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The veterinary medicinal products market supply gap: A practical insight based on the Regulation (EU) 2019/6

O défice de oferta no mercado dos medicamentos veterinários: uma visão prática baseada no regulamento (UE) 2019/6

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ABSTRACT

The Regulation (EU) 2019/6 establishes that the veterinary prescriptions should follow a cascade, according to their availability of the market. In sum, the veterinarian is authorized to use a medicine for human use only if there is no product available for the same or other therapeutic indication, in the same or another animal species. This study aims to analyse the application of Regulation (EU) 2019/6 in the pharmacological prescription at the Veterinary Hospital of the University of León. A total of 121 clinical cases, 89 dogs (73.55%) and 32 cats (26.45%) were included. Results revealed that 95 medicines were prescribed, 51 (53.68 %) as veterinary medicines and 44 (46.32 %) as human medicines. From the human medicines, 22 (50.00%) did not have a veterinary alternative in the market; four (9.00%) presented a veterinary medicine in the appropriate formulation for the species; 10 (23.00%) had no alternative in the desired formulation; and 8 (18.00%) had no alternatives for the target species. This study suggested that the cascade was not strictly followed, and several reasons may justify it, such as the lack of veterinary products, different formulations, and differences in costs. An effective, safe and sustainable use of the therapeutic option available can only be accomplished with a rational use of the prescription cascade and a correct use of the Regulation (EU) 2019/6.

KEYWORDS: medical prescription; pharmacology; Pharmacy; therapeutics; veterinarian.

RESUMO

O Regulamento (UE) 2019/6 estabelece que as prescrições veterinárias devem seguir uma cascata, de acordo com a sua disponibilidade no mercado. Em suma, o médico veterinário só está autorizado a utilizar um medicamento de uso humano se não existir um produto disponível para a mesma ou outra indicação terapêutica, na mesma ou noutra espécie animal. Este estudo tem como objetivo analisar a aplicação do Regulamento (UE) 2019/6 na prescrição farmacológica no Hospital Veterinário da Universidade de León. Foram incluídos 121 casos clínicos, 89 cães (73,55%) e 32 gatos (26,45%). Os resultados revelaram que foram prescritos 95 fármacos, 51 (53,68%) como medicamentos veterinários e 44 (46,32%) como medicamentos humanos. Dos medicamentos humanos, 22 (50,00%) não possuíam alternativa veterinária no mercado; quatro (9,00%) apresentavam medicamento veterinário na formulação adequada para a espécie; 10 (23,00%) não possuíam alternativa na formulação desejada; e 8 (18,00%) não possuíam alternativas para a espécie alvo. Este estudo sugeriu que a cascata não foi seguida rigorosamente, e vários motivos podem justificar esse fato, como a falta de produtos veterinários, diferentes formulações e diferenças de custos.

PALAVRAS-CHAVE: prescrição médica; farmacologia; farmácia; terapêutica; veterinário.

INTRODUCTION

A veterinary medicinal product can be defined as a substance, or combination of substances, which follows one (or more) of the following principles: 1) has curative or preventive properties for diseases in animals, 2) has the purpose of attenuating their symptoms, 3) is used or administered to the animal to establish a medical diagnosis, 4) restores, corrects or modifies a physiological function by exerting a pharmacological, immunological or metabolic action, or 5) is used for the euthanasia of animals (REGULATION EU 2019/6 2018).

At the European level, the body coordinating veterinary medicine is the European Medicines Agency (EMA), responsible for coordinating scientific resources for evaluating, supervising, and pharmacovigilance of medical products. EMA was first established in 1995, with the primary goal of protecting and promoting human and animal health by monitoring the authorization of medicines, including veterinary products. In other words, this agency aims to support the development of and access to veterinary medicines, and provides information for health professionals, patients, and in the case of animals, their owners (EUROPEAN MEDICINES AGENCY 2023).

