Preliminary clinical observations on the use of piroxicam in the management of rectal tubulopapillary polyps

Rectal tubulopapillary polyps were diagnosed in eight dogs following proctoscopy and mucosal pinch biopsy. Histological examination of the pinch biopsies revealed evidence of malignant transformation in three of the cases. The remaining cases were diagnosed as benign polyps. Inflammatory changes were observed in four cases. Seven dogs were treated with piroxicam suppositories and one with oral piroxicam. All dogs were re-examined after four to six weeks of piroxicam therapy and the extent of haematochezia, tenesmus and faecal mucus production was reduced in all cases. The owners of seven of the dogs considered the improvement in clinical signs to be good or excellent. Cases with and without evidence of inflammation responded equally well. This finding supports the hypothesis that piroxicam has an antineoplastic effect due to apoptosis and alteration in the cell cycle. Medical management with piroxicam may provide a non-invasive treatment option for dogs with rectal polyp formation in which surgical treatment is likely to be associated with complications such as incontinence, infection and wound breakdown, or where the owner declines such treatment.

INTRODUCTION

Rectal and colonic neoplasms are uncommon in dogs (Schäffer and Schiefer 1968, Seiler 1979, Patnaik and others 1980, Holt and Lucke 1985). Rectal tumours are reported more frequently than those of the colon (Schäffer and Schiefer 1968), and adenomatous tubulopapillary polyps and adenocarcinomata are the most common neoplasms identified (Head and Else 1981, Holt and Lucke 1985, White and Gorman 1987). Malignant transformation of benign polypoid lesions has been recorded in dogs (Valeriutis and others 1987). Multiple adenomata that have been present for considerable periods of time are generally considered more likely to undergo malignant transformation to adenocarcinomata (Van Stolk and others 1998). Early diagnosis and treatment is associated with a dramatic reduction in disease-related mortality (Straw 1989). Sections of the submucosa are required to differentiate between benign and malignant disease (Holt and Lucke 1985). Therefore, the collection of mucosal pinch biopsies at proctoscopy may fail to identify all cases in which malignant transformation has occurred.

The clinical signs associated with rectal tumours can be severe (Schäffer and Schiefer 1968, Patnaik and others 1980) owing to the presence of a large friable mass which bleeds easily when abraded by the passage of faeces and which may result in partial rectal obstruction (Church and others 1987). Surgical removal of rectal tumours by a variety of methods has had variable success due to postoperative complications or persistence of clinical signs (Holt and Lucke 1985, Church and others 1987, Holt and Durdey 1999). The majority of dogs with rectal neoplasia are euthanased due to an inability to control clinical signs (Church and others 1987).

The use of non-steroidal anti-inflammatory drugs in the prevention, treatment and reduction of progression of rectal tumours has recently received increasing interest in both the human and veterinary fields (Kune and others 1988, Rosenberg and others 1991, Thun and others 1991, Logan and others 1993, Muscat and others 1994, Rosenberg and others 1998, Sandler and others 1998). Human studies have shown that regular use of aspirin and other non-steroidal anti-inflammatory drugs reduces the risk of colorectal neoplasia by up to 50 per cent (Kune and others 1988, Rosenberg and others 1991, Thun and others 1991, Logan and others 1993, Muscat and others 1994, Rosenberg and others 1998, Sandler and others 1998). Human studies have also shown that regular use of aspirin and other non-steroidal anti-inflammatory drugs reduces the risk of colorectal neoplasia by up to 50 per cent (Kune and others 1988, Rosenberg and others 1991, Thun and others 1991, Logan and others 1993, Muscat and others 1994, Rosenberg and others 1998). Humans receiving non-steroidal anti-inflammatory drugs have also been found to show a reduced risk of malignant transformation of rectal adenomatous to adenocarcinomata (Sandler and others 1998). Oral administration of the non-steroidal anti-inflammatory drug piroxicam has been shown to reduce the incidence of rectal carcinoma in rats (Pollard and Luckhart 1984). Piroxicam has also reduced the progression of transitional cell carcinoma of the canine urinary tract in rats (Pollard and Luckhart 1984).
bladder (Knapp and others 1994) and induced a partial remission of other canine tumour types (Knapp and others 1991).

