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Veterinarians Need Better Options:
Currently Prescribed Metronidazole Formulations to Treat Diarrhea in Dogs Are Not Ideal

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Abstract

Metronidazole is an antibiotic developed and approved for human use that is also used by veterinarians (off label) to treat diarrhea (and other illnesses and conditions) in companion animals (specifically dogs, cats, and horses). Metronidazole is provided in 2 forms, as either an immediate-release (IR), rather large tablet that is bitter-tasting and difficult for companion animals to swallow, or as metronidazole benzoate in an oral suspension, which is less bitter-tasting and easier to administer than the parent compound. As is the case for many drugs used in veterinary medicine, metronidazole has not been approved by the Food and Drug Administration Center for Veterinary Medicine (FDA-CVM) for animal use and, to date, the pharmacokinetics of these formulations in animals have not been studied. In a study at Zomedica Pharmaceuticals Corp., plasma concentrations of 9 formulations of metronidazole in male beagles using high-performance liquid chromatography (HPLC) was examined. Concentrations of the metronidazole benzoate formulation did not achieve the same levels as its parent compound, suggesting that the efficacy of the benzoate derivative formulation is not equivalent.

Problem Statement/Introduction

Medications used by veterinarians are often originally developed for use in humans and have not been optimized to treat companion animals.

Problem #1: ***The efficacy of metronidazole to treat diarrhea has not been established in dogs.***
Veterinarians rely on using off-label drugs that are optimized for human use when no approved alternatives exist. In fact, metronidazole and its derivative metronidazole benzoate are among the most highly prescribed antimicrobials in veterinary medicine. However, these medications have not been approved by the FDA-CVM for use in companion animals, and veterinarians must use efficacy and safety data from human trials and translate this information into clinical practice to determine proper dosages for companion animals. Therefore, veterinarians cannot be sure that their 4-legged patients are receiving an appropriate dose. Additionally, proper dosage is especially tricky for smaller breeds and puppies, as weight-based dosing means that the tablets may need to be divided more than once.

Problem #2: ***The drug delivery of metronidazole is not optimized for canines.***
Drugs that are designed for humans are not optimally formulated to maximize compliance in dogs. While this drug does not seem to impact human patient compliance, it is well known that dogs have difficulty swallowing the large, bitter tablets that are approved for human use.

Problem #3: *Veterinarians must rely on compounding pharmacies.*
Currently, metronidazole prescribed by veterinarians is often converted by compounding pharmacies into a formulation that can be more easily administered to dogs. In fact, metronidazole benzoate oral suspension is one of the most frequently compounded drugs for dogs. The benzoate derivative is believed to be less bitter-tasting than the IR pill, but its efficacy has not been established for canines.

Supporting Data

Plasma concentrations of 3 different formulations of metronidazole in an immediate release (IR) tablet, 3 different formulations of metronidazole *benzoate* in IR tablets, and 3 different formulations of metronidazole *benzoate* in an oral suspension (OS), for a total of 9 different formulations were determined. Each formulation was administered once to each group (n=4) as close to 15 mg/kg as possible given the constraints of formulation, and blood samples were collected before dosing (0 hour) and then at 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, and 24 hours post-dose. HPLC is a simple, robust method that was developed and validated to measure the concentration of metronidazole present in human plasma.[1-4] Thus, HPLC was used to measure metronidazole in plasma from male beagle dogs in our study.

The average plasma concentration for each formulation is shown in Figure 1. The area under the plasma concentration curve (AUC), maximum plasma concentration (C_{max}), and the maximum time at C_{max} (T_{max}) were calculated and are shown in Table 1. Results of this study showed that the parent compound significantly outperformed the benzoate, in that the Cmax was greater than three times that of the benzoate, and the AUC greater than twice that of the benzoate, suggesting that the derivative may not be as effective.

Suggested Solutions

An urgent need exists to establish safe and effective doses of metronidazole to treat diarrhea in dogs, rather than relying on efficacy and safety data extrapolated from human studies and using tablets or suspensions produced for human use. Veterinary medicine also needs a better option for drug delivery designed specifically for canines. Presently, veterinarians must choose between a bitter-tasting metronidazole IR tablet and a better-tasting, but less-effective, metronidazole benzoate tablet or suspension.

Zomedica Pharmaceuticals Corp. currently has 2 drugs progressing through the FDA-CVM approval process:

1. **ZM-012**, a novel, canine-specific tablet formulation to replace the large, bitter-tasting generic tablet designed for humans.
2. **ZM-007**, an oral suspension formulation that provides veterinarians a means by which to accurately dose smaller breeds and puppies without relying on compounding pharmacies.

By taking ZM-007 and ZM-012 through the rigorous FDA-CVM approval process, Zomedica Pharmaceuticals Corp., intends to validate these drugs as safe and effective for veterinary use in dogs; and ultimately provide products specifically formulated for companion animals to positively impact patient care and practice management.

"Our goal with these formulations is to give veterinarians full confidence that the medication they are using to treat their canine patients is indeed safe and effective rather than relying on data from human trials."

Conclusions

This study demonstrated that all formulations of metronidazole benzoate (both the IR tablet and the oral suspension) produced significantly lower plasma concentrations and performed significantly more poorly than did all formulations of the metronidazole IR tablet. Thus, medicating dogs with the benzoate derivative carries the risk of treatment failure. Further studies are required to determine the ideal dose of metronidazole and its associated mechanism of action in dogs. Newer, more-tailored treatment options are needed to meet the needs of canine patients suffering with diarrhea that are safe, effective and easy to administer.

