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An analysis of the relative frequencies of reported adverse events associated with NSAID administration in dogs and cats in the United Kingdom

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ABSTRACT

This study aimed to analyse UK pharmacovigilance data to quantify adverse events (AEs) associated with the non-steroidal anti-inflammatory drug (NSAID) molecules found in veterinary medicines authorised for use in dogs and cats. It was hypothesised that the frequency of AEs would be lower when associated with cyclo-oxygenase-2 selective (coxib), compared to non-selective (non-coxib) NSAIDs. The UK Veterinary Medicines Directorate (VMD) supplied frequencies of AEs derived from Periodic Safety Update Reports subdivided by formulation and species for each NSAID molecule.

Frequencies of AEs were similar between species. The five most reported AEs were emesis, death, anorexia, lethargy, and diarrhoea. Reported frequency of emesis, renal insufficiency and death was higher with injectable compared to oral NSAIDs ($P = 0.043$). Reported frequency of emesis, lethargy and death was higher with coxib, compared to non-coxib NSAIDs ($P = 0.029$). Median (range) interval since authorisation was shorter for coxibs at 5 (2.5–9) years compared to non-coxibs at 15 (12–25) years. A negative correlation between time elapsed since authorisation and the frequency of AEs was identified ($r_s = -0.11$ to -0.94). Higher frequency of reported AEs with injectable NSAIDs may be related to perioperative administration. The AE frequency associated with coxib and non-coxib NSAIDs may be confounded by changes in reporting habits over time.

This study highlights the value of interrogating passive surveillance data to identify low frequency AEs and the need to facilitate improvement in recording and collecting AEs in small animal practice.

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Introduction

Prescription of non-steroidal anti-inflammatory drugs (NSAIDs) to dogs and cats is commonplace for perioperative analgesia (Farnworth et al., 2014; Hunt et al., 2015) and management of painful inflammatory conditions such as osteoarthritis (Sanderson et al., 2009; Sparkes et al., 2010). Concern exists amongst veterinary surgeons (Capner et al., 1999; Hugonnard et al., 2004) and pet owners[1,2] about potential adverse effects (AEs) of NSAIDs in pet animals.

An AE is defined by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) as '*any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after use of a Veterinary Medicinal Product (VMP) (off-label and on-label uses)*'. Most NSAID AEs are mild and self-limiting (Forsyth et al., 1998; Leong and Chan, 2006), although serious AEs, defined by the VICH as '*an event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect*', coincident with NSAID administration are reported (Duerr, 2004; Enberg et al., 2006).

It has been proposed that selective cyclo-oxygenase 2 (COX-2) inhibitors decrease NSAID AEs (Simmons et al., 2004). Increased tolerability of COX-2 selective (coxib), compared to non-selective (non-coxib), NSAIDs in dogs (Wooten et al., 2009; Reymond et al., 2012) or cats (Kamata et al., 2012; Sano et al., 2012) has, however, not been reported.

Recently, two reviews of NSAID AEs in dogs have been published. Monteiro-Steagall et al. (2013) concluded that '*most studies were not appropriately designed to determine the safety of NSAIDs, and involved a healthy non-geriatric population of research dogs*', whilst

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[1] See: http://www.dailymail.co.uk/news/article-2127028/Could-drug-cost-beloved-pet-life-kill-YOUR-dog-Vet-raises-alarm-arthritis-pill-prescribed-millions-animals.html. (accessed 27 February 2015).

[2] See: http://ths.gardenweb.com/discussions/2499315/i-suspect-metacam-side-effects-other-options. (accessed 27 February 2015).

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Innes et al. (2010) commented that '*robust data on the safety of long-term NSAID use are lacking in large numbers of dogs*'. No published studies address the frequency of NSAID AEs in cats. Randomised controlled clinical studies are powered to investigate the efficacy of a drug, and are unlikely to generate valid estimates of the incidence of rare AEs (Tramèr et al., 2000). Moreover, reporting of AEs within clinical trials may not always be complete (Edwards et al., 1999).

The UK Veterinary Medicines Directorate (VMD) administers a passive AE surveillance programme and summary reports are published regularly (Dyer et al., 2011, 2012). Marketing Authorisation Holders (MAHs) submit Periodic Safety Update Reports (PSURs) to the VMD and these incorporate instances of non-serious AEs that have been reported to the MAH, but may not have generated an AE report to the VMD.

Under-reporting of AEs is likely. Dean et al. (2013) found that the number of reports of feline injection site sarcomas to the VMD in 2007 was fewer than the number identified during a period of active surveillance for the condition. However, the data collated by the VMD represent the most comprehensive record of AEs available for NSAIDs, and was therefore considered appropriate for this analysis. It is recognised that whilst passive surveillance schemes are subject to reporting biases (Wallenstein and Fife, 2001; Hartnell and Wilson, 2004), their value lies in the comparison of the frequency of AEs associated with products which would be expected to be subject to similar biases; and in the identification of 'signal' data of low frequency or unanticipated AEs (Williams, 2012).

