Development of an adverse events questionnaire for the study of long-term treatment with NSAIDs in canine cancer patients

Research project Veterinary Medicine at University Utrecht

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Prefactory note

During the Master of Veterinary Medicine at the Faculty of Veterinary Medicine of the University of Utrecht, all students have to take part in a research project. This paper is the report of the participation of M.J. van der Burg in the following research project: 'Study of pain in canine cancer patients: Carporal vs. Robenacoxib' at the Department of Veterinary Medicine of Companion Animals at the University of Utrecht.

This research project is designed to determine if robenacoxib (Onsior) can play a part in the palliative treatment of canine cancer patients. Unfortunately, due to a delay in the start of this research project, this report does not contain any results to confirm or reject the usefulness of robenacoxib in palliative treatment of canine cancer patients. This report takes notice of the study design and the development an adverse events questionnaire necessary for the research project.

Contents

Summary

In this paper, we discuss the development of an adverse events (AEs) questionnaire for the registration and documentation of adverse events (AEs) in a clinical trial with nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain in canine cancer patients. The aim of the research project is to assess the usefulness of robenacoxib in comparison to carprofen in the palliative treatment of canine cancer patients. The assessment of the treatment efficacy is done by scoring quality of life (QoL), pain and AEs. In literature, QoL scoring systems en pain scoring systems can be easily found (Lynch, 2010) (Iliopoulou, 2013) (Lavan, 2013). But in most clinical trials, AEs are recorded spontaneously or by interviewing owners (Edamura, 2012) (Vial, 2012) (Flor, 2013). We developed an AE questionnaire owners can fill out at home every week during the treatment period. The research question of this thesis is whether we succeeded in developing an AE questionnaire for the clinical trial with NSAIDs. During the development of the AE questionnaire another research question emerged. Namely, if the AE questionnaire might also be useful for owners with canine cancer patients undergoing chemotherapy at the Clinic of Companion Animals at the University of Utrecht.

In order to create the AE questionnaire, a selection of expected AEs in treatment with NSAIDs was made. This selection is based upon the mechanisms of action of NSAIDs and the known AEs reported by the European Medicines Agency (European Medicines Agency, 2011). We adapted the VCOG CTCAE v1.1, a grading system for AEs observed during chemotherapy in cats and dogs (Veterinary Cooperative Oncology Group, 2011). After translation and a first review, the developed questionnaire was tested twice. The first time its adequacy was tested in a group of canine patients without AEs. The second time its adequacy was tested in a group of canine cancer patients treated with chemotherapy. Based upon the first test, the final version of the AE was formed. Finally, owners of the second test group were asked for feedback on the AE questionnaire. In both tests, we find that owners think that the AE questionnaire we developed is clear and easy to fill out. The results of the survey reported that owners do not think that filling out the AE questionnaire is time consuming. But only 50% (4/8) of the owners think the AE questionnaire has added value.

In this study, we find that the AE questionnaire is adequate for the use in the research project with NSAIDs. However, we believe that the AE questionnaire should be adapted before it can be used in a clinical setting with canine cancer patients undergoing chemotherapy.

1 Introduction

Cancer is a worldwide known and occurring complex group of diseases. Cancer does not only affect humans, but is also seen in our beloved companion animals. Different causes of cancer are known in humans, such as genetics, tobacco, diet and physical activity, sun and UV exposure, radiation exposure, and many other carcinogens (American Cancer Society, 2013). Approximately half of all Dutch companion animals also develop cancer during their lifetime (LICG, 2010). And this is mostly because our companion animals become older, due to advancements in control of infectious animal diseases, improvements in nutrition and improvements of overall health care.

Just as in humans, many options for treatment are possible, for example surgery, chemotherapy, radiation therapy, and combinations of these options are available. However, not all veterinary cancer patients are eligible for these options. The alternative is palliative treatment until quality of life has deteriorated in such a way that euthanasia is the only option left. At the Faculty of Veterinary Medicine at the University of Utrecht, a study is set up in order to investigate if nonsteroidal anti-inflammatory drugs (NSAIDs), specifically carprofen and robenacoxib, can play a part in the palliative treatment of canine cancer patients, also referred to in this paper as 'Pain Study'. To investigate the effects, both positive and adverse, these NSAIDs have on canine cancer patients, scoring forms for pain, quality of life (QoL), and adverse events (AEs) have to be filled out by the owners of the participating dogs.

Several different QoL scoring systems can be found in literature (Lynch, 2010) (Iliopoulou, 2013) (Lavan, 2013). However none of these were in Dutch. The QoL scoring system described by Lynch et al. (2010) is translated and adapted to the purpose of this study. For pain scoring, the Glasgow Pain Score form is applied (University of Glasgow, 2008). However, for the documentation and scoring of AEs caused by NSAIDs no specific form can be found. Therefore, developing an AE questionnaire understandable and clear for the owners, but also reliable and useful for this study had to be our aim. For this purpose, we modified the Common Terminology Criteria for Adverse Events (CTCAE) following chemotherapy of biological antineoplastic therapy in dogs and cats version 1.1 developed by the Veterinary Cooperative Oncology Group (VCOG) (Veterinary Cooperative Oncology Group, 2011). The research question of this paper is whether we succeeded in developing an AE questionnaire for the Pain Study. Another research question emerged during the development of the AE questionnaire, namely if the AE questionnaire might also be useful for owners with canine cancer patients undergoing chemotherapy at the Clinic of Companion Animals at the University of Utrecht.

In the following chapters we discuss the development of the AE questionnaire for the registration of AEs in the study with NSAIDs as palliative treatment in canine cancer patients. In Chapter 2 we provide background information on cancer and pain in canine cancer patients, on NSAIDs, their mechanisms of action, and their effects on several organ systems and we outline the study design of the study this questionnaire is intended for. Then, in Chapter 3, we discuss all steps taken during the development of the AE questionnaire. Chapter 4 contains the results we found. And in Chapter 5, we discuss our interpretation of certain result and the difficulties we came across during the development. Finally, in Chapter 6, we give an answer to both research questions.

2 Background information

2.1 Cancer in canine patients

Canine cancer patients are becoming more and more common. The main cause is an increase in the mean age of dogs. Other causes consist of hormonal influences, genetic predispositions and environmental factors. According to the Dutch National Information Centre Companion Animals (Landelijk Informatie Centrum Gezelschapsdieren) 47% of the dogs and cats will develop a form of cancer during their life (LICG, 2010).[1]

Treatment of cancer in companion animals is to extend life and to improve quality of life (QoL). This is in contrast with treatment of human cancer patients, in which the main goal is to cure the patient. Options for treatment of cancer in canine patients are multi-disciplinary: surgery, chemotherapy and radiotherapy are three main groups (Nelson, 2009). Depending on which type of cancer is diagnosed, one or more of the treatment options can be applied. For example, dogs with multi-centric lymphoma often respond very well to chemotherapy alone. However, osteosarcoma in the proximal humerus can be treated by amputation of the leg combined with chemotherapy or by bone-sparing surgery combined with radiation therapy and chemotherapy.

The costs and benefits of these treatments vary substantially. Survival time, quality of life, adverse events and costs of the treatment are factors contributing to these costs and benefits. Owners have to weigh these factors and decide whether or not they want treatment for their dog. And if so, they have to consult with their veterinarian what kind of treatment is best. Thus it may be that an owner decides not to treat their dog. However, no treatment may not be the correct term for this option because owners often want to keep their dog as comfortable as possible for as long as possible with palliative treatment until they have to euthanize their dog.

Palliative treatment, depending on the form of cancer and the clinical signs, consists of antiemetic agents, anti-inflammatory agents, analgesia, hormonal therapy, nutritional support, and even antibiotics when deemed necessary. Clinical signs in canine cancer patients are be caused by the tumour or by paraneoplastic effects of the tumour. An important clinical sign, but also a more difficult one to interpret, is pain. Pain significantly reduces the QOL in canine cancer patients. However, it is not clear which types of cancer cause pain and how severe the pain is. To our knowledge, there is little research on this topic, especially in comparing pain profiles in different types of cancer. And we believe this is one of the causes for undertreatment of canine cancer pain. The undertreatment of cancer pain continues to be very common and has many causes, among which are lack of recognition of pain and suffering, inadequate or irregular historical questioning (QoL questions), diagnostic dilemmas and the lack of both baseline and follow-up assessment (Looney, 2010). One way to determine pain in canine cancer patients is to compare it to pain in human cancer patients. According to questionnaires performed among human cancer patients, pain prevalence among patients with newly diagnosed cancer is 28%, in patients with existing disease above 50% and in patients with advanced tumours and paraneoplastic disease even 80% (Bonica, 1990). The World Health Organisation (WHO) has developed a report concerning the causes and

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[1] In Dutch, *Landelijk Informatie Centrum Gezelschapsdieren*. This organisation provides information for owners of companion animals in the Netherlands and is financed by the Dutch government, the Dutch Animal Protection organisation, the University of Wageningen and the Faculty of Veterinary Medicine of the University of Utrecht.

treatment of pain in human cancer (World Health Organisation, 1996). The causes listed for pain in patients with cancer are pain caused by the cancer itself, pain related to the cancer, pain related to anticancer treatment, and pain caused by a concurrent disorder. In human cancer, many patients with advanced cancer experience pain due to more than one of these causes (World Health Organisation, 1996).