The antineoplastic effects of piroxicam and other non-steroidal anti-inflammatory drugs may be related to inhibition of prostaglandin E₂ production, resulting in enhanced local immune responses and stimulation of cytoprotective prostaglandin production (Muscat and others 1994). Piroxicam also induces apoptosis of adenocarcinoma cells and reduces tumour growth by altering distribution within the cell cycle so that a higher proportion of cells remain within the 'Go' phase (Shiff and others 1996).

Rectal tumours in dogs generally carry a guarded prognosis owing to the incidence of malignant transformation and significant complications following surgical treatments. The aim of this study was to assess the clinical efficacy of piroxicam therapy in the medical management of rectal tubulopapillary polyps in dogs.

**MATERIALS AND METHODS**

**Initial examination**

All dogs included in the study were presented to the Royal (Dick) School of Veterinary Studies with a history of large intestinal disease and a mass palpable on rectal examination. The history and clinical findings of each dog were recorded. The extent of haematochezia, rectal tenesmus and faecal mucus production was scored using an established scale of severity (Dixon and Bird 1981, Simpson and others 1994). Routine haematological and serum biochemical analysis, and routine faecal analysis and culture for selected faecal pathogens were performed. Dogs with evidence of systemic disease were excluded from the study. A total of eight dogs were included in this preliminary study.

Food was withheld for 24 hours before colonoscopy and proctoscopy. Enemas were administered one and 12 hours before endoscopy, which was performed following sedation with acepromazine (ACP; C-Vet) 0.05 mg/kg and buprenorphine (Vetgesic; Reckitt and Colman) 0.01 mg/kg, administered by intramuscular injection. Dogs were placed in left lateral recumbency, and proctoscopy and colonoscopy were performed using a 9 mm diameter flexible videoendoscope (Olympus, PV10). Following visualisation of the rectal mass, photographs were taken before the collection of multiple pinch biopsies from the mass surface and its point of attachment with the rectal wall. The colonic mucosa was assessed by visualisation and pinch biopsies were collected from random areas of apparently normal mucosa. Biopsies of the rectal mass and the colon were placed in separate containers of 10 per cent formol saline (Fig 1). All samples were submitted for histological examination.

**Table 1. Summary of signalment and presenting signs in eight dogs with rectal polyps**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Breed</th>
<th>Presenting signs</th>
<th>Duration of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>11</td>
<td>West Highland white terrier</td>
<td>Haematochezia, tenesmus, increased faecal frequency</td>
<td>Several years</td>
</tr>
<tr>
<td>2</td>
<td>FN</td>
<td>9</td>
<td>Springer spaniel</td>
<td>Haematochezia, tenesmus</td>
<td>6 weeks</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9</td>
<td>Cocker spaniel</td>
<td>Haematochezia, tenesmus</td>
<td>34 months</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>8</td>
<td>Cocker spaniel</td>
<td>Haematochezia, tenesmus</td>
<td>22 months</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>10</td>
<td>Hungarian vizla</td>
<td>Haematochezia, tenesmus, increased faecal frequency</td>
<td>11 months</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>9</td>
<td>Basset hound</td>
<td>Haematochezia, tenesmus</td>
<td>8 months</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>9</td>
<td>West Highland white terrier</td>
<td>Severe tenesmus</td>
<td>8 days</td>
</tr>
<tr>
<td>8</td>
<td>MN</td>
<td>4</td>
<td>West Highland white terrier</td>
<td>Haematochezia, tenesmus, increased faecal frequency</td>
<td>20 months</td>
</tr>
</tbody>
</table>

M Male, F Female, N Neutered

**Treatment**

Following histological confirmation of the presence of tubulopapillary polyps, all dogs except case 4 were placed on 20 mg piroxicam suppositories (Feldene suppositories; Pfizer) at a dose equivalent to 0.24 to 0.46 mg/kg/day. Suppositories were administered every second or third day. Case 4 received oral piroxicam tablets (Feldene tablets; Pfizer) at a dose of 0.34 mg/kg on alternate days.