The aim of this study was to investigate the reported relative frequencies of adverse events (AEs) associated with NSAIDs in dogs and cats. We hypothesised that coxibs would be associated with fewer gastrointestinal AEs, compared to non-coxibs.

Materials and methods

Terminology

We considered that the NSAIDs available comprised individual *molecules* (e.g. carprofen, meloxicam, robenacoxib), which were formulated by MAHs into authorised *preparations*, which could be injectable or oral *formulations*.

The VMD supplied cumulative frequencies of AEs, calculated since the date of marketing authorisation (MA) of each molecule (Table 1) and classified in a spreadsheet file (Excel 2007, Microsoft) according to terms for clinical signs given in the European Medicines Agency's Veterinary Dictionary for Drug Related Affairs (VeDDRA).[3] Data were supplied regarding reported AEs in dogs and cats for the molecules carprofen, cimicoxib, cinchophen/prednisolone, firocoxib, ketoprofen, mavacoxib, meloxicam, paracetamol/codeine, robenacoxib, and tepoxalin. Data for each molecule were made up of a composite of data from each authorised preparation.

Table 1
Length of time since granting of marketing authorisation (years) and proportion of product assumed prescribed to cats and dogs by the Marketing Authorisation Holders and Veterinary Medicines Directorate for the purpose of calculating the frequency of adverse events.

Active	Date of MA	Years since MA	Proportion administered to dog (%)	Proportion administered to cat (%)
Carprofen injection	15/03/93	20	80	20
Carprofen oral	17/03/93	20	100	0
Cimicoxib	18/02/11	2.5	100	0
Cinchophen	01/12/92	21	100	0
Firocoxib	13/09/04	9	100	0
Ketoprofen injection	18/05/92	21	60	40
Ketoprofen oral	29/04/92	21	5 mg 75 20 mg 100	5 mg 25 20 mg 0
Mavacoxib	09/09/08	5	100	0
Meloxicam injection	24/06/96	17	75	25
Meloxicam oral cat	20/04/07	8	0	100
Meloxicam oral dog	28/09/92	21	100	0
Paracetamol	15/04/93	20	100	0
Robenacoxib injection	16/12/08	5	75	25
Robenacoxib oral cat	16/12/08	5	0	100
Robenacoxib oral dog	16/12/08	5	100	0
Tepoxalin	13/03/01	12	100	0

MA, marketing authorisation.

Table 2
Products and time periods for which periodic safety update report data were not available to the Veterinary Medicines Directorate.

Product	Active	Dates during which PSUR data were unavailable
Zenecarp 5% injection	Carprofen	October 1997–January 2000
Ketofen 1% solution for injection	Ketoprofen	September 1993–December 1995
Metacam 1.5 mg/mL oral suspension for dogs	Meloxicam	January 2002–June 2002
Metacam 5 mg/mL solution for injection for dogs and cats	Meloxicam	January 2002–June 2002
Zubrin 30, 50, 100 and 200 mg oral lyophilisates for dogs	Tepoxalin	October 2001–September 2002

PSUR, periodic safety update report.

In molecules for which injectable and oral formulations were available (ketoprofen, carprofen, meloxicam and robenacoxib), frequencies for injectable and oral formulations were presented and analysed separately. Data for oral meloxicam and robenacoxib were presented separately for cats and dogs, as species-specific MAs permitted attribution of AEs to each species. Reports where the product was not assessed to have been likely responsible for the signs observed (i.e. causality coded N under the ABON system) (Woodward, 2005) were excluded.

The VMD estimated the number of doses of each NSAID preparation sold by dividing the total volume of product sales by the estimated average volume per dose. For tablets it was assumed one tablet constituted one dose. For injectable formulations and oral suspensions the average volume per dose was estimated, assuming average weights of 20 kg for dogs and 5 kg for cats. In the case of products authorised for use in more than one species, the number of doses sold was calculated using estimates of the proportion administered to each species, provided by MAHs (Table 1), as follows:

$$\text{Number of doses of product/formulation sold} = \frac{\text{Volume of product sold}}{\text{Average dose of product}}$$

The frequency of each reported AE for each NSAID was calculated by dividing the total number of reports of each VeDDRA term by the estimated number of doses sold since MA. Data unavailable for the NSAID preparations and periods are shown in Table 2.

$$\text{Frequency of reported AE for each molecule} = \frac{\text{Number of reports of AE}}{\text{Number of doses of product/formulation sold}}$$

For each molecule the 10 most common VeDDRA terms were identified (Table 3); these were predominantly AEs currently listed in the relevant NSAID Summary of Product Characteristics (SPCs) product literature, which accompany authorised NSAID products. The frequencies of the most commonly reported AEs were compared between different formulations, and classes, of NSAIDs. The duration of MA was calculated from the original date of MA of each molecule, obtained from the VMD website.[4] To provide a clinically useful metric, the reported frequency of each VeDDRA term was used to calculate the predicted number of AE reports per million doses of molecule sold.

