

Use of a trigger tool to identify adverse drug events in dogs

Uso de rastreadores para identificar eventos adversos a medicamento em cães

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Abstract

Background: The highlight of the shortcomings in the regulation and surveillance of veterinary drugs in Brazil is the absence of a system to report adverse drug events (ADEs). **Objective:** Evaluate the use of triggers in dogs to detect ADEs by estimating the prevalence of ADE and identifying the possible triggers. **Method:** We screened medical records for ADEs and degree of harm caused by an ADE, using known triggers, with the Global Trigger Tool: translated, adapted and validated for use in animal health. The triggers comprised two-fold increase in blood urea nitrogen or serum creatinine levels compared to baseline, administration of vitamin K, administration of diphenhydramine or promethazine, excessive sedation or hypotension, administration of an antiemetic, abrupt cessation of medication, or others. The association between the occurrence of ADEs and variables, such as age, race, duration of hospitalization, polypharmacy, and clinical outcome was evaluated. **Results:** 148 medical records were analyzed. The trigger tools identified the known triggers 109 times in 68 medical records. Additionally, 14 ADEs were identified; the prevalence of ADEs was 9.5%. Positive predictive values of the triggers were 12.8%, and "vitamin K administration" had the best performance. The duration of hospitalization (p-value = 0.030) and polypharmacy (p-value < 0.001) were associated with the occurrence of ADEs. **Conclusion:** Approximately 46% of the hospitalized dogs presented with at least one trigger. One out of five hospitalized dogs suffered from temporary harm due to an ADE. The duration of hospitalization and polypharmacy were found to be risk factors for ADEs in dogs.

Keywords: drug safety, patient safety, veterinary drugs, veterinary pharmacovigilance, triggers.

Resumo

Introdução: O destaque das deficiências na regulamentação e vigilância de medicamentos veterinários no Brasil é a ausência de um sistema de notificação de eventos adversos a medicamentos (EAM). **Objetivo:** Avaliar o uso de rastreadores em cães para detectar EAM, estimando a prevalência de EAM e identificando os possíveis rastreadores. **Método:** Rastreamos prontuários médicos para identificar EAM e grau de dano causado por um EAM, usando rastreadores conhecidos, com a Global Trigger Tool: traduzida, adaptada e validada para uso em saúde animal. Os rastreadores consistiram no aumento de duas vezes nos níveis de nitrogênio ureico no sangue ou creatinina sérica em comparação com a linha de base, administração de vitamina K, administração de difenidramina ou prometazina, sedação excessiva ou hipotensão, administração de um antiemético, interrupção abrupta da medicação ou outros. Foi avaliada a associação entre a ocorrência de EAM e variáveis como idade, raça, tempo de internação, polifarmácia e evolução clínica. **Resultados:** Foram analisados 148 prontuários. Os rastreadores foram gatilhados 109 vezes em 68 registros médicos. Ademais, 14 EAM foram identificados e a prevalência de EAM foi de 9,5%. O valor preditivo positivo do rastreador foi 12,8%, e "administração de vitamina K" teve o melhor desempenho.



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O tempo de internação (p-valor = 0,030) e a polifarmácia (p-valor <0,001) foram associados à ocorrência de EAM. Conclusão: Aproximadamente 46% dos cães hospitalizados apresentaram pelo menos um rastreador. Um em cada cinco cães hospitalizados sofreu danos temporários devido a um EAM; e o tempo de internação e a polifarmácia foram identificados como fatores de risco para EAM em cães.

Palavras-chave: farmacovigilância veterinária, medicamentos veterinários, segurança medicamentosa, segurança do paciente, rastreadores.

Introduction

Despite the recent changes in pharmacovigilance and legislation to improve patient safety, the shortcomings in regulation and surveillance of veterinary drugs still exist in Brazil, even after the affiliation of Brazil with the International Conference of Harmonization (Varallo et al., 2019). In addition, the absence of a system to report adverse drug events (ADEs) in the field of animal health in Brazil is noteworthy.

Studies have shown implications of ADEs in the field of animal health as well as its impacts on the environment (Woodward, 2005a; Fusco et al., 2010; Kumar et al., 2017). Prevalence studies, and data from previously reported cases world-wide showed the occurrence of ADEs in different animal species, primarily in companion animals (i.e., dogs and cats) (Mouiche et al., 2019; Müntener et al., 2019), that was related to the use of vaccines, antiparasitic drugs, antimicrobials, and non-steroidal anti-inflammatory drugs (Maddison, 1996; Woodward, 2005b; Müntener et al., 2017).

