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Journal

Journal of Veterinary Pharmacology and Therapeutics, 39(4)

ISSN

0140-7783

Authors

Fitzpatrick, RL
Wittenburg, LA
Hansen, RJ
et al.

Publication Date

2016-08-01

DOI

10.1111/jvp.12286

Peer reviewed

HHS Public Access

Author manuscript

J Vet Pharmacol Ther. Author manuscript; available in PMC 2020 January 31.

Published in final edited form as:

J Vet Pharmacol Ther. 2016 August ; 39(4): 350–355. doi:10.1111/jvp.12286.

Limited sampling pharmacokinetics of subcutaneous ondansetron in healthy geriatric cats, cats with chronic kidney disease, and cats with liver disease

R. L. FITZPATRICK, **L. A. WITTENBURG**, **R. J. HANSEN**, **D. L. GUSTAFSON**, **J. M. QUIMBY**

Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, USA

Abstract

Ondansetron, a 5-HT_3 receptor antagonist, is an effective anti-emetic in cats. The purpose of this study was to compare pharmacokinetics of subcutaneous (SQ) ondansetron in healthy geriatric cats to cats with chronic kidney disease (CKD) or liver disease using a limited sampling strategy. 60 cats participated; 20 per group. Blood was drawn 30 and 120 min following one 2 mg (mean 0.49 mg/kg, range 0.27–1.05 mg/kg) SQ dose of ondansetron. Ondansetron concentrations were measured by liquid chromatography coupled to tandem mass spectrometry. Drug exposure represented as area under the curve (AUC) was predicted using a limited sampling approach based on multiple linear regression analysis from previous full sampling studies, and clearance (CL/F) estimated using noncompartmental methods. Kruskal–Wallis ANOVA was used to compare parameters between groups. Mean AUC (ng/mL·h) of subcutaneous ondansetron was 301.4 (geriatric), 415.2 (CKD), and 587.0 (liver). CL/F (L/h/kg) of SQ ondansetron was 1.157 (geriatric), 0.967 (CKD), and 0.795 (liver). AUC was significantly higher in liver and CKD cats when compared to geriatric cats ($P < 0.05$). CL/F in liver cats was significantly decreased ($P < 0.05$) compared to geriatric cats. In age-matched subset analysis, AUC and CL/F in liver cats remained significantly different from geriatric cats.

INTRODUCTION

Ondansetron is a 5-HT_3 receptor antagonist used as an anti-emetic frequently in human medicine. This medication has previously been shown to be an effective anti-emetic in cats, blocking dexmedetomidine-induced emesis (Santos *et al*., 2011; Wang *et al*., 2011), and xylazine-induced emesis (Jarolmasjed & Kolahian, 2010). Bioavailability varies widely between species as well as between routes of administration. A recent study performed evaluated the pharmacokinetics for different routes of administration (oral, subcutaneous, and intravenous) of ondansetron in healthy cats (Quimby *et al*., 2014). Based on the results of this study, it was shown that subcutaneous administration resulted in a more prolonged exposure than both oral and intravenous administration. Ondansetron is metabolized primarily by the liver (Roila & Del Favero, 1995), however, there is a minimal amount (<5%) metabolized by the kidney (Amantea *et al*., 1993). Previous pharmacokinetic studies

Jessica M. Quimby, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 300 West Drake Road, Fort Collins, CO 80523, USA. jquimby@colostate.edu.

in human medicine have shown that liver disease and age can alter the clearance (CL) of ondansetron in people and that kidney disease does not appear to have a significant effect on CL (Roila & Del Favero, 1995). The effects of age, kidney disease, and liver disease on the CL of ondansetron in cats are unknown. The purpose of this study was to compare the pharmacokinetics of subcutaneous ondansetron in healthy geriatric cats, cats with CKD, and cats with liver disease. A limited sampling strategy was used in this study based on the pharmacokinetic modeling from the previous study evaluating ondansetron in cats (Quimby *et al.*, 2014). Our hypothesis was that cats with liver disease would have increased drug exposure and decreased CL compared to the other two groups based on previous studies in people with liver disease.

