Title

Estimation of defined daily doses of antimicrobials for dogs and cats treated for bacterial cystitis.

Journal

The Canadian veterinary journal. La revue veterinaire canadienne, 63(8)

ISSN

0008-5286

Authors

Weese, J

Bergman, Philip

Battersby, Ian

et al.

Publication Date

2022-08-01

Peer reviewed

Estimation of defined daily doses of antimicrobials for dogs and cats treated for bacterial cystitis

J. Scott Weese, Philip J. Bergman, Ian Battersby, Talon McKee, Dennis Ballance, Anne Kimmerlein

Abstract

Objective

To calculate prescribed daily doses (PDDs) for selected antimicrobials and evaluate application of defined daily doses (DDDs) using an antimicrobial purchasing dataset.

Animals

Data from dogs and cats treated for bacterial cystitis at a veterinary practice network were evaluated.

Procedure

A dataset containing antimicrobial prescriptions for dogs and cats diagnosed with bacterial cystitis was evaluated. Median dose and frequency and median weight of treated animals were used to calculate PDDs. To account for differences in use between dogs and cats, an adjusted DDD was calculated based on adjustment for proportional use in dogs *versus* cats.

Results

PDDs for dogs and cats were determined and adjusted DDDs were calculated and applied to an antimicrobial purchasing dataset from 886 veterinary clinics, demonstrating the difference between mass-based and DDD data.

Conclusions

DDDs can be estimated using prescription datasets, accounting for differences in weights (between and within species) and relative use between dogs and cats. These can be applied to broader (sales, purchase) datasets to provide a more detailed understanding of how antimicrobials are used.

Clinical relevance

DDDs could be a useful measure for assessing mass-based antimicrobial use datasets as part of antimicrobial stewardship surveillance efforts.

Résumé

Estimation des doses quotidiennes définies d'antimicrobiens pour les chiens et les chats traités pour une cystite bactérienne

Objectif

Calculer les doses quotidiennes prescrites (PDDs) pour certains antimicrobiens et évaluer l'application de doses quotidiennes définies (DDDs) à l'aide d'un ensemble de données d'achat d'antimicrobiens.

Animaux

Les données de chiens et de chats traités pour une cystite bactérienne dans un réseau de pratiques vétérinaires ont été évaluées.

Procédure

Un ensemble de données contenant des prescriptions d'antimicrobiens pour les chiens et les chats diagnostiqués avec une cystite bactérienne a été évalué. La dose et la fréquence médianes et le poids médian des animaux traités ont été utilisés pour calculer les PDDs. Pour tenir compte des différences d'utilisation entre les chiens et les chats,

Centre for Public Health and Zoonoses, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada (Weese); VCA Clinical Studies, Los Angeles, California, USA (Bergman, McKee, Ballance, Battersby); Davies Veterinary Specialists, Hitchin, Hertfordshire, UK (Battersby); VCA Inc, Sacramento, California, USA (Kimmerlein).

Address all correspondence to Dr. J. Scott Weese; email: jsweese@uoguelph.ca

une DDD ajustée a été calculée sur la base d'un ajustement pour une utilisation proportionnelle chez les chiens par rapport aux chats.

Résultats

Les PDDs pour les chiens et les chats ont été déterminées et les DDDs ajustées ont été calculés et appliqués à un ensemble de données d'achat d'antimicrobiens provenant de 886 cliniques vétérinaires, démontrant la différence entre les données basées sur la masse et les données DDD.

Conclusions

Les DDD peuvent être estimées à l'aide d'ensembles de données de prescription, en tenant compte des différences de poids (entre et au sein des espèces) et de l'utilisation relative entre les chiens et les chats. Celles-ci peuvent être appliquées à des ensembles de données plus larges (ventes, achats) pour fournir une compréhension plus détaillée de la façon dont les antimicrobiens sont utilisés.

Pertinence clinique

Les DDDs pourraient être une mesure utile pour évaluer les ensembles de données sur l'utilisation massive d'antimicrobiens dans le cadre des efforts de surveillance de la gestion des antimicrobiens.

(Traduit par Dr Serge Messier)

Can Vet J 2022;63:851–854

Antimicrobial stewardship is an emerging field in veterinary medicine that is attempting to address the "silent pandemic" of antimicrobial resistance and the need to better understand and optimize antimicrobial use (AMU) in animals. A core component of antimicrobial stewardship is monitoring AMU (1), as an understanding of how antimicrobials are used is the foundation for evaluating those practices, identifying areas for improvement, developing targets, and evaluating impacts of interventions. Yet, AMU data can be challenging to obtain for dogs and cats. Even with electronic medical records systems, specific patient-level prescribing data are not often readily available, whereas higher-level metrics such as overall mass of antimicrobials can sometimes be more readily obtained from purchasing or sales data. Regardless, use of antimicrobial mass data can be challenging based on variations in recommended dosing ranges, lack of information about typical dosing patterns, differences in animal size, and differences in relative use of antimicrobials in dogs and cats, limiting the ability to put overall mass data into context.

