COMPARISON OF ROBENACOXIB AND CARPROFEN IN THE PALLIATIVE MANAGEMENT OF CANCER PAIN

Research Project report by J.E. Spierenburg
Supervisors: Prof. dr. J.K. Kirpensteijn and Dr. S.A. van Nimwegen

Abstract

Robenacoxib is a nonsteroidal anti-inflammatory drug and a selective cyclooxygenase (COX) -2 inhibitor, registered for treatment of osteoarthritis and post-operative pain in dogs. In a randomized cross over investigator-blinded trial with client-owned dogs diagnosed with a form of cancer, we compare treatment with robenacoxib versus carprofen. Adverse effects (AEs), pain and Quality of Life (QoL) are assessed to determine which drug is the better choice in palliative management of the canine cancer patient. In the pain study, dogs were treated 28 days with one NSAID, had a wash out period of 1 day and were treated 28 days with the other NSAID. Physical examination and blood analysis were performed during a clinic visit every two weeks and every week forms assessing AEs, pain and QoL were filled out by the owner.
This research project report discusses results of the first four patients participating in this pain study. Results in this paper are blinded, because of continuation of the study.
The first patient showed no differences between treatments and only mild AEs and changes in scores, which were most likely caused by the effects of radiation therapy. The second dog survived 6 weeks and showed a difference in the two periods of the pain study, which may have been an idiosyncratic reaction of the dog to the NSAID secondly used. The third dog survived 3 weeks, thus was only treated with one NSAID; AEs and poor scores were most likely caused by progression of the tumour. The fourth dog showed no differences between treatments; AEs and changes in scores were most likely related to other causes than treatment.
Recruitment of patients and use of the forms are discussed and recommendations are given for the continuation of the pain study.

Introduction

Cancer is a common cause of death in older companion animals. High percentages of human cancer patients suffer from pain affecting their quality of life. The prevalence of pain in canine cancer patients is not known, but it is expected that many dogs with cancer have reduced quality of life because of pain. (1)

Cancer is preferably treated with surgery, radiation therapy or chemotherapy. However, it may not be possible to use these options, because of the type of tumour, presence of metastasis or wishes and possibilities of the owner. In that case the veterinarian is assigned to help the animal keep an acceptable quality of life for as long a period as possible. Untreated pain causes excessive sympathetic stimulation, which can have a negative effect on gastrointestinal functions and effect motility and mucosal integrity. Also the immune system can be impaired because of elevated cortisol levels, and negative effects on the cardiopulmonary, neuroendocrine system and fluid homeostasis can occur. Hormones released in reaction to prolonged stress can result in a general catabolic state and impair healing. Assessment and treatment of pain is an important part of palliative management in canine cancer patients. Untreated pain may affect survival times

negatively. Terminal patients may not receive satisfactory treatment of pain, because of difficulties to asses pain, or because of fear for adverse effects when using analgesics. (1, 2)

Nonsteroidial anti-inflammatory drugs (NSAIDs) are often used in human and veterinary medicine, because of their analgesic, anti-inflammatory and antipyretic properties. They inhibit cyclooxygenase (COX), which oxidizes arachidonic acid to prostaglandins and thromboxane. There are two isoforms of COX: COX-1 and COX-2. COX-1 maintains physiological functions like production of gastric mucus and regulation of renal blood flow. COX-2 is induced at places of tissue damage or inflammation. Prostaglandins that are formed work as inflammation mediators and amplify nociceptive input and its transmission to the spinal cord. Thus COX-2 is thought to be responsible for pain after injury. Adverse effects of NSAIDs, involving gastrointestinal ulceration, bleeding disorders and renotoxity, are attributed to the inhibition of COX-1. This finding had leaded to development of selective COX-2 inhibitors: NSAIDs of the coxib class. The hypothesis was that selective COX-2 inhibitors would have the same efficacy as non-selective NSAIDs without the adverse effects. Although it is now recognised that COX-2 also is expressed constitutively in several tissues, so specific COX-2 inhibitors will not be free of adverse effects, data still indicates that they cause less gastrointestinal ulceration than non-selective NSAIDs. (3-5)

Hepatic adverse effects secondary to treatment with NSAIDs are most likely to be an idiosyncratic reaction to a specific drug, than hepatic toxicity of the NSAID itself. Pre-existing liver disease may be exacerbated by the use of NSAIDs. (6, 7)

Luna et al. (2007) compared treatment with different NSAIDs during 90 days with placebo. Carprofen was found to have less AE's than the other NSAIDs tested. Carprofen was given at therapeutic dosage (4mg/kg/day). Bleeding times at 30 and 90 days were significantly higher than baseline, but this was found to be clinically relevant. At 90 days, 3 of 6 dogs were found to have occult blood in faeces and 1 dog had gastric lesions, which was significantly more than dogs receiving placebo. (8)

Robenacoxib is a selective COX-2 inhibitor, developed for use in veterinarian medicine, registered for treatment of osteoarthritis and post-operative pain in dogs. King et al. (2010) found that robenacoxib had highest selectivity for inhibition of COX-2 versus COX-1 of NSAIDs tested. Robenacoxib was found to be much more selective than carprofen.(9) In rats, robenacoxib (specific COX-2 inhibitor) was as efficacious in reducing pain, inflammation and fever as diclofenac (non-selective NSAID), but had significant less gastrointestinal ulceration. (4) In a canine model of synovitis, robenacoxib was found to have a dose-related inhibition of COX-2 and no inhibition of COX-1, was significantly superior to placebo and non-inferior to treatment with meloxicam. (5)

King et al. (2011) studied safety of robenacoxib by treating healthy beagle dogs with placebo or 10-40 mg/kg robenacoxib once daily for one month (study 1); or placebo or 2-10 mg/kg robenacoxib once daily for six months (study 2). Dosages used were several times higher than therapeutic dosages. This study found no significant differences between placebo or therapy in frequency of AE's, blood analysis variables or findings at post-mortem examination. Bleeding times from dogs treated with robenacoxib in study 2 were not significantly different from dogs receiving placebo. There was no evidence for toxicity for the gastro-intestinal tract, liver or kidneys. Robenacoxib was found to have an excellent safety profile in healthy beagle dogs. (10)

Edamura et al. (2012) compared robenacoxib with carprofen for the treatment of osteoarthritis in the dog. Dogs treated with robenacoxib and carprofen had significantly better functional disability scores than they had before treatment. Robenacoxib scored better than carprofen numerically, but difference was not significant. Tolerability was good for both Robenacoxib and carprofen. (11)

Reymond et al. (2012) found that treatment of osteoarthritis with robenacoxib was non-inferior in efficacy and tolerability to treatment with carprofen. No difference was found in the frequencies of adverse effects occurring. Adverse effects that were observed were observed in 46% of robenacoxib group and 52% of carprofen group and consisted mostly of mild adverse effects affecting the gastro-intestinal tract. (7)

Gruet et al. (2011) found that treatment with robenacoxib of postoperative pain and inflammation in dogs undergoing orthopaedic surgery was non-inferior in efficacy and tolerability to treatment with meloxicam. Only mild adverse effects were found during the study, mostly affecting the gastro-intestinal tract, with no significant difference between treatments and which were not necessarily related to treatment. (12)

In this pain study, we compare robenacoxib, a NSAID in the coxib group, with carprofen, a non-selective NSAID in the palliative management of dogs with cancer. We investigate differences between both NSAIDs in efficacy in improving quality of life and in causing adverse effects. Our aim is to determine which drug is the better choice in palliative management of the canine cancer patient.

