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Phase I trial of piroxicam in 62 dogs bearing naturally occurring tumors*

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Summary. Piroxicam, a nonsteroidal antiinflammatory drug, was given to 62 dogs bearing naturally occurring tumors in a phase I clinical trial. Dose escalation was performed, with oral doses ranging from 0.5 mg/kg every 48 h (q48h) to 1.5 mg/kg q48h being tested. Dose-limiting gastrointestinal irritation/ulceration occurred in all four animals that received 1.5 mg/kg q48h. The maximum tolerated dose was 1 mg/kg q48h. Subclinical renal papillary necrosis occurred in two dogs (initial dosages, 1 and 1.5 mg/kg q48h, respectively). Following dose escalation, an additional group of dogs was treated with 0.3 mg/kg piroxicam q24h per os, the accepted canine dosage prior to this trial. Inclusion of this treatment group enabled evaluation of the toxicity of and tumor response to a daily dosage regimen. No complete remissions occurred in this trial. Partial remission was documented in three of ten dogs exhibiting transitional-cell carcinoma, in three of five animals bearing squamous-cell carcinoma, in one of three dogs displaying mammary adenocarcinoma, and in the one dog that exhibited a transmissible venereal tumor. The results of this study support the additional evaluation of piroxicam in a phase II clinical trial in dogs bearing naturally occurring tumors.

Introduction

Piroxicam, a nonsteroidal antiinflammatory drug in the oxicam family, is most commonly prescribed for the relief of arthritis pain in man [1]. It has also been evaluated as a potential antineoplastic or chemopreventive agent [2, 8, 11–16]. Piroxicam has been reported to have an inhibitory effect on the growth of chemically induced [8, 11–15] and transplanted tumors [16] in rodents. In a human clinical trial, the drug was given as a single agent to 31 cancer patients exhibiting known pulmonary metastasis; 1 complete response and 5 "minor regressions" were reported [2].

We have previously observed complete tumor remission in two dogs bearing naturally occurring cancer (one malignant hemangiopericytoma, one metastatic carcinoma) following treatment with piroxicam (0.3 mg/kg q24h) as a single agent. Partial remission occurred at week 4 of therapy in both cases, and complete remission was achieved at 5 and 6 months of treatment, respectively. Both dogs were in complete remission when they died of unrelated causes at 6 and 14 months, respectively, of piroxicam therapy. The present paper reports the results of a phase I clinical trial designed for the further evaluation of piroxicam therapy in dogs bearing naturally occurring neoplasia.

Materials and methods

Eligibility criteria. Dogs entered into the trial were required to exhibit histologically confirmed, measurable tumors. The trial was open to dogs that (1) had failed standard therapy, (2) could not undergo standard therapy due to medical complications or owner refusal, or (3) bore tumors for which standard therapy did not exist. A minimal interval of 3 weeks was required between prior chemotherapy and entry into the present trial. Dogs were required to be partially or fully ambulatory; to be capable of eating and drinking with minimal assistance, if any; to be maintaining reasonable body weight (weight loss, <15%); and to achieve an expected minimal survival of 6 weeks. Informed consent from the dog owner was required. The trial was conducted with the approval and according to the guidelines of the Purdue Animal Care and Use Committee.

Evaluation of response and toxicity. Dogs were evaluated at the Purdue University Veterinary Teaching Hospital (PUVTH) on days 0, 28, and 56 of the trial. These evaluations included a complete physical examination, including body weight and tumor measurements; radiography of the primary tumor site and expected sites of metastasis; contrast cystography (in dogs with bladder tumors); complete blood and platelet counts; a serum biochemistry profile; and urinalysis. The tumor stage was determined and recorded according to the World Health Organization TNM classification [9]. Serum samples were obtained on day 28 for determina-

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Table 1. Characteristics of the 62 dogs entered in the present study