In human health, triggers are of good use in screening and detection of ADEs (Giordani et al., 2012; Rozenfeld et al., 2013). For instance, the Global Trigger Tool is an instrument widely used to actively screen for ADEs using known triggers. In addition, it measures the degree of harm caused by ADEs (Griffin & Resar, 2004; Griffin & Resar, 2009). However, to date, there have been no studies on the development and/or use of triggers in the field of animal health.

The identification of ADEs has improved human patient safety (Varallo et al., 2014). Considering the lack of strategies for the detection and monitoring of ADEs in animal health, and the high prevalence of ADEs in dogs (Maddison, 1996; Woodward, 2005b; Müntener et al., 2017), we hypothesized that the use of triggers may be effective in obtaining post-marketing data on veterinary drugs. Therefore, in this study, we aimed to assess the use of triggers in order to detect and estimate the prevalence of ADEs, and to identify the triggers for ADEs in dogs.

Materials and methods

Ethics approval and study design

This cross-sectional study was conducted based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, in order to detect ADEs in hospitalized dogs, at the Veterinary Hospital of the Federal University of Goiás, from April 1, 2017 to November 30, 2017.

This study was approved (protocol number: 006955/2017, 090/16) by the Committee on Ethics in the Use of Animals (CEUA), Federal University of Goiás. All the applicable guidelines, such as international, national, and institutional guidelines for the care and use of animals were followed.

Setting and participants

The study was conducted in the inpatient ward at the Veterinary Hospital of the Federal University of Goiás, which has a capacity of 21 beds, and has 24-hour supervision. The dogs that were admitted for at least 48 hours in the inpatient ward were included in this study. The dogs that underwent only fluid replacement therapy were excluded from the study. Furthermore, dogs with incomplete medical records were also excluded because this would cause the screening of ADEs and causality assessment to be unviable.

Twenty medical records were randomly selected per month, according to the recommendations of the Global Trigger Tool. Each month, the patient information was registered in the admission control book of the inpatient ward. The patients that met the inclusion criteria were listed sequentially, and the electronically available patient information was collected (<https://www.randomizer.org>).

Measurement of data

The screening and detection of ADEs through triggers was conducted according to the adapted and validated version of the Global Trigger Tool for animals, specifically for dogs (Fonseca et al., 2018). The Global Trigger Tool is an instrument used in retrospective or prospective review of known triggers, in order to detect ADEs in selected patients (Griffin & Resar, 2009).

This study was conducted in two stages. The first stage was the random selection and data collection from the medical records through a standardized questionnaire, conducted by one pharmacist researcher (B.C.O.F). Patient data, such as sex, race, age, duration and outcome of hospitalization (discharge or death), drugs prescribed, polypharmacy, and the presence of triggers were collected. Polypharmacy among the patients, was defined as the use of four or more drugs (World Health Organization, 2019).

The selected triggers were as follows: (i) increased blood urea nitrogen or serum creatinine levels by two-fold compared to the baseline, (ii) administration of vitamin K, (iii) administration of diphenhydramine or promethazine, (iv) excessive sedation and hypotension, (v) administration of an antiemetic, (vi) abrupt cessation of medication, or (vii) other (ADE detected but not associated with one of the triggers listed above).

The variations in vital signs were analyzed to identify episodes of excessive sedation and hypotension associated with the administration of a sedative, analgesic, or muscle relaxant. Intentional overdose was not considered as an ADE. The second stage was the causality analysis and assessment of the degree of harm caused by ADEs. When an ADE was detected, a causality assessment was conducted through a discussion between the specialists (two pharmacists, and one veterinarian). To avoid biases in the causality assessment, a fourth researcher was consulted when there was no consensus between the other three researchers.

The degree of harm caused by the ADEs was categorized (Griffin & Resar, 2009) into: E (ADE contributed or resulted in temporary harm to the patient and required medical intervention), F (ADE contributed or resulted in temporary harm to the patient and required brief or prolonged hospitalization), G (ADE contributed to or resulted in permanent harm to the patient); H (needed medical intervention to sustain life), and I (ADE contributed to or resulted in the patient's death).