The Regulation (EU) 2019/6 establishes the rules for the placing on the market, manufacture, import, export, supply, distribution, pharmacovigilance, control, and use of veterinary medicine products. This Regulation aims to harmonise the rules for authorising veterinary medicines and placing them in all the countries that belong to the European Union (REGULATION EU 2019/6 2018). According to this Regulation, the prescription by veterinary professionals (working with non-food-producing animal species) should follow the following principles:

- Veterinarians should always prescribe a veterinary product (authorised in their country) specific to that animal species and therapeutic indication.
- However, if there is no authorised veterinary product (for the purpose) in their country, veterinarians may exceptionally treat the animals with another medical product. In this case:
    - At first, veterinarians may prescribe a veterinary medical product authorised under this Regulation in another Member State for use in the same or another animal species for the same or another therapeutic indication.
    - If a veterinary medicinal product with the above characteristics is unavailable, a medicinal product for human use is usually authorised.
    - If the above alternatives still do not exist, a veterinary medicinal product may be compounded under the terms of a veterinary prescription.

The importance of following these principles is multifactorial. The differences between species (humans and animals) lead not only to the marketing of medicines with different formulations and dosages, but also, for example, to the use of different excipients. Absorption, transport, metabolization and excretion undergo significant changes between different species, even if they are taxonomically similar. The use of medicines formulated for the species in question is undoubtedly safer, with fewer adverse reactions and greater therapeutic efficacy. For some medicines, such as antimicrobials, the importance of differentiated use between veterinary and human medicine is important to avoid the resistance (BEYENE and TESEGA 2014). The correct usage of veterinary medicines is also essential for controlling the presence of residues of veterinary medicines in meat and meat products and promoting the safety of human food (LANUSSE 2021).

Despite the relevance of this topic for all veterinarians in the European Union, there is a current lack of studies on applying Regulation (EU) 2019/6, particularly in pet clinical practice. Thus, this study aims to analyse the application of Regulation (EU) 2019/6 in the pharmacological prescription at the Veterinary Hospital of the University of León.

METHODOLOGY

Hospital and casuistic

The Veterinary Hospital of the University of León opened in 2013 and works as a reference hospital. It is mainly composed of experienced and specialised professionals, with the main goals of contributing to the clinical training of veterinary students in both large and small animal practices and providing social support to all activities related to the Veterinary Clinic of Castilla y León (UNIVERSIDAD DE LEÓN 2023). The high hospital's activity follows the requirements of the European Association of Establishments for Veterinary Education (EAEVE), offering services in the following clinical areas: Cardiorespiratory, Cellular therapy,

Clinical Pathology, Dermatology, Diagnostic Imaging (radiology, ultrasound, magnetic resonance imaging, tomography and endoscopy), Gastroenterology, General surgery, Genomics (Diagnostic and Therapy), Infectious diseases, Nephro-urology, Neurosurgery, Oncology, Ophthalmology, Orthopaedics and Traumatology (UNIVERSIDAD DE LEÓN 2020).

Clinical cases

A total of 121 clinical cases, admitted from September to December 2022, 89 dogs (73.55%) and 32 cats (26.45%), from the small animal surgery and hospitalisation units, were included in this study. The population included patients of various breeds, and with different diseases and reasons for admission to the hospital. The animals' age ranged from 1.5 months to 17 years old. In total, 30 dogs and five cats were submitted to a surgical hospitalisation, while 59 dogs and 27 cats were submitted to non-surgical hospitalisation. The animals were followed up, and the respective therapeutic protocols were analysed. Table 1 summarises the information of these cases regarding the sex, reproductive status, the mean duration of hospitalisation (surgical and non-surgical), and the clinical outcome.

Table 1. Summary of the biological and clinical details of the 121 clinical cases included in this study. "Dead" in the clinical outcome refers to both natural death and euthanasia.

Species (N=121)	Sex	Reproductive Status	Mean surgical hospitalisation (days)	Mean non-surgical hospitalisation (days)	Clinical outcome
Dogs 89 (73.55%)	Female 57 (47.11%)	Intact 52 (58.43%)	3.34	4.53	Discharged 54 (44.63%)
		Neutered 5 (5.62%)			Dead 3 (3.37%)
	Male 32 (26.45%)	Intact 30 (33.71%)	3.95	5.91	Discharged 31 (25.62%)
		Neutered 2 (2.25%)			Dead 1 (1.12%)
Cats 32 (26.45%)	Female 18 (14.87%)	Intact 14 (43.75%)	4.43	4.00	Discharged 18 (14.88%)
		Neutered 4 (12.50%)			Dead 0 (0%)
	Male 14 (11.57%)	Intact 10 (31.25%)	4.08	3.00	Discharged 13 (10.74%)
		Neutered 4 (12.50%)			Dead 1 (3.13%)