One approach to refine AMU surveillance is the use of defined daily doses (DDDs). This is commonly used in human medicine and defined as *"The assumed average maintenance dose per day for a drug used for its main indication in adults"* (https://www.who.int/tools/atc-ddd-toolkit/about-ddd). It is a theoretical measure based on estimated dosing regimens and body weights, with accuracy of the measure being dependent on the applicability of those estimates to the patient population for a given antimicrobial dataset. By using DDDs, it is possible to estimate the amount of use of an antimicrobial from overall mass, by converting a weight-based measure to a representation of the number of treatment days. Furthermore, DDDs can provide a stable measure to assess antimicrobial use among times, facilities, and regions.

In animals, there can be challenges to the use of DDDs based on wider weight ranges among species and because there is often disproportionate use in growing animals, where weights are more changeable compared to adult populations (2). Various metrics are used for measuring AMU in food animals, such as DDD animal (DDDA), used daily doses (UDD), number of standardized regimens and mass of active ingredient, with variable reporting, such as per animal, per kg of animal, per animal-days, per production cycle, or per population correction unit (PCU) (2–4).

There has been limited study of antimicrobial use metrics in companion animals. As AMU in companion animals is more similar to that in humans than that in livestock, DDDs are potentially a more useful measure than metrics designed for food animals. Because sizes of food animals are more similar within a treated population (usually the same species and production type), dosing recommendations tend to be more uniform and have greater compliance. However, establishing DDDs poses challenges as the proportional weight differences within a population of adult dogs and cats are much greater than those in humans and there may be abundant extra-label use of antimicrobials and variations in dosing regimens. Furthermore, whereas DDDs are species-specific, available antimicrobial data (*e.g.,* sales, purchasing) are typically composite data from dogs and cats in companion animal clinics. Differences in dosing recommendations and relative use in dogs *versus* cats can also impact assessment of overall AMU purchasing or sales datasets. Therefore, development of DDDs for dogs and cats requires an understanding of the use of antimicrobials within each species, and, if DDDs are to be applied to a broader dataset of combined dog and cat data, relative use between species must be understood to develop a composite measure.

The objectives of this study were to estimate DDDs from a population of dogs and cats treated with antimicrobials for acute sporadic cystitis.

Electronic medical records from a veterinary practice corporation with clinics in the United States and Canada were queried between January 2, 2016 and December 3, 2018 (5,6). Canine and feline patient visits with a diagnosis of sporadic bacterial cystitis (or variations such as urinary tract infection or bladder infection) and in which an antimicrobial was prescribed were retrieved. "Suspect" or "possible" entries were included because they were accompanied by an antimicrobial prescription for that condition. If a comorbidity that might impact antimicrobial decision-making (*e.g.,* wound infection, dermatitis) was reported, the record was excluded. Cases identified as recurrent

Table 1. Median dosing, animal weights, and daily doses, as well as species-specific and adjusted overall defined daily doses for selected antimicrobials prescribed for sporadic bacterial cystitis in dogs and cats.

	Canine				Feline					
	n	Median dose (mg/kg)	Median weight (kg)	Median daily dose (mg)	*n*	Median dose (mg/kg)	Median weight (kg)	Median daily dose (mg)	Dogs: cats treated	Adjusted DDD
Enrofloxacin	100	5.8 q24h	15.9	136	80	4.8	4.5	22.7	434:80	118.4
Amoxicillin	100	17.6 q21h	15.6	500	76	12.5 q8h	4.9	127.5	325:76	429.4
Pradofloxacin	0	NA	NA	NA	60	7.4 q24h	4.0	27.5	0:60	27.5
Amoxicillin/clavulanic acid	100	15 q12h	11.8	375	100	14.2	4.9	125	2617:1118	300.2
Marbofloxacin	100	3.7 q24h	12.2	50	100	4.0	4.8	25	726:335	42.1
Cefpodoxime	100	6.9 q24h	20.1	150	22	7.5 q24h	6.1	50	1032:22	147.9
Trimethoprim-sulfa	70	22.9 q12h	30	960	0	NA	NA	NA	70:0	960
Cephalexin	100	23 q12h	26.8	1000	0	NA	NA	NA	215:0	1000
Ciprofloxacin	69	15.7 q12h	28.7	750	0	NA	NA	NA	69:0	750
Cefovecin*	100	8 mg/kg	7.6	61*	100	8 mg/kg	5.5	44*	401:2966	46*

* Defined treatment course dose, not daily dose.
NA — Not applicable.

or chronic by the diagnostic field entry or presence of a previous visit in the dataset were also excluded.

