellets. All rats were then maintained on control diet for 49 days and then transferred on the test diets for a...
further 102 days. One hundred and six days after these diets finished the rats were killed by CO₂ inhalation and post-mortem examinations carried out.

Any tissues or organs showing evidence of neoplasia and all urinary bladders were fixed in neutral formalin, sectioned, stained with haematoxylin and eosin and examined microscopically.

Samples of powdered fern (10g) or pellets (20g) were extracted into 1:1 methanol:water (100ml) by shaking for three hours on a flat-bed shaker and then centrifuged at 4000rpm for two hours. The samples were analysed, without further cleanup, by high performance liquid chromatography (HPLC) on a Zorbax C-8 (15 cm x 4.6 I.D.) homepacked column using water:methanol (67:33) at 1 ml/min. The retention time for PT was 25 minutes. Detection was by UV absorption at a wavelength of 220 nm.

RESULTS

Soon after the commencement of the trial the bodyweights of the LB and TB groups rapidly declined (Fig. 1). These rats were changed to the control diet for 14 days following which thiamine was added to their water. The bodyweights rapidly recovered and no further serious weight problems were encountered in these groups. Five rats died during the last two months of the experiment, one from LB and four from the TB groups. The LB rat had severe pneumonia as its only lesion. Of the TB rats, one death was due to trauma, two had massive squamous cell carcinomas of the upper oesophagus or pharynx and the fourth had tumours of the ileum and urinary bladder. The remaining rats were examined after CO₂ euthanasia. Many of these has neoplasia of the urinary bladder, ileum, mammary gland, liver and lymph nodes. Most were in the rats from the TB group and only one small tumour in one rat from the control group was observed, a haemangioma in the uterus. The distribution of tumours in the organs of rats from the different groups is shown in Table I. Often there were several tumours in a single urinary bladder (Fig. 2a) or ileum (Fig. 2b) but multiple tumours in organs are not recorded in the data. Judging from microscopic appearance and the gross findings the tumours varied from benign localised to highly malignant invasive tumours. The types of tumour present are indicated in Table I.

Chemical analysis for PT showed it was present in both the dried powdered bracken and the pellets made from it. Much higher concentrations of PT were found in the samples from the Taumarunui site. The concentrations of PT found are shown in Table II.

<p>| TABLE I: PREVALENCE AND VARIETY OF TUMOURS IN ORGANS OF RATS FED PELLETS CONTAINING BRACKEN FERN FROM TWO LOCALITIES |
|--------------------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>No. of rats</th>
<th>Urinary bladder (1,2,5,7)</th>
<th>Ileum (3,4,6)</th>
<th>Mammary gland (4)</th>
<th>Liver (4)</th>
<th>Oesophagus (5)</th>
<th>Lymph node (6)</th>
<th>Lungs (8)</th>
<th>Other (7)</th>
<th>Total Rats</th>
<th>Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Local bracken</td>
<td>19*</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Taumarunui bracken</td>
<td>20*</td>
<td>15</td>
<td>14</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>17</td>
<td>42</td>
</tr>
</tbody>
</table>

*One rat eliminated - deaths due to trauma/pneumonia.
#Uterine haemangioma. All rats were females.

Figures in parenthesis indicate types of tumour associated with each organ. In this table the presence of one or more tumours in a rat organ is counted as a single occurrence. The following tumours were identified in the rats:

Transitional cell papilloma (1), transitional cell carcinoma (2), adenoma (3), adenocarcinoma (4), squamous cell carcinoma (5), lymphosarcoma (6), haemangioma (7), undifferentiated sarcoma (8).
TABLE II: CONCENTRATIONS OF PTAQUILOSIDE FOUND IN HARVESTED BRACKEN FERN FROM TWO SITES AND RAT FEED PELLETS MADE FROM BRACKEN FERN (25% W/W).

<table>
<thead>
<tr>
<th>Pellets November 1984</th>
<th>Control</th>
<th>Concentration of ptaquiloside μg/g DMB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Fern April 1985</td>
<td>NA</td>
<td>12.5</td>
</tr>
<tr>
<td>Pellets April 1985</td>
<td>ND</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>355</td>
</tr>
</tbody>
</table>

There were less mammary tumours in our rats than has been reported in some experiments.

ACKNOWLEDGMENTS

The authors wish to thank Professor Kiyoyuki Yamada, Chemistry Dept, Nagoya University for the gift of a sample of ptaquiloside. We wish to thank Angela Matthews and Katherine Howard for technical assistance.

This work was assisted by a research grant from the New Zealand Cancer Society.

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