MATERIALS AND METHODS

Animals

Cats were categorized into one of the following three groups: healthy geriatric, chronic kidney disease (CKD), and liver. Group 1 included 20 healthy geriatric cats, defined as having a normal complete blood count, chemistry, urinalysis, and thyroid level. Exclusion criteria for healthy geriatric cats include other systemic illness (diabetes, inflammatory bowel disease, hyperthyroidism, cancer, liver disease, heart disease) and a urine specific gravity < 1.035 or a creatinine > 1.5 mg/dL. The cats in group 1 were recruited from the patient population owned by students and staff. Group 2 included 20 cats diagnosed with chronic and stable kidney disease with a creatinine between 1.7 and 6 mg/dL. Group 3 included 20 cats diagnosed with liver disease based on elevation of any of the serum liver enzymes and/or total bilirubin. Cats with mild to moderate elevated alanine transaminase (ALT) levels had to have a normal thyroid level. Cats also had to be clinically hydrated to be included in the study. The cats in groups 2 and 3 were recruited from the patient population at the Colorado State University veterinary teaching hospital. An *a priori* power calculation was performed using the standard deviation of ondansetron AUC in normal cats (53 ng/mL·h) (Quimby *et al.*, 2014) and revealed that with an alpha of 0.05, 17 cats would be needed in each group to obtain a power of 80%. This study was approved in advance by the Institutional Animal Care and Use Committee (IACUC) at Colorado State University and all owners gave informed consent.

Dosing and sampling

Each cat received 2 mg of ondansetron (2 mg/mL injectable; West/Ward Pharmaceuticals, Eatontown, NJ, USA) administered subcutaneously. Dose selection was intended to allow comparison to a previous study describing ondansetron pharmacokinetics in cats (Quimby *et al.*, 2014). Blood samples were collected 30 min and 120 min following the subcutaneous injection. Methodology for determining timepoints is described below. Serum was collected via centrifugation immediately after clot formation and frozen in aliquots at −80 °C until analysis.

Limited sampling modeling

The ondansetron serum concentration vs. time data for six cats administered a fixed 2 mg dose by subcutaneous injection was utilized for calculation of drug exposure ($AUC_{0–12}$ h) by

noncompartmental methods. The resulting AUC values were found to be normally distributed by Q–Q plot and subsequently analyzed as a response to time point ondansetron concentration values as predictors by best subset multiple linear regression. This method evaluates all single time points as well as all possible combinations of multiple time points (2, 3, 4, 5, 6, or 7) as predictors of the outcome ($AUC_{0–12}$ h). Data utilized in the best subset linear regression analysis were those time points corresponding to postadministration samples and were designated as 15, 30, 60, 120, 240, 480, and 720 corresponding to the number of minutes the samples were collected after administration. The combinations of statistical correlation, number of samples required, and length of time required postadministration were all considered in choosing the optimal limited sampling scheme. All regression analysis was carried out using Minitab® v 15.1.1.0 software (Minitab, State College, PA, USA). The results of best subset multiple linear regression revealed that using two points as predictors of AUC (30 and 120 min) could provide the best combination of statistical correlation ($r^2 = 0.978$) while minimizing sample number and time postadministration. Increasing the number of early time points by adding the 15 and 60 min samples only increased the correlation by approximately 2%. The final model utilizing the identified time points is described by the equation

$$\mathrm{AUC} = -0.7 + \left(1.12 * C_{30\,\mathrm{min}}\right) + \left(5.69 * C_{120\,\mathrm{min}}\right)$$

where $C_{30\ \mathrm{min}}$ and $C_{120\ \mathrm{min}}$ represent the serum concentrations at 30 and 120 min, respectively, following subcutaneous administration. This equation was used to estimate AUC in study samples. Because ondansetron was administered via an extravascular route, absorbed dose is equal to dose × bioavailability (F), thus CL is represented as CL/F and was calculated as Dose/AUC.