Signalment, body weight, diagnosis, and antimicrobial drug regimen (drug, dose, and duration) were recorded. Records that did not indicate patient weight or dosing regimen were excluded.

For both dogs and cats, a random selection of 100 patient visits was made for each prescription of amoxicillin, amoxicillin-clavulanic acid, enrofloxacin, marbofloxacin, cefovecin, ciprofloxacin, cephalexin, cefpodoxime, and trimethoprim-sulfonamide. However, if the dataset had < 100 prescriptions, the total number available was used. Prescribed daily doses were determined. Median dosage (mg/kg), dosing frequency, and daily amount administered (dose × weight × number of administrations per day) were calculated for each drug and each species. For calculation of DDD, the median daily amount prescribed to the individual animal (PDD) was used. As cefovecin is highly protein bound and licenced for administration every 14 d, data for this drug represent a defined treatment course, not DDD.

Because there are differences in how commonly various antimicrobials are used in dogs *versus* cats, and potential differences within species (*e.g.,* more common use of a certain drug in large dogs due to cost considerations), species-level DDDs were adjusted to account for the impact of differences in patient size and relative use of each drug in dogs and cats. The total number of prescriptions of each drug for dogs and cats was determined. The adjusted DDD was calculated as:

[Canine DDD × (number of dogs treated with a given antimicrobial/total number of animals treated with that antimicrobial)] + [Feline DDD × (number of cats treated/total number of animals treated with that antimicrobial)]

To compare antimicrobial mass and DDDs, the adjusted DDD was applied to an antimicrobial purchasing dataset for selected antimicrobials from 886 small animal veterinary clinics that belonged to the same veterinary corporation. Total antimicrobial purchases from December 30, 2018 to April 24, 2021 were evaluated. The total mass of antimicrobial that was purchased was converted to DDDs using the adjusted DDDs.

A total of 6582 canine and 5051 feline patient visits for sporadic cystitis were present in the overall dataset. Median dose, weight, and daily administered amount (define daily dose) for the random selection of up to 100 prescriptions per drug are presented in Table 1. Adjusted overall dog and cat DDDs are also presented in Table 1, accounting for differences in relative use between dogs and cats and differences in animal size.

Purchasing data for amoxicillin/clavulanic acid, enrofloxacin, cephalexin, marbofloxacin, pradofloxacin, cefovecin, and ciprofloxacin were obtained from 885 clinics. Amoxicillin data were not analyzed because DDDs based on use for lower urinary tract disease may not represent broader amoxicillin use. Comparison of mass and DDDs is presented in Figure 1.

These DDD data must be considered in the context of their population. These DDD calculations were made from a dataset of dogs and cats treated with antimicrobials for sporadic bacterial cystitis. The use of a large dataset from 2 countries helps offset potential regional or clinic-specific differences and it is likely that the dosing practices for these specific drugs in other regions or clinics would be similar, but this needs to be explored further. These data are also based on treatment of sporadic bacterial cystitis. However, prescribed dosages and duration, and relative use in dogs *versus* cats, may be likely similar for this condition compared to other common conditions, except for amoxicillin. Treatment recommendations for amoxicillin differ for lower urinary tract disease *versus* other diseases (7), with twice-daily administration being commonly used lower urinary tract disease but 3 times a day administration recommended for other infections. Therefore, use of this amoxicillin DDD should be restricted to datasets that only involve lower urinary tract disease.

There could also be inter- or intra-regional impacts on the adjusted DDDs if there are differences in relative use of certain antimicrobials between dogs and cats and differences in median animal weights. Study of other datasets and consideration of these potential confounders is important when using the individual or combined DDDs, and region-specific DDDs may be required for some antimicrobials. Within clinic or network comparison of DDDs over time or in response to an intervention targeted veterinarians' prescribing practices would likely be