The hypothesis for the pain study is: Canine cancer patients that receive robenacoxib as a palliative treatment, have significantly lesser scores on adverse effects and significantly better scores for pain and quality of life than dogs treated with carprofen.

This paper will discuss results of the first four patients participating in the pain study. Results are still blinded in this paper, as the key for blinding could not be broken yet, because of continuation of the study. The recruitment of patients and use of the forms will be discussed and recommendations are given for the continuation of the study. Information and recommendations for a new research project student are annexed, in Dutch.

Materials & Methods

This study is a randomized cross over investigator-blinded trial with client-owned dogs diagnosed with a form of cancer. Dogs entered the study according to inclusion-/ exclusion criteria. Inclusion criteria were: Dogs with a primary diagnosis of cancer, confirmed by FNAB or biopsy, who were expected to survive for at least 6 months. Exclusion criteria were: Concomitantly usage of other NSAIDs, corticosteroids or potentially nephrotoxic medication, severe organ failure, cardiac-, hepatic-, renal- or gastro-intestinal disease, blood dyscrasias, mast cell tumour, concurrent radiation- or chemo therapy, pregnant females and hypersensitivity to any of the excipients.

New patients were recruited by checking clinic appointments at the University Clinic for Companion Animals in Utrecht, especially from the surgery and oncology department and searching in our digital patients system for terminal cancer patients. Veterinarians from the clinic were asked to watch out for patients that would be able to enter the study. Veterinarian practices in and around Utrecht received a letter with information about the study and the request to contact the research team if they would have a patient that would be willing to join the study.

When dogs with cancer that would not receive other treatment were found, owners were given verbal and written information about the study and asked if they would be willing to participate.

Selected dogs were checked for metastases at the first examination by thoracic radiograph, abdominal ultrasound or CT scan. If dogs were found to have metastases, during treatment period radiographs or ultrasound were repeated to check growth. This was performed in the middle of the treatment period or on other clinic visits, upon exacerbation of clinical symptoms.

Before the study, the selected dogs were randomly selected into two groups. Dogs were treated for a period of 57 days, from which they were treated 28 days with one product, had a wash out period of 1 day and were treated 28

days with the second product. One group started treatment with robenacoxib, 1mg/kg 2dd and switched to carprofen, 2 mg/kg 2dd. The other group started with carprofen and switched to Robenacoxib. All drugs were prepared and delivered to the client by our pharmacy. Owners were instructed not to discuss the product, appearance or packaging with the investigator.

Throughout the study, several forms were used to score the quality of life and to register the observed adverse events. We applied the Glasgow Pain Score forms, both the short (Pain) and the long (Quality of Life; QoL) version, to score the quality of life of the dogs participating in this study. For registration and interpretation of observed adverse events (AEs), the VCOG-CTCAE v1.1 form (13) was adapted so it could be used for this study. For every AE the following details were described: duration, clinical signs, severity, outcome, causality assessment, action(s) taken and their outcome. In case of death or very severe AEs, further examination would have been required (pathology, histology). Next to the AE form, which was filled in weekly, a daily AE form was developed for the owner, so they could note any AE directly and to help them remembering all AE occurring that week when filling out the weekly AE form.

During the treatment period, every dog was physically examined five times: at the start of the treatment period (day 0), at day 14, day 28, day 42 and day 57 of the treatment period. These examinations were performed by a veterinarian or a veterinary student.

When owners agreed to enter the study, they signed a Compliance Statement and a letter was send to their own veterinarian to inform about participation of the dog in the study. The forms AE, Pain and QoL were filled out together with the owner. This was done by reading the questions with all the answers to the owner and asking them which answer they would choose. The owner was asked to confirm all the questions and answers were clear. At the first visit, the owner received a folder with a letter with information about the study and contact information and at least two sets of forms, consisting of a daily AE form, AE form, Pain and QoL. The owner was asked to fill out any AE on the daily AE form. Also every week (day 7, 14, 21, 28, 35, 42, 49 and 57), they were asked to fill out the AE, Pain and QoL form. Every week the dog was not visiting the clinic, the owner was called to check how the dog was doing, if AE's were noted and if they had any difficulties filling out the forms. Every two weeks, the dog visited the clinic.

During the clinic visits, history was taken (first visit), physical examination was performed and the tumour measured. Blood analysis was performed and consisted of haematocrit, leucocytes differentiation, thrombocytes, creatinine, uric acids, total protein, ALT, ALP, bile acids, bilirubin, cholesterol, triglycerides, calcium, phosphate, sodium and potassium.

Scoring of AE was done according to the VCOG-CTCAE v1.1 form (13). With the adaptation of the form, score 0 was added for no AE in that category and score 5 (death) was left out. Pain was scored from 0 to 24, with 0 for no pain. QoL was scored 1-5 for each question, with 110 as maximum score for QoL.

Table 1: Overview of examinations and forms during study

Day	History	Physical examination*	Tumour measurement	Pain form	QoL form	AE form
0	X	X	X	X	X	X
7				X	X	X
14		X	X	X	X	X
21				X	X	X
28		X	X	X	X	X
35				X	X	X
42		X	X	X	X	X
49				X	X	X
57		X	X	X	X	X

*Physical examination: includes blood analysis and during the first time FNAB of the tumour and metastases check.

Results

During the period of May – October 2013, 4 dogs could be recruited and participated in the study. Most of the dogs with cancer visiting the clinic are referred for specialist treatment like surgery, radiation therapy or chemotherapy, so they could not participate because of concurrent treatments. Palliative care for cancer patients is mostly done by a primary veterinarian, but we did not receive reaction of any the veterinary practices that had received an information letter. A couple of veterinarians from those practices that had personal contact with the research team promised to watch for patients, but unfortunately no patients were found.

Patients also were not able to enter the study because of the exclusion criteria, especially because mast cell tumours were not allowed. Other patients received corticosteroids or tramadol and were unable to switch to NSAIDs. Some owners were unwilling to participate because they thought it would be too heavy a burden for the dog to visit the clinic every two weeks and also to take blood samples every visit, others thought the medication to be too heavy a burden for the dog. Some owners were not convinced their dog was in pain and therefore not willing to give him painkillers. One owner resigned after intake, because the dog would be hypersensitive for NSAIDs.

The owners that entered the study were motivated to do everything for their dog they could. Distance was not a problem, owners were motivated to visit the clinic every two weeks, also if that would take some time and driving.

Owners were able to fill in the right forms at the right times. They did not think it was difficult to fill them in. Sometimes they found it difficult to choose between two options, then they wrote remarks under the question. Remarks were taken into account with recording of AE and with the scoring of QoL and Pain.

Scores for QoL and Pain did not always match with clinical signs found at clinic visits, especially for some owners.

First patient

The first patient that entered the pain study was a female neutered Welsh Springer Spaniel of 10 years old. She had a very rapid growing lump on her tarsus since 4 months. Histologic examination showed a rhabdomyosarcoom grade III. She was referred to the University Clinic for Companion Animals in Utrecht and a CT-scan was performed to investigate invasiveness of the tumour and check for metastases. No metastases were found and except for the tumour and being a bit more lethargic for some time, the dog was healthy. As the tumour was too big for complete surgical resection, it was decided to treat it with combination therapy of Holmium therapy, then chirurgic marginal resection and afterwards radiation therapy. She was already treated with NSAIDs during this period. The dog entered the study one day after surgery and started radiation therapy 10 days later. Because of the radiation therapy the dog did not meet the inclusion- / exclusion criteria, but she entered as a pilot for the study.

The dog had complete remission for 3 months and then relapsed. No metastases were found. The leg was then amputated.