Another way to categorize cancer pain is to divide it in somatic pain and visceral pain, both are forms of nociceptive pain, and neuropathic pain. Somatic pain is caused by activation of pain receptors in cutaneous and deep tissue such as skin, muscle and bones and is often seen in bone metastases. This pain is localized in contrast to visceral pain, which is diffuse and difficult to identify (Looney, 2010). Visceral pain is caused by activation of pain receptors in organs and viscera. Causes for this type of pain are direct infiltration, compression, distension or stretching. This pain can be found in cancer of the organs, such as liver cancer and pancreatic cancer. Neuropathic pain is caused by injury or damage to the peripheral or central nervous system. This is observed in tumour compression or infiltration of peripheral nerves, nerve roots or the spinal cord. It may also be caused by treatment of cancer by means of surgery, chemotherapy or radiotherapy (Chapman, 2012) (Payne, 2011). It is likely that canine patients experience pain that is similar to that of human cancer patients. They have the same or resembling types of cancer and similar underlying mechanisms for pain sensation.

A different way to determine pain in canine cancer patients is through a QoL scoring system. In the Pain Study an adapted version of the questionnaire developed by Lynch et al. (2010) is used to determine the presence of pain and assess treatment effect. Several of these QoL scoring systems are available in the literature (Lynch, 2010) (Iliopoulou, 2013) (Lavan, 2013). The QoL score is based on a questionnaire that includes questions on overall happiness, tail and ear stance, sleep-wake pattern, appetite, defecation habits, urination habits, hygiene and mental state. This score is a somewhat objective indication of the QoL of the patient at that moment. For example, the adapted QoL scoring system of Lynch et al. (2010) has a scale of 1 to 5 per question (five answers possible), where a score of 1 indicates the worst QoL and a score of 5 indicates the best QoL. The total score is the sum of the scores per question and is an indication for the overall QoL of a patient.

When it is determined that a canine cancer patient is in pain, the next step is to decide which analgesic therapy is suited for this patient. Cancer pain treatment in human patients is based on the analgesic ladder of the WHO. The analgesic ladder consists of three steps. Step 1 is for pain of mild intensity, step 2 for pain of mild-to moderate intensity, and step 3 for pain of moderate to severe pain intensity. Each step indicates which analgesic treatment options should be used (World Health Organisation, 1996). When using this ladder to assess the adequate treatment, it is important to know the intensity of pain experienced by the patient. Human patients can give an indication but for our animal patients we have to assess pain intensity based on the information from the owner and a physical examination. Several options for treatment of canine cancer pain are steroids and non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, opioids, alpha-2 agonists, NMDA-receptor antagonists, radiation therapy for analgesia or surgery (Looney, 2010). Nociceptive pain is treatable with this these treatment options. However, neuropathic pain is not as responsive to these treatment options. Epidural, spinal or perineural blockades, antiepileptic drugs, antidepressants and antiarrhythmic drugs are important options for neuropathic pain. In this paper, we focus on the use of NSAIDs. Other treatment options will not be further discussed.

2.2 NSAIDs

In the study, for which the AE questionnaire is intended, two NSAIDs are compared with regard to the QoL in canine cancer patients. Although NSAIDs have been widely investigated for their use in inflammatory diseases and postoperative analgesia (Edamura, 2012), less is known about their usefulness in canine cancer pain. NSAIDs are a group of cyclooxygenase (COX) enzyme inhibitors. COX oxidizes arachidonic acid to prostaglandins and thromboxane.

In order to understand which AEs can occur and to decide which AEs must be included in our questionnaire, we will now discuss the pharmacokinetics, the mechanisms of action and the effects of NSAIDs. These are, when possible, discussed specifically for carprofen and robenacoxib and their effect on several organ systems.

2.2.1 Pharmacokinetics

NSAIDs tend to be well-absorbed after oral administration, with some exceptions, such as fircoxib. Hence carprofen and robenacoxib are well-absorbed after oral administration. However, according to the leaflet of approval of Onsior (robenacoxib), a higher systemic bioavailability of robenacoxib has been observed when tablets were administered without food. Most NSAIDs are highly bound to plasma proteins, but clinical implications of high protein binding are limited (KuKanich, 2012). Both carprofen and robenacoxib have a relatively small volume of distribution and are highly bound to plasma proteins. Robenacoxib has a plasma protein binding of more than 99% (Medicines Evaluation Board, 2008) (European Medicines Agency, 2011).

The primary route of elimination of NSAIDs is through metabolisation in the liver by means of conjugation reactions and metabolic reactions such as cytochrome P450 metabolism. Also, some elimination of NSAIDs occurs through renal elimination, but this is a secondary route of elimination. Conjugate products of carprofen are mainly excreted through biliary secretions (Medicines Evaluation Board, 2008). Robenacoxib is also excreted predominantly (65%) via the biliary route (European Medicines Agency, 2011). Based on this information, hepatic disease may decrease the rate of elimination, and therefore, an increase of the terminal half-life and total drug exposure can be found. This could increase gastrointestinal (GI) and renal AEs.

Terminal half-life of carprofen after oral administration is approximately 9 hours. The analgetic effect of every dosage lasts for at least 12 hours (Medicines Evaluation Board, 2008). Terminal half-life in blood after oral administration of robenacoxib is 1.2 hours. Robenacoxib persists longer and at higher concentrations at sites of inflammation than in blood (European Medicines Agency, 2011).

2.2.2 Mechanism of action

The NSAIDs are a group of therapeutics that have, despite their wide variety in structures, a similar mechanism of action, namely the inhibition of cyclooxygenase (COX) enzyme. COX oxidizes arachidonic acid to eicosanoids. These eicosanoids, i.e. prostacyclines, leukotrienes and thromboxanes, play an important role in inflammatory processes but also in common physiological processes. Therefore it is no surprise that COX is present in many tissues within the body and up-regulation of COX is caused by a variety of stimuli (Lascelles B. K.-L., 2009). Two primary isoforms of COX have been identified, COX-1 mainly known as a constitutive form and COX-2 as an inducible form (Simmons, 2004). However, more recent studies have shown that both isoforms are constitutive and inducible (Wooten J. B., 2008) (Lascelles B. K.-L., 2009). A third isoform of cyclooxygenase, COX-3, has been found in the canine cerebral cortex, and in lesser amounts in other tissues. Yet, physiological

effects of this third isoform have not been identified (Kis, 2005). Thus, due to unlikely clinical relevance we will continue to focus on COX-1 and COX-2.

As mentioned, COX plays a role in the production of eicosanoids. COX-1 produces many different eicosanoids, but most important are prostaglandin (PG) E_2 and thromboxane A_2, as they establish many clinically important effects (Simmons, 2004). PGE_2 invokes several physiological responses including sensitisation of nociceptors, vasodilatation and multiple effects on the GI tract including an increase in mucus production, a decrease in gastric acid secretion, an increase in turnover of mucosal cells, and an increase in bicarbonate secretion in the duodenum. Thromboxane A_2 can be primarily associated with platelets and results in increased platelet aggregation and vasoconstriction, and with this, an enhancement of coagulation and the formation of blood clots are established. As a result, exclusive inhibition of COX-1 results in an anticoagulant effect (Simmons, 2004). Aside from this, COX-1 is also constitutively expressed in the cerebral cortex where its inhibition may contribute to the central analgesic and antipyretic effects of NSAIDs (Braga, 1990).

The other isoform of COX, COX-2, also produces a variety of eicosanoids including PGE_2, prostacyclin (PGI_2) and 15-epi-lipoxin A_4, also known as aspirin triggered lipoxin (ATL). And as in the eicosanoids produced by COX-1, production of COX-2 eicosanoids results in many clinical effects (Simmons, 2004). PGE_2 produced by COX-2 results in the same physiologic effects as PGE_2 produced by COX-1. PGI_2 is produced in endothelial cells and results in vasodilation and inhibition of platelet aggregation, which is an antagonistic effect to thromboxane A_2 (Simmons, 2004). Therefore, exclusive inhibition of COX-2 produces a pro-coagulant effect. PGI_2 has also been identified in inflamed tissues and in the GI tract where it produces similar gastroprotective effects as PGE_2 (Simmons, 2004). Both PGE_2 and PGI_2 alter renal physiology by increasing sodium excretion, inhibiting sodium reabsorption, and altering chloride transport. And they also stimulate renin release and establish a profoundly altered total renal blood flow and regional blood flow within the kidneys of dogs (Simmons, 2004). Due to constitutive expression of COX-2 in the dorsal horn of the spinal cord, COX-2 contributes to the propagation of nociceptive stimuli, with the result that inhibition of COX-2 also produces central analgesic effects (Nishiyama, 2006).