Sample preparation and mass spectrometry

Samples were prepared and analyzed as previously described (Quimby *et al.*, 2014) with the exception of a few refinements described as follows. Initial stocks of ondansetron and zolpidem were prepared in 1:1 methanol/Milli-Q water (1 mg/mL) for standard curve and quality controls. A standard curve for ondansetron was then prepared ranging from 0.75 to 500 ng/mL in 1:1 methanol/Milli-Q water. Five microlitre of each appropriate standard was then added to 50 μL of blank serum and spiked with 5 μL internal standard (zolpidem at 250 ng/mL). Quality controls of low, medium, and high concentrations (2.5, 50, and 250 ng/mL) were prepared in a similar manner. Five microlitre internal standard and 5 μL 1:1 methanol/Milli-Q water were added to 50 μL of each unknown sample. Proteins were precipitated from all samples with addition of 175 μL of ice cold methanol, vortex mixed for 5 min, centrifuged at 14 000 ***g*** at 4 °C for 10 min and 175 μL was transferred to fresh 2 mL micro-centrifuge tubes. Samples were concentrated to dryness on a speed vacuum then reconstituted in 100 μL of 80:20 [v:v], 10 mM ammonium acetate: acetonitrile. Samples were then transferred to autosampler vials with poly propylene inserts for injection onto the LC system.

Mass spectra were obtained with a MDS Sciex 3200 Q-TRAP triple quadrupole mass spectrometer (Applied Biosystems, Inc., Foster City, CA, USA) with a turbo ionspray source

interfaced to an Agilent 1200 Series Binary Pump SL HPLC system (Santa Clara, CA, USA). Samples were chromatographed with a Sunfire C8, 5 lm, 4.6 × 50 mm column (Waters Corporation, Milford, MA, USA) protected by a C18 guard cartridge, 4.0 × 2.0 mm (Phenomenex, Torrance, CA, USA). An LC gradient was employed with mobile phase A consisting of 10 mM ammonium acetate with 0.1% acetic acid and mobile phase B consisting of acetonitrile. Chromatographic resolution was achieved by increasing mobile phase B linearly from 20% to 50% from 1 to 3 min, maintaining at 50% from 3 to 3.5 min, decreasing linearly from 50% to 20% from 3.5 to 4 min, followed by re-equilibration of the column at 20% B from 4 to 5 min. The LC flow rate was 1 mL/min, the sample injection volume was 20 μL, and the analysis run time was 5 min. Operating in positive ion electrospray mode, source-dependent parameters were optimized as follows: turbo ionspray temperature, 550 °C; ion spray voltage, 5500 V; curtain gas, N_2, 20 units; collision gas, N_2, 2 units; nebulizer gas, N_2, 60 units; and auxiliary gas, N_2, 60 units. The compound-dependent parameters for ondansetron and zolpidem, respectively, were optimized as follows; declustering potential, 39 and 49 V; entrance potential, 8.3 and 10.1 V; collision energy, 35 and 42 V; collision cell entrance potential, 22.2 and 31.7 V; collision cell exit potential, 2.2 and 2.0 V. The predominant product ion for ondansetron was *m/z* 170.2. Samples were quantified by internal standard reference method in the MRM mode monitoring ion transitions *m/z* 294.2 → 170.2 for ondansetron and *m/z* 308.2 → 235.4 for the internal standard, zolpidem. The dwell times for each ion transition were 250 ms. Q_1 and Q_3 were both operated in unit resolution mode.

Protein binding

In a subset of healthy geriatric cats ($n = 5$) and cats with liver disease ($n = 5$) serum protein binding (PB) of ondansetron was determined via ultrafiltration through an Amicon®Ultra centrifugal filter unit (regenerated cellulose, 10 000 NMWL) purchased from Millipore (Bedford, MA, USA) as previously described (Lee *et al.*, 2003). Briefly, filter units were pretreated by incubating 400 μL of 5% Tween-80 in phosphate buffered saline (PBS) (pH 7.4) in top of filter unit for 5 min and then centrifuged for 10 min at 3000 ***g***. Filter tops were then rinsed with 400 μL of PBS. Serum samples (200 μL) were incubated at room temperature for 1 h, 50 μL was removed for total ondansetron measurement, and remaining was centrifuged for ~25 min at 3000 ***g*** until 50 μL of filtrate was in the bottom of the tube and used for free drug sample measurement. Nonspecific PB was determined to be zero performing the same procedure with ondansetron spiked in PBS (pH 7.4). Samples were quantified by LC/MS/MS as described above.