The owner had no problems filling out the forms and tried to consider whether AEs were because of radiation therapy or therapy with NSAIDs.

Table 2.1: First patient Adverse Effects scores

Week	0	1	2	3	4	5	6	7	8
Appetite	0	0	0	0	0	1	0	0	0
Vomiting	0	0	0	0	0	0	0	1	0
Nausea	0	0	0	0	0	0	1	0	0
Diarrhoea	0	0	0	0	0	0	0	0	0
Obstipation	0	0	0	0	0	0	0	0	0
Stomach ache	0	0	0	0	0	0	0	0	0
Weight loss	0	0	0	0	0	0	0	0	0
Urination habits	0	0	0	0	0	0	0	0	0
Allergic reactions	0	0	0	0	0	0	0	0	0
Fever	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	0	0	0	0	0
Bleeding	0	0	0	0	0	0	0	0	0
Activity	1	1	1	1	2	1	1	1	1
Consciousness	0	0	0	1	1	1	0	0	0
Behaviour	0	0	0	0	0	1	1	0	0

The change of behaviour without negative effect during week 5 and 6 was lameness. The dog was walking on 3 legs and was given Tramadol in addition to the NSAID.

Table 2.2: First patient scores for Pain and Quality of Life

Week	0	1	2	3	4	5	6	7	8
Pain	2	0	0	0	3	1	2	0	0
QoL	95	106	100	82	84	89	87	97	99

Table 2.3: First patient blood analysis

Week	0	score	2	score	4	score	6	score	8	score
Ht	0,34	1	0,44	-	0,44	-	0,49	-	0,47	-
Leucocytes	14,0	-	6,2	-	5,7	-	5,2	-	5,5	-
Segmented neutrophils	11,3	↑	4,1	-	4,0	-	3,6	-	3,9	-
Band neutrophils	0	-	0	-	0	-	0	-	0	-
Lymphocytes	1,4	-	1,1	-	1,0	-	1,1	-	1,1	-
Monocytes	0,9	-	0,2	-	0,4	-	0,2	-	0,2	-
Eosinophils	0,4	-	0,7	-	0,2	-	0,4	-	0,4	-
Basophils	0	-	0	-	0	-	0	-	0	-
Thrombocytes	262	-	377	-	350	-	177	-	263	-
Creatinine	100	-	114	-	112	-	110	-	-	-
Uric acid	3,4	-	4,1	-	4,8	-	5,2	-	-	-
Total protein	62	-	61	-	-	-	65	-	67	-
ALT	23	-	32	-	33	-	36	-	44	-
ALP	64	-	47	-	41	-	54	-	45	-
Bile acids	7	-	21	↑	17	↑	18	↑	20	↑
Bilirubin	3,7	1	4,7	1	<1,7	-	<1,7	-	3,3	-
Cholesterol	3,6	-	5,0	-	5,7	-	5,0	-	5,4	-
Triglycerides	0,55	-	0,50	-	0,48	-	0,45	-	1,40	-
Calcium	2,48	-	2,52	-	2,57	-	2,62	-	2,61	-
Phosphorus	1,02	-	1,09	-	1,18	-	1,14	-	0,95	-
Sodium	147	-	143	-	143	-	147	-	146	-
Potassium	3,4	-	4,1	-	4,1	-	4,1	-	4,0	-

Second patient

The second dog was a Labrador, neutered female of 12 years old. She was losing weight despite good appetite and was retching or clearing her throat. Her veterinarian found elevated liver values and the dog was referred. Liver biopsy showed copper-associated chronic hepatitis and the dog was treated for this with metalcaptase. After 3 months, retching and clearing of her throat had become productive coughing with mucus and sometimes blood. She also vomited. On X-ray a consolidated lung lobe was seen. FNAB was taken and a broncheoalveolar carcinoma was found. A caudal lung lobe resection was performed, but after 3 months, coughing had returned. On X-ray metastases in the operated lung were found. The owner considered reoperation, but decided not to. Then the dog entered the pain study. She did have pre-existing liver disease, but as we would monitor liver values, she was allowed to enter the study.

The dog did well in the first part of the study, she did couch and clear her throat but had good appetite and was happy going for a walk. During the clinic visits, the dog moved normal but slow and was alert. The owner noted that the dog could walk for 45 minutes, but at her own pace. During the first weeks, no difference was seen at the clinic visits and also the owner noted that there was no change. From week 3, she vomited once a week. At week 4, thoracic radiographs were made, on which growth of metastases was visible and extension of metastases to another lung lobe. During week 5, after switching NSAIDs, clinical signs worsened; the dog was coughing more and was more lethargic and anorectic and vomited one time. The dog had an extra clinic visit at week 5, because the owner was very worried about her appetite. Because of anorexia, another type of food was tried during the clinic visit, which she ate with good appetite. Codeine was prescribed to treat coughing. That evening she vomited her food. Between week 5 and 6, a great difference was seen at the clinic visit. At week 6 the dog was lethargic, walking extremely slow and was depressed; she reacted less and had a depressed expression on her face. She was also coughing up mucus with blood. She vomited the morning of the clinic visit; the vomitus was yellow with a small fragment of red. Because the dog was also coughing up mucus with blood and the red part of the vomitus was not mixed with the yellow part, it was not clear if the blood came from the respirational or gastrointestinal tract. Because of clinical signs, decided was to euthanize the dog at home. The owner was realistic that the situation was untenable. The dog received for two days the NSAID she had received during the first part of the study, because palatability of the first NSAID used was better than the second for this dog, to give the owner some time saying goodbye. Back on the first NSAID however, the dog got back her appetite, wanted to eat her normal food again and was less lethargic. The owner considered delaying euthanasia, but decided not to.

Because of the decision for euthanasia, we were unable to do blood analysis at week 6. Therefore we unfortunately only have results of blood analysis during the first period of treatment.

The owner very much tried to keep secret which NSAID was given, but because of certain questions and answers given and certain properties of the tablets, investigators did find out. So results of this dog were not blinded for the author of this paper.

The owner of this dog very much appreciated the care and attention she and her dog received. She was very concerned about her dog and was very thankful to be able to call at any time to talk if the dog did not do well or she had a question about something. She was emotional when she saw things changing in her dog. She was glad that her dog was examined every two weeks and that she was able to have an extra clinic visit when the dog was not eating well.

The owner of this dog scored differently for Pain and QoL at different weeks for things that had not changed between the weeks. The difference between the scores of week 0 and 1 is because she first noted that the dog was moving

slowly and lethargic and sleeping more, while in week 1 and 2 she noted this as normal. She also noted on the form and during clinic visit that there was no difference between the weeks. The dog coughed all the time, but she only noted this as change of behaviour in week 0. The dog had loose hairs, which the owner said were normal for her in this period of the year, but one week she scored the question about the coat as agreed, the other week as disagree, while the coat did not change. At week 5 and 6, the scores do reflect worsening of clinical signs, but the great difference between week 5 and 6 seen at the clinic visits is not that much seen in the scores.

Table 3.1: Second patient Adverse Effects scores

Week	0	1	2	3	4	5	6
Appetite	0	0	0	0	0	1	2
Vomiting	0	0	0	1	1	1	1
Nausea	0	0	0	0	0	1	2
Diarrhoea	0	0	0	0	0	0	0
Obstipation	0	0	0	0	0	0	0
Stomach ache	0	0	0	0	0	0	0
Weight loss	0	0	0	0	0	0	0
Urination habits	0	0	0	0	0	0	0
Allergic reactions	0	0	0	0	0	0	0
Fever	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0
Pruritus	0	0	0	0	0	0	0
Bleeding	0	0	0	0	0	0	0
Activity	1	0	0	0	0	0	1
Consciousness	0	0	0	1	0	0	2
Behaviour*	1	0	0	1	0	2	2

*Change of behaviour without negative effect at the first clinic visit: coughing; in week 3: sleeping more. Change of behaviour with negative effect in week 5: more dyspnoeic, in week 6: much decreased appetite; only willing to eat cooked meat or bread, dyspnoeic, couching up mucus with blood.