An increase in COX-2 expression, and thus an increase in PGE_2 en PGI_2 production, can be found in injured tissue, resulting in sensitization of peripheral nociceptors with enhanced pain transmission, as with COX-1 mediated by PGE_2. (Simmons, 2004). Recent studies have stated that both COX-1 and COX-2 are up-regulated in the synovium of dogs with naturally occurring hip osteoarthritis (Lascelles B. K.-L., 2009). Up-regulation of COX-2 can also be found in the endothelial cells within the hippocampus during fevers, which may explain the anti-pyretic effect of some NSAIDs.

Another form of eicosanoids are lipoxins, which produce anti-inflammatory effects and are thought to be produced to modulate the inflammatory response (Parkinson, 2006). As stated before, 15-epi-lipoxin A_4, also known as Aspirin Triggered Lipoxin (ATL) is produced by COX-2. ATLs have potent anti-inflammatory and gastroprotective effects. Aspirin administration in a study by Fiorucci et al. (2002) showed an elevated production of 15-epi-lipoxin A_4 via COX-2. They also administered aspirin in combination with a selective COX-2 inhibitor, which resulted in substantially more severe gastric injury (Fiorucci, 2002). This demonstrates the gastroprotective response of ATLs. Besides that, ATLs have antagonistic effects on bronchoconstriction and vasoconstriction induced by leukotriene C_4 and

they also antagonize the effect of leukotriene D_4 mediated decreases in glomerular filtration rate (Parkinson, 2006).

The 5-lipoxygenase (LOX) is another enzyme of the arachidonic acid cascade. LOX produces a variety of leukotrienes which have been associated with vasoconstriction, increased vascular permeability, bronchoconstriction, and attraction of inflammatory cells such as neutrophils, lymphocytes, and eosinophils (Bertolini, 2001). In a study of Rainsford (1993) support was found for the postulate that non-selective COX-inhibition by NSAIDs diverts arachidonic acid to the LOX pathway, leading to AEs of the GI tract.

The more studies into NSAIDs are done, the more evident it becomes that they may influence other processes not associated with the COX enzymes as well. For example, some NSAIDs have been shown to inhibit activator protein 1, which plays a role in a variety of processes including immune function, inflammation, and tumour formation and progression (Tegeder, 2001). Also, some NSAIDs seem to inhibit the activation of Nuclear Factor kappa-B which regulates pro-inflammatory enzymes, cytokines, chemotactic factors and cellular adhesions factors (Tegeder, 2001). However, the extent of these effects have not yet been clarified.

2.2.3 Effects on organ systems

Gastrointestinal tract

AEs of the GI tract due to NSAID administration can range from vomiting, anorexia and diarrhea to mild gastritis/enteritis and severe GI ulceration, bleeding and death. Most common of these AEs are vomiting and diarrhoea, and these are the main reason for a dog to be taken off a particular NSAID. In animals with vomiting, diarrhoea, and anorexia no GI erosions or ulcers may be found as clinical signs are poorly correlated with GI tract injury (Dow, 1990). Wooten et al. (2010) examined the GI tract of clinically healthy dogs and found in 4/27 dogs GI erosions despite the lack of clinical signs. This suggests that the absence of clinical signs does not guarantee the absence of GI erosions. Therefore, careful monitoring of AEs during treatment is also important in clinical healthy animals. Clinical signs that may be suggestive of GI ulceration include depression, reduced appetite, anorexia, vomiting, diarrhoea and melena (Wooten J. L., 2010).

NSAIDs can cause AEs of the GI tract through direct and indirect mechanisms. The direct way is through irritation of the GI mucosa and the indirect way through inhibition of COX-1 and COX-2 and thus the resulting inhibition of PGE_2. Other mechanisms with the potential to result in GI AEs include the production of leukotrienes (via LOX shunting), inhibition of PGI_2, and inhibition of ATL (KuKanich, 2012). Most NSAIDs are weak acids and, as such, can directly irritate the GI mucosa after oral administration or following biliary secretion regardless of the route of administration (Carter, 1980). Both PGE_2 en PGI_2 have important gastroprotective effects including increased mucosal blood flow, increased mucus production, increased bicarbonate production, decreased acid secretion and increased turnover of gastrointestinal epithelial cells (Simmons, 2004). Inhibition of PGE2 and PGI2 results in inhibition of these gastro-protective effects, which makes the GI tract more vulnerable.

In the canine GI tract both COX-1 and COX-2 are constitutively expressed. Inhibition of both isoforms by a non-selective COX inhibitor can lead to GI AEs. Inhibition of only one of these isoforms, by a selective COX inhibitor, results in minimal GI AEs. This can be explained by the fact that both isoforms produce PGE_2 and inhibition of one isoform can be partially compensated by the other isoform. For

example, three days of aspirin administration to dogs, which inhibits COX-1 to a greater extent than COX-2, results in a significant induction of COX-2 in the canine duodenum, whereas the amount of COX-1 remains unchanged in the stomach and intestines (Wooten J. B., 2008). The newer, COX-2 selective, NSAIDs appear to have a decreased frequency of GI AEs in dogs, compared to older NSAIDs such as aspirin, ketoprofen, and flunixin (Luna, 2007). This might be due to COX-1 sparing properties of the newer NSAIDs, resulting in continued PGE_2 production in the GI tract by COX-1. However, there are no studies comparing every NSAID available for dogs in a clinical set up, so comparing them and their AEs is difficult.

Wooten et al. (2010) find an up-regulation of COX-2 in damaged and healing tissues of the GI tract. It is thought that COX-2 promotes healing of the GI tract through multiple mechanisms, for example by increasing angiogenesis, inhibition of cellular kinase activity, increasing production of PGE2 and increasing of vascular endothelial growth factor (Hirose, 2002). Therefore, inhibition of COX-2 in an animal with pre-existing damage of the GI tract can result in delayed of even inhibited healing of the GI tissues, regardless of COX-1 inhibition. This can lead to even more severe AEs including perforation and death (Goodman, 2009). Because of their effects on healing in gastric lesions, NSAIDs should preferably not be used or otherwise be used with caution in animals that have pre-existing GI damage such as ulceration, gastric surgery or concurrently use of glucocorticoids, as they are at an increased risk for severe GI AEs from NSAIDs (Lascelles B. B., 2005).

Kidneys
COX, both COX-1 and COX-2, is constitutively expressed in the kidneys of dogs (Sellers, 2004). PGE_2 en PGI_2 play an important role in the kidneys. For instance, they alter renal physiology by increasing sodium excretion, by inhibiting sodium reabsorption, and by altering chloride transport. Also, PGE_2 and PGI_2 stimulate renin release and alter total renal blood flow and regional blood flow (Simmons, 2004) (Rodriguez, 2000). In case of volume depletion, hypotension, or hyponatremia, up-regulation of COX-2 occurs resulting in a decrease of vascular resistance caused by higher PGE_2 concentrations (Khan, 1998).

In a study with rats, researchers find that COX-selectivity of NSAIDs is not associated with renal AEs. They have compared the effect of a selected group of NSAIDs with different COX-2/COX-1 selectivity, but find no relationship between COX-2/COX-1 selectivity and urinary electrolytes excretion (Harirforoosh s. J., 2005). Further study in rats suggests that accumulation of NSAIDs within the kidney is most probably associated with renal AEs (Harirforoosh S. A.-H., 2006). However, this was found in rats and the extent of species-specific differences in the accumulation of NSAIDs in the kidney is not yet clear. Another study by Luna et al. (2007) did not find any evidence of renal injury in long-term administration of several NSAIDs in healthy dogs. These findings, along with those of several other studies, suggest that long-term administration of NSAIDs in healthy, normovolemic, and normotensive dogs result in minimal renal AEs (Ryan, 2006) (Luna, 2007) (Mansa, 2007).

However, there are certain risk factors for the development of renal AEs by NSAIDs. Cases in which renal damage caused by COX inhibitors was found, are mostly associated with high doses of NSAIDs or simultaneously present complicating factors such as dehydration, shock or pre-existing renal disease (Lobetti, 2000) (Rodriguez, 2000) (KuKanich, 2012). Also, inhalant anaesthesia is not an unexpected risk factor, because isoflurane, halothane, and desflurane cause a dose-dependent decrease in renal blood flow (Hartman, 1992). And as NSAIDs cause a decrease in sodium

reabsorption and an increase in sodium excretion through PGE_2 and PGI_2, pre-existing sodium depletion is amplified and with that comes a higher risk of renal AEs. The effects of NSAIDs on the renal function of dogs with underlying renal disease have not been studied yet. However, it is hypothesized that dogs with pre-existing renal disease have increased COX-2 expression as a compensatory mechanism and administration of NSAIDs in these cases could lead to acute decompensation (Simmons, 2004).