Statistical methods

Prism 5 for Mac OSX (GraphPad) was used for statistical analysis. Data were assessed for normality using frequency histograms and Kolmogorov–Smirnov normality analysis. The data were not normally distributed; non-parametric methods were used throughout. Comparisons of the median frequency of an AE between groups or formulations (e.g. coxib vs. non-coxib; oral vs. injectable) were performed using Mann–Whitney *U*-tests. A Spearman non-parametric correlation was used to evaluate the correlation between the duration of MA and the frequency of each AE. Numerical

[3] See: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094802.pdf (accessed 20 July 2015).

[4] See: http://www.vmd.defra.gov.uk/ProductInformationDatabase/Default.aspx (accessed 18 June 2015).

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Table 3
Ten most frequent adverse events reported for each non-steroidal anti-inflammatory drug, in order of descending frequency from left to right.

Product	Most frequently reported AE									Tenth most frequently reported AE
Carprofen oral	Emesis	Death	Lethargy	Hepatopathy	Diarrhoea	Anorexia	RI	HD	Melaena	Jaundice
Carprofen injection	Death	Emesis	Lethargy	Anorexia	RI	Diarrhoea	ATR	Hepatopathy	ISRNOS	LOC
Cimicoxib	Emesis	Diarrhoea	HD	Anorexia	Melaena	Lethargy	RI	Death	Haematemesis	Polydipsia
Cinchophen	Emesis	ATR	Death	Anorexia	Diarrhoea	Lethargy	Polydipsia	Alopecia	Epistaxis	Melaena
Firocoxib	Emesis	Death	Lethargy	RDNOS	Anorexia	Diarrhoea	Hepatopathy	HD	Abdominal pain	Anaemia NOS
Ketoprofen oral	Death	Emesis	Lethargy	Anorexia	Haematemesis	Gastric ulcer	Hypersalivation	Melaena	Convulsion	LOC
Ketoprofen injection	Death	Emesis	RI	Lethargy	Anorexia	Dyspnoea	Ataxia	Polydipsia	Haematemesis	Gastric ulcer
Mavacoxib	LOE	Emesis	Anorexia	Diarrhoea	RI	Lethargy	Death	Hepatopathy	HD	Abdominal pain
Meloxicam oral cat	RI	Emesis	Anorexia	Lethargy	Death	Diarrhoea	Dehydration	Hepatopathy	Ataxia	Polydipsia
Meloxicam oral dog	Emesis	Death	Lethargy	Anorexia	Diarrhoea	HD	RI	Haematemesis	Hepatopathy	Melaena
Meloxicam injection	Emesis	RI	Death	Lethargy	Anorexia	Diarrhoea	HD	Dehydration	Polydipsia	Hyperthermia
Paracetamol	Death	Anorexia	Hepatopathy	Melaena	Emesis	UI				
Robenacoxib oral cat	Emesis	Lethargy	Anorexia	Death	LOE	ATR	Dehydration	RI	Oliguria	Loss of condition
Robenacoxib oral dog	Emesis	Hepatopathy	Polydipsia	Anorexia	Lethargy	ATR	Polyuria	Diarrhoea	Death	LOE
Robenacoxib injection	LOE	Vocalisation	Hypersalivation	Convulsion	Death	Tachypnoea	Urticaria	Emesis	Diarrhoea	Tachycardia
Tepoxalin	Emesis	Death	Diarrhoea	Melaena	HD	Anaemia NOS	Haematemesis	Anorexia	LOC	Lethargy

AE, adverse event; ATR, abnormal test result; HD, haemorrhagic diarrhoea; ISRNOS, injection site reaction (not otherwise specified); LOC, loss of consciousness; LOE, lack of efficacy; NOS, not otherwise specified; RDNOS, renal disorder (not otherwise specified); RI, renal insufficiency; UI, urinary incontinence.

data are presented as median (range). Statistical significance was considered at P values < 0.05 for all tests.

Results

In total, encompassing all molecules, there were 2231 AE reports related to oral administration of NSAIDs in dogs, resulting from approximately 748,000,000 doses given. In cats, 190 AE reports resulted from approximately 60,000,000 administered doses of oral NSAIDs. For injectable NSAIDs, 952 reports were received for cats and dogs, resulting from approximately 46,500,000 doses. The annual number of AE reports, encompassing all drug classes, is shown in Table 4 (G. Davis, personal communication, 2013).