Disclosures and Acknowledgments

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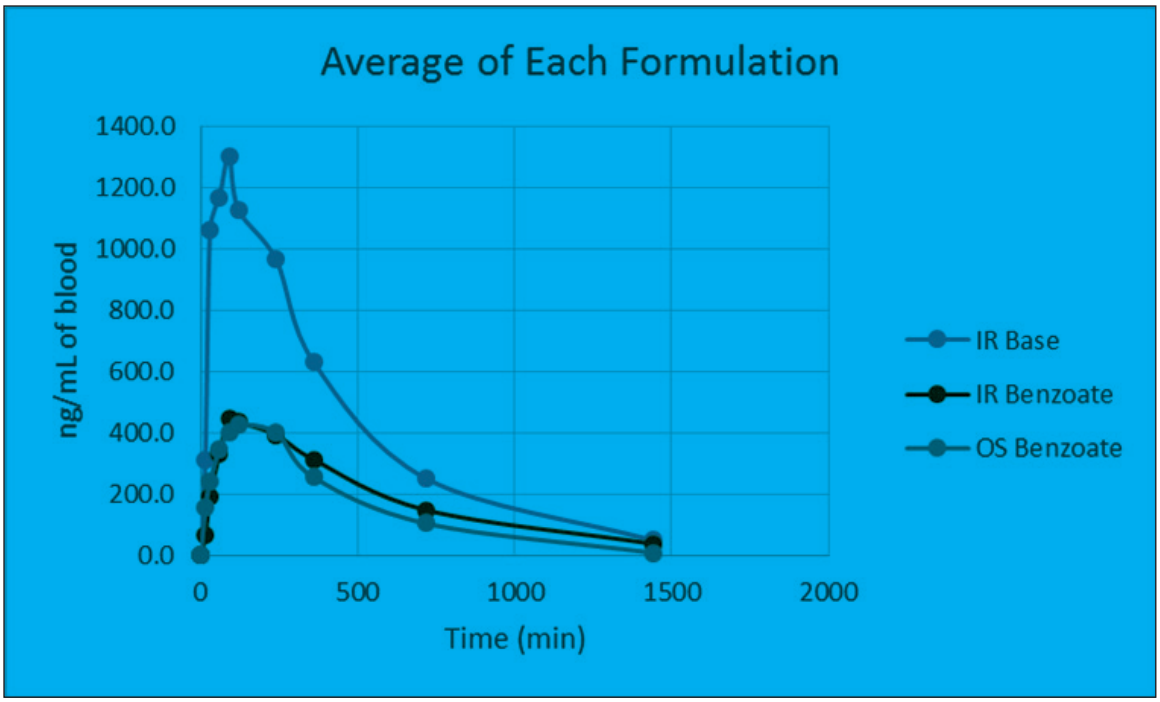
REFERENCES

1. Do Nascimento, TG, de Jesus Oliveira, E, Macêdo, RO. Simultaneous determination of ranitidine and metronidazole in human plasma using high performance liquid chromatography with diode array detection. *J PharmBiomed Anal*. 2005;37:777–783.
2. Menelaou A, Somogyi AA, Barclay ML, Bochner F. Simultaneous quantification of amoxicillin and metronidazole in plasma using high-performance liquid chromatography with photodiode array detection. *J Chromatogr B*. 1999;731:261–266.
3. Obodozie OO, Ebeshi, BU, Mustaoha KB, Kirim RA, Ekpenyong M, Inyang US. The effects of an investigational antimalarial agent, NIPRD-AM1 on the single dose pharmacokinetics of metronidazole in healthy human volunteers. *Eur J Drug Metab Pharmacokinet*. 2011;35:103–108.
4. Tavakoli N, Varshosav J, Dorkoosh F, Zargarzadeh, MR. Development and validation of a simple HPLC method for simultaneous *in vitro* determination of amoxicillin and metronidazole at a single wavelength. *J Pharm Biomed Anal. 2007;43:325–329*.

Figure 1. Average Plasma Concentrations for All Metronidazole Formulations



IR = immediate release; OS = oral suspension.

Table 1. Pharmacokinetics of Single-Tablet or Oral-Gavage of Metronidazole in Male Beagles

	Group[a]								
	Metronidazole IR 15 mg/kg			Metronidazole benzoate IR 25 mg/kg			Metronidazole benzoate OS 25 mg/kg		
Parameter	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
C_{max}, ng/mL									
Mean	1,650	1,390	1,550	471	589	365	419	403	501
SD	261	145	288	201	387	133	232	91.2	70.7
%CV	15.8	10.4	18.5	42.7	65.8	36.4	55.4	22.7	14.1
T_{max},[b] hr									
Median	NA	1	NA	NA	NA	NA	2	NA	NA
Range	0.5-1.5	0.5-1.5	0.5-1	1.5-6	1.5-4	1.5-4	2-4	2-4	1-4
%CV	NA	NA	NA	NA	NA	NA	NA	NA	NA
AUC_{0-24}, hr • ng/mL									
Mean	10,200	11,100	9,080	4,550	5,720	3,620	4,260	3,130	4,190
SD	1,100	1,110	1,530	1,450	2,910	1,260	2,140	793	752
%CV	10.8	10.0	16.9	31.8	50.8	34.9	50.2	25.3	17.9

AUC_{0-24} = area under the plasma concentration curve from 0-24 hours; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; IR = immediate release; NA = not applicable; OS = oral suspension; SD = standard deviation; T_{max} = maximum time at C_{max}.

[a] Doses were averaged among 4 animals per group.

[b] Median value only reported if actual collection interval.