**Follow-up**

All dogs were re-examined after four to six weeks of piroxicam therapy. Clinical and rectal examinations were repeated and the extent of haematochezia, rectal tenesmus and faecal mucus production was reassessed. Proctoscopy and colono-

![Figure 1. Proctoscopic views of the rectal mass observed in case 7 following treatment with piroxicam. (A) Before treatment the mass fills more than 50 per cent of the rectal lumen. (B) Three months after treatment with piroxicam; the mass fills less than 20 per cent of the rectal lumen.](image-url)
The eight dogs included in the study were repeated, and photographs and pinch biopsies of the rectal mass were collected.

**RESULTS**

The eight dogs included in the study comprised three West Highland white terriers, two cocker spaniels, one springer spaniel, one Hungarian vizsla and one basset hound. Their ages ranged from four to 11 years (mean 8.6 ± 2.1 years). Six were male and two were female, and the duration of clinical signs ranged from eight days to several years (Table 1).

All eight dogs had haematochezia and faecal tenesmus, and seven out of eight had increased faecal mucus (Table 1). At presentation, haematochezia and faecal tenesmus were severe in all dogs (mean score ± standard deviation 8.94 ± 1.57 and 7.81 ± 2.25, respectively) (Table 2). Faecal mucus production was variable (mean score ± standard deviation 5.75 ± 3.20, median score 5.5), ranging from none to severe (Table 2). Histological examination of biopsies collected from the colon revealed no evidence of colitis. Biopsies collected from the rectal masses revealed evidence of malignant transformation in three of the cases. The remainder were diagnosed as benign tubulopapillary polyps (Table 3).

Re-evaluation after four to six weeks of piroxicam therapy revealed a reduction in the extent of haematochezia and faecal tenesmus (mean score ± standard deviation 2.44 ± 2.44 and 2.38 ± 3.90) in all cases (Table 2). Faecal mucus production was also reduced in each case (mean score ± standard deviation 1.38 ± 3.13, median score 0); however, in case 7, the faecal mucus production was still high (Table 2). The owners of seven of the dogs considered the improvement in clinical signs to be good or excellent. The remaining owner felt that there had been no clinical improvement following therapy with piroxicam suppositories. Case 1 had one bout of vomiting during therapy. Piroxicam suppositories were withdrawn for one week and then reinstituted. Case 1 was euthanased by the referring veterinary surgeon six months after piroxicam therapy was initiated following a diagnosis of renal failure. Postmortem examination was not performed. No other side effects were reported.

The rectal mass appeared to have reduced in size at follow-up endoscopy after four to six weeks of piroxicam therapy in all dogs. Although the numbers are too small for statistical analysis, dogs with histological evidence of malignant change appeared to have the same severity of clinical signs (both at initial examination and follow-up) as those without evidence of malignant change. Similarly, dogs with histological evidence of inflammation appeared to have the same severity of clini-

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**Table 2. Summary of severity of symptoms at initial presentation and after piroxicam therapy in eight dogs with rectal polyps**

<table>
<thead>
<tr>
<th>Case</th>
<th>Score at presentation</th>
<th>Score at follow-up</th>
<th>Owner's perception of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mucus</td>
<td>Tenesmus</td>
<td>Blood</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>4.5</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>5-5</td>
<td>6</td>
<td>5-5</td>
</tr>
<tr>
<td>5</td>
<td>5-5</td>
<td>6</td>
<td>5-5</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>5-5</td>
<td>7-5</td>
<td>9</td>
</tr>
</tbody>
</table>

Mean: 5.75; SD: 3.2; Median: 5-5; Note: Scores based on a sliding scale of severity in which 0 is the lowest score (no clinical signs) and 10 is the highest score (severe clinical signs).