Across molecules, 11 terms appeared consistently within the 10 most frequently reported terms. The predicted number of these 11 VeDDRA terms, per million doses sold, was calculated (Table 5). The ranked orders of terms for dogs and cats differed slightly. For oral formulations in cats (robenacoxib 6 mg tablets, meloxicam 2 mg/mL oral solution), six VeDDRA terms were common to both molecules. These were, in decreasing order of frequency, emesis, anorexia, lethargy, death, renal insufficiency, and dehydration. The 11 most frequently reported VeDDRA terms associated with oral NSAIDs in dogs were emesis, death, anorexia, lethargy, diarrhoea, hepatopathy, renal insufficiency, haemorrhagic diarrhoea, melaena, haematemesis, and polydipsia. Comparison of the frequency of AEs associated with oral NSAIDs revealed no significant differences between cats and dogs (Table 6). Convulsions were reported for the majority of NSAIDs in cats and dogs (Tables 3,5).

Comparisons between the frequencies of AEs reported for injectable and oral NSAIDs in both species are shown in Figs. 1–3. The analysis included only drugs for which both injectable and oral formulations were available (ketoprofen, carprofen, meloxicam, robenacoxib). Emesis, renal insufficiency, and death were reported significantly ($P = 0.043$) more frequently with injectable formulations.

The frequencies of reported AEs in dogs were compared between daily-administered oral coxibs (cimicoxib, firocoxib, robenacoxib) and non-coxibs (carprofen, ketoprofen and meloxicam). Emesis, lethargy and death were significantly ($P = 0.029$) more frequently reported in the coxib group (Figs. 4–6). For preparations used specifically in cats (robenacoxib 6 mg tablets, meloxicam 2 mg/mL oral), the limited number of products available precluded statistical comparisons (Table 5).

The frequencies of AEs reported with the monthly-administered mavacoxib were approximately 30 × higher than those observed for other coxibs (Table 5). There was a moderate to strong negative correlation between the frequency of the majority of reported AEs and time since MA (Table 7). As an illustration, Fig. 7 shows the relationship between frequency of reported emesis (the most common AE) and duration of MA. The median duration of MA for coxibs was shorter at 5 (2.5–9) years than non-coxibs at 14.5 (8–21) years ($P = 0.0018$).

Table 4
Total numbers of reports of adverse event for all drug classes submitted to the Veterinary Medicines Directorate by year.

Year	Number of adverse events reported in animals	Number of adverse events reported in humans	Total number of reported adverse events
1985	7	9	16
1990	87	37	124
1995	950	177	1127
2000	1618	117	1735
2005	1971	129	2100
2010	3586	98	3684
2011	3754	123	3877
2012	4127	160	4287
2013	5343	145	5488

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Table 5
Predicted number of reports of adverse events per 1,000,000 administrations of drug, calculated from reported data to Veterinary Medicines Directorate. For mavacoxib the bracketed figure refers to a 1/30 of the per 1,000,000 administrations result in order to permit a comparison with drugs that are administered daily.

Product	Emesis	Death	Anorexia	Lethargy	Diarrhoea	Hepatopathy	Renal insufficiency	Haemorrhagic diarrhoea	Melaena	Haematemesis	Polydipsia	Convulsions	Dehydration
Carprofen oral	91	51	36	43	40	42	31	13	12	8	8	7	4
Carprofen injection	476	552	319	421	153	136	259	76	64	64	76	42	85
Cimicoxib	1971	282	751	469	845	NR	469	751	657	188	188	NR	NR
Cinchophen	12	6	5	3	5	1	NR	1	2	1	NR	1	NR
Firocoxib	170	113	74	83	65	65	52	52	39	30	9	13	17
Ketoprofen oral	48	60	24	36	NR	NR	12	NR	24	24	NR	24	12
Ketoprofen injection	458	595	183	183	NR	NR	320	NR	137	137	137	NR	92
Mavacoxib	51,849 (1728)	14,233 (474)	18,808 (627)	16,775 (559)	18,808 (627)	14,233 (474)	17,791 (593)	12,708 (424)	4575 (153)	4575 (153)	3558 (119)	1525 (51)	1017 (33.9)
Meloxicam oral cat	107	61	93	76	34	24	110	2	7	3	17	5	25
Meloxicam oral dog	109	67	48	54	43	22	36	38	19	24	7	10	9
Meloxicam injection	943	684	606	679	303	107	870	235	73	93	166	44	186
Paracetamol	18	18	18	NR	NR	18	NR	NR	18	NR	NR	NR	NR
Robenacoxib oral cat	400	267	267	267	NR	NR	133	NR	NR	NR	NR	NR	133
Robenacoxib oral dog	515	157	358	314	269	448	90	67	22	22	381	22	NR
Robenacoxib injection	884	1325	442	442	884	NR	442	NR	NR	442	NR	1325	NR
Tepoxalin	421	349	102	87	334	15	NR	160	203	116	NR	NR	NR

NR, not reported.

Table 6
Comparison of the predicted numbers of adverse event reports per million administrations of oral non-steroidal anti-inflammatory drugs in dogs and cats.

