JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. **34,** 108–115. doi: 10.1111/j.1365-2885.2010.01201.x.

Pharmacovigilance in veterinary medicine in Chile: a pilot study

D. IRAGÜEN*
S. URCELAY† &
B. SAN MARTÍN*

**Laboratory of Veterinary Pharmacology, Department of Clinical Sciences, Faculty of Veterinary Science, Universidad de Chile, Santiago, Chile; †Department of Animal Preventive Medicine, Faculty of Veterinary Science, Universidad de Chile, Santiago, Chile*

Iragüen, D., Urcelay, S., San Martín, B. Pharmacovigilance in veterinary medicine in Chile: a pilot study. *J. vet. Pharmacol. Therap.* **34,** 108–115.

In Chile, there is no present government policy to survey and analyse adverse drug reactions (ADRs) in the field of veterinary medicine. The intent of this study is to assess, for the first time, ADR frequency in treated animals. To this purpose, a 6-month period pilot study based on WHO recommendations was conducted to monitor ADRs in cats and dogs for frequently used drugs and common labelled signs. Of a total of 149 detected ADRs, 29 (6 in cats and 23 in dogs) were notified by means of ADR report forms, while the rest was identified after reviewing patient clinical records, thus evidencing strong under-reporting problems. More than 70% of ADRs were related to antimicrobials, vaccines and tranquilizers. In dogs, there was a significant effect on ADRs' presentation when acepromazine, amoxicillin, carprofen, ivermectin, sextuple vaccine (polyvalent vaccine that confers immunity against canine distemper virus, canine parvovirus, *Leptospira canicola, L. icterohemmoragiae*, canine adenovirus type 2 and canine parainfluenza virus) and phytomenadione (subcutaneous injection) were administered. In the case of cats, a significant influence on ADRs was detected when acepromazine, amoxicillin or vitamin K was administered. Present results suggest the need for a pharmacovigilance programme in veterinary medicine for timely ADR-presenting drug detection and drug safety improvement.

(Paper received 21 October 2009; accepted for publication 16 March 2010)

D. Iragüen, Avda. Santa Rosa 11735, La Pintana, Santiago, Chile.
E-mail: diraguen@uchile.cl

INTRODUCTION

Adverse drug reactions (ADRs) are harmful, unintended reactions often occurring at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function (Woodward, 2005; European Union, 2008). According to the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), ADRs are 'events whether or not considered to be product-related that is unfavourable and unintended and that occurs after any use of a veterinary medicinal product (VMP) (on-label or off-label uses). Included are events related to a suspected lack of expected efficacy according to approved labelling or noxious reactions in human after being exposed to VMPs' (VICH, 2008).

Safety of medicines can only be regarded as provisionally established during drug development. Of special interest are drugs approved for commercialization, mainly because safety data is based on studies performed in animals whose exposure would not normally correspond to that of animals treated in clinical practice. For instance, concomitant administration of drugs may be the source of drug interactions leading to ADRs (Amatori *et al.*, 2004; Kuroha *et al.*, 2004; Orito *et al.*, 2008; Yap *et al.*, 2008).

Pharmacovigilance was first defined for human medicine by World Health Organization (WHO) as any activity conducting to obtain systematic indication of probable casualty relations between drug administration and ADRs in a population (WHO, 1972). This definition has been also applied to veterinary medicine. Veterinary pharmacovigilance monitors the safety of veterinary medicines, including vaccines (VAC) used for the prophylaxis, diagnosis or treatment of diseases in animals once they reach the market after authorization. The task of veterinary pharmacovigilance is to ensure the protection of the environment as well as the safety of veterinary medicines in animals, animal-derived food and people in contact with veterinary medicines (EMEA, 2006).

It has been recognized that pharmacovigilance is an international activity with increased exchange of information and cooperation around the world. The VICH represents an international effort at harmonizing technical requirements for product registration. Members are the United States of America (USA),

European Union (EU), Japan and Canada. The scope of pharmacovigilance in the VICH topic GL24 document is defined as the management of the detection and investigation into the clinical effects of marketed VMPs mainly concerned with the safety and efficacy in animals and the safety in people exposed to these products. It deals with the spontaneous reporting system for the identification of possible adverse events following the use of marketed VMPs (VICH, 2008).

In general terms, in a spontaneous reporting system, the reporter communicates with the Marketing Authorization Holders (MAH), the MAH submits ADRs' reports to the Regulatory Agencies (RA) and the RA notifies the MAH of ADRs' reports it has received (VICH 2008). An ADR report consists of information about adverse medical events occurring in patients presumably because of drug administration.

