Overview of suspected adverse reactions to veterinary medicinal products reported in South Africa (March 2003 – February 2004)

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ABSTRACT

The Veterinary Pharmacovigilance and Medicines Information Centre is responsible for the monitoring of veterinary adverse drug reactions in South Africa. An overview of reports of suspected adverse drug reactions received by the centre during the period March 2003 to February 2004 is given. A total of 20 reports was received. This had declined from the previous year. The general apathy with regards to the reporting of adverse drug reaction has prompted the Medicines Control Council to make reporting a legal obligation on all members of the veterinary and medical profession as from August 2004. The majority of reports involved suspected adverse reactions that occurred in dogs and cats. Most of the products implicated were Stock Remedies. Veterinarians predominantly administered these products. Only two reports were received from a veterinary pharmaceutical company.

Key words: spontaneous reports, suspected adverse drug reactions, veterinary medicinal products veterinary pharmacovigilance.

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INTRODUCTION

Veterinary medicinal products in South Africa are currently registered under two Acts and are administered by two separate regulatory authorities:

The Medicines and related Substances Control Act (Act No. 101 of 1965), is administered by the Medicines Control Council of the National Department of Health. These products are termed Veterinary Medicines and represent scheduled veterinary remedies.

The Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947) administered by the National Department of Agriculture. These products are termed Stock Remedies and represent veterinary over-the-counter remedies.

The reporting of Adverse Drug Reactions (ADRs) is currently controlled under both acts with the onus being on the pharmaceutical company marketing a product, to report these ADRs to the regulatory authorities. Although this is a condition of registration, the spontaneous reporting by pharmaceutical companies and even the veterinarians is poor and requires improvement. As such the new amendments to Act 101, August 2004, has made the reporting of ADRs by companies, veterinarians and other health care professionals a legal obligation. It is a provision of registration of Act 36 for pharmaceutical companies to legally report any ADRs to the Registrar of the Act.

The Veterinary Pharmacovigilance and Medicines Information Centre (VP & MIC), which was initially started at the Faculty of Veterinary Sciences, with private funding, has now been adopted as the official monitoring centre for veterinary medicines on behalf of Act 101. The VP & MIC is currently negotiating with the Registrar, Act 36, to also take responsibility for the monitoring, evaluating and reporting of ADRs.

MATERIALS AND METHODS

The Veterinary Pharmacovigilance and Medicines Information Centre relies on spontaneous reports of suspected adverse drug reactions. Reporting is voluntary and reports may be received from veterinarians, paraveterinary professionals, pharmacists, the general public, health care professionals and Registration Holders.

Reporters are requested to complete and submit a form, which is published in the Index of Veterinary Specialities (IVS). Reports can also be faxed or e-mailed on request. Upon receipt, each report is marked with a date and given a sequential number. The minimum information required to be given in each report is: an identifiable source (name and contact details of the reporter), animal details (species, sex, age), suspected product (name and/or registration number) and reaction details. Other information, if available, includes a history of previous treatments, any concomitant treatments and other details on the product such as batch number, etc. If some of this information does not appear on the report, the reporter is contacted and requested to submit these details.

Reports that contain all the abovementioned information are entered into a computerised database. Thereafter, the report is presented at the a meeting of the Veterinary Pharmacovigilance Working Group. At these meetings each report received since the previous discussion, is evaluated and assigned a causality classification (Table 1).

Reports are then forwarded to the relevant regulatory authority together with an evaluation and recommendation. The Registration Holder is also informed of any report of a suspected adverse reaction to one of their products, which they have not submitted themselves.

RESULTS

The Veterinary Pharmacovigilance and Medicine Information Centre received only 20 reports of suspected adverse drug reactions for the period March 2003 to February 2004, implicating 31 medicinal products. These reports are summarised and classified according to the species in which the reactions occurred (Table 2), the registration of the implicated products under current South African legislation (Table 3), the person administering the implicated product to the animal (Table 4) and the source of the report submitted to

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Table 1: **Criteria used for assigning causality.**

Causality classification	Criteria
Certain	There is a plausible time relation between the administration and the adverse event that cannot be explained by the concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) is clinically plausible and the event is definitely pharmacological or phenomenological, using a satisfactory rechallenge procedure if necessary.
Probable	There is a plausible time relationship between the administration of the drug and the adverse event, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follow a clinically reasonable response on withdrawal. A positive re-challenge is not required to meet this definition.
Possible	There is a plausible time relationship between the administration of the drug and the adverse event, but the event could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	An adverse event with a temporal relationship to drug administration that would make a casual relationship improbable, and for which other drugs, or chemicals or underlying disease provide plausible explanation.

Table 2: **Reports of suspected adverse drug reactions received for the period March 2002 – February 2003 and the period March 2003 – February 2004 classified according to species.**

Species	March 2002 – February 2003 (n = 40)		March 2003 – February 2004 (n = 20)	
	Number of reports	Percentage	Number of reports	Percentage
Canine	25	62.5	11	55
Feline	6	15	6	30
Bovine	3	7.5	2	10
Equine	2	5	0	0
Ovine/caprine	2	5	0	0
Poultry	1	2.5	0	0
Porcine	0	0	0	0
Human	1	2.5	0	0
Game	0	0	1	5

the VP & MIC (Table 5). These results are compared with those of previous years[2]. Active ingredients implicated for the current period are also summarised by causality, and classified by the species in which the reactions occurred (Table 6).