Adverse event	Predicted number of AE reports in dogs per 1,000,000 oral NSAID administrations	Predicted number of AE reports in cats per 1,000,000 oral NSAID administrations	*P*
Renal insufficiency	44 (31–469)	122 (110–133)	0.93
Emesis	170 (18–1970)	254 (107–400)	0.69
Anorexia	74 (24–751)	180 (93–267)	0.93
Lethargy	83 (36–469)	172 (76–267)	0.90
Death	113 (51–349)	164 (61–267)	0.92

AE, adverse event; NSAID, non-steroidal anti-inflammatory drug.

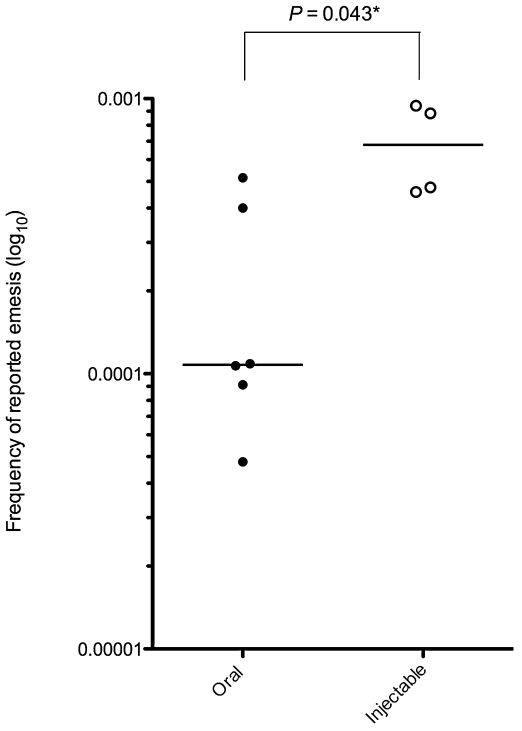

Fig. 1. Frequency (log_{10} scale) of emesis reported in dogs and cats in association with oral or injectable NSAIDs. Points represent frequencies for individual drugs and line indicates median.

Table 7
Spearman correlation coefficients for individual adverse events related to the number of years since granting of marketing authorisation.

AE	Spearman correlation coefficient (r_s)	*P*
Emesis	–0.793	0.005
Death	–0.691	0.002
Anorexia	–0.889	0.0005
Lethargy	–0.911	0.0005
Diarrhoea	–0.611	0.114
Hepatopathy	–0.675	0.069
Renal insufficiency	–0.916	0.002
Haemorrhagic diarrhoea	–0.611	0.114
Melaena	–0.431	0.218
Haematemesis	–0.339	0.359
Polydipsia	–0.943	0.017
Convulsions	–0.111	0.840

AE, adverse event.

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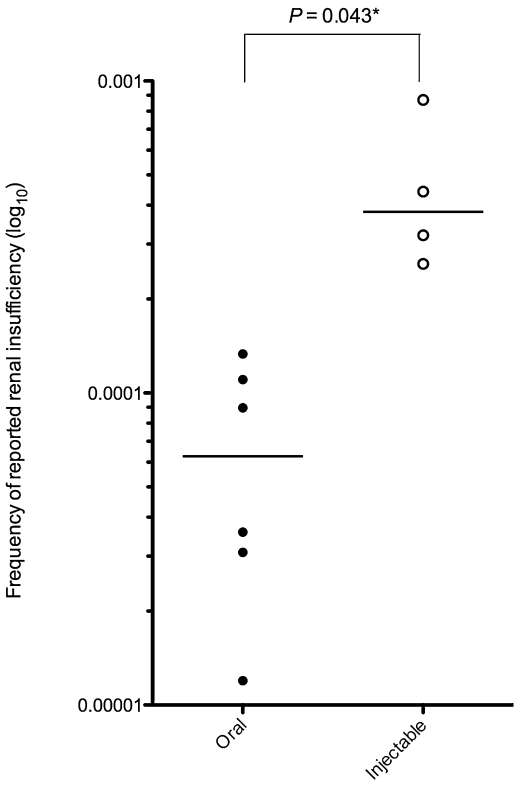

Fig. 2. Frequency (log_{10} scale) of renal insufficiency reported in dogs and cats in association with oral or injectable NSAIDs. Points represent frequencies for individual drugs and line indicates median.