In the United States, the Food and Drug Administration (FDA) Center for Veterinary Medicines (CVM) monitors voluntary reports of ADRs. FDA-CVM encourages pet owners and VMP users to report to the manufacturer of a suspect product. The manufacturer must complete the FDA 1932 form and forward the report to the CVM. Federal regulations require drug manufacturers to forward to the FDA all information concerning ADRs' reports to their companies (Keller *et al.*, 1998; FDA, 2009b). In addition, if the drug is not FDA approved for animal administration or if it is approved but the reporter does not wish to contact the manufacturer, the report may be submitted directly to the FDA on Form 1932a, a preaddressed, prepaid postage form that can be completed and dropped in the mail (FDA, 2009b). Such reporter information remains confidential. Presently, USA has been gathering ADR information since 1987, therefore having the largest ADR database. It is freely accessible, and available information includes administered drugs, route of administration, species presenting the reaction and clinical signs presented by animals (FDA, 2009a).

In the EU, pharmacovigilance is an integral part of the postmarketing surveillance of VMPs. Its scope includes all aspects of safety and, in particular, adverse reactions in treated animals and exposed humans, adverse environmental events and those resulting from violations of maximum residue limits (Woodward, 2005).

The European Medicines Agency (EMEA) and its veterinary scientific committee, the Committee for Veterinary Medicinal Products, are responsible of the postmarketing surveillance of VMP in the EU. Monitoring of the safety of authorized products is conducted through the EU's network of national veterinary medicines agencies, in close cooperation with veterinary professionals and the pharmaceutical companies themselves. The CVMP plays an important role in this EU-wide pharmacovigilance activity by closely monitoring potential safety concerns and, when necessary, can make recommendations to the European Commission, which has the ultimate responsibility for granting, refusing, revoking or suspending marketing authorizations (EMEA, 2009).

In Chile, there is no pharmacovigilance programme in veterinary medicine whatsoever. Therefore, essential information such as frequency, severity of treated animal ADRs and reliable data about frequent ADR-producing drugs remains unknown. In this article, a small-scale pharmacovigilance programme is proposed. To the purposes of the present validation-type study, the concept small scale is threefold. First, it refers to the number of veterinarians involved. Secondly, it is bounded to the ADRs capable to be detected in a relatively short time period (6 months). In third place, it is pointed towards early-occurring and known reactions. ADRs' presentation was monitored in cats and dogs for most frequently used drugs and for ADRs identified prior to drug marketing authorization. Results of a successful implementation in a small pilot group are discussed as well.

MATERIALS AND METHODS

The study was performed in two phases. The first one consists of a survey intended to gather information related to drugs used in small animal clinical practice by means of a questionnaire handed to participating veterinarians. The second one corresponds to a pilot pharmacovigilance programme, applied to a reduced number of veterinary clinics and drugs producing ADRs. Materials and methods considered for both phases are explained in the following sections.

Phase 1: veterinary clinics

A total of 129 veterinarians were asked to participate in the survey. They were accepted to participate in the study provided: (i) they had more than 150 feline or canine patients per month, (ii) they kept written or computerized records of all patients and (iii) they would allow reviewing available patient records. A total of 75 veterinarians from 19 veterinary clinics finally agreed to participate in the survey. All veterinarians and veterinary clinics met the study criteria and therefore were included in the research.

Survey questionnaire

A survey instrument consisting of a questionnaire about most frequently used drugs in cats and dogs was developed. The questionnaire was personally delivered to the veterinarians of selected veterinary clinics.

To identify most frequently used groups of drugs in small animal clinical practice, veterinarians were instructed to assign an integer frequency value from 1 to 7 (one corresponding to drugs less frequently administered and seven to drugs most frequently administered) to each group of drugs according to the frequency of prescription in cats and dogs. A drug administration index for each drug group j ($1 \leq j \leq 10$), referred to herein as DAI_j, was defined as:

$$\mathrm{DAI}_j = \frac{\sum_{k=1}^{7} k \times A_{j,k}}{\sum_{k=1}^{7} A_{j,k}} \quad (1)$$

Here, $A_{j,k}$ is the number of occurrences corresponding to each drug frequency administration value k ($1 \leq k \leq 7$) and drug

Table 1. Designation for groups of drugs for drug administration index (DAI) computation as described in equation (1)

Drug group number (j as in equation 1)	Description
1	Antimicrobials
2	External antiparasitic drugs
3	Internal antiparasitic drugs
4	Vaccines
5	Anti-inflammatory drugs
6	General Anaesthetics
7	Tranquilizers
8	Antifungal
9	Vitamins
10	Hormones

group j. Drug groups are described in Table 1. It is noted that in our study, the expression $\sum_{k=1}^{7} A_{j,k}$ remains the same for all drug groups.

A frequency analysis using Microsoft Excel was performed on administered drugs within each drug group. This included on-label and off-label drug use along with ADR historical data according to each drug group.

Because of the fact that ADRs are low-frequency events, drug selection was performed according to the following criteria: (i) drugs belonging to group of most frequently administered drugs, (ii) even when they were not frequently administered, the drug must have a high ADR production frequency, (iii) ADRs to be monitored must have been identified by most participating veterinarians, before marketing authorization and (iv) corresponding reactions should appear in a short time period after drug administration.

