Overview of suspected adverse reactions to veterinary medicinal products reported in South Africa (March 2004 – February 2006)

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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 2004 to February 2006 is presented. A total of 21 reports was received in the 2-year period, continuing the decline in the number of reports to a lower figure than in any previous year. This is surprising considering the legal obligation of the veterinary professionals to report all adverse drug reactions. Once again 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.

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 2 Acts and are administered by 2 separate regulatory authorities:

- The Medicines and Related Substances Control Act (Act No. 101 of 1965), administered by the Medicines Control Council of the National Department of Health. These products are called Veterinary Medicines and represent scheduled veterinary remedies.
- The Fertilisers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947) administered by the National Department of Agriculture. These products are called Stock Remedies and represent over-the-counter veterinary 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. This is a condition of registration in terms of Act 36 of 1947 and is obligatory in terms of the Regulation 37 of Act 101 of 1965. Nevertheless, the reporting of adverse reactions by both pharmaceutical companies and veterinarians continues to be poor and requires improvement.

The Veterinary Pharmacovigilance and Medicines Information Centre, 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 101/65 and Act 36/47.

MATERIALS AND METHODS

The Veterinary Pharmacovigilance and Medicines Information Centre relies on reports of suspected adverse drug reactions. Reporting is obligatory for registration holders of both veterinary medicines and stock remedies as well as members of the veterinary profession.

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 serial number. The minimum information required to appear on each report is: an identifiable source (name and contact details of reporter), animal details (species, sex, age), suspected product (name and/or registration number) and reaction details. 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 above-mentioned information are entered into a computerised database. Thereafter, the report is presented at the next 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 21 reports of suspected adverse drug reactions for the period March 2004 to February 2006, implicating 24 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 the Veterinary Pharmacovigilance and Medicines Information Centre (Table 5). These results are compared with those of previous years[4]. 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

Once again there was a marked decrease in the number of reports received by the Veterinary Pharmacovigilance and Medicines Information Centre (VP & MIC) during the period March 2004 to February 2006 compared to the previous year, prompting the release of this biannual report (decreased from 20 in the previous

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

Casuality classification	Criteria
Certain	There is a plausible time relation between the administration and the adverse event, which 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 re-challenge 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 fulfil 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.

Table 2: **Reports of suspected adverse drug reactions received for the period March 2002 – February 2004 and the period March 2004 – February 2006 classified according to species.**

Species	March 2002 – February 2004 (*n* = 60)		March 2004 – February 2006 (*n* = 21)	
	Number of reports	Percentage	Number of reports	Percentage
Canine	36	60.0	10	47.6
Feline	12	20.0	3	14.3
Bovine	5	8.3	4	19.0
Equine	2	3.3	1	4.8
Ovine/caprine	2	3.3	1	4.8
Poultry	1	1.7	0	0
Porcine	0	0	0	0
Human	1	1.7	0	0
Wildlife	1	1.7	2	9.5

Table 3: **Comparison of the registration of products implicated in reports of suspected adverse drug reactions for the period March 2002 – February 2004 and the period March 2004 – February 2006.**

Product registration	March 2002 – February 2004 (*n* = 89)		March 2004 – February 2006 (*n* = 24)	
	Number of products	Percentage	Number of products	Percentage
Stock Remedies (Act 36/47)	56	62.9	13	54.2
Veterinary Medicines (Act 101/65)	20	22.4	10	41.7
Products used extra-labelly	13	14.7	1	4.2

Table 4: **Reports of suspected adverse drug reactions received for the period March 2002 – February 2004 and the period March 2004 – February 2006 classified according to persons administering the drugs.**

Person administering drugs	March 2002 – February 2004 (*n* = 60)		March 2004 – February 2006 (*n* = 21)	
	Number of reports	Percentage	Number of reports	Percentage
Veterinarian	30	50	9	42.9
Owners	25	41.6	10	47.6
Other	4	6.6	2	9.5
Paraveterinary professional	1	1.8	–	–

Table 5: **Reports of suspected adverse drug reactions received for the period March 2002 – February 2004 and the period March 2004 – February 2006 classified according the origin of the report submitted to the Veterinary Pharmacovigilance and Medicines Information Centre.**

Person submitting report	March 2002 – February 2004 (*n* = 60)		March 2004 – February 2006 (*n* = 20)	
	Number of reports	Percentage	Number of reports	Percentage
Pharmaceutical company	3	5	1	5
Veterinarian	52	87	18	90
Veterinary specialist	2	3	1	5
Others	2	3	0	0

1-year period to 21 for the current 2-year period). The reason for the poor reporting is unknown. As in previous years, the majority of reports received pertained to those products used in small animals[4].