Liver

Apart from the effects on the kidneys and the GI tract, NSAIDs can also have effects on the liver. Hepatotoxicity caused by drugs may be either intrinsic or idiosyncratic in nature (Lewis, 1984). Intrinsic hepatotoxicity by NSAIDS can be caused by massive overdosing of NSAIDs, when for example a dog eats a whole package of NSAIDs. Idiosyncratic toxicity can be found when label dose is used and has been reported for carprofen in 21 dogs by MacPhail et al. (1998). Onset of clinical signs in these dogs varied from a few days to several weeks (MacPhail, 1998).

Although hepatotoxicity is a class warning for NSAIDs, even for veterinary NSAIDs, no reports identifying a particular NSAID with increased risk of idiosyncratic hepatic toxicity can be found (KuKanich, 2012). In human medicine, three NSAIDs have more commonly been associated with liver disease, i.e. diclofenac, sulindac, and aspirin (Bjorkman, 1998). More research into hepatotoxicity of veterinary NSAIDs should be done. Several studies investigated the long-term administration of several NSAIDs in dogs with osteoarthritis or clinically healthy dogs. None of these studies suggest that long-term treatment with NSAIDs is associated with hepatocellular toxicity. Most AEs were observed in the early stages of NSAID treatment. Only a low percentages (3,2-5%) of dogs did not tolerate NSAID treatment well and had to leave the study due to AEs of any kind (Ryan, 2006) (Luna, 2007) (Mansa, 2007).

2.2.4 Carprofen and robenacoxib

Carprofen is an older, frequently used NSAID. It is argued that carprofen is a weak COX-inhibitor and, therefore, even though it is not a very selective COX-2 inhibitor (*in vitro* IC50 COX-1/COX-2 : 1,8 (ratio of concentrations required to produce 50% inhibition of COX activity)), not many side effects are observed (Kay-Mugford, 2000). Carprofen is commonly used for treatment of inflammatory diseases, especially arthritis or for post-operative pain management after orthopaedic or soft tissue surgery (Medicines Evaluation Board, 2008).

Robenacoxib is a NSAID of the coxib class. It is a very potent and selective inhibitor of COX-2 (*in vitro* IC50 COX-1/COX-2: 140) and should have minimal adverse reactions. Robenacoxib is registered for the treatment of pain and inflammation associated with chronic osteoarthritis in dogs (European Medicines Agency, 2011).

2.3 Research protocol

At the Faculty of Veterinary Medicine of the University of Utrecht a research project has been set up for the palliative treatment of canine cancer patients: '*A study of pain in canine cancer patients: robenacoxib vs. carprofen.*' This study compares the effect of robenacoxib and carprofen in relation to the QoL of the patient that receives treatment. Any adverse reactions observed during the treatment period are monitored and registered. The aim of this study is to determine which drug is the better choice in palliative management of the canine cancer patient.

2.3.1 Study design

The study is set up as a randomized cross over investigator-blinded trial with 20 client-owned dogs diagnosed with a visible/palpable form of cancer. Before the study, the selected dogs are randomly selected into two groups of 10 dogs. The treatment period covers 57 days and the selected dogs are not allowed to receive any other form of anti-cancer treatment. One group receives product A during 28 days followed by product B during another 28 days. The other group receives product B during 28 days followed by product A during another 28 days. Between both products there is a wash out period of 1 day. Both NSAIDs have a predetermined dose. Robenacoxib, is administered at a dose of 1 mg/kg BID and carprofen is administered at a dose of 2 mg/kg BID.

2.3.2 Protocol

During the treatment period, every dog is physically examined five times: at the start of the treatment period (day 0), at day 14, day 28, day 43 and day 57 of the treatment period. A veterinarian or a veterinary student performed these examinations. QoL, pain and AEs are monitored by questionnaires, translated for and adapted to this study, filled out by the owners. Every week (day 7, 14, 21, 28, 35, 43, 50 and 57) a short form of Glasgow pain score, a QoL form and an AEs form is going to be filled out. Every two weeks, the history, a physical examination and blood work are collected. The blood work consists of haematocrit, leuco's/diff, thrombocytes, ureum, creatinine and liver enzymes. Subsequently, the tumour is measured and all observed side effects are documented and evaluated.

2.3.3 Selection/exclusion criteria

In this study, the dogs are selected by satisfying several criteria. Each dog must be in overall good health without clinical signs of systemic disease, except for the primary diagnosis of cancer. The diagnosis of tumour needs to be based on history, clinical examination, fine needle aspiration biopsy (FNAB) and/or histological biopsy. If the laboratory values are outside the reference range, but within the expectations for a given dog, this dog is still considered.

The type of cancer included in this study is defined as *visible/palpable*. This is a very wide range, not only in types of cancer, but also in pain profile. Tumours of the bone are considered the most painful of tumours. When chosen not to perform surgery or chemotherapy, the only two options left are euthanasia or palliative treatment. This is why it is important to know how effective robenacoxib and carporal are in these cases. Tumours of the skin are often considered as not painful unless ulceration is present. However, owners with dogs with larger lipomas often complain that their dog is not doing well, while nothing out of the ordinary can be found. So even in these cases improvement might be gained.

Dogs that currently receive corticosteroid or other pain medication treatment are excluded or have to go through a standard wash out period of 7 days, unless label of use states differently. Also, dogs are excluded from this study when they have severe organ failure, or receive concurrent chemo- or radiation therapy, or are expected to live less than 30 days, or are considered to be unsuitable for inclusion.

Dogs are withdrawn from the study if the owner fails to comply with the protocol, or in case of serious side effects, or therapy failure (and additional intervention is needed).

2.3.4 Registration of results

Throughout the study, several forms are used to score the QoL and to register the observed AEs. We apply the Glasgow Pain Score form, the short version (University of Glasgow, 2008), and an adapted QoL form (Lynch, 2010) to score the QoL of the dogs participating in this study. For registration and interpretation of observed AEs, the VCOG-CTCAE v1.1 form is adapted so it can be used for this study (Veterinary Cooperative Oncology Group, 2011). The development of this adapted AE questionnaire will be thoroughly discussed further on in this paper. For every AE the following details should be described: duration, clinical signs, severity, outcome, causality assessment, action(s) taken and their outcome. In case of death or very severe AEs, further examination is required (pathology, histology).

2.3.5 Statistics

With an alpha of 0.05 and a beta of 0.10, a standard deviation of 15% and an expected difference between groups of 30%, 20 dogs is sufficient for each group. The QoL score is the main variable used for the power analysis. The results between groups are evaluated with a paired T-test after normalization (if necessary) of the data. P-values less than 0.05 will be considered statistically significant.

3 Materials and methods

3.1 Development of the AE questionnaire

To evaluate the effect of both carprofen and robenacoxib on QoL it is important to register QoL, pain and any AE observed during the treatment period. For both QoL and pain, scoring systems have been developed and can be found in literature (Lynch, 2010) (Iliopoulou, 2013) (Lavan, 2013). However, documentation and scoring of AEs seems to be more difficult. No specific, standardized AE scoring form for NSAIDs has been found in literature. Therefore, we chose to use a scoring system for AEs in chemotherapy treatment and adapt it to an AE questionnaire for the scoring of AEs occurring during NSAID treatment (Veterinary Cooperative Oncology Group, 2011).

The AE questionnaire we discuss in this paper is based upon the Common Terminology Criteria for Adverse Events (CTCAE) following chemotherapy of biological antineoplastic therapy in dogs and cats version 1.1 developed by the Veterinary Cooperative Oncology Group (VCOG) (Veterinary Cooperative Oncology Group, 2011). The VCOG CTCAE v1.1 contains a wide variety of AEs, graded in severity from grade 1 (mild) to grade 5 (death related to AE), with a description of specific characteristics for every grade of an AE. The AEs have been categorized into domains such as administration site condition, allergic/immunologic event, blood/bone marrow, cardiac arrhythmia, cardiac general, coagulation, constitutional clinical signs, dermatologic/skin, ear and labyrinth disorders, endocrine, gastrointestinal, haemorrhage/bleeding, hepatobiliary/pancreas, metabolic/laboratory, muscoloskeletal/soft tissue, neurology, ocular/visual, pain, pulmonary/respiratory, renal/genitourinary, neoplasms benign, malignant and unspecified, sexual/reproductive function, vascular. Attribution of an AE to a treatment or an intervention can be exercised by another five categories from unrelated (1) to definite (5) and should be done by the treating clinician or by the investigators (Veterinary Cooperative Oncology Group, 2011).