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**Table 3. Summary of the histopathological assessment of pinch biopsy samples collected from eight dogs with rectal polyps**

<table>
<thead>
<tr>
<th>Case</th>
<th>Histopathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Papillary-like proliferation of epithelial cells. Evidence of inflammation. No indication of malignancy.</td>
</tr>
<tr>
<td>2</td>
<td>Evidence of epithelial proliferation which appears to be benign. No inflammatory component present.</td>
</tr>
<tr>
<td>3</td>
<td>Proliferation of epithelial cells, cellular pleomorphism and mitotic figures observed. Mild inflammatory response also observed. Suggestive of malignant transformation</td>
</tr>
<tr>
<td>4</td>
<td>Fronds of epithelial cells arranged irregularly with areas of fibrous tissue and some inflammatory response. No evidence of malignancy</td>
</tr>
<tr>
<td>5</td>
<td>Epithelial cells forming tubular structures, some of which are dysplastic and some areas have mitosis present. Cells supported on a friable oedematous connective tissue with some evidence of inflammation. No evidence of malignancy</td>
</tr>
<tr>
<td>6</td>
<td>Marked proliferation of epithelial cells as papillary-like processes with mild inflammatory response. Early invasion of the stroma suggestive of malignancy</td>
</tr>
<tr>
<td>7</td>
<td>Tubulopapillary polyp formation with sufficient atypia to be classified as malignant</td>
</tr>
<tr>
<td>8</td>
<td>Epithelial proliferation arranged in papillary fronds on a fibrovascular stroma. No evidence of inflammation or malignancy.</td>
</tr>
</tbody>
</table>

Scores based on a sliding scale of severity in which 0 is the lowest score (no clinical signs) and 10 is the highest score (severe clinical signs). From Dixon and Bird (1981) and Simpson and others (1994).
West Highland white terriers appear to be overrepresented in this study, a finding which concurs with the results of a previous study (Holt and Lucke 1985). The mean age of affected dogs was 8.6 years, which is similar to that previously reported (Schäffer and Scheife 1968, Valerius and others 1987, Holt and Durdey 1999). Males were overrepresented by a ratio of 3:1, which also concurs with results of previous studies (Holt and Lucke 1985, Church and others 1987, Valerius and others 1987). The severity of clinical signs did not appear to correlate with the duration of signs before presentation. Haematochezia, faecal tenesmus and increased mucus production were commonly reported and are known to be associated with both rectal and colonic disease. The absence of colonic disease on colonoscopy and histological examination of colonic biopsies would suggest that colitis was not a predisposing factor in the development of rectal tumours in these cases.

Surgical treatment of rectal neoplasia has been associated with poor survival rates, primarily due to a failure to control clinical signs and postoperative complications, including stricture formation, infection, wound breakdown and incontinence (Church and others 1987). Cautery methods require a general anaesthetic and multiple treatments and can be associated with perforation (Holt and Durdey 1999). Medical therapeutic options have been limited and the use of drugs commonly employed in the treatment of colitis has failed to result in clinical improvement (Thompson and others 1992). High concentrations of piroxicam, which is not a product licensed for veterinary use, have been shown to result in a significant reduction in growth of human colon adenocarcinoma cell lines in vitro. Piroxicam causes apoptosis of human colon adenocarcinoma cells and alters the distribution of cells within the cell cycle such that a higher proportion of cells remain in 'G0' (Shiff and others 1996). The fact that other anti-inflammatory drugs used in the treatment of colitis do not result in an improvement in colonic and rectal tumours suggests that the role of piroxicam is not solely anti-inflammatory. The use of piroxicam suppositories is likely to be associated with a higher local drug concentration than that achieved following oral administration. Any local antineoplastic effect of piroxicam should therefore be enhanced by rectal administration.

To minimise the potential for side effects associated with systemic absorption of rectally administered piroxicam, the rectal dose was tailored to approximate to the recommended daily oral dose (0.3 mg/kg piroxicam). Due to the size of the suppositories available, the dosing interval was increased to ensure that this average daily dose was not exceeded. Dogs therefore received either a half or one piroxicam 20 mg suppository every two or three days depending on their weight. Case 4 received oral piroxicam therapy at a dose of 0.34 mg/kg on alternate days. Since case 4 had the lowest total clinical sign scoring (17) before treatment, it is possible that the concentrations of piroxicam achieved by systemic absorption were sufficient to result in significant clinical improvement in this dog.