Table 3.2: Second patient scores for Pain and Quality of Life

Week	0	1	2	3	4	5	6
Pain	3	0	0	0	0	5	2
QoL	82	102	102	92	91	70	64

Table 3.2: Second patient blood analysis

Week	0	score	2	score	4	score
Ht	0,36	1	0,40	1	0,41	1
Leucocytes	8,7	-	7,7	-	8,1	-
Segmented neutrophils	5,5	-	4,8	-	5,0	-
Band neutrophils	0	-	0	-	0	-
Lymphocytes	1,8	-	1,9	-	1,9	-
Monocytes	0,9	-	0,5	-	0,4	-
Eosinophils	0,5	-	0,5	-	0,8	-
Basophils	0,0	-	0,0	-	0,1	-
Thrombocytes	391	-	350	-	298	-
Creatinine	68	-	71	-	69	-
Uric acid	1,6	↓	2,6	↓	3,0	-
Total protein	74	↑	77	↑	-	-
ALT	85	1	350	3	460	3
ALP	1760	3	2065	4	1705	3
ALP (65)	1063	↑	1501	↑	1016	↑
Bile acids	1	-	6	-	11	↑
Bilirubin	11,9	3	9,4	2	7,9	2
Cholesterol	5,9	-	6,0	-	6,2	-
Triglycerides	2,77	↑	4,14	↑	0,56	-
Calcium	2,66	-	2,69	-	2,74	-
Phosphorus	1,49	-	1,63	-	1.67	-
Sodium	146	-	146	-	145	-
Potassium	4,9	-	4,6	-	4,8	-

Third patient

The third dog was a 11 year old Papillion. Three months before referral, her veterinarian performed an unilateral mammary chain resection and ovariohysterectomy because of mamma tumours. The tumours could not be completely removed, because then not enough skin would have been left to close the wound. The caudal part of the wound was healing badly. Treatment with prednisolone, antibiotics and dermiel salve did not resolve the problem and the dog was referred. At the first clinic visit, other small nodules in the mammae were found and on thoracic radiographs metastases were found. As the dog was on prednisolone, this was gradually reduced and the dog entered the study a week later. At the start of the study, the owner noted that she thought the dog was deteriorating; she was less fanatic and didn't want to play and walk as long as she used to. In a week the wound had become more red and exudative, because of that two weeks of amoxicillin/clavunalate was given. During the first weeks of the study, clinical signs worsened. The dog was more lethargic and often licking the wound. She was panting more, but not coughing. At the 2 weeks clinic visit, the wound again looked more red and exudative. The dog seemed to suffer most from pain from the wound, as she was licking it constantly and the owner thought it was very unpleasant for the dog to wear a bodysuit. A swab was taken of the wound for bacterial culture and antibiogram; to check for resistant bacteria, and amoxicillin/clavunalate was continued. No resistant bacteria were found. The owner was advised to let the dog wear a bodysuit as the wound was more unpleasant than the bodysuit, but the dog worked very hard to move it and would still lick the wound. Thoracic radiographs were taken, which showed growth and multiplication of lung metastases. At week 3, the owner called that clinical signs had worsened very fast and the dog was now dyspnoeic. The dog had had some episodes during the night that she could not get her breath and was very frightened. The owner went to her own veterinarian, were the dog was found to be

cyanotic. The dog was euthanized at home on the next day. Because she only survived for 3 weeks in the study, she only received one NSAID. The dog was not seen by the research team in week 3, the owner send the forms of that week by mail.

Scores for Pain and QoL were not optimal for this dog from the start of the study and deteriorated quickly during the weeks.

The owner of this dog was very concerned about her. She was pleased with the clinic visits and said to trust the research team to have good care for her dog. She did not like the blood samples, but understood they were necessary. She was emotional when she saw the dog becoming less and less the dog she knew. The owner scored high for AE's and Pain and low for QoL. The clinic visit of week 2 for this dog took place on the same day as the clinic visit of the second dog in week 6. During the clinic visit, clinical signs of the second dog were more severe than clinical signs of the third dog at that moment, but the third dog had worse scores.

Table 4.1: Third patient Adverse Effects scores

Week	0	1	2	3
Appetite	0	0	1	2
Vomiting	0	0	0	0
Nausea	0	0	0	0
Diarrhoea	0	0	0	0
Obstipation	0	1	1	0
Stomach ache	0	0	0	0
Weight loss	0	0	0	0
Urination habits	0	0	0	0
Allergic reactions	0	0	0	0
Fever	0	0	0	0
Alopecia	0	0	0	0
Pruritus***	0	2	3	3
Bleeding	0	0	0	0
Activity	1	1	2,5	3**
Consciousness	0	0	0	1
Behaviour*	1	1	2	2

*Change of behaviour without negative effect at the first clinic visit: itching from the wound; in week 1: withdrawn. Change of behaviour with negative effect in week 2: more withdrawn; in week 3: twice had an dyspnoeic episode, could not get her breath and was frightened.** In week 3, the owner fed the dog at her place, but she was still housetrained. ***The owner interpreted the licking of the wound as itching. The dog was only licking the wound, not other parts of her body and she was not scratching.

Table 4.2: Third patient scores for Pain and Quality of Life

Week	0	1	2	3
Pain	3	4	10	11
QoL	98	78	59	62

Table 4.3: Third patient blood analysis

Week	0	score	2	score
Ht	0,54	-	0,57	-
Leucocytes	12,4	-	13,3	-
Segmented neutrophils	10,3	-	11,2	↑
Band neutrophils	0	-	0	-
Lymphocytes	1,3	-	1,2	-
Monocytes	0,4	-	0,5	-
Eosinophils	0,2	-	0,2	-
Basophils	0,1	-	0,2	↑
Thrombocytes	390	-	444	-
Creatinine	59	-	57	-
Uric acid	8,6	-	7,5	-
Total protein	70	-	69	-
ALT	60	-	57	-
ALP	84	-	80	-
Bile acids	86	↑	23	↑
Bilirubin	4,1	1	3,7	1
Cholesterol	4,4	-	4,3	-
Triglycerides	0,86	-	0,71	-
Calcium	2,96	-	2,75	-
Phosphorus	1,51	-	1,71	-
Sodium	147	-	152	↑
Potassium	3,5	1	4,3	-

Fourth patient

The fourth dog was a male Miniature Schnauzer of 9 years old. His own vet noticed a mass from the gingiva of his mandible during dental cleaning. From biopsies the mass was found to be a malignant melanoma. On X-ray the mandibular bone was affected. The dog was referred and CT scan was performed, which showed involvement of the mandibular bone and no visible thoracic metastases. The mandibular lymph node was somewhat enlarged, but FNAB showed no visible metastases. Apart from the tumour, the dog was healthy, no clinical signs were visible. Because of financial considerations the owner decided for palliative care and entered the study. In the first weeks the dog became less willing to eat his food in the morning, but ate normal in the evening. When playing with a ball, he was bleeding a bit from his mouth. At the clinic visit at week 4, the tumour had grown and the dog had excessive salivation, which was light brown/red of colour. His beard was wet from salivation and foetor ex ore had become worse. The dog was less able to keep itself clean, because he would spread saliva with blood when licking himself. Sometimes he was a bit lethargic. Because of this situation, the owner decided to do a partial mandibular resection. Because of inflammation of the tumour, amoxicillin/clavunalate was given. Start of antibiotics was around the same time as switching NSAIDs.