3.1.1 Selection and translation of relevant AEs

The VCOG-CTCAE v1.1 is very extensive in the number of AEs described. For the Pain Study not all of these AEs are expected to be observed. Therefore, we made a first selection of AEs based upon the mechanism of action of COX-inhibitors as described in Chapter 2.2, and based on the registered AEs for carprofen and robenacoxib (Medicines Evaluation Board, 2008) (European Medicines Agency, 2011). After making the first selection, selected AEs were translated into Dutch by a veterinary student. The translation was performed mostly with basic knowledge of English, and when necessary a medical dictionary, an online dictionary and an online translation website were used. No back-translation was applied. After translation, the AE questionnaire was reviewed by the main investigator of the Pain Study, and several other participating investigators of the Pain Study.

3.1.2 Development of a clear AE questionnaire

Following selection and translation the AE questionnaire was submitted to several veterinarians, a psychologist with experience in developing questionnaires and a small group of dog owners without veterinary knowledge. They reviewed the AE questionnaire on the formulation of the questions and on the clarity of the questions.

3.1.3 Testing the adequacy in patients without AEs

Because the AE questionnaire should be adapted to AEs observed in treatment with COX-inhibitors, the questionnaire was first presented to owners of canine patients treated with a NSAID for a short

period of time. These were mostly patients with chronic ear infection and surgery patients with standard post-operative analgesia. None of these patients displayed AEs during treatment. We observed whether owners had difficulty filling out the AE questionnaire. And we asked them if they thought questions/AEs were unclear to them.

3.1.4 Testing the adequacy in patients with AEs

After the first test of adequacy in a group of clinically healthy dogs with short-term treatment with NSAIDs, another group of dogs was selected to determine the adequacy of the AE questionnaire in patients with AEs. In this part we investigate if the formulated questions are accurate, clear, and extensive enough when AEs are present. But also if filling out the form once a week at home caused any problems. For this purpose, a group of canine patients with a greater risk of AEs after treatment was selected. This group is composed of canine cancer patients undergoing chemotherapy. Although canine cancer patients treated with chemotherapy do not show as many and severe AEs as human cancer patients treated with chemotherapy, it is a group of patients in which most patients do show some AEs during treatment. Therefore, nine owners of canine cancer patients treated with chemotherapy at the University Clinic of Companion Animals in Utrecht were approached to participate. Owners were asked to fill out the questionnaire once a week. When no appointment at the policlinic was scheduled, they were contacted by phone once a week. After the owners filled out the AE questionnaire, we processed all answers. We observed whether owners had had any difficulty filling out the AE questionnaire. And we compared the answers owners gave on the AE questionnaire to the answers they gave during policlinic visitations.

3.2 Feedback on the AE questionnaire by survey

In order to determine if the AE questionnaire can also be applied in a clinical setting with chemotherapy patients, a survey among the owners of the chemotherapy group was held. In this survey owners were asked for feedback on the AE questionnaire. The survey comprised questions about the usefulness, clearness, and relevance of the questions asked in the AE questionnaire, the convenience of weekly filling out the AE questionnaire, the time it took to fill out the AE questionnaire, if the AE questionnaire helped to recollect AEs observed during the week, if it helped to alert owners to the possible AEs, if the AE questionnaire had value to them, if they appreciated filling out the AE questionnaire together the first time and if they appreciated to have weekly contact about the health status of their dog. These questions were scored on a 5-level Likert scale. Finally, owners were asked if they had suggestions for additions to the questionnaire, or if they thought anything on the AE questionnaire was unclear and they would like to see different.

4 Results

4.1 Development of the AE questionnaire

4.1.1 Selection and translation of relevant AEs

The first selection consisted of 39 AEs: allergic reaction/hypersensitivity, lethargy/fatigue/general performance, fever, hypothermia, weight loss, alopecia, pruritus, abdominal distention, anorexia, ascites, colitis, constipation, dehydration, diarrhoea, enteritis, flatulence, gastric ulceration, ileus, anal incontinence, nausea/ptyalism, vomiting, spontaneous haemorrhage/bleeding, petechiae/ecchymosis, liver dysfunction/failure, pancreatitis, consciousness, pain, acute kidney injury, chronic kidney disease, glucosuria, proteinuria, polyuria, pollakiuria, urinary output diminished, urinary retention, urine colour change, tumour pain, and neoplasms benign, malignant and unspecified.

After translation, some AEs were combined into one AE. For example, fever and hypothermia were combined into fever, polyuria, pollakiuria, diminished urinary output, urinary retention and urine colour change into urination habits, diarrhoea, enteritis, flatulence, colitis, and anal incontinence into diarrhoea, and spontaneous haemorrhage/bleeding and petechiae/ecchymosis into bleeding. Other AEs were excluded because detection by owners would be difficult. AEs, such as ascites, dehydration, gastric ulceration, ileus, liver dysfunction/failure, pancreatitis, acute and chronic kidney disease, glucosuria, proteinuria, and neoplasms were all excluded for this reason. Exclusion of these AEs from the AE questionnaire does not mean they were not included as AEs that may occur during the research period. Presence of these AEs was tested every two weeks by clinical physical examination, blood work and tumour examination and measurement. Also, pain and tumour pain were left out to avoid double questions, because these aspects are covered by the Glasgow Pain Score form.

The final selection of AEs consists of 16 domains: appetite, vomiting, nausea, diarrhoea, obstipation, stomach ache, weight loss, urination habits, allergic reactions, fever, alopecia, pruritus, bleeding, activity, consciousness, and behaviour.

4.1.2 Development of a clear and comprehensible questionnaire

Based on the feedback of veterinarians, a psychologist and a group of ten dog owners without veterinary knowledge, the questionnaire was adapted. In terms of basic, our AE questionnaire has the same structure as the VCOG CTCAE v1.1 (Veterinary Cooperative Oncology Group, 2011). Every AE in the VCOG CTCAE v1.1 has 5 grades, ranging from grade 1 (mild) to grade 5 (death caused by AE). In the AE questionnaire not all grades of the VCOG CTCAE v1.1 have been adopted. Every grade 5, death caused by AE, has been omitted. The reason for this omission was to not frighten owners. On one hand because the NSAIDs used in the Pain Study have been registered safe for normal use and death caused by an AE due to NSAID treatment is not expected. On the other hand, grade 5 was not omitted because in case of death of one of the participating dogs, the owner can often not attribute death to one of the AEs. That is a job for the clinician or the investigator. Therefore, reporting of death suffices.

The five grades of an AE on the VCOG CTCAE v1.1, each consist of a description. When a description fits the clinical signs shown by a patient, that grade is chosen. Not all grades of the selected AEs of the VCOG CTCAE v1.1 are applicable in the setting of the Pain Study, mostly because owners cannot evaluate them. The same applies for the descriptions of every grade of the AEs included in the AE

questionnaire. The following AEs have been reduced to three grades or less of the original grading: nausea/ptyalism, abdominal distention, weight loss, urination habits, allergic reaction/hypersensitivity, alopecia, pruritus, bleeding, consciousness, and lethargy/fatigue/general performance. Another grade was added to every AE domain, namely grade 0, i.e. no clinical signs of that particular AE.

In order to combine multiple AEs, as discussed in the previous section, it was suggested to add extra questions to the AE domains. To be able to compare the answers to these questions, the added questions are closed questions where possible. An example for the AE diarrhoea can be found in Figure 4.1. The question consists of multiple sub questions. Sub question a) is an adapted form of the AE from the VCOG CTCAE v1.1. Sub questions b) to f) are extra questions derived from reducing multiple AEs to one. Further adjustments in wording, mostly in jargon, were made based on the received feedback of the owners with no veterinary background knowledge. Also instructions for the owner on how to fill out the AE questionnaire were added. The layout of the AE questionnaire was as much as possible adjusted to the layout of the QoL score form and the Glasgow Pain Score short form.

Figure 4.1 Question 4 of the AE questionnaire, diarrhoea

4.1.3 Testing the adequacy in patients without AEs

During the testing of the adequacy of the AE questionnaire in clinically healthy patients, all AE questionnaires were filled out together with a veterinary student on the clinic. In total, 12 owners with dogs treated with NSAIDs were asked to fill out the questionnaire. 17% (2/12) of the owners did not fill out the questionnaire themselves. In these cases a veterinary student asked the questions on the AE questionnaire and filled out the answers for them. The other 83% (10/12) of the owners filled out the AE questionnaire themselves, with a veterinary student present in case the owner had questions about the questionnaire.

All but one of the AE questionnaires were filled out only once, mostly at the start of the treatment with NSAIDs. Only 8% (1/12) of the owners was contacted three days later to ask if anything had changed in the health status of their dog. None of the dogs treated with NSAIDs showed any AEs related to NSAID treatment. And because none of these dogs showed any AEs during treatment with

the NSAIDs, the first five owners did not read the grades above grades 0 to 1 (no clinical signs - mild clinical signs). To test if all descriptions were formulated in a clear way, owners also had to read the other grades. In order to achieve this, the grades of every AE were turned around. So at first every AE started with no clinical signs observed, i.e. grade 0. And after turning the grades, every AE started with the highest grade, life-threatening or severe clinical signs. This way, it was thought, the owners would also read the more severe grades.