In seven of the eight cases, the owners reported a marked improvement in clinical signs, as evidenced by improvement in the sliding scores, following piroxicam treatment. One dog (case 1) developed a bout of vomiting. Symptoms resolved following dietary rest and did not recur following reintroduction of piroxicam. This case subsequently developed renal failure, which resulted in euthanasia six months after starting piroxicam treatment. Gastric lesions and renal papillary necrosis have been recorded following oral dosing with piroxicam (Galbraith and McKellar 1991, Knapp and others 1991, 1994). The dose used in case 1 (0.32 mg/kg/day) was, however, similar to that currently recommended for daily oral dosing. Since plasma piroxicam concentration following per rectum administration of piroxicam in dogs has not been determined, increased systemic absorption and enterohepatic circulation (Galbraith and McKellar 1991) may have resulted in higher plasma levels in this case. Pre-existing subclinical renal insufficiency cannot however be ruled out, despite normal biochemistry before treatment.

Cases 3 and 8 received higher dose rates of piroxicam than case 1 (0.46 and 0.35 mg/kg/day, respectively) and showed no evidence of side effects. Despite the use of lower piroxicam dose rates in cases 6 and 7 (0.24 and 0.25 mg/kg/day, respectively), palliation of clinical signs was still recorded.

Further studies are required to determine the dose of rectal piroxicam that results in maximal palliation of clinical signs while minimising the risk of side effects. Since failure to control the clinical signs associated with rectal tubulopapillary polyps is the most common reason for euthanasia (Church and others 1987), the palliation of clinical signs without recognised side effects has the potential to prolong survival and improve quality of life in dogs with these polyps.

At follow-up proctoscopy, piroxicam therapy appeared to result consistently in a reduction in the size and friability of the masses (Fig 1). Although this improvement was based on a subjective assessment, these results coupled with the improvement in clinical signs observed by the owners (as severity scores) would suggest that piroxicam does have a direct effect on rectal polyps. While reduction in both the size and friability may be associated with an anti-inflammatory effect of the drug, only half the patients in this study had evidence of inflammatory changes on histopathology, while all cases showed a similar reduction in tumour mass. This finding
supports the hypothesis that piroxicam has an antineoplastic effect due to apoptosis and alteration in cell cycle.

Predisposing factors for the development of rectal malignancy have not been identified in the dog but are thought to include dietary, familial and environmental factors in humans (Straw 1989, Thun and others 1991). Malignant transformation of rectal adenomas has been reported to occur in up to 50 per cent of canine rectal tumours (Patnaik and others 1980) and is thought to be more common when polyps have been present for prolonged periods (Van Stolk and others 1998). In the present study, evidence of early malignant change was recorded in three cases, but did not appear to be associated with prolonged duration of clinical signs before presentation. Since invasion of the submucosal layer is considered to be the most important criterion in the diagnosis of malignancy, collection of mucosal pinch biopsies has been considered a poor investigation for detecting rectal malignancy (Holt and Lucke 1985).

Proctoscopic collection of pinch biopsies may be performed under sedation in most dogs and is not usually associated with postprocedural complications. The presence of malignant changes in mucosal pinch biopsies from three cases in this study would suggest that malignancy can be detected in mucosal biopsies. It is possible, however, that some cases with malignant transformation were not identified in this study because samples did not include submucosal. Further investigation into proctoscopic biopsy methods is required to determine the optimum technique for the early detection of rectal malignancy.

The presence of malignant change in cases 3, 6 and 7 did not appear to affect the response to piroxicam therapy. Such findings on mucosal biopsy should not therefore be used as a criterion for euthanasia. Regular use of oral non-steroidal anti-inflammatory drugs has been shown to reduce the risk of development of rectal malignancy and prevent malignant transformation of benign tubulopapillary polyps in humans and rats (Pollard and Luckhart 1984, Kune and others 1988, Rosenberg and others 1991, Thun and others 1991, Logan and others 1993, Muscat and others 1994, Rosenberg and others 1998, Sander and others 1998). Long-term follow-up is therefore required to establish whether piroxicam therapy reduces the risk of malignant transformation of benign rectal polyps in dogs.

Conclusions

Medical management with piroxicam may provide a non-invasive treatment option both for dogs with rectal tubulopapillary polyps in which surgical treatment is likely to be associated with significant side effects and for the control of clinical signs.

Acknowledgements

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