Three days after the clinic visit, the dog came for operation. Excessive salivation had reduced; his beard was now almost dry and the owner had noted that the dog was less lethargic and had better appetite in the morning. A partial mandibular resection was performed, also the mandibular lymph node was removed. At histologic examination, metastases in the lymph node were found. After operation, the dog received tramadol for 5 days as additional pain medication. After operation, he recovered quickly. He had some difficulty eating, especially the last bit on the plate, but had good appetite. Occasionally he dropped some saliva. The owner noted the sound of the bark of his dog had

changed after operation. He was active and wanted to play.

In week 7, the dog got a fever (40,1˚C) and lost his appetite. Also the dog did not defecate. He vomited one time, after the owner gave him cooked chicken, which he never ate before. The owner visited his own veterinarian in the weekend, who found no connection of clinical signs with the operation or the tumour. The wound looked normal and abdomen soft on palpation. The veterinarian prescribed metronidazole. After the weekend, temperature had turned back to normal. Appetite improved, but was still variable. The dog did not lose weight and was active. At the clinic visit, no abnormalities were found at physical examination.

The owner will now try if there is a difference when stopping NSAIDs. At the moment, there is no evidence of metastases. The dog will have a check-up clinic visit in 3 months, or earlier when clinical signs would occur.

The owner was content with the clinic visits and care and attention given. He needed some extra help when to give what medication and when to fill out which form, but did not encounter any problems after that. He coincidentally mentioned the name of the NSAID, so results were not blinded for the author of this paper.

Table 5.1: Fourth patient Adverse Effects scores

Week	0	1	2	3	4	5	6	7	8
Appetite**	0	1	0	0	1	0	0	3	2
Vomiting	0	0	0	0	0	0	0	1	0
Nausea***	0	0	0	0	1	0	0	0	0
Diarrhoea	0	0	0	0	0	0	0	0	0
Obstipation	0	0	0	1	0	1	0	1	1
Stomach ache	0	0	0	0	0	0	0	1	0
Weight loss	0	0	0	0	0	0	0	0	0
Urination habits	0	0	0	0	0	0	0	0	0
Allergic reactions	0	0	0	0	0	0	0	0	0
Fever	0	0	0	0	0	0	0	2	0
Alopecia	0	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	0	0	0	0	0
Bleeding*	0	0	0	0	0	0	0	0	0
Activity	0	0	0	0	0	0	0	1	0
Consciousness	0	0	0	0	0	0	0	0	0
Behaviour****	0	0	0	0	0	1	1	1	1

*The dog was bleeding a bit from the tumour when playing, but as he did not have haemorrhage in the skin or faeces, score 0 was given. **In week 3, he was eating more careful, sometimes dropping food. In week 4 he only ate in the evening and was more affectionate. ***At week 4, he had excessive salivation with some blood, thus scored 1 on that AE, but he was not nauseous.**** Change of behaviour without negative effect in week 5: having difficulty to pick up all the food from his plate, barks less, is a bit uneasy; in week 6: is a bit more affectionate; in week 7: eats very little, so also not much faeces; week 8: variable appetite, but improved compared to week 7.

Table 5.2: Fourth patient scores for Pain and Quality of Life

Week	0	1	2	3	4	5	6	7	8
Pain	0	0	0	0	2	1	0	3	0
QoL	107	108	93	101	98	103	103	90	103

Table 5.3: Fourth patient blood analysis

Week	0	score	2	score	4	score	6	score	8	score
Ht	0,50	-	0,42	-	0,43	-	0,46	-	0,41	1
Leucocytes	15,1	↑	16,8	↑	21,6	↑	9,9	-	13,0	-
Segmented neutrophils	11,2	↑	13,5	↑	17,7	↑	7,5	-	10,6	-
Band neutrophils	0	-	0	-	0	-	0	-	0	-
Lymphocytes	2,6	-	2,0	-	2,1	-	1,6	-	1,4	-
Monocytes	0,8	-	1,0	↑	1,2	↑	0,4	-	0,5	-
Eosinophils	0,3	-	0,2	-	0,6	-	0,3	-	0,3	-
Basophils	0,2	↑	0,1	-	0,0	-	0,0	-	0,0	-
Thrombocytes	204	-	185	-	182	-	349	-	230	-
Creatinine	91	-	83	-	78	-	77	-	74	-
Uric acid	6,6	-	4,1	-	3,9	-	5,9	-	5,0	-
Total protein	70	-	72	-	73	-	70	-	71	-
ALT	-	-	49	-	43	-	197	2	50	-
ALP	49	-	57	-	67	-	175	1	138	1
ALP (65)	-	-	-	-	-	-	12	-	<5	-
Bile acids	1	-	10	↑	2	-	10	↑	10	↑
Bilirubin	4,0	1	5,4	2	2,8	-	<1,7	-	<1,7	-
Cholesterol	4,6	-	4,1	-	3,6	-	5,9	-	7,1	-
Triglycerides	0,37	-	0,29	↓	0,23	↓	1,23	-	0,81	-
Calcium	2,74	-	2,72	-	2,75	-	2,73	-	2,59	-
Phosphorus	0,83	-	1,05	-	1,15	-	1,19	-	0,99	-
Sodium	146	-	149	-	148	-	146	-	148	-
Potassium	3,8	-	4,1	-	4,3	-	4,2	-	4,0	-

Discussion

Materials and methods

Recruitment of patients

Recruitment of patients was difficult and took more time than expected. We did not have any patient from the clinics we send information letters. This may be because veterinarians were not motivated to recruit patients or because they would not remember the study when seeing a terminal cancer patient. In the University Clinic for Companion Animals, surgeons were informed about the study and asked to watch for possible patients in a meeting. Also a student from the research team would follow up any possible patient with lumps visiting the clinic and see if they would meet criteria and the owner would be willing to participate. During operation of the fourth patient, the orthopaedic surgeon noted he had not been informed about the study and did see cancer patients regularly. Thus possibly more patients can be recruited by also informing the orthopaedic surgeons and watching orthopaedic patients by students of the research team.

Adverse effects form

For the AE form, most of the time the score the owner had filled out at the form, agreed with what was found when questioned during the clinic visit. The first and fourth owner noted on the form when they thought an AE was not because of the NSAID, like lameness because of radiation therapy and bleeding because of the tumour.

Owners many times used the last question; change of behaviour, to note any AE that was not mentioned somewhere else, like lameness and coughing. In the adaptation of the VCOG-CTCAE v1.1 form (13), AE's that were not known to be an AE from the use of NSAIDs were left out. The question may be changed to differentiate between behaviour and other AE's, or left like this as it was not a real problem in interpretation.

Pain and Quality of Life form

Scoring varied between owners. The first owner very much tried not to score effects of radiation therapy and to score in the same way every week. Scoring was in accordance to physical examination at clinic visits. The second owner was less consistent with filling out the forms. She scored things that had not changed sometimes as being normal and sometimes abnormal. She may have had difficulty scoring objectively because of emotion. She was very worried about her dog, especially at week 0, when she had just heard the dog had metastases, and at week 5, when the dog did not want to eat her normal food. In those weeks, scores were lower than expected from clinical signs seen at the clinic visit. Also in the third patient, scores were lower than expected from clinical signs seen at the clinic visits. In the fourth patient, it is notable that scores were worse during the period in week 7 when the dog was ill, than in the period before operation when the dog was suffering from the tumour.