Phase 2: pharmacovigilance pilot study

A total of 19 veterinary clinics from 14 districts in Santiago city agreed to participate in the pharmacovigilance survey. A visit to all veterinary clinics was programmed, and a document with relevant information was handed to veterinarians. The latter included ADR definition, clear indication of purposes and duration of the study, drugs intended to be monitored during the pilot study, those ADRs that needed to be reported and the reporting system required to be used.

Veterinarians were requested to report detected ADRs in cats and dogs treated with any of the drugs considered in the study, identified either by themselves or by pet owners. The latter were instructed on the possible reactions their pets might present according to the administered drug and, in case of reaction occurrence, to bring the pet to the corresponding veterinary clinic.

ADRs to be reported were those previously identified by pharmaceutical laboratories in clinical studies prior to drug marketing authorization. In addition, veterinarians were asked to inform ADRs by means of filling an ADR reporting form, previously handed to them. Once the latter document was fully completed, it was submitted to the author by electronic or postal mail. Phone contact for ADR notification was also accepted.

The ADR reporting form was adapted from that used in the EU (EMEA, 2005). The pilot pharmacovigilance study was 6 month long, from April to September 2006. Once the pharmacovigilance programme was finished, veterinary clinics were again visited for two purposes: (i) to obtain the number of cats and dogs attended in the clinics in the period covered by the pilot study (cohorts) that received each drug and (ii) for reviewing patient records to identify ADRs in cats and dogs not reported by veterinarians. This served as a means to assess the accuracy of the whole reporting process.

Prospective observational study

A prospective cohort study was performed. Two cohorts, consisting of cats and dogs, were defined. Animals were attended in veterinary clinics and treated with one or more selected drugs. A 2×2 contingency table was calculated for each combination (administered drug vs. ADR) upon which a quantitative method was considered. A statistical χ^2 analysis was performed (95% confidence level with 1 degree of freedom) and odds ratio (OR) was calculated (95% CI). The analysis was performed using the software Infostat (2004).

RESULTS

Phase 1

A total of 75 questionnaires were delivered to veterinarians, with 92% fully answered. Groups of drugs most frequently administered in dogs and cats are shown in Fig. 1. Relative frequencies of the most commonly administered drugs for each corresponding group are presented in Table 2.

On-label and off-label use of VMPs is shown in Fig. 2. According to the information provided in the questionnaires, high frequencies regarding off-label use were detected for antimicrobials (AMC), internal antiparasitic drugs (INT-AP)

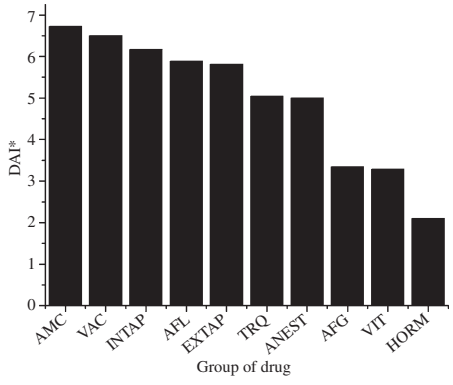

Fig. 1. Groups of drugs most frequently used in small animal clinical practice. AMC, antimicrobials; VAC, vaccines; INT-AP, internal antiparasitic drugs; AFL, anti-inflammatories; AP EXT, external antiparasitic drugs; TRQ, tranquilizers; ANEST, general anaesthetics; AFG, antifungal; VIT, vitamins; HORM, hormones. *Drug administration index (DAI) was calculated using equation (1).

Table 2. Relative frequencies (R.F. %) of drugs most frequently used in small animals' clinical practice. Drugs were identified for each group of drugs

Group of drug	Generic 1	R.F. (%)	Generic 2	R.F. (%)
Antimicrobials	Amoxicillin	25.7	Enrofloxacin	20.4
Vaccines	Rabies	33.1	Sextuple vaccine	29.5
Antiparasitic drugs	Ivermectin	25.9	Levamisole	22.2
Anti-inflammatory	Ketoprofen†	41.6	Carprofen	24.0
Sedatives	Acepromazine	52.4	Diazepam	21.8
General anaesthetics	Ketamine	43.1	Thiopental	35.8
Antifungal	Griseofulvin	39.3	Ketoconazole	29.9
Vitamins	B vitamins	34.6	Vitamin K‡	30.7
Hormones	Estradiol	50.0	Progesterone	23.3

†Oral administration. ‡Fitomenadione, subcutaneous administration.