None of the owners had any trouble filling out the AE questionnaire. For most owners it took no more than ten minutes to fill out the AE questionnaire. After filling out the questionnaire, owners were asked if they thought any of the questions were unclear or vaguely formulated. However, none of the owners thought that the AE questionnaire was unclear and all thought the questions were clearly formulated. Nevertheless, we did adapt the AE questionnaire after this test of adequacy. Nienke Endenburg PhD is a psychologist who also teaches at the Faculty of Veterinary Medicine and has experience in developing questionnaires. She thought the layout of the AE questionnaire could be improved. We used her advice to adjust the AE questionnaire. This adapted version of the AE questionnaire was used in the next test.

4.1.4 Testing the adequacy in patients with AEs

We chose the chemotherapy patient group to test the adequacy of the AE questionnaire when AEs are present. This group consists of 9 chemotherapy patients of whom 89% (8/9) received chemotherapy for the treatment of lymphoma and 11% (1/9) received chemotherapy for the treatment of canine transmissible venereal tumour. During the testing of the questionnaire, one of the dogs was euthanized because chemotherapy did not have the expected results. This was one of the patients diagnosed with lymphoma. The filled out forms could not be retrieved from the owner, so this dog was excluded from the study.

All owners were first approached during an appointment at the Medical Oncology policlinic at the University Clinic of Companion Animals in Utrecht. In 88% (7/8), owners filled out the AE questionnaire the first time in attendance of a veterinary student. 12% (1/8) of the owners did not have the time to fill out the AE questionnaire together. This owner was contacted the next week to inquire after unclarities in the AE questionnaire. The owner managed to fill out the AE questionnaire on her own and did not need any extra explanation. 75% (6/8) of the owners brought the questionnaire home to fill it out during the week(s) following their appointment. And 25% (2/8) of the owners were contacted by phone to fill out the AE questionnaire in the weeks following. Depending on the treatment protocol and how far along the patients were with the treatment, patients had to return to the clinic once a week, once in two weeks or even once in every three weeks. This resulted in a variety of times owners filled out the AE questionnaire. The minimum number was two times, the maximum number was four times. The mean number of AE questionnaires filled out per dog is 2.75 times (Table 4.1).

Besides filling out the AE questionnaire, owners were also asked to fill out a QoL score form and a Pain score form. Both score forms have been adapted to the Pain Study by another veterinary student. Development and adaption of these forms will not be further discussed in this paper. However, the mean scores acquired of both these forms can be found in Table 4.1.

As expected, and unlike the first test group, the chemotherapy patient group showed AEs. Table 4.2 reports the mean score per AE per patient, the standard deviation of the mean score per AE, and the

minimum score and the maximum score observed per AE. 13% (1/8) of the patients did not show any AEs during two weeks of treatment. None of the participating patients showed an allergic reaction or had any signs of bleeding during the time they participated. Only one patient scored a grade 3 in an AE, this was in urination habits. During chemotherapy, this patient was simultaneously treated with prednisolon (source: Patient file). This might explain the high score in urination habits. Attribution of this AE to chemotherapy treatment falls most likely in category (1): unrelated.

During processing of the filled out AE questionnaires, no signs of difficulty were found. This finding was confirmed by the feedback owners gave in the survey about the AE questionnaire in Chapter 4.2. Owners were encouraged to write down extra observations that were not included in the AE questionnaire. Most owners only used this option to state exactly when AEs were observed during the week. One dog (12%) developed a pneumonia during the test period. However, for pneumonia no respiratory AEs, such as coughing, dyspnoea and wheezing, are included on the AE questionnaire. Therefore, this owner wrote this extra on the AE questionnaire. Comparison of the answers given during policlinic visitations and the answers given on the AE questionnaire, showed no big discrepancies. Most differences were found in time of occurrence of an AE, and in the more subtle AEs such as daily activity and behaviour.

Table 4.1 Characteristics of the participating patients and the results of the QoL and Pain Score

Variables			Mean	St.dev.	Min.	Max.	Nr. of participants
Age (in years)			5.00	2.50	2	9	8
Nr. of forms filled out per dog			2.75	0.71	2	4	8
Pain Score	nr.	1	0.25	0.46	0	1	8
		2	0.38	0.52	0	1	8
		3	0.40	0.55	0	1	5
		4	0	0	0	0	1
QoL Score	nr.	1	100.50	11.64	79	110	8
		2	98.50	10.31	84	110	8
		3	95.60	11.39	78	107	5
		4	100.00	0	100	100	1

Note: In the QoL Score, the highest score achievable, and thus the best QoL, is a score of 110 (ranging from 110 to 0). In the Pain Score, the lowest score, and thus the least pain, is a score of 0 (ranging from 24-0).

Table 4.2 Mean scores per patient per AE

Adverse Events	Patient 1	2	3	4	6	7	8	9	Mean	St.dev.	Min.	Max.
Appetite	0	0	0.33	0	0.33	1	0	0	0.21	0.35	0	2
Vomiting	0	0	0	0	0.33	0.67	1	0	0.25	0.39	0	1
Nausea	0	0.5	0	0	0.33	0.33	0	0	0.15	0.21	0	1
Diarrhoea	0	0.5	0	0	0.33	0.67	0	0	0.19	0.27	0	1
Obstipation	0	0	0	0	0	0.33	0	0	0.04	0.12	0	1
Stomach ache	0	0	0	0	0	0.33	0	0	0.04	0.12	0	1
Weight loss	0	0	0	0.67	0.67	0.67	0	0	0.25	0.35	0	1
Urination habits	0	0	0	0	2.33	0	0	0	0.29	0.82	0	3
Allergic reactions	0	0	0	0	0	0	0	0	0.00	0.00	0	0
Fever	-	-	0	0	-	0.5	-	-	0.17	0.18	0	1
Alopecia	0	0	0	0	1	0	0	0	0.13	0.35	0	1
Pruritus	0	0	0	0	0	0	0.5	0	0.06	0.18	0	1
Bleeding	0	0	0	0	0	0	0	0	0.00	0.00	0	0
Activity	0.75	0	0.67	1	1.17	0	0.5	0	0.51	0.47	0	2
Consciousness	0.25	0	0	1	0	0	0	0	0.16	0.35	0	1
Behaviour	0.5	0	0.67	1	1	0	0	0	0.40	0.45	0	1

4.2 Feedback on the AE questionnaire by survey

All eight owners of the chemotherapy group were again approached to answer a survey by phone. All of them had completed two or more AE questionnaires before they were contacted for the survey. The time between filling out the AE questionnaires and filling out the survey about the AE questionnaire, ranged from one week to two months. However, all owners said they remembered the questionnaire well enough to answer the survey questions.

Table 4.3 reports the results of the survey about the AE questionnaire. Of all questions the mean scores, standard deviation and minimum and maximum scores are reported. All owners disagreed with the statement that filling out the AE questionnaire is time-consuming. Therefore, none of the owners answered question 6 (see Appendix 9.1). All owners tended to agree or fully agreed with the statement that filling out the AE questionnaire was not difficult. And 88% (7/8) thought the AE questionnaire was clear, the other 12% (1/8) was neutral regarding the clearness. 75% (6/8) of the owners appreciated to keep a weekly track of the AEs they observed in their dog. The other 25% (2/8) of the owners, tended to agree or were neutral to this statement. In the statements regarding the helpfulness in observing and remembering AEs, and the value of the AE questionnaire, answers ranged from agree to disagree. Only 12% (1/8) of the owners thought that the AE questionnaire helped with otherwise forgotten AEs. The other 88% (7/8) were either neutral regarding this statement or disagreed with this statement. However, 38% (3/8) of the owners agreed with the statement that the AE questionnaire helped with the recollection of observed AEs. The other 62% (5/8) of the owners were neutral regarding this statement or disagreed.

Even though the AE questionnaire is intended for and adapted to canine cancer patients treated with NSAIDs, 75% (6/8) of the owners agreed or tended to agree with the statement about the relevance of the AEs on the AE questionnaire. The other 25% (2/8) of the owners were neutral regarding this statement. 75% (6/8) of the owners appreciated the weekly contact by phone about the health status of their dog. 25% (2/8) was neutral regarding this statement.

There was a low response to the open questions about suggestions for any additions to the AE questionnaire and about any vagueness owners had come across in the AE questionnaire. One owner thought that questions could be expanded. However, she could not point out which questions should be expanded and what the questions lacked in their current form. One other owner mentioned that it was not clear to her when a new AE questionnaire had to be filled out. No signs of this unclarity were observed in the filled out AE questionnaires of this owner.