	Animals (*n*)
Median age (range)	10 (2–17) years
Male: female	28 : 34
Prior therapy:	
Surgical excision	20
Radiotherapy	4
Chemotherapy	8
None	30
Tumor types:	
Transitional-cell carcinoma[a]	10
Melanoma[a]	10
Osteosarcoma	9
Fibrosarcoma	6
Hemangiopericytoma	6
Squamous-cell carcinoma	5
Mammary adenocarcinoma	3
Perianal-gland adenocarcinoma	3
Anal-sac adenocarcinoma	2
Lymphoma	2
Mast-cell tumor	2
Nasal carcinoma	1
Mammary adenoma	1
Transmissible venereal tumor	1
Synovial-cell sarcoma	1
Lipoma	1

[a] 1 dog exhibited transitional-cell carcinoma of the bladder and a melanoma of the toe

Table 2. Relevant findings of postmortem examinations of 44 dogs treated with piroxicam

Finding	Dogs (*n*)
Original tumor present	43
Gastrointestinal disease:	
Gastritis	2
Gastric ulceration	1
Duodenal ulceration	2
Perforated duodenal ulcer/peritonitis	2
Renal disease:	
Renal papillary necrosis	2
Chronic interstitial nephritis	6
Renal amyloidosis	1
Other disease resulting in death of the dog:	
Ruptured pulmonary abscess/pyothorax	1
Traumatic injuries	1

tion of the steady-state serum piroxicam concentration. Dogs that demonstrated a complete or partial remission at 56 days remained on study and were reevaluated at PUVTH at 1- to 3-month intervals. Animals that had not responded to piroxicam by day 56 had the option of undergoing different therapy (off study). Complete necropsies were performed at the time of death.

Dogs were carefully observed for evidence of gastrointestinal toxicity, which was graded as follows. Grade 0 toxicity was defined as no evidence of gastrointestinal irritation. Grade 1 toxicity was defined as episodes of anorexia lasting for <12 h per 24-h period. Grade 2 toxicity was defined as any or all of the following: episodes of anorexia lasting for >12 h per 24-h period, the occurrence of melena, and 1–2 episodes of vomiting per 24-h period. Grade 3 toxicity included any or all of the following: >2 episodes of vomiting per 24-h period, the occurrence of cranial abdominal pain, and the development of gastrointestinal ulceration (confirmed by endoscopy, surgery, or necropsy).

All tumors were measured in three perpendicular axes, and tumor volumes were calculated. Complete remission was defined as the disappearance of all clinically evident tumor for a minimum of 4 weeks and the reossification of lytic bone lesions. Partial remission was defined as a decrease of $\geq$ 50% in the summed tumor volume, with no increase occuring in the size of any preexisting lesion and no appearance of any new lesion. Progressive disease was defined as an increase of $\geq$ 50% in the volume of any lesion or the appearance of new lesions. Stable disease was defined as any response amounting to less than either a partial remission or progressive disease.

Treatment plan. Piroxicam was given orally on an outpatient basis. The starting dosage of piroxicam was 0.5 mg/kg every 48 h (q48h); this dose was increased by 0.5 mg/kg for each group of 15 dogs until the maximum tolerated dose had been determined. When grade 2 or 3 gastrointestinal toxicity or other significant organ toxicity occurred in four of five animals at a given dose, the dose escalation was terminated and the next lower dose was considered to be the maximum tolerated dose. Following the completion of this dose escalation, an additional group of dogs received 0.3 mg/kg q24h (the accepted canine dosage prior to this trial) for an evaluation of this daily dosage regimen. If grade 2 or 3 gastrointestinal irritation occurred, piroxicam was temporarily discontinued and cimetidine (5 mg/kg q4–6h) and sucralfate (0.25–1 g/dog q6–8h) were given; on resolution of the irritations piroxicam was reintroduced at 50% of the original dose.

Serum piroxicam analysis. Serum samples were collected on day 28, frozen, and shipped to an outside laboratory (Danbury Hospital, Special Chemistry Laboratory, Danbury, Conn.) for piroxicam quantitation by high-performance liquid chromatography (HPLC) [18]. This assay showed a sensitivity of 0.5 µg/ml, recovery of 100%, and linearity for up to 20 µg/ml.