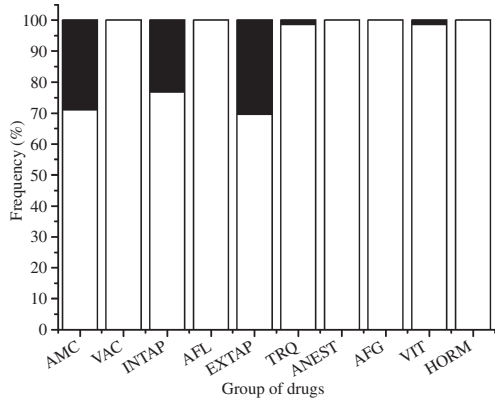

Fig. 2. On-label and off-label drug use for each drug group in dogs and cats. Black areas represent off-label use; white areas represent on-label use. AMC, antimicrobials; VAC, vaccines; INT-AP, internal antiparasitic drugs; AFL, anti-inflammatories; AP EXT, external antiparasitic drugs; TRQ, tranquilizers; ANEST, general anaesthetics; AFG, antifungal; VIT, vitamins; HORM, hormones.

and external antiparasitic drugs (EXT-AP), corresponding to 29%, 23% and 30%, respectively. In all cases, off-label use for AMC and INT-AP drugs was referred to the administration of a higher dose than that proposed by the manufacturer and approved by the regulatory process. Off-label use of EXT-AP drugs, where ivermectin was included, dose adjustments, route of administration and the use in species not recommended by the manufacturer were mentioned as off-label administration.

Previous experiences reported by veterinarians on ADRs' presentation in their patients revealed that VAC (17%), AMC (14%), anti-inflammatories (AFL) (13%), EXT-AP (13%), vitamins (VIT, 13%) and tranquilizers (TRQ, 11%) were the most frequent ADR-producing drugs. Other drugs as INT-AP, hormones (HORM), antifungal (AFG) and general anaesthetics (ANEST) appeared with lower frequencies (19%, considering remaining groups of drugs together). Following the defined criteria for drug selection (see Materials and Methods), amoxicillin, ketoprofen (oral administration), carprofen, ivermectin, acepromazine, vitamin K, rabies vaccine and sextuple vaccine were used in the second phase of the study. Sextuple vaccine was

Table 3. Drugs and adverse drug reactions (ADRs) selected for phase 2 of the study

Group of drugs	Generics	ADRs
Antimicrobials	Amoxicillin	Gastrointestinal: vomiting, diarrhoea Allergic reactions: anaphylaxis
Vaccines	Rabies vaccine – sextuple vaccine	Acute allergic reactions: angioedema, anaphylaxis
Anti-inflammatories	Ketoprofen† – carprofen	Gastrointestinal: vomiting, diarrhoea, gastric or duodenal ulcers
External antiparasitic drugs	Ivermectin	Ataxia, depression, midriasis
Tranquilizers	Acepromazine	Hypotension
Vitamins	Vitamin K‡	Acute allergic reactions: angioedema, anaphylaxis

†Oral administration. ‡Fitomenadione, subcutaneous administration.

only used in dogs and is a polyvalent vaccine that confers immunity against canine distemper virus, canine parvovirus, leptospirosis (*Leptospira canicola* y *L. icterohemmoragiae*), canine adenovirus type 2 and canine parainfluenza virus. ADRs to be monitored are detailed in Table 3.

Phase 2

At this stage, ADRs were already identified by veterinarians or owners depending on administered drug. The latter were informed by veterinarians on what ADRs their pets could possibly present. For instance, if the patient (dog) received ivermectin as treatment (600 μg/kg oral administration), the owner should have pay attention whether the dog was depressed. In case ketoprofen was used (oral administration), the owner was instructed to report possible vomits or diarrhoea. Corresponding ADR report forms were completed solely by the veterinarian and submitted to the author.

The number of ADRs detected in the two animal species considered is shown in Table 4. As expected, there was a low ADR report rate by means of ADR Report Form submission in dogs and cats (20% and 17.6%, respectively).

ADRs detected in dogs and cats for each monitored drug are presented in Table 5. The most frequent ADRs in dogs occurred after sextuple vaccine administration (not used in cats).

Table 4. Adverse drug reactions (ADRs) detected in dogs and cats

Animal species	ADRs' report form	Review of clinical records	Total
Cats	6	28	34
Dogs	23	92	115

Data were obtained by means of ADR report form submitted to the author or by reviewing clinical records in the veterinary clinics.

Table 5. Frequencies of adverse drug reactions (ADRs) detected in dogs and cats for each of the selected drugs

	Total of ADRs detected† (%)	
Drug	Dogs (n = 115)	Cats (n = 34)
Sextuple vaccine	34 (29.6)	–
Amoxicillin	25 (21.7)	15 (44.1)
Acepromazine	25 (21.7)	6 (17.6)
Ivermectin	15 (13.0)	–
Vitamin K‡	12 (10.4)	6 (17.6)
Ketoprofen§	2 (1.7)	7 (20.6)
Carprofen	2 (1.7)	0 (0)
Rabies vaccine	0 (0)	0 (0)

Relative frequencies are presented in parenthesis. †ADRs detected includes reactions collected from ADR report forms and information contained in patient clinical records. ‡Fitomenadione, subcutaneous administration. §Oral administration.

Amoxicillin showed high frequencies of ADRs detected in dogs and cats (21.7% and 44.1%, respectively).