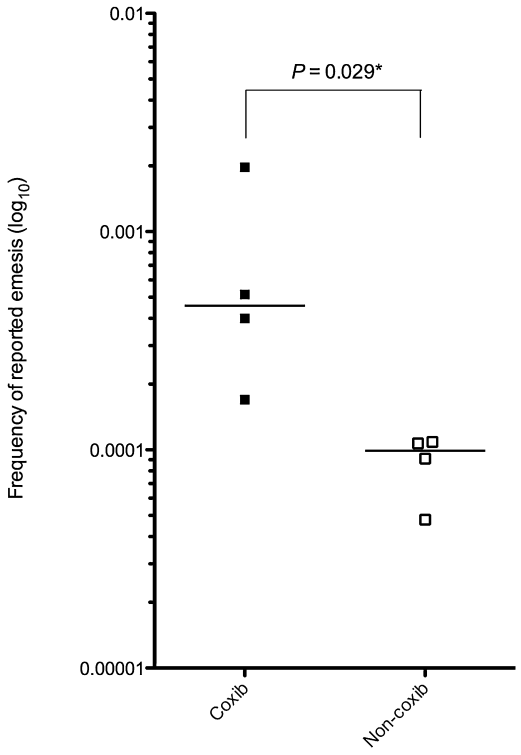

Fig. 4. Frequency (log_{10} scale) of emesis reported in dogs in association with coxib or non-coxib NSAIDs. Points represent frequencies for individual drugs and line indicates median.

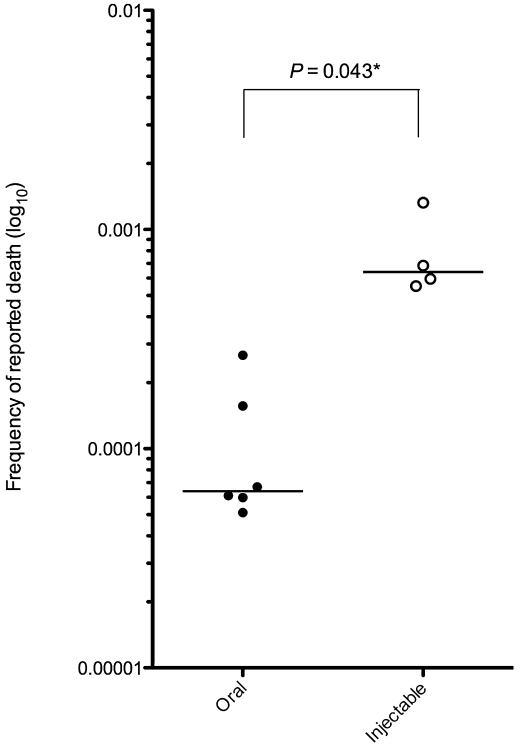

Fig. 3. Frequency (log_{10} scale) of death reported in dogs and cats in association with oral or injectable NSAIDs. Points represent frequencies for individual drugs and line indicates median.

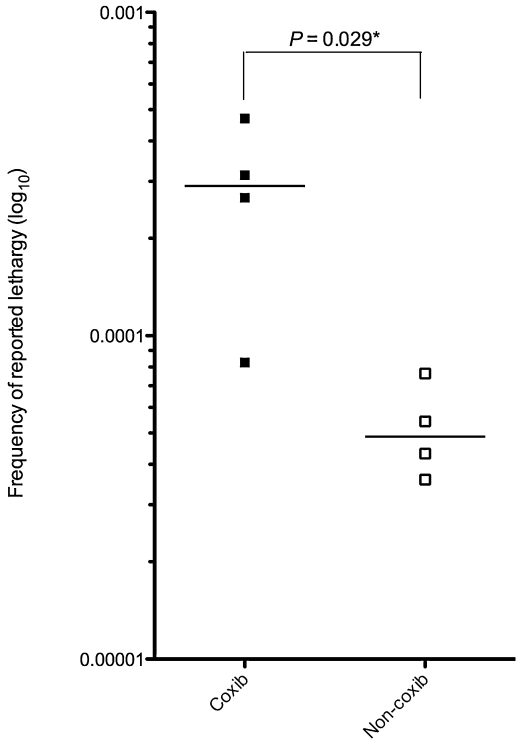

Fig. 5. Frequency (log_{10} scale) of lethargy reported in dogs in association with coxib or non-coxib NSAIDs. Points represent frequencies for individual drugs and line indicates median.

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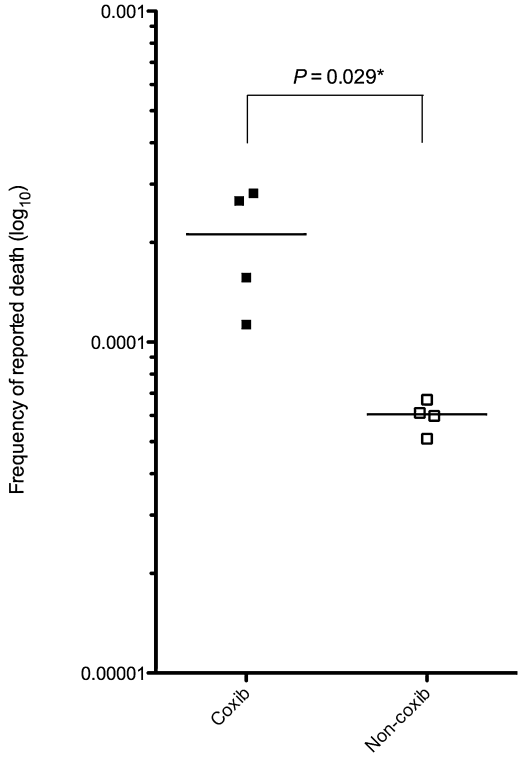

Fig. 6. Frequency (log_{10} scale) of death reported in dogs in association with coxib or non-coxib NSAIDs. Points represent frequencies for individual drugs and line indicates median.