Analytical methods

In Spain, the Spanish Agency for Medicines and Health Products (AEMPS) is the regulatory body for both human and veterinary medicines. The Veterinary Medicines Information Centre (CIMAVET), which is part of AEMPS, makes it possible to consult all the veterinary medicines authorised in Spain and aims to provide information on each one. The CIMAVET website can be found at https://cimavet.aemps.es/cimavet/publico/home.html. This was the database used in this study to verify the availability of veterinary medical products and their characteristics (e.g. formulations, target species…).

A detailed descriptive statistical analysis was carried out using Microsoft® Office Excel 365 software.

RESULTS

A total of 962 prescriptions were made for these 121 animals, 564 (58.63%) referring to veterinary medicine products and 398 referring to human medicine products (41.37%). On the other hand, 95 different medicines were prescribed for these animals, and 44 (46.32%) were prescribed as human medicines and 51 (53.68%) as veterinary medicines. For dogs, 88 different medicines were prescribed: 42 human medicines (47.73%) and 46 veterinary medicines (52.27%). Considering cats, 24 human medicine forms (48.98%), and 25 veterinary medicine forms (51.02%) were prescribed during this study, totalling 49 different medicines.

Drugs that act on the nervous system were the most prescribed pharmacological group (n=30; 31.58%), including analgesics, anaesthetics, sedatives, antidepressants, antiepileptics, psychostimulants, dopaminergic agents, and anxiolytics. The second most prescribed group of medicines were those for the gastrointestinal tract and metabolism (n=17; 17.89%). This group includes antacids, antiemetics, insulins,

laxatives, proton pump inhibitors and vitamins. The different prescribed medicine groups are summarised in Table 2.

Table 2. Prescribed human and veterinary medicines during the study period.

Group (according to ATCvet*)	Total	Human medicines	Veterinary medicines
Nervous system	30	14 (46.67%)	16 (53.33%)
Gastrointestinal tract and metabolism	17	7 (41.18%)	10 (58.82%)
Systemic antibiotics	14	4 (28.57%)	10 (71.43%)
Cardiovascular system	9	5 (55.56%)	4 (44.44%)
Respiratory system	5	4 (80%)	1 (20%)
Blood and hematopoietic organs	5	4 (80%)	1 (20%)
Sensory organs (Oftalmology)	4	3 (75%)	1 (25%)
Musculoskeletal system	3	1 (33.33%)	2 (66.67%)
Systemic hormone preparations	3	1 (33.33%)	2 (66.67%)
Dermatology	2	- -	2 (100%)
Genitourinary system and sexual hormones	2	1 (50%)	1 (50%)
Deworming, insecticides and repellent medicines	1	- -	1 (100%)

*ATCvet - Anatomical Therapeutic Chemical Classification System for veterinary medicinal products.

According to AEMPS, considering the 44 human medicines prescribed for these animals, one-half (n=22; 50.00%) did not have an equivalent veterinary alternative in the Spanish market. For the remaining half, only four (9.00%) presented a veterinary medicine available on the market that met the requirements for the target species and the appropriate formulation. For ten (23.00%), there was no alternative veterinary medicine in the desired formulation. Finally, in the case of eight (18.00%) prescribed human medicines, no veterinary alternatives were available for the target species.

DISCUSSION

As mentioned above, veterinarians should follow a prescribing cascade, according to the Regulation (EU) 2019/6, which, in brief words, states: if there is no veterinary medicinal product authorised for a therapeutic indication for a companion animal, the veterinarian may, as a first option, use a veterinary medicinal product authorised for use in the same or another animal species, for the same or another indication. Only as a second option the vet is authorised to use a medicine for human use. According to our results, the cascade was not strictly followed, and several reasons may justify it.