The cohort of dogs (n = 2939) and cats (n = 740) resulting from the 6-month period of the pilot study is shown in Tables 6 and 7, respectively. In dogs, there was a significant positive effect on ADRs' presentation when acepromazine (χ^2 = 115.86; OR 22.24), amoxicillin (χ^2 = 34.63; OR 5.48), carprofen (χ^2 = 7.43; OR 9.37), ivermectin (χ^2 = 109.66), sextuple vaccine (χ^2 = 35.67; OR 4.55) and vitamin K (χ^2 = 46.02; OR 7.29) were administered ($P < 0.05$). Rabies vaccine (χ^2 = 2.12) and ketoprofen (χ^2 = 3.40) showed no influence on ADRs.

In the case of cats, a positive significant influence on ADRs was detected when acepromazine (χ^2 = 28.84; OR 3.99–35.25), amoxicillin (χ^2 = 12.11; OR 1.83–10.75) and vitamin K (χ^2 = 27.59; OR 3.72–30.03) were administered ($P < 0.05$). There was no significant influence on ADRs when rabies vaccine (χ^2 = 2.88; OR 0–1.26), carprofen (χ^2 = 0.83; OR 0–38.88) or ketoprofen (χ^2 = 2.75; OR 0.86–6.03) was administered.

DISCUSSION

Pharmacovigilance deals with the detection, evaluation, understanding and prevention of ADRs or any other drug administration-related problem. Its focus on event detection provides useful evidence about failures on safety, quality and efficacy of medicinal products (Woodward, 2005). In Chile, veterinary pharmacovigilance activities are not performed at present. Even data showing the use of veterinary drugs, in terms of frequency, is scarce. This local scenario suggested the present research that, in its first phase, was intended to gather information about most frequently used drugs in small animals, specifically cats and dogs. Collected data allowed us to select drugs to be included in phase two, a small-scale pilot pharmacovigilance programme. Most frequently used drugs were selected to ensure ADR identification by veterinarians. In addition, ADRs previously

Table 6. Cohort of dogs after a 6-month ADR detection follow-up period

Administered drug	Treated + ADR	Treated − ADR	Untreated† + CS	Untreated‡ − CS	OR	95% CI	P-value
Acepromazine	25	358	8	2548	22.24	10.15–48.72	< 0.0001
Amoxicillin	25	643	16	2255	5.48	2.93–10.24	< 0.0001
Rabies vaccine	0	586	13	2340	0	0–1.58§	> 0.05*
Carprofen	2	283	2	2652	9.37	1.62–54.32	0.006
Ivermectin	15	317	0	2607	Ind	–	< 0.0001
Ketoprofen¶	2	472	2	2463	5.22	0.90–30.20	> 0.05*
Sextuple vaccine	34	731	22	2152	4.55	2.66–7.79	< 0.0001
Vitamin K††	12	104	44	2779	7.29	3.78–14.06	< 0.0001

*Not significant ($P > 0.05$). †Untreated + CS: patient seen by the practice for the identified clinical signs (CS) but received no medications. ‡Untreated − CS: untreated patient that showed no clinical signs. §Confidence intervals calculated using Yates correction (Fleiss, 1973). ¶Oral administration. ††Fitomenadione, subcutaneous administration.

Table 7. Cohort of cats after a 6-month ADR detection follow-up period

Administered drug	Treated + ADR	Treated − ADR	Untreated† + CS	Untreated‡ − CS	OR	95% CI	P-value
Acepromazine	6	49	7	678	11.86	3.99–35.25	< 0.0001
Amoxicillin	15	234	7	484	4.43	1.83–10.75	0.0005
Rabies vaccine	0	187	12	541	0	0–1.26§	> 0.05
Carprofen	0	7	16	717	0	0–38.88§	> 0.05
Ketoprofen¶	7	184	9	540	2.28	0.86–6.03	0.974
Vitamin K††	6	43	9	682	10.57	3.72–30.03	< 0.0001

*Not significant ($P > 0.05$). †Untreated + CS: patient seen by the practice for the identified clinical signs (CS) but received no medications. ‡Untreated − CS: untreated patient that showed no clinical signs. §Confidence intervals calculated using Yates correction (Fleiss, 1973). ¶Oral administration. ††Fitomenadione, subcutaneous administration.

identified in clinical trials and known by veterinarians were included in this research.

DAI values computed from survey data showed that AMC, VAC, INT-AP, EXT-AP, AFL and ANEST were the most frequently used groups of drugs in small animals. This is shown in Fig. 1. Published reports on ADRs indicate that among these groups, VAC, EXT-AP and nonsteroidal anti-inflammatory drugs were responsible for 39%, 16.7% and 12.3% of ADRs reported to the Veterinary Medicines Directorate, respectively (Dyer *et al.*, 2008). Müntener *et al.* (2009) reported that high percentages of ADRs' reports corresponded to antiparasitic drugs (47%) and AFL (23%). The latter have also a correlation with the most frequently used therapeutics classes in dogs. Based in our results and on the mentioned references, selected drugs to be monitored in phase 2 of the study would allow successful identification of ADRs in dogs and cats.