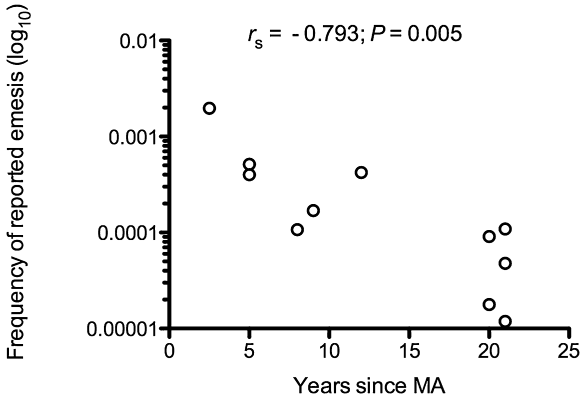

Fig. 7. Frequency (log_{10} scale) of emesis reported in dogs and cats plotted against time since marketing authorisation in years, demonstrating negative correlation.

Discussion

These data represent the most complete assessment possible of AE reports following NSAID administration in companion species in the UK. Pain management, which may include NSAID prescription, represents a significant contribution of the veterinary profession to animal welfare (Lascelles and Main, 2002). Knowledge of the frequency of reported NSAID AEs contributes to the ability of prescribers to balance benefits with risks of treatment, and informs discussions with animal owners. Until more active surveillance of AEs to NSAIDs is possible, the data presented are vital to aid decision-making around administration.

The frequency of reported NSAID AEs was low, and similar between molecules. Injectable formulations, compared with oral formulations, and coxibs compared with non-coxibs, were associated with a higher frequency of reported AEs. However, there are likely to be biases related to the circumstances in which the formulations were prescribed and AEs reported, which may well account for these differences.

Gastrointestinal disturbance, renal insufficiency, anorexia, lethargy and death were the most commonly reported AEs in cats and dogs; the data do not suggest either species to be at increased risk of any of these AEs. A systematic review of NSAID AEs in dogs by Monteiro-Steagall et al. (2013) reported that gastrointestinal AEs were most common, but these authors found renal insufficiency and death were not reported, suggesting those AEs were unlikely to occur within small to moderate studies. Owing to their seriousness, these AEs, if observed during clinical use, are likely to be reported and so appear relatively frequently in pharmacovigilance data. This supports the validity of assessing the frequency of reported AEs segregated by VeDDRA coding, rather than by assessing the total number of reports.

The frequency of emesis was less than one report per 500 doses of product sold. In clinical studies in dogs the incidence of vomiting has ranged from 1 in 25[5] to 1 in 4[6] (Reymond et al., 2012). Gastrointestinal disorders are well recognised (often self-limiting) NSAID-related AEs that are detailed in SPCs of all veterinary NSAIDs. Emesis may therefore be regarded as a 'normal' side effect of NSAIDs, thus the likelihood of reporting is low; the frequency reported here probably underestimates the likelihood of emesis associated with NSAIDs. Under-reporting of AEs within spontaneous reporting systems is well documented; in medical practice within the UK it has been estimated to be up to 98% (Fletcher, 1991). However, the degree of under-reporting decreases with increasing severity of AE, shorter length of time post MA, and the occurrence of an unlisted AE (Alvarez-Requejo et al., 1998).

Frequency of death reported was less than one per 500 injectable doses, and one per 2000 oral doses sold, however death ranked highly in the order of AEs for all of the NSAID molecules and formulations. Convulsions were reported with the majority of NSAID molecules, and have not previously been reported associated with licensed NSAIDs in dogs and cats. Seizures associated with ibuprofen and aspirin have been reported in the human medical literature (Hernández-Díaz and Rodríguez, 2000); additionally, the potential for certain NSAID molecules to potentiate epileptogenic γ-aminobutyric acid (GABA) antagonism of certain fluoroquinolone antibiotics has been reported (Kim et al., 2009). These data are insufficient to conclude that NSAIDs have the potential to increase convulsive activity in dogs and cats, but highlight the value of surveillance systems in detecting 'signal' data of unanticipated AEs coincident with product administration, which may then be more rigorously investigated (Williams, 2012).