Statistical analysis. Association between piroxicam dosage and toxicity was evaluated using Fisher's exact test (Statistical Analysis Systems, SAS Institute, Cary, N. C.). Dosages of 0.3 mg/kg q24h and 0.5 mg/kg q48h were compared with regard to toxicity and tumor response using Fisher's exact test. The serum piroxicam concentrations measured in dogs receiving these two dosages were compared using Student's unpaired *t*-test. The level of statistical significance was set at $P \leq 0.05$.

Results

Subject accrual

In all, 62 dogs bearing 63 tumors were entered into the clinical trial. Their characteristics are summarized in Table 1. Of the 62 animals investigated, 2 died and 6 were euthanized before day 21, and 2 dogs were not returned for follow-up examinations. The 8 early deaths/euthanasias were due to tumor-related causes in 2 dogs, combined tumor- and piroxicam-related causes in 2 animals, and causes unrelated to the tumor or piroxicam in 4 dogs. Of the remaining 52 animals, 43 were followed for a minimum of 56 days (range, 56–480 days) and 9 were followed for a minimum of 28 days. One dog is presently alive. In all, 45 dogs remained on piroxicam therapy until death, enabling a median follow-up period of 105 days (range, 7–480 days). Of the 61 animals that died, necropsies were performed on 44 (Table 2), and 17 were not returned for necropsy as requested.

Table 3. Gastrointestinal toxicity of piroxicam

Dose	Dogs treated (*n*)	Dogs exhibiting toxicity grade				% of dogs exhibiting toxicity*
		0	1	2	3	
q48h[a]:						
0.5 mg/kg	17	14	0	1	2	17.6%
1.0 mg/kg	18	12	0	2	4	33.3%
1.5 mg/kg	4	0	0	1	3	100%
q24h[b]:						
0.3 mg/kg	23	22	0	0	1	4.3%

[a] 48-h dose interval
[b] 24-h dose interval
* The percentages of animals exhibiting toxicity differed significantly among the groups treated at a 48-h dose interval (Fisher's exact test, $P = 0.008$)

Table 4. Steady-state serum piroxicam concentrations on treatment day 28

Piroxicam dosage	Animals sampled (*n*)	Serum piroxicam concentration (μg/ml)	
		Mean ± SD	Range
0.5 mg/kg q48h	11	3.46±1.69	1.6–7.3
1 mg/kg q48h	13	4.96±2.79	0.6–11.2
1.5 mg/kg q48h	2	(3.5, 5.3)[a]	
0.3 mg/kg q24h	10	3.05±1.37	1.1–5.2

[a] Only 2 dogs were sampled; actual concentrations are given

Toxicity

Piroxicam toxicity consisted of dose-limiting and dose-related gastrointestinal irritation/ulceration and of subclinical renal papillary necrosis. The gastrointestinal (GI) toxicity data are summarized in Table 3. GI toxicity occurred after 7–120 days (median, 35 days) of piroxicam therapy and was observed in 14 dogs, 8 of which responded well to cimetidine and sucralfate therapy, temporary discontinuation of piroxicam, and reinstitution of piroxicam at the reduced (50% of the original) dose. In all, 4 of the 14 dogs were euthanized due to tumor progression and drug intolerance, and 2 animals bearing disseminated mast-cell tumors were euthanized when early, severe GI irritation occurred.

The two dogs bearing disseminated mast-cell tumors developed grade 3 GI toxicity after they had received only four doses (0.5 mg/kg q48h and 1 mg/kg q48h, respectively) of piroxicam each. Intense medical management (discontinuation of piroxicam and administration of cimetidine, sucralfate, antibiotics, and intravenous fluids) was instituted, but both dog owners requested euthanasia for their pets. Perforating duodenal ulcers were found on postmortem examination of both animals. The first four dogs treated with 1.5 mg/kg piroxicam q48h developed grade 2 or 3 GI toxicity. Dose escalation was discontinued at this point and the previous level of 1 mg/kg q48h was considered to be the maximum tolerated dosage.