It may be useful if the student from the research team investigating the dog at the clinic visit, would also score Pain and QoL, as for some owners worries and emotion, or lack of knowledge seems to have influenced the score, which makes interpretation very difficult. Scoring by the owner is very useful to know how the owner interprets the situation and what subjects need attention in palliative care. But to evaluate differences between two NSAIDs, a member of the research team may be able to score more objectively.

Results

First dog

In the first patient, the lameness was related to the radiation therapy. She was sleeping more during the period of radiation therapy and daily narcosis, so mostly likely was related to that. Lethargy was worse during radiation therapy, but also present before and after. Most likely it is related to the tumour or pain, as from history she was found to be lethargic for a longer time before starting NSAIDs.

In this dog, differences in Pain and QoL scoring and AE's between the first and second period of the study were most likely related to radiation therapy, thus no difference in tolerability and efficacy between NSAIDs was found. Treatment with NSAIDs was found to be not efficacious enough for pain secondary to radiation therapy.

The dog had elevated bile acids during the study. This may be related to treatment or to other causes. At week 0, bile acids were not elevated, but this is probably not an argument for therapy being the cause of elevation in the other weeks, as the dog was also treated with NSAIDs before entering the study.

Elevated leucocytes and reduced haematocrit and in week 0 in this dog were most likely related to inflammation and operation of the tumour respectively.

Contact with this owner was less intensive than with the other owners. This may be because of differences between owners, or because this owner still had hope of accomplishing complete remission; it is still possible the dog will not die because of the tumour.

Second dog

The second dog showed a difference between treatment periods. It is not clear to which extend this difference can be explained by the switching of medication or the progression of cancer. The forms filled in by this owner are somewhat difficult to interpret, because she scored very differently on some points, while at the same time she would comment that she did not find this week different from the week before. The owner was worried very much and would sometimes note the dog was not eating, when the dog was mostly eating less and only eating food made more tasty. Anorexia did not seem as profound as suggested at the extra clinic visit at week 5. But what can be said objectively, is that during the second period of the study, the dog did not want to eat her hepatic diet; only food that the owner made more tasty, and she became lethargic. When the dog was back on the NSAID of the first period for two days, she did eat her hepatic diet again and wanted to make longer

walks. So the second NSAID may have induced anorexia and lethargy, which the first NSAID did not. Palatability was better for the NSAID used in the first period of the study for this dog.

It is unlikely that coughing with mucus and blood can be caused by the second NSAID, so most likely the increase of coughing in the second period of the study is related to progression of cancer. Vomiting and nausea may be related to the NSAID, but it may also be that the dog was vomiting because of a fit of coughing, which may have happened in week 6, or overeating, which may have happened in week 5.

Reymond et all (2012) found that dogs (3 of 188) that showed serious hepatic adverse effects, had preliminary elevated liver values or biopsy findings of pre-existing liver disease, both in the group receiving robenacoxib as the group receiving carprofen. (7) The second dog did also have pre-existing liver disease. Unfortunately we do not have blood analysis results from this dog at week 6 and at the day of euthanasia, to see if there was an effect of the second NSAID, or the switching back to the first NSAID, on the liver values or other blood analysis results. Increase of liver values in this dog may be exacerbation of pre-existing liver disease by treatment with NSAIDs.

Haematocrit was reduced in this dog. This is likely to be due to other causes than therapy, as values improved in the course of the study.

Part of the differences in this dog between the two periods can be explained by progression of the tumour. Because of early euthanasia, lack of blood analysis in the second period and inconsistencies in the forms filled in by the owner it is difficult to judge which part should be interpreted as caused by the NSAID used. It is likely for this dog there is a difference in efficacy and tolerability between the two NSAIDs. This may be an idiosyncratic reaction of the dog to the NSAID secondly used.

For this owner, having attention and care for her and her dog was the most valuable part of the study. She was very thankful she was able contact somebody at any moment to talk to and discuss her worries. She needed confirmation she had done everything she could and made the right decisions. From this case, the importance of palliative care in terminal patients can be seen.

Third dog

In the third patient, the AE of itching may have been itching, or pain interpreted as itching by the owner. It was not related to the NSAID, but to the tumour/ inflamed wound. Lethargy and loss of appetite may be related to progression of the tumour, pain or treatment with NSAIDs. Because scores were already decreased in this dog when starting with NSAIDs and disease progression was very fast, most likely AE were related to the tumour. Straining on faeces may be related to treatment or other causes.

The dog had elevated bile acids and bilirubin. This is likely to be related to other cause than treatment, as values were already elevated before start of NSAIDs and improved during treatment.

Reduced potassium at week 0 and elevated sodium in this dog may be related to stress and/or pain (2), or to other causes. Also the non-healing of the wound may be caused by stress and/or pain (2), or the tumour, or other causes.

For this dog tolerability of the NSAID was good, as AE's were most likely caused by progression of cancer or were mild. Treatment with the NSAID did not succeed in improving scores for Pain and QoL. Scores were related to pain from the non-healing wound and progression of cancer. Treatment with the NSAID was not efficacious enough in this dog, as the dog was still suffering from the wound and tumour. It is questionable if other therapy could have been more effective, as the wound and tumour could not be removed. The dog did not survive long enough to see if preventing licking and treatment with antibiotics would reduce pain and improve scores.

The owner of this dog scored lower than expected from clinical signs seen during clinic visits. Scoring by the research team may have given a more objective impression of AEs, pain and QoL in this dog. But scoring by the owner does show that situation was untenable for her

like this. On the other hand, situation was severe for this dog, as in week 3 she was dyspnoeic and cyanotic. So perhaps this dog did not show much she was in pain and we might have underestimated pain in scoring.

For this owner, also palliative care was very important, as she was very worried about her dog and much appreciated the contact and clinic visits.

Fourth dog

In the fourth patient, all AE can be contributed to the tumour, as this was causing him to have difficulty eating and to lose some blood and saliva from his mouth. Straining on faeces may be related to treatment or to other causes.

The first period of reduced appetite was most likely related to the tumour, as the dog did eat in the evening when hungry enough and got back his appetite after operation.

The improvement of clinical signs just before operation (reduction of hypersalivation and improvement of appetite and activity) was at the same moment at switching of NSAIDs, but is most likely caused by start of antibiotics at the same time.

Elevated leucocytes in the first four weeks of the study are likely to be related to inflammation of the tumour and not to therapy with NSAIDs. The tumour showed progressive inflammation during the clinic visits; leucocyte counting shows resemblance with worsening of inflammation. At week 6, when the tumour was removed and the dog received antibiotics, leucocytes had turn back to normal.

At week 6, the dog had elevated ALT and ALP, and bile acids just outside reference values. At week 7, ALT had returned back to normal, ALP had improved and bile acids did not change. In the study of Gruet et all (2011), dogs undergoing orthopaedic surgery treated with robenacoxib or meloxicam had increased ALP 1 and 24 hours after extubation and 12 days after operation, but ALT was not increased, but decreased at 12 days for the robenacoxib group. The article does not mention values of blood analysis and they don't discuss possible causes. (12) In our dog, elevation of ALT and ALP may be related to different causes, possibly part of it to orthopaedic surgery. Elevation of liver values may be related to treatment with NSAIDs, but as elevation was transient and values improved while still on NSAIDs, it is more likely due to other causes.

The fever and second period of loss of appetite may be related to treatment but were most likely related to other cause. Fever resolved quickly and appetite improved with time, while still on NSAIDs.