Off-label use of AMC and antiparasitic drugs was practiced by about one-third of surveyed veterinarians. For AMC administration, this is a concerning situation, as drug safety and efficacy can be adversely modified when alternative routes of administration are used. Pharmaceutical formulations are designed to be administered in specific tissues, where their absorption process is optimal. Changes in the magnitude of absorption can lead to lower minimum inhibitory concentrations (MICs), therapy failure or the emergence of resistant pathogens, among other consequences (Hoekstra & Paulton, 2002; Malik *et al.*, 2005).

Even when ivermectin is classified as a highly effective endectocide against internal and external parasites (González *et al.*, 2009), veterinarians were instructed to consider ivermectin in the EXT-AP group when answering the questionnaire because of the fact that it is mostly orally administered for the treatment of external parasite infestations in dogs and is rarely used in the prevention of parasitism. Ivermectin has a wide therapeutic range mainly because of the presence of P-glycoprotein in the hematoencephalic barrier, which functions as a transmembrane efflux pump that limits drug uptake by the brain, thereby protecting against ivermectin neurotoxicity (Mealey, 2004; González *et al.*, 2009; Merola *et al.*, 2009).

In Chile, ivermectin is registered for parenteral and oral use in species not considering small animals. Oral administration of parenteral formulations of ivermectin has shown faster absorption and higher plasmatic levels when compared to subcutaneous administration in dogs (Gokbulut *et al.*, 2006). Furthermore, ivermectin is daily administered at 600 μg/kg during at least a month in the treatment of generalized demodicosis in dogs, leading to drug accumulation owing to its pharmacokinetics characteristics (Mueller, 2004; González *et al.*, 2009). Annual reports on ADRs in the USA indicate a high frequency of these reactions in dogs when administered orally (FDA, 2009a). In our study, 4.7% of treated dogs presented one or more ADRs to ivermectin, suggesting that off-label use may be considered an important factor causing ADRs in treated dogs. As mentioned earlier, according to national regulations, ivermectin administration in dogs is considered off-label.

The pharmacovigilance pilot study showed some aspects that need to be discussed. Following the recommendations of the World Health Organization (WHO, 2001), a spontaneous reporting system by means of an ADR Report Form was implemented. Only 19% of ADRs were identified by submitting of ADR Report Form. Reviewing clinical records is not currently an activity performed in pharmacovigilance programmes, but as veterinarians were not used to this report system, clinics were visited to collect data of all animals attended in the 6-month period.

ADRs under-reporting is a matter of concern in pharmacovigilance programmes. In South Africa, a legal obligation of the veterinary professionals to report all adverse reactions was established. Nonetheless, only 21 reports were received in a 2-year period, being this figure the lowest so far (Naidoo & Sykes, 2006). In the EU and in USA, there is no such obligation. However, veterinarians and animal owners are encouraged to report adverse events and products' failures to the corresponding government agencies (Woodward, 2005; FDA, 2009b).

This study determined a significant incidence for acepromazine, amoxicillin and vitamin K as drugs often associated with ADRs in cats and dogs. In the case of amoxicillin and vitamin K, most frequently described ADRs correspond to type B reactions, defined as dose-independent, hypersensitivity reactions. ADRs corresponding to acepromazine are of type A reactions (explained by the drug pharmacological effect) and dose dependent (Hunziker *et al.*, 2002; EMEA, 2004; Aagaard & Hansen, 2009).

In our study, AMC, VAC and TRQ were found to be responsible of more than 70% of detected ADRs. EMEA (2009) pointed out that AMC were responsible of 30% of total ADR notifications. In the United Kingdom, the Veterinary Medicines Directorate (VMD, 2009) informed for the first time 2009 that a 45% of total ADRs was a result of vaccine administration.

A high frequency of ADRs was expected to be found in AFL drugs. However, no significant association on ADRs' presentation was observed after ketoprofen administration. Only a significant association between ADRs' presentation and carprofen administration was found in dogs, probably because of the low number of ADR reports for both animal species. AFL drugs are widely used in veterinary medicine, and their corresponding ADRs are well documented (Narita *et al.*, 2005; Luna *et al.*, 2007; Niza *et al.*, 2007). The FDA-CVM processed 17 442 carprofen-associated ADRs during a 90-month period, 1381 etodolac-associated ADRs during a 60-month period and 285 meloxicam-related reports during a 12-month period (Hampshire *et al.*, 2004). Our results show that ADR reporting regarding AFL drugs along with the importance of conducting continuous safety monitoring activities must be encouraged to veterinarians. Moreover, pet owners should be involved in ADR activities by bringing them broader insights on how to recognize them.