Data analysis

Ondansetron quantitation was based on linear calibration curves in spiked blank serum using the ratio of ondansetron peak area to zolpidem peak area and $1/x^2$ weighting of linear regression. Parameters for the assessment of assay performance were calculated as previous described (Quimby *et al.*, 2014).

Statistical analysis

Pharmacokinetic parameters were compared between the three groups using a nonparametric ANOVA (Kruskal–Wallis) test with Dunn's *post hoc* analysis in Prism software (Prism 5; GraphPad, La Jolla, CA, USA). Parameters assessed included area under the curve (AUC) and CL/F. The creatinine, ALT, ALP, total bilirubin, and albumin between the three groups were also compared using a nonparametric ANOVA (Kruskal–Wallis) test with Dunn's *post hoc* analysis in the Prism software. Correlation between AUC and CL/F vs. clinicopathologic parameters creatinine, ALT, ALP, total bilirubin, and albumin was analyzed using linear regression in Prism software. Additionally, subset analysis was performed in which cats were age matched when possible within 1 year of reported age, and age-matched comparisons between liver and geriatric controls and CKD and geriatric controls were analyzed using a Mann–Whitney test in Prism software. Data were assessed for normality using D'Agostino and Pearson normality test and were not found to be normally distributed; hence, nonparametric tests were performed. For all analyses, a *P*-value < 0.05 was considered statistically significant.

RESULTS

Cats

In the healthy geriatric group there were 12 female cats (11 spayed, 1 intact) and eight male cats (all castrated) with an average age of 11.5 years (range 5–18 years) and median body weight of 4.4 kg (range 2.5–7.5 kg). Although not considered geriatric, a few cats (ages 5, 6, and 9) were enrolled that were under the age of ten to age-matched cats in the other two groups. In the CKD group, there were 10 female cats (all spayed) and 11 male cats (all castrated) with an average age of 14 years (range 5–20 years) and median body weight of 4.5 kg (range 1.9–7.0 kg). In the liver disease group, there were 10 female cats (all spayed) and 10 male cats (all castrated) with an average age of 10.2 years (range 2–15) and a median body weight of 4.5 kg (range 2.9–6.0 kg). There was no statistical difference in body weight between groups but dose-correction was performed as part of analysis. There was a statistically significant difference in age between the CKD group and both healthy geriatric and liver disease groups ($P < 0.05$). A subset of cats were able to be age matched between groups with a total of 15 pairs for the liver vs. geriatric group comparison and 13 pairs for the kidney vs. geriatric group comparison.

Dose-corrected clinicopathologic parameters for each group are presented in Table 1. The following parameters were evaluated and compared across the three groups, albumin, ALT, ALP, creatinine and total bilirubin. The ALT, ALP, and total bilirubin were all significantly elevated in the cats with liver disease when compared to the healthy geriatric cats and cats with CKD ($P < 0.05$). The creatinine levels were significantly higher in the CKD cats when compared to the other two groups ($P < 0.05$). Albumin levels were significantly lower in the CKD cats and cats with liver disease when compared to the healthy geriatric cats ($P < 0.05$). There was not a statistically significant difference in the albumin levels between the CKD cats and cats with liver disease.

Drug administration

There was no statistically significant difference noted in the dose of ondansetron administered across the three groups. The mean dose for the geriatric cats was 0.45 mg/kg (range 0.27–0.79 mg/kg), 0.54 mg/kg for the cats with kidney disease (range 0.29–1.05 mg/kg), and 0.47 mg/kg for the cats with liver disease (range 0.34–0.69 mg/kg). Vocalizing was observed upon injection in 4 of 60 cats, however, overall these reactions were infrequent and mild. No adverse side effects to the ondansetron were observed or reported during this study.