Statistical analysis

A chi-square test was applied to calculate the association between the categorical variables and the occurrence of ADEs. The p-value ≤ 0.05 was considered significant. In order to assess the use of the trigger tools in identifying an ADE, prevalence of the ADEs, and their positive predictive values (PPVs) were calculated within a confidence interval (CI) of 95%. All statistical analyses were performed in Epi Info™ 7.2 program.

Results

One hundred forty-eight dogs were included in this study. Most dogs were female [60.0% (89/148)] and of mixed-breeds [52.7% (78/148)]. The median age was six years with a range from zero to 16. Among all the dog breeds [47.3% (70/148)]: Shih Tzu (n = 11), Pinscher (n = 10), American pit bull (n = 05), boxer (n = 05), and poodle (n = 04) were the most frequent breeds.

The primary causes for hospitalization of these dogs were pyometra, parvovirus, and gastroenteritis. The average length of hospital stay was four days [standard deviation (SD) ± 2.9], and the clinical outcomes included hospital discharge for 87.0% of dogs, while 13.0% died due to natural causes or euthanasia. The medical records were reviewed, and 780 drugs were identified. A mean of 5.7 drugs were prescribed per dog (SD: ± 2.3 , range: 1-17). Among these drugs, 24.7% (n = 194) were antimicrobials, 22.9% (n = 179) analgesics, 10.3% (n = 80) gastric protectors, and 8.6% (n = 67) were antiemetics.

Half of the analyzed medical records [45.9% (68/148)] consisted of at least one trigger. Among the known triggers, the following were defined by the number of times they were identified: administration of an antiemetic (n = 67), increase in blood urea nitrogen or serum creatinine levels by two-fold compared to the baseline (n = 25), administration of diphenhydramine or promethazine (n = 08), administration of vitamin K (n = 05), abrupt cessation of medication (n = 01), and others (n = 03)

Fourteen ADEs were detected using the following known triggers: administration of vitamin K (n = 05), administration of an antiemetic (n = 04), and increase in blood urea nitrogen or serum creatinine level by two-fold compared to the baseline (n = 02), and others (n = 03). Among the 14 ADEs that were identified in our study population, we found a prevalence of 9.5% (95% CI, 5.7%-15.3%). Furthermore, the performance of the triggers was 12.8% (n = 14, 95% CI, 7.8%-20.4%), since the triggers were identified 109 times.

Out of the 14 ADEs identified in this study, only eight could be categorized; they fit into the category E. The association between the occurrence of ADEs and variables, such as length of hospital stay ($p = 0.030$) and polypharmacy ($p < 0.001$), were observed. Data on the presence of comorbidities in the patients were unknown because this information was unavailable in the hospital records. Thus, the association between the risk of ADEs and presence of comorbidities could not be assessed. This finding shows that these dogs did not undergo periodic health examinations (Table 1).

Discussion

In this study, we showed the unprecedented use of trigger tools in the screening of ADEs in the field of animal health. The occurrence of ADEs affected 14 hospitalized dogs involved in this research. It has been noted that in human health, prevalence studies have helped improve the identification of ADEs, and that 70% of these events could be avoided by active monitoring of drug use (Mastroianni et al., 2009). Recent studies have revealed that the use of triggers has contributed to increased detection of ADEs, up to 10.5% (Rozenfeld et al., 2013; Varallo et al., 2017). These findings highlight the need to develop and apply such standardized tools to obtain data for a more accurate evaluation of ADEs and its impact on animal health. The comparative analysis of data on ADEs is hampered by data scarcity in the literature on veterinary pharmacovigilance. However, official data provided by the ADE surveillance systems in developed countries show that ADEs occurred more frequently in companion animals, especially dogs (Woodward, 2005a; Müntener et al., 2017), and the number is gradually increasing. Furthermore, the data recorded through the ADE surveillance systems in developed countries aids in understanding the profiles and the occurrence of ADEs in animal patients. For instance, ADEs such as, nausea, diarrhea, and weight loss in cats have been associated with the use of oral cyclosporine (Heinrich et al., 2011), use of non-steroidal anti-inflammatory drugs cause serious ADEs in dogs and cats (Tjalve, 1997), and self-medication or off-label medication use is associated with ADEs (Gehring, 2001).

Reis et al. (2012) identified potential drug interactions in hospitalized dogs, and observed that some of them had the ability to cause serious and irreversible harm to the health of these patients (Reis et al., 2012). In this study, one of the identified ADEs was possibly associated with the drug interaction between furosemide and doxycycline that may increase serum urea and creatinine levels due to the reduction in renal function. In the present study, we found a low performance of triggers such as "antiemetic administration" and "increased blood urea nitrogen or serum creatinine" to cause harm.