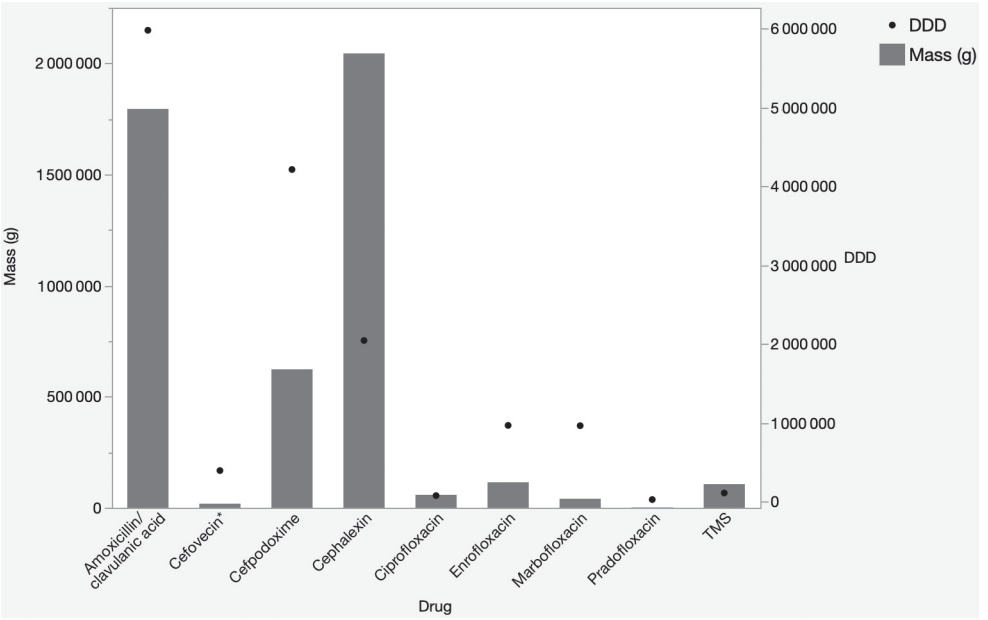

Figure 1. Total antimicrobial purchases (g) and adjusted defined daily doses (DDDs) from a clinic network purchasing database.

* Defined treatment course dose, not daily dose.

stronger than comparing between regions or networks, in which differences in relative use of antimicrobials between dogs and cats or differences in median weights may be more pronounced. There is also a need to be aware of potential changes in dosing patterns that could influence DDDs, such as a change in recommended mg/kg dosing or dosing frequency based on new data or guidelines. Should those occur, DDDs would have to be re-assessed.

When applied to antimicrobial purchasing data, it is clear how DDDs can provide different interpretations of the data. Cephalexin was the most abundantly used drug on a mass basis but was only third when adjusted for DDDs. The impact of DDDs was most striking for fluoroquinolones and 3rd generation cephalosporins, which are dosed infrequently and at lower mg/kg dosages than penicillins. Therefore, although it may appear that there is limited use of some antimicrobials on a mass basis compared to amoxicillin-clavulanic acid and cephalexin, applying DDDs reduced that apparent difference. This highlighted the potential importance of considering dosing, *via* DDD or a similar metric, when attempting to quantify and understand AMU at the animal level.

It was also interesting to see differences in weights for different prescribed drugs in dogs, with high median weights for trimethoprim sulfonamide, cephalexin, and ciprofloxacin. Reasons for drug choices were not queried, but cost is a likely explanation, as these drugs are generally less expensive and therefore less cost prohibitive for larger dogs. This highlighted the number of factors that must be considered when evaluating and addressing AMU data in companion animals.

Defined daily dose is a crude measure, but it can be useful for surveillance activities if the appropriateness of the dataset and potential limitations are considered. Often, obtaining detailed patient-level antimicrobial use information is difficult or impossible, whereas higher-level data such as overall drug purchase or sales data can be obtained. The use of DDDs can help provide context to overall drug purchase or sales data. Ultimately, accurate and easy-to-access patient-level data may be the main surveillance tool and that would be the most effective approach. However, in the interim, metrics such as DDD can be used to provide more insight into antimicrobial use, to set targets, and to evaluate impacts of interventions. CVJ

References

1. Barlam TF, Cosgrove SE, Abbo LM, *et al.* Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51–77.
2. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. Prev Vet Med 2004;64: 201–215.
3. Schrag NFD, Apley MD, Godden SM, Lubbers BV, Singer RS. Antimicrobial use quantification in adult dairy cows — Part 1 — Standardized regimens as a method for describing antimicrobial use. Zoonoses Public Health 2020;67 Suppl 1:51–68.
4. Werner N, McEwen S, Kreienbrock L. Monitoring antimicrobial drug usage in animals: Methods and applications. Microbiol Spectr 2018:6.
5. Weese JS, Webb J, Ballance D, McKee T, Stull JW, Bergman PJ. Evaluation of antimicrobial prescriptions in dogs with suspected bacterial urinary tract disease. J Vet Intern Med 2021;35:2277–2286.
6. Weese JS, Stull JW, Evason M, *et al.* A multicenter study of antimicrobial prescriptions for cats diagnosed with bacterial urinary tract disease. J Feline Med Surg 2021:1098612X211054815.
7. Weese JS, Blondeau J, Boothe D, *et al.* International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats. Vet J 2019;247:8–25.