Pharmacokinetics

The pharmacokinetic parameters that were compared between the three groups are summarized in Table 2. AUC was significantly greater in the cats with liver disease and cats with CKD when compared to the healthy geriatric cats ($P < 0.05$) (Fig. 1). The CL/F was also significantly lower in the cats with liver disease when compared to the healthy geriatric cats. ($P < 0.05$) (Fig. 2). Results were similar when a subset of age-matched cats were compared, with a statistically significant increase in AUC ($P = 0.007$) and a statistically significant decrease in CL/F ($P = 0.004$) in liver cats compared to age-matched geriatric controls (Table 3). However, in this subset analysis no significant difference was seen in CKD cats in comparison with healthy geriatric cats for either AUC or CL/F. No significant correlations were seen between AUC and CL/F vs. the clinicopathologic parameters creatinine, ALT, ALP, total bilirubin, and albumin. There was, however, a trend identified between increasing total bilirubin levels and increased drug exposure ($P = 0.06$) and decreased CL/F ($P = 0.06$) in the cats with liver disease.

Protein binding

When PB of ondansetron was assessed in a subset of healthy geriatric cats ($n = 5$) and cats with liver disease ($n = 5$) with statistically significant differences in serum albumin concentration, no significant difference in PB between groups was observed. Median bound ondansetron was 84.8% (range 80.7–88.6%) in normal cats and 88.2% (range 79.1–96.5%) in cats with liver disease. Median drug concentration of samples used for protein binding calculations was 58.8 ng/mL (range 41.6–99.9 ng/mL) in normal cats and 144 ng/mL (range 37.9–206 ng/nL) in cats with liver disease.

DISCUSSION

The purpose of this study was to compare the pharmacokinetics of subcutaneous ondansetron in healthy geriatric cats, cats with CKD and cats with liver disease using a limited sampling strategy. The results of this study demonstrated administration of SQ ondansetron to cats with liver disease resulted in increased AUC and decreased CL/F when compared to healthy geriatric cats. Administration of SQ ondansetron to cats with CKD disease resulted in increased AUC when compared to healthy geriatric cats, but this finding was not observed when age-matched subset analysis was performed. When possible, cats were age matched and in a subset analysis age was not identified to be a significant factor in the drug exposure or CL/F of ondansetron across the three groups.

Ondansetron has a high first pass hepatic metabolism in people with approximately 95% of the drug metabolized by the liver (Roila & Del Favero, 1995). Previous pharmacokinetic studies in people have shown that patients with liver disease have increased bioavailability (as high as 98%) and decreased CL (as low as 35% of normal patient clearance) of intravenous ondansetron (Figg *et al.*, 1996). As a result, patients with moderate to severe liver disease are dosed less frequently (Roila & Del Favero, 1995). Renal CL only accounts for less than 5% of total CL (Amantea *et al.*, 1993). Therefore it is thought that renal dysfunction is unlikely to have a significant effect on the pharmacokinetics of ondansetron. In the present study, AUC was found to be significantly increased in CKD cats when compared to healthy geriatric cats, but not when age-matched subset analysis was performed. As AUC could be altered as a results of a number of variables and no significant difference in CL/F was observed, it seems unlikely that these findings have clinical significance for dosing of ondansetron in CKD cats. Decreased CL has also been reported with increased age, however, this has not been shown to be significant enough to alter the dose of ondansetron in elderly human patients (Roila & Del Favero, 1995). The findings in this study evaluating the effects of age, liver disease and CKD in cats on the metabolism of ondansetron are consistent with what has previously been reported in the human literature. However, bioavailability was not assessed in this study design.

Based on a recent study evaluating the pharmacokinetics of ondansetron in healthy cats, the current twice daily dosing recommendations may not be sufficient to maintain adequate therapeutic serum levels of ondansetron levels (estimated 25–75 ng/mL) (Quimby *et al.*, 2014). In healthy cats, a dose interval of every 8 h is likely required to maintain adequate therapeutic serum drug levels. However, based on the increased drug exposure and decreased CL/F in cats with liver disease, twice daily dosing may be sufficient to maintain therapeutic serum drug levels, but this was not able to be confirmed by the information gathered in this study.