Silva et al. (2018) and Patel et al. (2020) identified antiemetic administration as the most frequent trigger in human patients that are hospitalized. However, antiemetic administration presented the lowest performance compared with the other triggers due to the large number of false-positive cases, corroborated by our findings (Silva et al., 2018; Patel et al., 2020). Furthermore, in another study conducted in humans, Brenner et al. (2012) evaluated abnormal laboratory parameters as triggers for the detection of ADEs in outpatients. Abnormalities in the international normalized ratio was the trigger that showed the highest performance, while triggers such as blood urea nitrogen and serum creatinine levels showed lower performances to detect ADEs (Brenner et al., 2012). Therefore, confounding factors associated with the use of triggers and the occurrence of ADEs is important in clinical practice, and further research is essential to optimize its use. The association between the occurrence of ADEs and variables, such as duration of hospitalization and polypharmacy, demonstrates a similar risk in human health (Varallo et al., 2014; Härkänen et al., 2015; Kojima et al., 2020).

The present study has several strengths. To our knowledge, this is the first Brazilian study that evaluated the use of triggers in the detection of ADEs to overcome the barriers resulting from the absence of an efficient ADE surveillance system in the field of animal health. In addition,

Table 1. Assessment of the association between the occurrence of adverse drug events and the variables: sex, duration of hospitalization (days), number of drugs administered, and clinical outcome (n = 148), at the Veterinary Hospital of the Federal University of Goiás, 2017.

Variable	Category	Patients with ADEs (n)	Patients without ADEs (n)	Total (n)	p-value		
Sex	Female	8	81	89	0.913		
	Male	5	54	59			
Age (years)	0-5	7	56	63	0.955		
	5-10	2	31	33			
	10-15	3	31	34			
	15-20	-	2	2			
	Unknown	1	15	16			
	Mixed-breeds	6	72	78			
	Pinscher	-	10	10			
	Shih-Tzu	1	10	11			
	American Pit Bull	-	5	5			
	Boxer	-	5	5			
	Poodle	-	4	4			
	Dalmatian	-	3	3			
	German Shepherd	2	3	5			
	Chow Chow	-	2	2			
Breed	Siberian Husky	-	2	2	0.277		
	Pug	-	2	2			
	Rottweiler	-	2	2			
	Schnauzer	-	2	2			
	German Spitz	-	2	2			
	Teckel	-	2	2			
	Yorkshire terrier	-	2	2			
	Basset hound	-	1	1			
	Cocker Spaniel	-	1	1			
	Great Dane	-	1	1			
	Brazilian queue	-	1	1			
	Golden retriever	2	1	3			
	Labrador	-	1	1			
	Belgian Shepherd	-	1	1			
	02-04	5	103	108			
	05-07	5	22	27			
	Duration of hospitalization (days)	08-10	1	6		7	0.031*
		11-13	1	1		2	
		14-16	1	2		3	
		17-19	-	1		1	
01-03		-	20	20			
04-06		5	79	84			
Number of drugs (n)	07-09	6	31	37	< 0.001*		
	10-12	-	5	5			
	13-15	1	-	1			
	16-18	1	-	1			
Clinical outcome	Hospital discharge	11	118	129	0.773		
	Death	2	17	19			

* statistical significance (p-value < 0.05). ADE: adverse drug event; n: number.

it helps to identify and raise hypotheses on safety in the field of animal health and veterinary drug use. The limitation of this study is the inability to obtain complete clinical characterization in dogs as well the classification of all the identified ADEs, owing to the incomplete data in the medical records.

Conclusion

Approximately 46% of the hospitalized dogs presented with at least one trigger. Out of every five patients presented harm due to an ADE of category E. The prevalence of ADEs in our study was found to be 9.5%. The triggers showed a performance of 12.8%. Among the evaluated triggers, vitamin K administration showed the highest performance. The duration of hospitalization and polypharmacy were identified as risk factors for the occurrence of ADEs. Our findings highlight the importance of identification, evaluation, and management of ADEs in field of animal health. Additionally, we emphasize the need for re-structuring of the regulations in veterinary pharmacovigilance in Brazil, and the importance of using trigger tools for timely detection of ADEs in order to minimize the harm caused to patients.

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