There were some limitations in the study that need to be taken into account. First, only a few drugs with high frequency of administration in small animals with known ADRs were included in the pilot study. In order that veterinarians were able to identify ADRs in a short period (6 months), this criterion was adopted. Second, even when pharmacovigilance programmes include both previously identified ADRs (prior

marketing authorization) and late or rare ADRs (not-labelled signs), this study only considered the former. This omission is justified by the primary intent of the study, which is to put a pilot-scale pharmacovigilance programme in Chile, serving as a means of validation for a country-wide programme. Anyhow, one of the pharmacovigilance major purposes, namely the continued monitoring of the safety of a product to ensure that the risks and benefits remain acceptable (Woodward, 2005), is preserved in this study. Third, the programme was applied only in the capital to a limited number of veterinary clinics. Despite the above-mentioned limitations, ADRs were identified by veterinarians and ADR reports were submitted to the authors. A natural continuation of this study would be to include the full list of veterinary medicines as well as the monitoring of known and unknown reactions.

Our results show that more than 70% of detected ADRs were probably caused by AMC, VAC and TRQ, being these findings in agreement with international literature. In the EU, from a total of 1675 ADRs' reports in small animals submitted to the EMEA in 2008, 30% were attributed to AMC (EMEA, 2009). In the United Kingdom, the Veterinary Medicines Directorate published that 45% of ADRs' reports were associated with vaccine administration (VMD, 2009).

In Chile, there is not a pharmacovigilance in veterinary medicine. However, in human medicine, a pilot programme began in 1995 with a regional coverage, receiving 63 spontaneous ADR reports. Currently, this programme has been expanded nation-wide, detecting 771 ADRs in 2001 (Morales *et al.*, 2002). Ethical reasons provide a strong motivation for the inception of a pharmacovigilance programme. Veterinary medicine should be no exception.

A pilot pharmacovigilance programme using small animals was performed in Chile. To the knowledge of the authors, this is the first instance of this kind of study. Our findings, including ADRs detected using a spontaneous reporting scheme along with ADRs associated to off-label use, suggest the need for broadening this study to other veterinary drugs and, in the future, implement a nation-wide pharmacovigilance programme for veterinary medicine.

REFERENCES

Aagaard, L. & Hansen, E.H. (2009) Information about ADRs explored by pharmacovigilance approaches: a qualitative review of studies on antibiotics, SSRIs and NSAIDs. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656469/pdf/1472-6904-9-4.pdf (accessed 8 September 2009).

Amatori, F.M., Meucci, V., Giusani, M., Soldani, G., Corraza, M. & Giorgi, M. (2004) Effect of grapefruit juice on the pharmacokinetics of cyclosporyne in dogs. *Veterinary Records*, **154,** 180–181.

Dyer, F., Spagnuolo-Weave, M., Cooles, S. & Tait, A. (2008) Suspected adverse reactions, 2007. *Veterinary Record*, **163,** 69–72.

EMEA (2004) The European Agency for the Evaluation of Medicinal Products. Harmonising the approach to casualty assessment for adverse reactions for veterinary medicinal products. EMEA/CVMP/552/03-FINAL, **8** pp.

EMEA (2005) The European Agency for the Evaluation of Medicinal Products. Guideline on EU veterinary suspected adverse reaction report form for veterinarians and health professionals. EMEA/CVMP/893/04-UK, 2 pp.

EMEA (2006) The European Agency for the Evaluation of Medicinal Products. Veterinary pharmacovigilance in the EU – a simple guide to reporting adverse reactions. EMEA/CVMP/PhVWP/110607/2005, 2 pp.

EMEA (2009) The European Agency for the Evaluation of Medicinal Products. Veterinary medicines. Available at: http://www.emea.europa.eu/index/indexv1/htm (accessed 15 December 2009).

European Union, (2004) *The rules governing medicinal products in the European Union*. Pharmacovigilance. Medicinal Products for Human and Veterinary Use http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-9/pdf/vol9_10-2004_en.pdf. (accessed 12 may 2010).

Fleiss, J.L. (1973) Assessing significance in a four-fold table. In *Statistical Methods for Rates and Proportions*. Eds. R.A. Bradley, J.S. Hunter, D.G. Kendall, G.S. Watson. John Wiley & Sons, New York. pp 14–22.

Food and Drug Administration (FDA) (2009a) Cumulative veterinary adverse event (ADE) reports. Available at: http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm (accessed 4 May 2009).

Food and Drug Administration (FDA) (2009b) How to report an adverse drug experience. Available at: http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm (accessed 10 August 2009).

Gokbulut, C., Karademir, U., Boyacioglu, M. & McKellar, Q. (2006) Comparative plasma disposition of ivermectin and doramectin following subcutaneous and oral administration in dogs. *Veterinary Parasitology,*, **135,** 347–354.

González, A., Sahagún, A.M., Diez, M.J., Fernández, N., Sierra, M. & García, J. (2009) The pharmacokinetics and metabolism of ivermectin in domestic animal species. *The Veterinary Journal*, **179,** 25–37.

Hampshire, V., Doddy, F., Post, L., Koogler, T., Burgess, T., Batten, P., Hudson, R., MsAdams, D. & Brown, M. (2004) Adverse drug event reports at the United States Food and Drug Administration Center for Veterinary Medicine. *Journal of the American Veterinary Medical Association*, **225,** 533–536.