Renal papillary necrosis was detected in two dogs on postmortem examination. Prior to death, clinical signs of renal disease were absent, and serum biochemistry profiles and urinalyses were normal in both animals. The first dog (bearing a perianal-gland adenocarcinoma) had been given piroxicam at 1.5 mg/kg q48h for 14 days followed by 0.5 mg/kg q48h for 136 days. The second animal (exhibiting a hemangiopericytoma) had received piroxicam at 1 mg/kg q48h for 30 days followed by 0.5 mg/kg q48h for 180 days.

Serum piroxicam concentrations

Serum piroxicam concentrations were determined in 36 dogs on day 28. These data are summarized in Table 4. Serum samples were collected for piroxicam analysis at 15–24 h after drug administration in most dogs; variation in this interval did occur in a few cases.

Tumor response

In all, 52 dogs were considered to be evaluable for tumor response. No complete remissions occurred. Eight partial remissions were documented in 3 of 10 dogs bearing transitional-cell carcinoma of the bladder, in 3 of 5 animals exhibiting squamous-cell carcinoma, in 1 of 3 dogs bearing mammary adenocarcinoma, and in the 1 dog that exhibited a transmissible venereal tumor (Table 5). The tumor re-

Table 5. Characteristics of dogs bearing tumors that showed a partial remission

Tumor type/site	WHO TNM stage[a]	Prior therapy	Piroxicam dosage	Duration of response (days)	Survival (days)
TCC/bladder	$T_2N_0M_0$	None	0.3 mg/kg q24h	330	510
TCC/bladder	$T_2N_0M_0$	Cisplatin, doxorubicin	1 mg/kg q48h	120[b]	270
TCC/bladder	$T_2N_0M_0$	None	0.3 mg/kg q24h	150	300
SCC/skin	$T_3N_0M_0$	None	0.5 mg/kg q48h	NA[c]	45
SCC/maxilla	$T_{3b}N_0M_0$	None	0.3 mg/kg q24h	120	150
SCC/tongue	$T_{3a}N_0M_0$	Cisplatin	0.3 mg/kg q24h	NA[c]	390
Mam. Adeno CA	$T_{3c}N_1M_1$	Cisplatin, doxorubicin	0.5 mg/kg q48h	100	105
TVT/skin	$T_4N_0M_0$	None	0.3 mg/kg q24h	NA[c]	165

[a] From Owen [9]
[b] Pet owner had been unable to give the dog piroxicam for 4 weeks prior to relapse
[c] Tumor was in remission when the dog died of causes unrelated to the tumor or therapy
TCC, Transitional-cell carcinoma; SCC, squamous-cell carcinoma; Mam. Adeno CA, mammary adenocarcinoma; TVT, transmissible venereal tumor

Table 6. Piroxicam dosage and tumor response measured on treatment day 56

Piroxicam dosage	Animals treated (*n*)	CR	PR	SD	PD	NA[a]
Dose escalation:						
0.5 mg/kg q48h	17	0	2	3	7	5
1 mg/kg q48h	18	0	1	8	8	1
1.5 mg/kg q48h	4	0	0	3	1	0
Every day dosing:						
0.3 mg/kg q24h	23[b]	0	5	5	9	4

[a] Follow-up not available

[b] 1 dog exhibited SD in a transitional-cell carcinoma and PD in a melanoma; this animal is listed once under PD

CR, Complete remission; PR, partial remission; SD, stable disease; PD, progressive disease

sponses and piroxicam dosages of all dogs are summarized in Table 6.

Discussion

This phase I clinical trial was performed to determine the appropriate piroxicam dosage that can be given to tumor-bearing dogs. Previous studies in normal dogs showed that the single dose of piroxicam that was lethal for 50% of the animals studied (LD_{50}) amounted to >700 mg/kg and that a dosage of 1 mg/kg daily for 373 consecutive days was toxic to 6/6 dogs [10]. Dose-related and dose-limiting GI irritation/ulceration was identified as the major form of piroxicam toxicity in dogs in the present trial. Cyclooxygenase-inhibiting drugs such as piroxicam can lead to GI irritation by decreasing the synthesis of prostaglandins of the E series. The role of E-type prostaglandins in providing gastric mucosa cytoprotection and in limiting gastric acid secretion has been well characterized [17]. Removal of this cytoprotection can result in a predisposition to gastric and duodenal irritation and ulceration [17].