Renal insufficiency was reported at low frequency in association with NSAID administration. Marino et al. (2014) reported that subclinical chronic kidney disease was identified in 50% of 86, randomly selected, client owned cats in the USA. It is possible that a significant population of cats harbour subclinical renal disease, and decompensation may occur coincident with an event which decreases glomerular filtration rate such as illness leading to dehydration (Greene et al., 2014). Whilst the frequency of reported renal insufficiency associated with NSAID administration may thus be artificially increased, it is advisable to ascertain hydration status prior to prescribing NSAIDs. The prevalence of clinical signs

[5] See: http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118041.pdf (accessed 27 February 2015).

[6] See: http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118026.pdf (accessed 13 February 2013).

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of renal disease in dogs in the UK has been reported to be 0.37% (O'Neill et al., 2013), however there is currently no published information on the prevalence of subclinical renal disease in dogs.

Injectable formulations of NSAIDs were associated with increased reporting of death and renal insufficiency, compared with oral formulations, and are commonly administered perioperatively. The incidence of mortality related to general anaesthesia in healthy cats and dogs has been reported as 1 in 900 and 1 in 2000, respectively (Brodbelt, 2006). It is possible that a number of the reported deaths associated with injectable NSAIDs were also associated with anaesthesia and/or surgery, confounding the interpretation of these data. Risk of renal injury is increased by episodes of hypotension, such as may develop under general anaesthesia (Jones and Budsberg, 2000). Experimentally, the combination of hypotensive anaesthesia and meloxicam did not produce renal insufficiency in dogs studied for 7 days following anaesthesia (Boström et al., 2006). Therefore it is likely that individual patient or environmental factors determine the initiation and extent of renal injury. Balanced anaesthesia and appropriate intravenous fluid administration (to maintain adequate mean arterial blood pressure) are likely to be the most effective strategy to decrease risk of renal injury associated with perioperative NSAID use (Oliver et al., 1981).

Although coxibs were associated with higher reported frequencies of lethargy, emesis and death than non-coxibs, these data probably suffer from bias related to the duration of MA. Compared with non-coxibs, coxibs have a shorter duration of MA and a negative correlation was observed between the reported frequency of AEs and the duration of MA. The original description of increased reporting of drug related AEs during the early post-MA period, followed by decreased reporting with time, was provided by Weber (1984), and these trends continue to be identifiable (Wallenstein and Fife, 2001; Hartnell and Wilson, 2004; Chhabra et al., 2013). Our data support previous findings that, with increasing MA duration, reporting of AEs declines. Although data relating to NSAIDs with a longer MA would also be expected to be affected by the Weber effect, a longer duration post initial marketing would decrease the cumulative frequency of AEs, resulting in the observed differences between more recently licensed and more established drugs.

There was a higher frequency of reported AEs associated with mavacoxib. As one administration of mavacoxib produces similar efficacy to 30 separate doses of a daily-administered NSAID (Cox et al., 2011), the reported frequency of AEs associated with each administration of mavacoxib would be expected to be approximately 30× higher than a daily-administered product of similar MA duration, and these results support this assumption. The apparent increased frequency of AEs with mavacoxib is likely to be caused by presentation of data on a per dose basis.

There are caveats to the interpretation of our data. Due to commercial sensitivity, and data protection, only the frequency of reported VeDDRA terms as a proportion of the number of doses sold since authorisation is presented. The estimate of the number of doses sold was an assumption, but any resulting inaccuracy was applied equally, allowing meaningful comparison of the frequencies between NSAID molecules and formulations. It was not possible to evaluate an untreated group to describe the frequency of AEs in this population. Association between product administration and AE occurrence does not demonstrate causality so the degree to which reported AEs were attributable to NSAID administration is uncertain. However, the majority of frequently reported AEs in this study correlate with documented effects of NSAIDs (Monteiro-Steagall et al., 2013).

PSUR data were not available for short periods for a small number of NSAID formulations. It is likely that these data related to transition periods between brand names, and did not represent active sales periods (G. Davis, personal communication, 2014). The marked increase in overall reporting of AEs to the VMD is likely to introduce bias into our data, which will be most pronounced for more recently licensed molecules. This may further contribute to the negative correlation identified between the duration of MA and the frequency of reported AEs.

Current data do not identify patient risk factors, such as increasing age, which may predispose to AEs. There is a need to undertake a large-scale prospective cohort study, conducted within first-opinion veterinary practice, in order to generate robust data on the incidence of NSAID related AEs. However, passive surveillance data are valuable in comparing products that would be expected to be subject to similar reporting biases, and in directing future research efforts. Frequencies of AEs identified in this dataset provide information that can be used to generate hypotheses for prospective studies. The more complete reporting of these data is important because both veterinarians and owners collate the AE information for the VMD, and the information should be shared with those that contributed to it.

Conflict of interest statement

Elanco Animal Health funded the research post of James Hunt but played no role in the study design, in the collection, analysis and interpretation of data, or in the manuscript writing or submission for publication. None of the authors has any other financial or personal relationships that could inappropriately influence or bias the content of the paper.

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