Hoekstra, K. & Paulton, R. (2002) Clinical prevalence and antimicrobial susceptibility of *Staphylococcus aureus* and *Staphylococcus intermedius* in dogs. *Journal of Applied Microbiology*, **93,** 406–413.

Hunziker, T., Bruppacher, R., Kuenzi, U.P., Maibach, R., Braunschweig, S., Halter, F. & Hoigné, R.V. (2002) Classification of ADRs: a proposal for harmonization and differentiation based on the experience of the Comprehensive Hospital Drug Monitoring Bern/St Gallen, 1974-1993. *Pharmacoepidemiology and Drug Safety*, **11,** 159–163.

Infostat (2004) *Infostat, Version 2004*. Infostat Group, FCA, Universidad Nacional de Córdoba, Argentina.

Keller, W., Bataller, N. & Oeller, D. (1998) Processing and evaluation of adverse drug experience reports at the Food and Drug Administration Center for Veterinary Medicine. *Journal of the American Veterinary Medical Association*, **213,** 208–211.

Kuroha, M., Shirai, Y. & Shimoda, M. (2004) Multiple oral dosing of ketoconazole influences pharmacokinetics of quinidine after intravenous and oral administration in beagle dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **27,** 355–359.

Luna, S.P., Basílio, A.C., Steagall, P.V., Machado, L.P., Moutinho, F.Q., Takahira, R.K. & Brandao, C.V. (2007) Evaluation of adverse effects of long-term oral administration of carprofeno, etodolac, flunixin meglumine, ketoprofeno, and meloxicam in dogs. *American Journal of Veterinary Research*, **68,** 258–264.

Malik, S., Peng, H. & Barton, M. (2005) Antibiotic resistance in staphylococci associated with cats and dogs. *Journal of Applied Microbiology*, **99,** 1283–1293.

Mealey, K.L. (2004) Therapeutic implications of the MDR-1 gene. *Journal of Veterinary Pharmacology and Therapeutics*, **25,** 257–264.

Merola, V., Khan, S. & Gwaltney-Brant, S. (2009) Ivermectin toxicosis in dogs: a retrospective study. *Journal of the American Animal Hospital Association*, **45,** 106–111.

Morales, M., Ruiza, I., Morgados, C. & González, X. (2002) Farmacovigilancia en Chile y el mundo. *Revista Chilena de Infectología*, **19,** S42–S45.

Mueller, R.S. (2004) Treatment protocols for demodicosis: an evidence-based review. *Veterinary Dermatology*, **15,** 75–89.

Müntener, C., Bruckner, L., Stürer, A., Althaus, F. & Schneider, A. (2009) Vigilance for veterinary medicinal products: declarations of suspected adverse reactions in the year 2007. *Schweizer Archiv fur Tierheilkunde*, **151,** 12–20.

Naidoo, V. & Sykes, R. (2006) Overview of suspected adverse reactions to veterinary medicinal products reported in South Africa (March 2004-February 2006). *Journal of the South African Veterinary Association*, **77,** 164–167.

Narita, T., Tomizawa, N., Sato, R., Goryo, M. & Hara, S. (2005) Effects of long-term oral administration of ketoprofen in clinically healthy beagle dogs. *The Journal of Veterinary Medical Science*, **68,** 258–264.

Niza, M.M., Félix, N., Vilela, C.L., Peleteiro, M.C. & Ferreira, A.J. (2007) Cutaneous and ocular adverse reactions in a dog following meloxicam administration. *Veterinary Dermatology*, **18,** 45–49.

Orito, K., Saito, M., Fukunaga, K., Matsuo, E., Takinawa, S., Muto, M., Mishima, K. & Fujiwara, M. (2008) Pharmacokinetics of zomizamide and drug interaction with phenobarbital in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **31,** 259–264.

Veterinary Medicines Directorate (VMD) (2009) Quarterly Summary Reports. Number of Animal Reports (%) by Product Type for Quarter 1 – 2009. Available at: http://www.vmd.gov.uk/sarquartsummaries/prq209.htm (accessed 16 August 2009).

VICH (2008) Guideline on Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Events Reports (AERs). VICH GL 24 (Pharmacovigilance: AERs), 7 pp.

WHO (1972) International drug monitoring: the role of national centres. *World Health Organization Technical Report Series*, **498,** 1–25.

World Health Organization (WHO) (2001) Vigilancia de la seguridad de los medicamentos. Guía para la puesta en funcionamiento de un Centro de Farmacovigilancia. The Uppsala Monitoring Centre, 32 pp.

Woodward, K.N. (2005) Veterinary Pharmacovigilance. Part 1. The legal basis in the European Union. *Journal of Veterinary Pharmacology and Therapeutics*, **28,** 131–147.

Yap, K.Y., Chui, W.K. & Chan, A. (2008) Drug interactions between chemotherapeutic regimens and antiepileptics. *Clinical Therapeutics*, **30,** 1385–1407.