Contact with this owner was intensive in discussing possible treatments for his dog and considering what would be the best possible option. The owner was happy being able to talk about his dog or about all kinds of other things.

Conclusion

More patients are needed to find if there is a significant difference for AE's, Pain and QoL between robenacoxib and carprofen. More publicity for the pain study may help in recruitment of patients.

Owners did not find it difficult to fill out the forms, but scoring was influenced, most likely because worries and emotions or lack of knowledge. A more objective scoring may be obtained by filling out forms together with the owner, or additional scoring by a member of the research team.

The patients participating in the pain study until now, had more variables because of concomitant treatment or disease which could be related to AE's or changes in scoring of Pain and QoL. This makes it difficult to judge if there is a difference between NSAIDs. Tolerability and efficacy were good for most patients. In the four patients participating until now, most likely AE's and changes in scoring of Pain and QoL are related to other causes than therapy, except for one dog, who showed a difference between first and second period, which may have been an idiosyncratic reaction to the NSAID used. No severe AEs like melena; although we did not test for occult blood in faeces; or hematemesis were found, except for one occasion, where the small

part of blood in the vomitus was most likely originating from the trachea. AEs that may have been related to treatment were mild. Changes in blood values were mild or most likely related to other causes.

Palliative care was found to be very important for most of the owners. As a veterinary practitioner, time to talk with owners will be much more sparse then when being a veterinary student doing a research project. Most owners in this study were found to have a need to talk about changes in their dog and about how to make the last part of the life of their dog as pleasant, or at least acceptable, as possible. Also the patient has a need that pain is assessed and relieved and quality of life is optimised when possible. Thus when dealing with terminal patients, it is important to try to meet this needs of the owner and patient as much as possible.

References

1. Lester P, Gaynor JS. Management of cancer pain. Vet Clin North Am Small Anim Pract. 2000 Jul;30(4):951,66, ix.

2. Gaynor JS. Control of cancer pain in veterinary patients. Vet Clin North Am Small Anim Pract. 2008 Nov;38(6):1429,48, viii.

3. Mathews KA. Nonsteroidal anti-inflammatory analgesics in pain management in dogs and cats. Can Vet J. 1996 Sep;37(9):539-45.

4. King JN, Dawson J, Esser RE, Fujimoto R, Kimble EF, Maniara W, et al. Preclinical pharmacology of robenacoxib: A novel selective inhibitor of cyclooxygenase-2. J Vet Pharmacol Ther. 2009 Feb;32(1):1-17.

5. Schmid VB, Spreng DE, Seewald W, Jung M, Lees P, King JN. Analgesic and anti-inflammatory actions of robenacoxib in acute joint inflammation in dog. J Vet Pharmacol Ther. 2010 Apr;33(2):118-31.

6. Monteiro-Steagall BP, Steagall PV, Lascelles BD. Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. J Vet Intern Med. 2013 Sep;27(5):1011-9.

7. Reymond N, Speranza C, Gruet P, Seewald W, King JN. Robenacoxib vs. carprofen for the treatment of canine osteoarthritis; a randomized, noninferiority clinical trial. J Vet Pharmacol Ther. 2012 Apr;35(2):175-83.

8. Luna SP, Basilio AC, Steagall PV, Machado LP, Moutinho FQ, Takahira RK, et al. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. Am J Vet Res. 2007 Mar;68(3):258-64.

9. King JN, Rudaz C, Borer L, Jung M, Seewald W, Lees P. In vitro and ex vivo inhibition of canine cyclooxygenase isoforms by robenacoxib: A comparative study. Res Vet Sci. 2010 Jun;88(3):497-506.

10. King JN, Arnaud JP, Goldenthal EI, Gruet P, Jung M, Seewald W, et al. Robenacoxib in the dog: Target species safety in relation to extent and duration of inhibition of COX-1 and COX-2. J Vet Pharmacol Ther. 2011 Jun;34(3):298-311.

11. Edamura K, King JN, Seewald W, Sakakibara N, Okumura M. Comparison of oral robenacoxib and carprofen for the treatment of osteoarthritis in dogs: A randomized clinical trial. J Vet Med Sci. 2012 Sep;74(9):1121-31.

12. Gruet P, Seewald W, King JN. Evaluation of subcutaneous and oral administration of robenacoxib and meloxicam for the treatment of acute pain and inflammation associated with orthopedic surgery in dogs. Am J Vet Res. 2011 Feb;72(2):184-93.

13. Veterinary cooperative oncology group - common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. Vet Comp Oncol. 2011 Jul 20.

Bijlage: Uitleg en aanbevelingen voor nieuwe student

Formulieren

Er zijn nog voorlopig voldoende setjes formulieren voor nieuwe patiënten, maar het is wel goed om even kritisch te kijken of er aanpassingen nodig zijn. In de brieven aan de eigenaar en dierenarts mag je eigen contactinformatie in plaats van de mijne en Prof. Dr. Kirpensteijn mag eruit. Doe ook je contactinformatie in de mapjes voor nieuwe patiënten, zodat een dierenarts je kan bellen als ze een nieuwe patiënt hebben.

Het eerste setje in de map heeft geen dagelijks formulier bijwerkingen, het eerste setje vul je namelijk bij de intake in samen met de eigenaar. Het dagelijkse formulier is eigenlijk puur voor de eigenaar om gedurende de week de bijwerkingen te noteren en onthouden, dit wordt niet gescoord. Sommige eigenaren vonden het lastig dat dit formulier van ma-zo loopt terwijl bijvoorbeeld woensdag hun begindag is, misschien is hier iets op te verzinnen?

De andere formulieren hebben de eigenaren steeds zelf ingevuld voorafgaand aan de controleafspraak. Dit ging op zich goed, maar voor sommige eigenaren was het erg moeilijk om objectief te oordelen en vulden ze iets dat niet veranderd was in verschillende weken op verschillende manieren in. Sommige eigenaren scoren bij een relatief kleine negatieve verandering gelijk heel hoog. Ik denk dat de scores die eigenaren geven nuttig zijn, maar je kan eens kijken of het toegevoegde waarde heeft zelf ook te scoren, ofwel samen met de eigenaar in te vullen zodat je meer door kan vragen. Bij het formulier bijwerkingen, de laatste vraag over gedragsveranderingen, hebben de meeste eigenaren dit gebruikt om alle bijwerkingen te noemen die niet ergens anders voorkwamen, dit schreven ze ernaast. Er is wel een ruimte voor niet genoemde bijwerkingen, maar zonder score van ernst. Eventueel kan je kijken naar een score daarbij zetten of anders formuleren, om gedragsveranderingen – andere bijwerkingen meer uit te splitsen.

Werving nieuwe patiënten

Kijk naar mogelijkheden voor meer bekendheid van het onderzoek. Langsgaan bij buurtpraktijken, informatie geven aan orthopedisch chirurgen. Poli's bijwonen naarmate er mogelijke patiënten komen, dit is vooral chirurgische oncologie op woensdag, maar houdt ook andere poli's / OK in de gaten op Vetware. Nieuwe patiënten moeten in principe voldoen aan de in- en exclusie criteria genoemd in 'Agreement Clinical Study' in Dropbox, maar in overleg worden sommige afwijkingen wel toegestaan.

De volgende patiënt wordt nummer 6; nummer 4 heeft na de intake besloten niet mee te doen, had wel al medicatie, dit is teruggestuurd en vernietigd. Er is dus eigenlijk geen nummer 4, maar ik denk dat je verder kan gaan met 6 en 4 open kan laten, omdat die bij de apotheek wel uitgegeven is.