Piroxicam therapy appeared to contribute to the rapid development of duodenal ulceration in the two dogs bearing disseminated mast-cell tumors (MCTs). Dogs exhibiting MCTs are predisposed to GI ulceration due to tumor release of histamine, which stimulates gastric acid production [6]. Although the potentiation of GI ulceration by nonsteroidal antiinflammatory drugs has not previously been reported in dogs bearing MCTs, this may have occurred in the present trial. Another possible explanation might be that tumor-cell death was occurring with histamine release from lysed tumor cells. Cutaneous tumor lesions in one of these two dogs had decreased in volume (by <50%) by the time of euthanasia. Until more information has become available, we do not recommend piroxicam administration in dogs bearing MCTs.

Renal papillary necrosis was detected on postmortem examination of two dogs. Clinical signs of renal disease had not occurred, and serum biochemistry profiles and urinalyses had remained normal in both cases. Renal papillary necrosis is considered to be characteristic of the renal toxicosis caused by prostaglandin-synthesis-inhibiting drugs [3]; it has been reported in normal dogs receiving piroxicam at 1 mg/kg q24h for 373 days [10]. Renal disease has occurred in association with piroxicam therapy in man [7]. Although the renal changes observed in the two dogs in the present trial were subclinical, more severe renal toxicity remains a matter of concern for dogs undergoing piroxicam treatment. Chronic interstitial nephritis was noted on postmortem examination of six dogs in this study. This condition is a common postmortem finding in older dogs exhibiting a variety of underlying diseases. The etiology of the interstitial nephritis observed in this study was unknown.

Our initial intent was to observe treated dogs for a minimum of 56 days. This period was considered to be acceptable for the detection of piroxicam toxicity and antitumor responses. During this phase I trial, many dog owners reported an increased level of activity and increased alertness in their dogs and therefore requested that their pets remain on piroxicam therapy beyond 56 days due to a notable increase in their quality of life. In all, 45 dogs received piroxicam therapy for life, enabling an extended follow-up period. Late GI irritation was detected in 2 animals at 120 and 105 days, respectively. All antitumor responses had become evident by day 28.

In the dose-escalation scheme, piroxicam was given every 48 h. This dose interval was considered to be appropriate due to the 43-h plasma half-life of piroxicam in dogs [5]. Following completion of the dose escalation, an additional group of dogs was treated with 0.3 mg/kg q24h. This dosage had been used in the two dogs that had achieved a complete remission prior to this trial. The 0.3 mg/kg q24h dosage and the 0.5 mg/kg q48h dosage did not differ in regard to the percentage of dogs exhibiting toxicity (Fisher's exact test, $P = 0.197$), the percentage of dogs achieving remission (Fisher's exact test, $P = 0.435$), and the resulting in vivo serum concentrations (Student's unpaired *t*-test, $P = 0.542$). It is fortunate that antitumor activity occurred at these lower, less toxic dosages. Either the 0.3 mg/kg q24h or the 0.5 mg/kg q48h dosage schedule would be appropriate for future canine clinical trials.

The steady-state serum piroxicam concentrations measured in dogs in this trial were similar to those previously obtained in normal humans [4]. This is not surprising because piroxicam metabolism is similar in man and dogs [4, 5, 10, 19]; the plasma half-life of the drug is 43 h in dogs, 45 h in man, and 9 h in rats [4, 5, 10, 19].

No complete remission was achieved in the present study. Partial remission occurred in eight dogs. Three possible explanations for the observed tumor regressions might involve (1) an antitumor effect of piroxicam, (2) a reduction in tumor volume due to a reduction in the inflammatory component of the tumor, and, less likely, (3) spontaneous tumor regression. Phase II clinical trials are indicated to define further the activity of piroxicam in naturally occurring tumors in dogs. Additional work is also needed to determine the potential mechanisms underlying the antitumor activity of piroxicam.

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