Decreased CL of ondansetron in people with liver disease is suspected to be related to a decrease in intrinsic metabolic function (Roila & Del Favero, 1995). Other suggested mechanisms include decreased hepatic blood flow and decreased first pass metabolism (Roila & Del Favero, 1995). A linear relationship was not identified between the parameters of liver disease in this study (ALT, ALP, and t. bili) and the drug exposure or CL/F in any of the groups, but specifically the cats with liver disease. There was however, a trend identified between increasing total bilirubin levels and increased drug exposure ($P = 0.06$) and decreased CL/F ($P = 0.06$) in the cats with liver disease. While this finding was not statistically significant, it could suggest that cholestatic disease has more of an impact on the pharmacokinetics of ondansetron than hepatocellular disease in cats. The studied parameters (ALT, ALP, t. bili) may not be the best evaluation of liver function. Fasting and 2-h postprandial bile acid levels were not evaluated in the cats with liver disease. Imaging of the liver was also not performed in all of the cats in the liver disease category.

A statistically significant difference in serum albumin levels was identified in healthy geriatric cats when compared to cats with liver and CKD. There was not a significant difference in the albumin levels of the cats with liver disease compared to the cats with CKD. We considered that the difference in drug exposure and CL/F between the groups

could be related to the albumin levels and possible protein binding. Unbound drug is generally eliminated faster either via glomerular filtration or metabolism, as it is more available to those processes (Gibaldi & Perrier, 1982). A lower albumin level may cause an increase in the volume of distribution, as more drug can distribute to tissues (Gibaldi & Perrier, 1982). This would then lead to a decrease in AUC, as drug goes out of the plasma and into tissues. Analysis of percentage of protein binding of ondansetron revealed no significant difference between cats with liver disease and healthy geriatric cats that had statistically significant differences in serum albumin. Thus, we deemed that the differences identified in the pharmacokinetic parameters of ondansetron in this study were unlikely related to differences in serum albumin levels.

In conclusion, when 2 mg of ondansetron was administered subcutaneously to healthy geriatric cats, cats with CKD and cats with liver disease, AUC was significantly greater in cats with liver disease and CKD compared to healthy geriatric cats. The calculated CL/F of ondansetron was also significantly decreased in cats with liver disease when compared to healthy geriatric cats. In age-matched subset analysis AUC and CL/F in liver cats remained significantly different from healthy geriatric cats. This suggests that there is increased drug exposure and prolonged CL/F of ondansetron in cats with liver disease, similar to what has previously been reported in human pharmacokinetic studies of ondansetron.

ACKNOWLEDGMENTS

This study was funded by a grant from the Angelo Fund for Feline Therapeutics and supported in part by the University of Colorado Cancer Center Shared Resource Support Grant (P30CA046934) supporting the Pharmacology Shared Resource. The authors are grateful to Ann Hess for statistical consultation.