Uitleg eigenaar

In principe doet de student de uitleg aan een mogelijk geïnteresseerde eigenaar. Goed voorbereiden dus, want er kan op elk moment een patiënt op de poli zijn of die je kan bellen die graag informatie wil. Waarom doen we dit onderzoek, wat willen we bereiken, wat houdt het in voor de eigenaar en wat heeft de hond eraan. Mij viel op dat een gemotiveerde eigenaar het geen probleem vind elke twee weken een afstand te rijden voor controle. Je kan een infobrief meegeven als ze erover na willen denken en nabellen.

Intake

Bij de intake tekent de eigenaar een akkoordverklaring. Het laatste stukje daarvan moest ik meestal even uitleggen. Het onderzoek is gratis, de kliniek (of eigenlijk Novartis…) betaalt voor de onderzoeken, echter

als de eigenaar uit zichzelf besluit niet meer mee te willen doen, kan hij alsnog een rekening krijgen van de gemaakte kosten. Dit gaat natuurlijk op wanneer de eigenaar zelf dit besluit neemt, niet als vanwege klinische verschijnselen van de hond besloten moet worden dat deze de medicijnen niet meer kan krijgen of het onderzoek gestopt moet worden.

Bij het eerste bezoek wordt anamnese afgenomen (formulier Chirurgie Diktes), lichamelijk onderzoek gedaan en de tumor onderzocht (voor zover nog niet gedaan DNAB, beeldvorming). Meestal is dit gedaan door studenten van de poli, omdat bij binnenkomst nog niet bekend is dat de patiënt aan het onderzoek gaat deelnemen. Als de eigenaar na het eerste bezoek een nieuwe afspraak maakt voor de intake, kan kort de anamnese en lichamelijk onderzoek herhaald worden, afhankelijk van hoeveel tijd er tussen zit. Altijd het oude formulier Chirurgie Diktes aanvullen bij elke controle, bovenaan kan je hokje 'controle' aanvinken. Bij de intake vul je het eerste setje formulieren met de eigenaar samen in. In principe vragen en antwoorden geheel voorlezen en vragen of er onduidelijkheden zijn. De volgorde van de intake kan je het beste af laten hangen of je alleen bent of met een groep studenten en wanneer de dierenarts tijd heeft, ik vond het vaak handig met formulieren af te sluiten, als je weer alleen bent met de eigenaar.

Als de tumor uitwendig zichtbaar is, hier een foto van maken en toevoegen aan dossier en elke controleafspraak herhalen. Zo is groei duidelijker te zien. En/of zo mogelijk opmeten.

Aan het eind van de intake krijgt de eigenaar een mapje mee met de informatiebrief aan de eigenaar en in ieder geval twee nieuwe pakketten formulieren. Handig is om per pakketje nietje erdoor te doen of dergelijke en erop te schrijven voor welke week het is. Ik liet het samen ingevulde pakket ook in de map, zodat ze nog kunnen kijken wat ze de eerste keer ingevuld hebben. De akkoordverklaring blijft in een mapje in de kliniek, samen met stickers en checklist van bloedonderzoek. Handig is om gelijk een controleafspraak over 2 weken te plannen.

Bloedonderzoek

Bij intake en elke controle wordt bloedonderzoek gedaan, je kan hiervoor hulp vragen aan dierverzorger (polikamer 14 of bellen). Aanvraag UVDL invullen:

- HT, leuko's, diff (EDTA)
- Trombo's (EDTA)
- Ureum + Creat
- Natrium + Kalium
- Calcium + Fosfaat
- AF + ALAT + Galzuren
- Bilirubine
- Totaal eiwit
- Cholesterol
- Triglyceriden

Dierenarts invullen en aanvraag versturen, buisjes in buizenpost met sticker. Ik had meestal 2ml buis EDTA en 4 ml heparine, dus 6 ml bloed nodig. TE hebben we uit heparine gedaan. Goed nakijken of alle vakjes aangevinkt zijn, wij blijken er af en toe één gemist te hebben. In principe moet de hond nuchter zijn voor bloedonderzoek, want eten heeft invloed op bepaalde waardes, dit dus goed communiceren naar de eigenaar.

Medicatie

Recept apotheek aanmaken:
R/Divers
S/ Pijn trial Jolle, (nummer van patiënt, volgende is #6)

Vooral heel duidelijk en vaak benadrukken dat de eigenaar niet met jou mag bespreken welke medicatie de hond krijgt/ hoe dit eruit ziet/ hoe vaak per dag en dergelijke. In principe is de bedoeling dat de hond zowel carporal als robenacoxib 2dd krijgt, zodat hier geen verschil onderling in zit. Echter is de uitleg en manier van klaarmaken verschillend afhankelijk van wie dit doet in de apotheek. Volgens de bijsluiter is robenacoxib 1dd (en dan dubbele dosering natuurlijk), in ieder geval bij één eigenaar is het op die manier voorgeschreven. Bij een eigenaar die na de intake besloot niet meer mee te doen, was de medicatie ook voor de eigenaar blind gemaakt. Verschillende variaties mogelijk dus. Bij vragen kan je contact opnemen met de apotheek.

Controleafspraken

Vragen naar veranderingen, bijwerkingen afgelopen weken, lichamelijk onderzoek doen en bloed afnemen. Ingevulde formulieren innemen en minimaal twee nieuwe pakketten meegeven.

Contact buiten de controleafspraken

Elke week dat de eigenaar niet langskomt, even bellen om te vragen hoe het gaat. Vooral de eerste week belangrijk om uit te vragen of het allemaal lukt met medicatie ingeven en formulieren invullen. Ik had een eigenaar die begrepen had elke week te moeten wisselen van medicijn, waar we dus net op tijd achter kwamen. Mailcontact kan ook handig zijn. Contact kan in het tabblad communicatie in Vetware ingevuld worden. Als er bijzonderheden zijn, overleggen met Bas.

Aandacht en zorg

Ik heb gemerkt dat voor de meeste eigenaren aandacht en zorg de belangrijkste meerwaarde was om mee te doen aan het onderzoek. Veel eigenaren waren erg bezorgd en waren erg blij en dankbaar dat ze altijd iemand konden bereiken om over hun zorgen te praten. Ik ben op vreemde tijdstippen gebeld met lastige vragen waarop niet altijd een goed antwoord is. Het uitdagende van dit onderzoek is dus vooral om goede begeleiding te geven in de laatste levensfase van een hond. Mensen laten praten over verdriet en meedenken hoe het leven van de hond nog aangenamer gemaakt kan worden en bij euthanasie geruststellen dat het goed is zo. Het is intensief maar erg leerzaam.

Scores

In Dropbox staan formulieren hoe de formulieren pijn en kwaliteit van leven gescoord worden. Er is een Excel bestand waar de resultaten ingevuld kunnen worden. De bijwerkingen zijn in dit bestand kort beschreven per week, echter volgens het VCOG-CTCAE bestand krijgen de onderdelen ook een score 0-4, dus dit heb ik voor mijn verslag gebruikt. Bloedonderzoek staat niet in het resultatenbestand. Misschien kan het bestand met aanpassingen overzichtelijker gemaakt worden. Er is een apart bestand met scores voor afwijkingen in bloedonderzoek, volgens het VCOG-CTCAE bestand. Niet alle afwijkingen hebben een score, hiervoor heb ik alleen verhoogd/verlaagd benoemd.

Veel succes en neem gerust contact op als je vragen hebt!

Hanneke Spierenburg

j.e.spierenburg@gmail.students.uu.nl (vanaf december hannekewestbroek@gmail.com)