The majority of these reports also implicated products registered as Stock Remedies under Act 36 of 1947. This has decreased from 78 % to 54 % in the current period. The greater occurrence in the over the counter remedies is most likely linked to the larger volumes at which they are used but may also be a skewed perception resulting from the paucity of report submission. For the current year, owners administered most of the drugs implicated. The number of reports of ADRs to medicines administered by owners had decreased from the previous period (from 63 % to the current 48 %).

Only 1 report was received from industry. Even though the pharmaceutical companies were legally bound to submit reports to the Medicines Control Council (MCC), only 1 company submitted a report in terms of Act 101. With the current amendments to Act 101, all registered drugs require re-registration at 5-yearly 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 may be argued that ADRs are not common in South Africa. This seems unlikely as a single commonly used product received over 3000 reports in the United States of America while over 700 reports were received in total by the UK regulators of veterinary remedies for the period 2002[6]. It is thus difficult to understand the reasons for poor reporting in South Africa.

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 into consideration the poor overall reporting to the centre. Even though both Act 101/65 and Act 36/47 currently make reporting ADRs compulsory, this trend of poor reporting continues within the profession.

The proportion of reports of suspected adverse reactions to products used extra-labelly (*i.e.* not registered for use in animals) has decreased from 18 % to 0.04 % 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.

Notably 1 of the products mentioned in current and previous reports is carprofen[3,4]. Although the number of reports may appear excessive, the reactions were not unexpected and are covered on the package insert. ADRs to this drug most likely reflect the widespread use of an important veterinary anti-inflammatory. It has also been well documented that Labradors and Retrievers are more susceptible to hepatic side-effects following the use of the drug and it should be used with care in these animals[5].

Other important changes in South Africa have resulted from the newly proposed amendment suggested for the Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972[2]. According to the proposed amendments, certain drugs will no longer be allowed for use in food-producing animals due to safety concerns for the consumer (Table 7). Notably metronidazole, nitrofurans and phenylbutazone have been added to the list. For metronidazole this has resulted from the mechanism of the drug's anaerobic spectrum of activity *viz.* only anaerobic bacteria have the ability to bioactivate the compound[1]. Once activated, this metabolite kills the organism by damaging the bacterial

Table 6: **Active ingredient implicated and their causality in cats, dogs, cattle and wildlife received for the period March 2004 – February 2006.**

Active Ingredient	Total	Definite	Possible	Probable	Unlikely
Cats					
Medetomidine	2		1		1
Vaccine reaction	1				1
Dogs					
Amitraz	1	1			
Carprofen	1			1	
Cephelexin	1			1	
Diminazene	1			1	
Imidoclopid	1				1
Lornoxicam		1			
Permethrin	1			1	
Potassium chloride	1				1
Prednisolone	1	1			
Vaccine reaction	2				2
Cattle					
Monensin	1			1	
Potentiated sulphonamide	1				1
Vaccine	1			1	
Vitamin A	1			1	
Wildlife					
Detomidine	1			1	
Etorphine	2			1	1
Equine					
GGE	1				1
Halothane	1			1	
Ketamine	1			1	
Ovine					
Nitroxynil	1			1	

Table 7: **Active ingredients for which no maximum residue levels will be set in food producing animals (Proposed amendments to Act 54/72).**

Substance	Foodstuffs
Aristolochia spp. and preparations	Eggs, fat, kidney, liver, meat and milk
Carbadox	Eggs, fat, kidney, liver, meat and milk
Cefuroxime*	Milk
Chloroform	Eggs, fat, kidney, liver, meat and milk
Chlorpromazine	Eggs, fat, kidney, liver, meat and milk
Colchicine	Eggs, fat, kidney, liver, meat and milk
Dapsone	Eggs, fat, kidney, liver, meat and milk
Diethylstilboestrol	Eggs, fat, kidney, liver, meat and milk
Ipronidazole	Eggs, fat, kidney, liver, meat and milk
Metronidazole	Eggs, fat, kidney, liver, meat and milk
Nitrofurans (Including furazolidone)	Eggs, fat, kidney, liver, meat and milk
Organic arsenicals	Eggs, fat, kidney, liver, meat and milk
Phenylbutazone	Eggs, fat, kidney, liver, meat and milk
Phoxim*	Eggs, fat, kidney, liver, meat and milk

*The new MRL applies for use in cattle only.

DNA. At present it is believed that the metabolite, on release from the dead bacterium, could induce damage to mammalian DNA in the vicinity with the end result of carcinogenicity.

Phenylbutazone has been added for a similar reason[1]. It has long been known that this drug can introduce an irreversible bone marrow suppression in humans. Since the effect is dose independent, trace amounts of residues in food may cause this severe side-effect. As such the risks of exposure far outweigh the benefits of the drug in production animals.

CONCLUSION

At present the reporting of adverse reactions in South Africa by the veterinary profession is on the decline. Until such time as South African veterinarians take note of the importance of ADRs, drug utilisation in animals will not be made safer.

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