DISCUSSION AND CONCLUSIONS

There was a marked decrease in the number of reports received by the Veterinary Pharmacovigilance and Medicines Information Centre during the period March 2003 to February 2004 compared with the previous year (decreased from 40 reports to 20 reports). As in previous years, the majority of reports received pertained to products used in small animals[1,2]. The reason behind the poor reporting is unknown. This poor history of reporting by veterinarians was a reason for Act 101 making reporting a legal requirement.

The majority of these reports also implicated products registered as Stock Remedies under Act 36 of 1947. This has increased from 62 % to 65 % in the current period. This increase cannot be regarded as significant and is still disappointing. The greater occurrence in the over-the-counter remedies is most likely linked to the larger volumes at which they are used i.e. large-scale utilisation makes the occurrence of ADRs more common.

Table 3: **Comparison of the registration of products implicated in reports of suspected adverse drug reactions for the period March 2002 – February 2003 and the period March 2003 – February 2004.**

Product registration	March 2002 – February 2003 (n = 40)		March 2003 – February 2004 (n = 31)	
	Number of products	Percentage	Number of products	Percentage
Stock remedies (Act 36/47)	36	62	20	65
Veterinary medicines (Act 101/65)	11	19	9	30
Products used extra-label	11	19	2	5

Table 4: **Reports of suspected adverse drug reactions received for the period March 2002 – February 2003 and the period March 2003– February 2004 classified according to persons administering the drugs.**

Person administering drugs	March 2002 – February 2003 (n = 40)		March 2003 – February 2004 (n = 20)	
	Number of reports	Percentage	Number of reports	Percentage
Veterinarian	16	40	14	70
Owners	20	50	5	25
Other	3	7.5	1	5
Paraveterinary professional	1	2.5	0	0

Table 5: **Reports of suspected adverse drug reactions received for the period March 2002 – February 2003 and the period March 2003 – February 2004 classified according the origin of the report submitted to the Veterinary Pharmacovigilance and Medicines Information Centre.**

Person submitting report	March 2002 – February 2003 (*n* = 40)		March 2003 – February 2004 (*n* = 20)	
	Number of reports	Percentage	Number of reports	Percentage
Pharmaceutical company	1	2.5	2	10
Veterinarian	35	87.5	17	90
Paraveterinary professional	1	2.5	0	0
Veterinary specialist	1	2.5	1	5
Others	2	5	0	0

For the current year, veterinarians administered most of the drugs implicated. The number of reports of ADRs to medicines administered by owners had decreased from the previous period (from 50 % to the current 30 %). This decrease comes from a small data base and the reason, if any, cannot be determined.

Only two reports were received from industry. Even though the pharmaceutical companies were legally bound to submit reports to the Medicines Control Council (MCC), only one company submitted a report in terms of Act 101. With the current amendments to Act 101, all registered drugs require re-registration at 5 year intervals. The failure of a company to submit this important safety data to the MCC, via the VP & MIC, could perhaps negatively influence their renewals of registration. It is thus difficult to understand the reasons behind their poor reporting.

As mentioned above, a separate governmental body administers Act 36/47. According to the Act, companies are obliged to submit all ADR to the registrar of the Act. It is, however, not necessary for pharmaceutical companies to submit these reports via the VP & MIC. Thus the reporting by companies to the centre may not reflect the occurrence of adverse drug reactions or reporting in the country. The number of reports received by the Registrar, Act 36, is not known.

The number of reports submitted by veterinarians in the field has remained constant (from 87 % to 90 % in the current period). This figure fails to take consideration of the poor overall reporting to the centre. With the amendments to Act 101 it is hoped that reporting will increase from within the profession.

The proportion of reports of suspected adverse reactions to products used extra-label (i.e. not registered for use in animals) has decreased from 19 % to 5 % in the current period. The reporting of extra-label induced ADRs is promoted by the centre. Even though the prescriber is legally responsible for any reaction that may result, the recording and publishing of such data make their overall use safer.

From the 31 active ingredients implicated none of these products appeared to cause any unexpected side effects, necessitating a drug safety update report. However, diminazene which is used in the treatment of tick bite fever (babesiosis) has once again been flagged as a drug of concern. The authors would like to point out that this drug is not registered for prophylactic use in dogs. With its low margin of safety, the dose needed has to be accurately calculated by the weight of animal. Although the doses are listed per 10/20 kg of bodyweight, the estimation of the dose has been implicated as a cause of death. For this reason it is advised that a positive diagnosis be made before treating a dog with diminazene and that the dose be accurately calculated based on the body mass of the animal.

Table 6: **Active ingredient implicated and their causality in cats, dogs, cattle and wildlife received for the period March 2003 – February 2004.**

Active Ingredient	Total	Possible	Probable	Unlikely	Unclassifiable
Cats					
Alfaxalone/alphadalone	1	1			
Cypermethrin/piperonyl butoxide	3		3		
Lufenuron	4			4	
Propofol	1			1	
Xylazine	2	1			1
Dogs					
Carprofen	1	1			
Diminazene	1			1	
Levamisole	1		1		
Medetomidine	1	1			
Neomycin	1			1	
Niclosamide	1			1	
Pentobarbitone	1			1	
Pyrantel pamoate	1	1			
Thiabendazole	1			1	
Vaccine	7		2	1	4
Cattle					
Vaccine	2	1	1		
Wildlife					
Azaperone	1			1	
Detomidine	1	1			
Etorphine	1	1			
Naltrexone	1			1	

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