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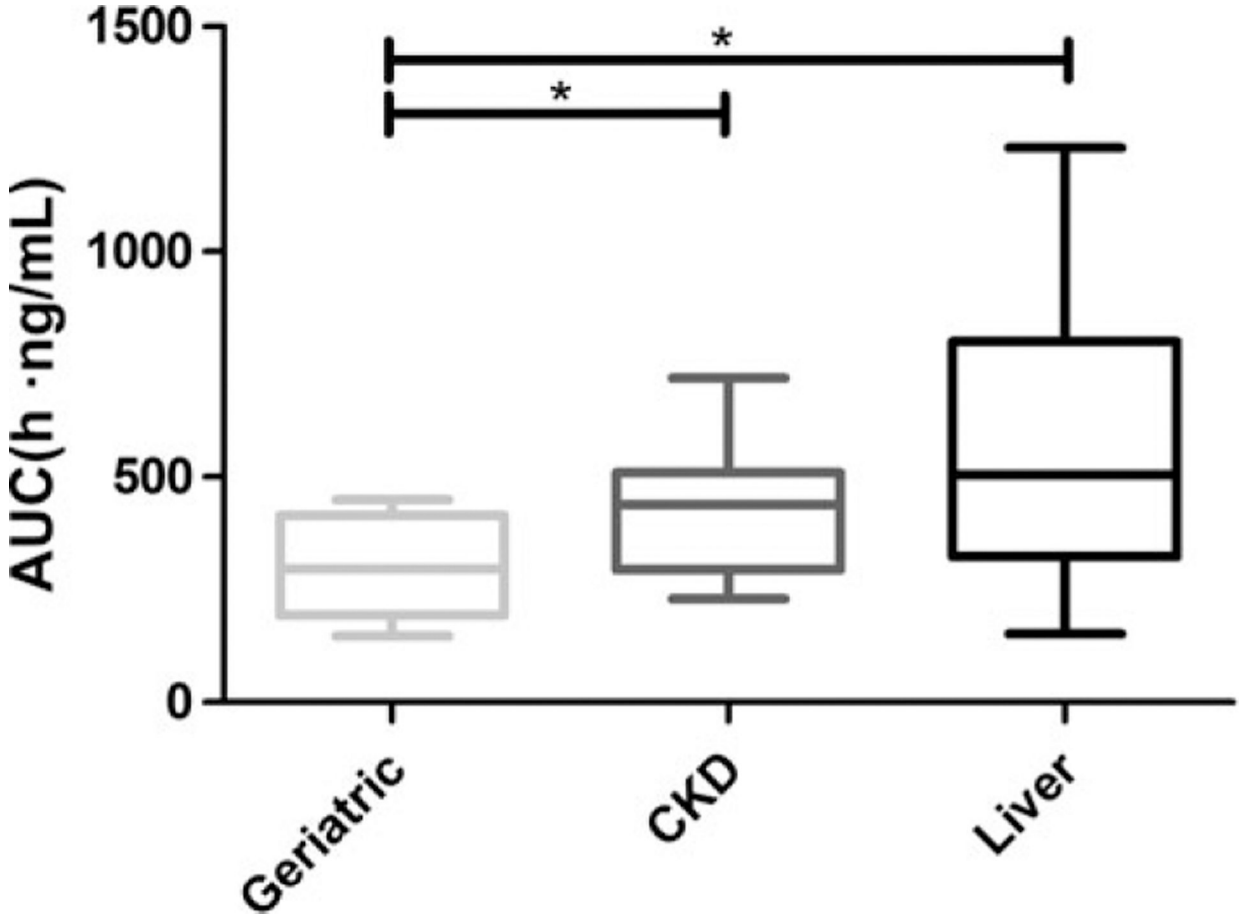

Fig. 1.

When 2 mg ondansetron was administered subcutaneously once and limited sampling pharmacokinetic modeling performed, AUC was significantly greater in the cats with liver disease ($n = 20$) and CKD ($n = 20$) when compared to the healthy geriatric cats ($n = 20$) (*$P < 0.05$). Data are displayed as mean ± SD.