Table 4.3 Results of the survey about the AE questionnaire

Questions	Mean	St.dev.	Min.	Max.
1 Tracking weekly adverse events	4.63	0.74	3	5
2 Clearness AE questionnaire	4.75	0.71	3	5
3 Easiness of filling out the AE questionnaire	4.88	0.35	4	5
4 Relevance of questions on AE questionnaire	4.38	0.92	3	5
5 Filling out of AE questionnaire is time-consuming	1.00	0.00	1	1
6 Bothersome	-	-	-	-
7 Helpfulness in remembering adverse events	3.00	1.85	1	5
8 Helpfulness in otherwise forgotten adverse events	2.25	1.49	1	5
9 Appreciation of weekly contact	4.38	0.92	3	5
10 Value of the AE questionnaire	3.38	1.69	1	5
11 Helpfulness in observing of adverse events	3.13	1.89	1	5
12 First time filling out AE questionnaire	4.13	0.99	3	5

Note: Owners were able to answer the statements according to a 5-Likert scale, ranged from agree, tend to agree, neutral, tend to disagree, disagree. We gave a score to these answers ranging from 5 to 1 respectively.

5 Discussion

In this study, the AEs and their grades we used were derived from the VCOG CTCAE v1.1 (Veterinary Cooperative Oncology Group, 2011). We adapted the selection into an AE questionnaire so owners, participating in the Pain Study, could register at home observed AEs. In most clinical trials however, occurrence of AEs is recorded only by interviewing the owner and observing patients during physical examination. For example, Edamura et al. (2012) compared robenacoxib and carprofen for the treatment of osteoarthritis in dogs in a randomised clinical trial. In this study, the clinician investigator examined each dog three times and also collected and recorded data on AEs by interviewing the owner every two weeks (Edamura, 2012). In a study of the efficacy and safety of water soluble micellar paclitaxel for the treatment of mast cell tumours in dogs, AEs were reported spontaneously at any time point during the study. The investigators of this study graded AEs according to VCOG-CTCAE v1.0 (Vial, 2012). Flor et al. (2013) investigated whether tramadol plus metamizole combined or not with anti-inflammatory drugs is a clinically effective treatment for moderate to severe chronic pain in canine cancer patients. In this study, the investigators also interviewed the owner to detect AEs. No report of classification of the observed AEs was made (Flor, 2013). None of these studies made use of a questionnaire for owners to detect and report AEs during treatment period. It could be argued that developing an AE questionnaire for owners is unnecessary and only time-consuming. However we believe that the use of an AE questionnaire for owners to report observed AEs gives a more accurate indication of all occurring AEs during treatment period.

The original VCOG CTCAE v1.1 is composed in order to offer a standardised way to report AEs in clinical trials with chemotherapy. The adaption of this document into a questionnaire for owners to report clinical signs they observe in their dogs during treatment with NSAIDs is a big step. If we look at the available literature about translation guidelines for questionnaires, many steps can be taken. In this study, we only made use of a forward translation and pre-tested a first version of the AE questionnaire on a select group of mostly professionals. More steps, such as translation by professional translators, back-translation and a larger pre-test are suggested by Acquadro et al. (2008) (Acquadro, 2007). However, the review by Acquadro et al. (2008) is focused on translation methods for use in multinational clinical trials. Our AE questionnaire is solely translated into Dutch. Therefore, we believe the steps we have taken during translation will suffice.

In the first test of adequacy, in a group of patients without AEs, 23% (3/13) of the questionnaires were filled out by a veterinary student. In these cases the student read the questions out loud for the owners. Ideally, to assess the adequacy of the AE questionnaire in this test, the owner has to fill out the form himself or herself. The same goes for the questionnaires filled out by a veterinary student in the second test of adequacy. Therefore it could be argued that these questionnaires have to be excluded from our assessment. However, in these cases owners heard all grades per AE and could directly appoint any unclarity in formulation. So we chose to include the results of these questionnaires for this reason.

In Chapter 4.1.3, it was pointed out that owners of the patients without AEs only read the low grade descriptions. In order to test if all descriptions were formulated in a clear way, we wanted owners to also read the higher-grade descriptions. To overcome this problem, the grades of every AE were turned around. After turning the grades around, most owners started to read the high-grade description first. But once owners saw through this, they again only read the low-grade descriptions. Other ways to overcome this problem could be by letting one AE start with a low grade and the next

with a high grade. Or by giving owners the specific instruction to first read all grade descriptions before picking one.

In the second test of adequacy, 75% (6/8) of the owners took a package of questionnaires home to fill out during the weeks between visits at the University Clinic for Companion Animals at Utrecht. All owners strictly filled out the AE questionnaire every week. Beforehand, our concern was that filling out the AE questionnaire would be time-consuming and therefore some owners would not be motivated to fill out the AE questionnaire every week. However, we experienced their willingness to cooperate and we find that owners do not experience the AE questionnaire as time consuming. However, the maximum of AE questionnaires filled out per owner was four times (Table 4.1). For the Pain Study, owners have to fill out at least eight AE questionnaires. It could be that owners are less inclined to fill out the AE questionnaire that often. Therefore owners have to be stimulated in this.

In Table 4.2 the mean scores of all AEs per patient are reported. We find that two AEs, bleeding and allergic reactions were not observed in any of the chemotherapy patients. It can be argued to exclude these AEs of the AE questionnaire because of these results. However, the group of patients used for this test does not correspond with the group the AE questionnaire is intended for. Also, the research group used for the second test is too small to deduce from. Therefore we believe that exclusion based on the scores found in this test is not indicated.

In order to acquire feedback on the AE questionnaire, participating owners filled out a survey. A marginal note about the survey should be made before the results of survey can be interpreted. Namely, the time between filling out the AE questionnaire and answering the survey was variable, ranging from one week to two months. All owners said they remembered the AE questionnaire well enough to answer the survey questions. However, we take into account that the low response in the open questions of the survey may be the result of the time between the AE questionnaire and the survey. And therefore answers to other questions in the survey, could be different when asked directly after finishing the last AE questionnaire. In a future study we suggest that the survey is held directly after finishing the last AE questionnaire.

From the survey, we conclude that most owners think the AE questionnaire is clear and easy to fill out. However, only a few owners think the AE questionnaire helped them in remembering observed AEs. Our question if this AE questionnaire could be applied in a clinical setting with canine chemotherapy can be argued in many ways. One of the owners suggested that the AE questionnaire could be useful for owners of patients starting with chemotherapy. She thought the questionnaire might make an owner more alert to AEs. However, the owners of patients in a more advanced phase of treatment might not need the AE questionnaire. This might also explain the wide range of answers owners gave in the survey. Owners new to chemotherapy treatment of their pets could be provided with AE questionnaires to fill out during the first month of treatment. More research into the demand among owners should be performed. Also the AEs on the questionnaire should be adapted to AEs observed in chemotherapy patients.

Other suggestions we have for future studies comparable to the one described in this study are the following. We suggest that in a future study larger research groups should be used, all owners should fill out the same number of questionnaires and for the same period of time that is required in the study the questionnaire is intended for.

6 Conclusion

In this study, we find that the AE questionnaire satisfies the needs of the Pain Study. And therefore, this questionnaire can be used to register the AEs observed in the Pain Study. Study results indicate that the questions in the AE questionnaire developed for the Pain Study are clearly formulated. In case of occurring AEs, the AE questionnaire seems to be extensive enough. No significant discrepancies between answers given in the AE questionnaire and answers given during policlinic visitation can be found. If anything, more accurate information can be drawn from the AE questionnaire.

For application of the developed AE questionnaire in a clinical setting with chemotherapy patients, the AE questionnaire should be adapted. In our study with chemotherapy patients, we find that a wider selection of AEs is necessary. Therefore, the selection of AEs should be adapted to the chemotherapy protocol or to the chemotherapy agents applied. Also, to determine if there is a demand for such a questionnaire among chemotherapy patient owners, more research is needed.

7 Acknowledgement

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9 Appendix

9.1 Survey AE Questionnaire

Enquête m.b.t. het Formulier Bijwerkingen voor eigenaren

		eens	beetje eens	neutraal	beetje oneens	oneens
1	Ik vind het prettig om wekelijks bij te houden welke bijwerkingen van de chemo ik bij mijn hond heb gezien.					
2	Ik vind het Formulier Bijwerkingen duidelijk.					
3	Ik vind het Formulier Bijwerkingen makkelijk in te vullen.					
4	Ik vind de vragen op het Formulier Bijwerkingen relevant.					
5	Ik vind dat het invullen van het Formulier Bijwerkingen veel tijd in beslag neemt.					
6	Zo ja: Ik vind dit vervelend.					
7	Ik heb het idee dat het Formulier Bijwerkingen mij heeft geholpen bij het onthouden van de verschijnselen die ik bij mijn hond heb gezien.					
8	Ik heb op het Formulier Bijwerkingen verschijnselen ingevuld die ik anders was vergeten.					
9	Ik vind het fijn om elke week (kort) contact te hebben m.b.t. de gezondheidstoestand van mijn hond.					
10	Het invullen van het Formulier Bijwerkingen heeft voor mij toegevoegde waarde.					
11	Het Formulier Bijwerkingen hielp mij om beter op mogelijke bijwerkingen te letten.					
12	Ik vond het fijn om het Formulier Bijwerkingen de eerste keer samen in te vullen.					