This lack of availability of veterinary medicines occurred in 22 (50%) of the medicines administered in this study. The pharmaceutical industry has a significant shortage of medicines for pets, because most of the veterinary medicines marketed are for food species or a large target population. If pharmaceutical companies do not foresee a sufficiently lucrative product market, they will not develop new veterinary medicines. The process of developing and gaining regulatory approval for medicine development is complex and costly.

Furthermore, the market and consumers of veterinary medicines is usually smaller compared to the human pharmaceutical market. Therefore, pharmaceutical companies frequently invest more resources in developing and producing medicines for human use. Additionally, the financial incentives for developing veterinary medicines are usually lower compared to those for human medicines, which also affect the motivation of pharmaceutical companies to do research and develop animal-specific medicines. This creates

a void in the market, forcing veterinarians to find solutions and adapt existing medicines for other species and/or other therapeutic indications (NEWMAN 2018). The problem is even more significant for exotic pets, given the limited market they represent (WINZENBURG et al. 2004). However, even for the most common companion species, such as dogs and cats, this study shows that the available commercial supply is insufficient.

It was also found that there was an alternative veterinary medicine for four (9%) of the medicines used, which met all the target species and formulation requirements. However, on average, the medicine was €0.60 cheaper than the veterinary medicine available on the Spanish market (NOGUEIRA 2023). It seems that the selection of a human medicine over a veterinary medicine for the same active ingredient may result from the socio-economic conditions of the owners and the need to control the costs of hospitalising animals. Animals play an important role in families, but due to the current economic crisis, it is often the case that families end up unable to afford costly veterinary treatments, as the cost jeopardises the financial balance of the household (BOLLER 2021). As a result, and due to the explicit economic constraints and, consequently, the inability of many guardians to bear the total cost of the necessary treatment for the disease, the veterinarian selects pharmacological alternatives according to the financial resources available to the guardians. However, this procedure calls into question Regulation (EU) 2019/6, which does not include the economic aspect in the cascade decision.

Of the eight (18%) medicines administered for the intended active ingredient, the veterinary medicine alternatives available targeted bovine, porcine, equine and poultry species. In the case of ten (23%) medicines, the easiest-to-administer formulation was not available as a veterinary medicine. The formulations and pharmaceutical forms of veterinary medicines available on the market interfere with its choice. Therefore, the type of formulation selected for each animal and its route of administration must consider the animal for which it is intended, its physiology, metabolism, behaviour, and SIZE (HARDEE & BAGGOT 2019).

In this study, 95 different medicines included in the various categories of the ATCvet code were prescribed (Table 2). Drugs that act on the nervous system were the most prescribed pharmacological group (31.58%). The high percentage of medicine prescriptions in this group is justified primarily by the number of clinical cases in neurology, but also by the importance of medicines used for pain control. Pain control is essential and transversal to any disease. Relieving the animal's pain is not only essential for comfort, but it is also an important factor for a successful recovery (GRUEN et al. 2022). The gastrointestinal tract and metabolism group comes in the second place as the most frequently prescribed medicines (n=17; 17.89%). This prescription results from the veterinarians' concern about the severe consequences of nausea, vomiting, and loss of appetite after surgical procedures and disease discomfort. The persistence of these signs can seriously damage the animal's recovery and potentially lead to loss of fluids and electrolytes, dehydration, and acid-base disturbances (ELWOOD et al. 2010).

Future studies with a broader time frame and involving more veterinary hospitals would provide a more comprehensive and complete perspective of veterinary prescription practices at a regional or national level. Drugs formulated for humans may not be suitable for an animal's physiology and metabolism and lead to toxic effects and lack of treatment effectivity (VAN NORMAN 2019). Therefore, the road to excellence and therapeutic efficacy in veterinary medicine also involves the development and practical use of more specific veterinarian medicines.

CONCLUSION

According to the results observed, one of the main challenges to absolute compliance with Regulation (EU) 2019/6 is the unavailability of veterinary medicines. When veterinary medicines are on the market, their formulations and target species are limited. As a result, there is still a gap in the supply of new veterinary medicines that need to be filled by the pharmaceutical industry. Veterinarians play a decisive role in correctly using veterinary medicines, and it is their responsibility to perform a coherent and regulated prescription and use. General therapeutic success in animal patients and global health are highly dependent of a correct use of the prescription cascade.

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