13 Eventuele aanvullingen op het formulier:

_____

_____

_____

14 Eventuele onduidelijkheden in het formulier:

_____

_____

 -_____

9.2 AE Questionnaire

Formulier Bijwerkingen

Naam eigenaar: ....

Naam patiënt: ....

Datum: ....

Vul hieronder de toestand van uw hond van de afgelopen week in.

1) **Verminderde eetlust:**

   Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond eet niet gedurende meer dan 5 dagen achtereenvolgend.	Mijn hond eet minder/niet gedurende 3-5 dagen achtereenvolgend.	Mijn hond eet minder/niet gedurende maximaal 3 dagen achtereenvolgend.	Mijn hond eet minder dan normaal en/of mijn hond eet alleen als ik het eten lekkerder maakt.	Mijn hond eet normaal.

2) **Braken:**

   Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond braakt continu.	Mijn hond heeft meer dan 10x keer per dag gebraakt.	Mijn hond heeft 3-10 keer per dag gebraakt.	Mijn hond heeft maximaal 3x per dag gebraakt.	Mijn hond heeft niet gebraakt. *

* Indien u deze stelling heeft gekozen kunt u verder gaan met vraag 3.

b) Mijn hond heeft ondersteunende behandeling i.v.m. braken nodig: ja/nee *

* Indien u nee heeft ingevuld kunt u verder gaan met vraag 2d.

c) Zo ja, wat voor behandeling:

d) Mijn hond heeft deze week … dagen gebraakt.   *(vul het aantal dagen in)*

3) **Misselijkheid/ speekselen:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a) Mijn hond speekselt en/of smakt gedurende meer dan 5 dagen achtereenvolgend.	Mijn hond speekselt en/of smakt gedurende 3-5 dagen achtereenvolgend.	Mijn hond speekselt en/of smakt gedurende maximaal 3 dagen achtereenvolgend.	Mijn hond is niet misselijk en/of mijn hond heeft geen last van overmatig speekselen.

4) **Diarree:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a) Mijn hond kan de ontlasting in huis niet ophouden.	Mijn hond poept per dag meer dan 6 x vaker dan normaal.	Mijn hond poept per dag 3-6 x vaker dan normaal. De dagelijkse activiteit van mijn hond is normaal.	Mijn hond poept per dag maximaal 3 x vaker dan normaal.	Mijn hond poept normaal.

b) Wat is de consistentie van de ontlasting van mijn hond?   normaal/minder/stevig/dun/wisselend

c) Heb ik bloed bij de ontlasting van mijn hond gezien?   ja/nee

d) Wat is de kleur van de ontlasting van mijn hond?

e) Mijn hond heeft last van winderigheid: nee/matig/veel

f) Mijn hond heeft diarree: ja/nee

5) **Verstopping (constipatie):**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond heeft last van ernstige verstopping: hierdoor is de dagelijkse activiteit van mijn hond verminderd.	Mijn hond heeft vaker last van verstopping.	Mijn hond heeft soms last van verstopping: persen op de ontlasting.	Mijn hond heeft een normale stoelgang.

b) Mijn hond krijgt medicatie die tegen verstopping helpt: ja/nee *

* Indien u <u>nee</u> heeft ingevuld kunt u verder gaan met vraag 6.

c) Zo ja, welke medicatie:

6) **Buikpijn:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond heeft ernstige buikpijn.	Mijn hond heeft matige buikpijn (bijv. kromme rug, pijnlijk bij aanraking).	Mijn hond heeft geen buikpijn.

7) **Gewichtsverlies:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond is zichtbaar afgevallen: meer dan 15 % van het totale gewicht.	Mijn hond is zichtbaar afgevallen: tussen de 10-15% van het totale lichaamsgewicht.	Mijn hond is (zichtbaar) afgevallen: minder dan 10% van het totale lichaamsgewicht.	Mijn hond is niet afgevallen.

b) Mijn hond krijgt ondersteunende voeding i.v.m. vermagering:　　ja/nee

8) **Plasgedrag:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond geeft aan vaker naar buiten te moeten: meer dan 10 x per dag.	Mijn hond geeft aan vaker naar buiten te moeten: 6-10 x per dag.	Mijn hond geeft aan vaker naar buiten te moeten: in totaal echter nog wel minder dan 6 x per dag.	Mijn hond heeft normaal plasgedrag.

b) Wat is de kleur van de urine van mijn hond?

c) Mijn hond plast 's nachts in huis:　　　　　　ja/nee

d) Mijn hond plast grotere plassen dan normaal　　　　ja/nee

9) **Allergische reactie:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond heeft uitslag op de huid (pukkeltjes, bultjes, rode vlekken) na toedienen medicatie.	Mijn hond heeft geen allergische reactie op toediening van het medicijn.

10) **Koorts:**

a) Neemt u de temperatuur van uw hond op?   ja/nee *

     * Indien u <u>nee</u> heeft ingevuld kunt u verder gaan met vraag 11.

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

b)

Mijn hond heeft een temperatuur tussen de 41-42 graden Celsius, gedurende langer dan 6 uur.	Mijn hond heeft een temperatuur tussen de 40-41 graden Celsius, van voorbijgaande aard (gedurende minder dan 6 uur).	Mijn hond heeft een temperatuur tussen de 39,5-40 graden Celsius.	Mijn hond heeft een normale temperatuur (38-39 graden Celsius).	Mijn hond heeft een temperatuur van minder dan 38 graden Celsius

11) **Kaalheid:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond heeft over het hele (of een groot deel van het) lichaam een dunnere vacht of is zelfs kaal.	Mijn hond heeft een dunnere vacht of is zelfs kaal op een of meerdere gelokaliseerde plaatsen.	Mijn hond heeft een glanzende, volle vacht zonder kale plekken.

12) **Jeuk:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond heeft last van ernstige en langdurige jeuk. Komt ook voor tijdens het eten, spelen, bewegen en slapen.	Mijn hond heeft last van matige of uitgebreide jeuk en dit komt regelmatig voor. Het kan 's nachts voorkomen, maar niet tijdens het eten of spelen.	Mijn hond heeft last van milde of gelokaliseerde jeuk.	Mijn hond heeft geen jeuk.

13) **Bloeding:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)	Over een groot deel van de huid van mijn hond zijn kleinere, dan wel grotere bloedingen te zien. Of mijn hond heeft zwarte ontlasting.	Op de huid van mijn hond zijn meerdere kleine bloedingen of een (enkele) grotere bloeding (-en) te zien. Of mijn hond heeft een zichtbare bloeduitstorting.	Op de huid van mijn hond zijn enkele kleine bloedingen te zien (tot 5 mm).	Mijn hond heeft geen last van bloeding(-en).

14) **Vermoeidheid/ algemene dagelijkse activiteit:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)	Mijn hond komt niet meer overeind: moet gedwangvoederd worden en geholpen worden met urineren/ontlasten.	Mijn hond vertoont ernstige futloosheid: urineert en ontlast op de ligplaats of in huis, eet alleen als voedsel op de ligplaats wordt aangeboden.	Mijn hond vertoont matige futloosheid: komt alleen overeind om te eten, wandelingen zijn kort: hoofdzakelijk urineren en ontlasten.	Mijn hond vertoont milde futloosheid: ligt vaker te slapen en is minder actief gedurende de wandeling. Dit gedrag vind ik echter nog acceptabel.	Mijn hond slaapt niet vaker dan normaal en kan tijdens de wandeling goed meekomen.

15) **Bewustzijn:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Mijn hond is in een coma: kan niet wakker worden gemaakt.	Mijn hond heeft een verminderd bewustzijn of is verdoofd: lastig wakker te maken.	Mijn hond slaapt gedurende de dag voornamelijk, maar dit heeft geen invloed op eten, drinken, urineren of ontlasten.	Mijn hond is goed bij bewustzijn.

16) **Gedrag:**

Zet een kruis in het vakje onder de stelling die het meest van toepassing is.

a)

Ik heb een verandering in het gedrag van mijn hond opgemerkt en dit is schadelijk voor mijn hond of mijn gezin.	Ik heb een verandering in het gedrag van mijn hond opgemerkt, met negatief effect op mijn hond of mijn gezin.	Ik heb een verandering in het gedrag van mijn hond opgemerkt, maar dit heeft geen (negatief) effect op mijn hond of mijn gezin.	Het gedrag van mijn hond is niet veranderd.

17) **Overige bijwerkingen:**

a) Zijn mij nog andere bijwerkingen/ veranderingen aan mijn hond opgevallen?

....

....

Bedankt voor het invullen!