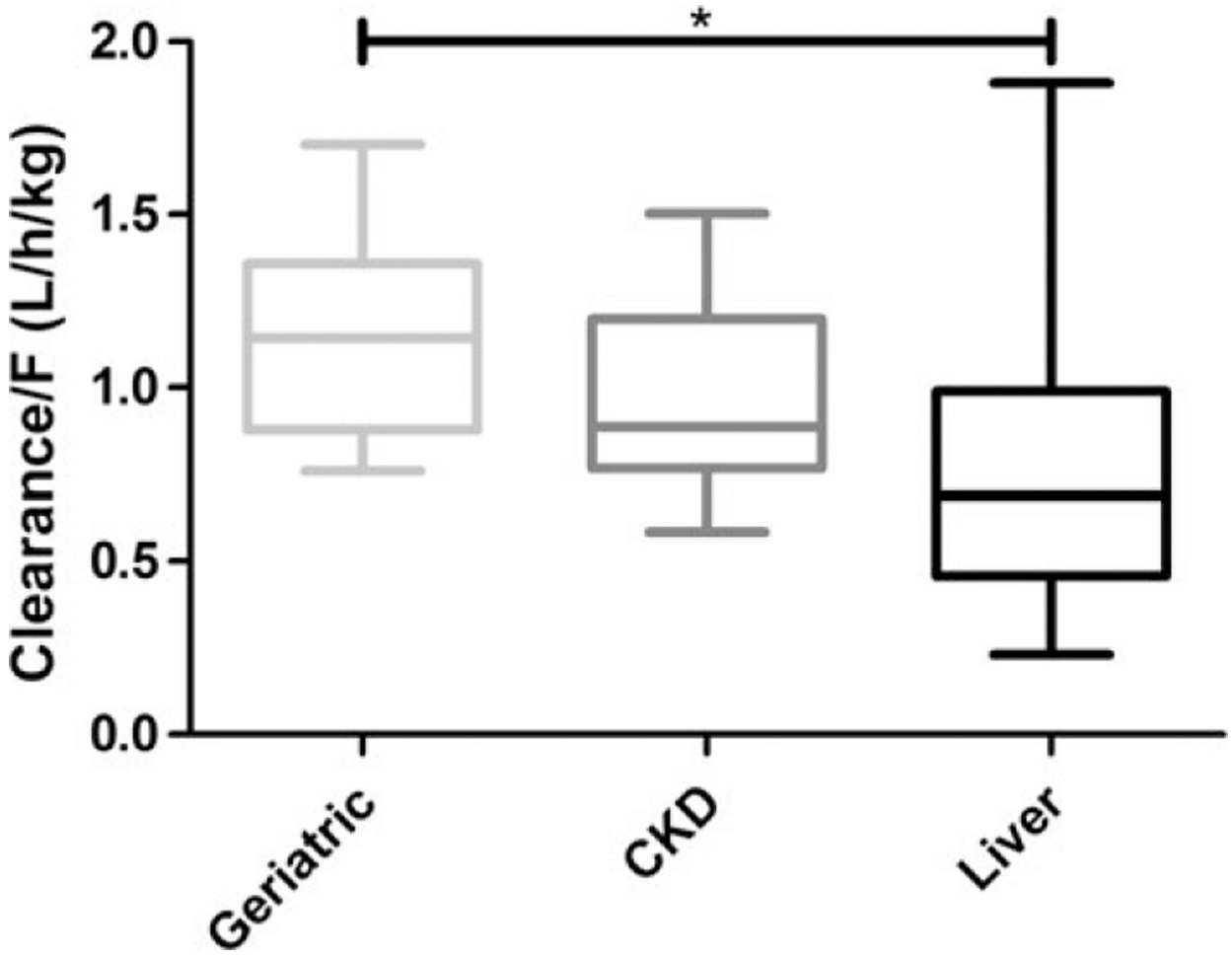

Fig. 2.

When 2 mg ondansetron was administered subcutaneously once and limited sampling pharmacokinetic modeling performed, CL/F was significantly lower in cats with liver disease ($n = 20$) when compared to healthy geriatric cats ($n = 20$) ($^*P < 0.05$). Data are displayed as mean ± SD.

Table 1.

Mean and SD for the laboratory work parameters in healthy geriatric cats, cats with CKD, and cats with liver disease at the time of ondansetron administration

	Geriatric	CKD	Liver
Albumin (g/dL)	3.87 ± 0.2	3.5 ± 0.3#	3.3 ± 0.38#
ALT (IU/L)	63.35 ± 33.9	57.1 ± 25.1	336.2 ± 241.4*
ALP (IU/L)	26.8 ± 9.6	32.67 ± 13.1	194.3 ± 189.4*
Creatinine (mg/dL)	1.3 ± 0.3	3.2 ± 0.8**	1.17 ± 0.3
T. bilirubin (mg/dL)	0.55 ± 0.05	0.05 ± 0.05	3.43 ± 4.28*

The ALT, ALP, and total bilirubin were all significantly elevated in the cats with liver disease when compared to the healthy geriatric cats and cats with CKD (*$P < 0.05$). The creatinine levels were significantly higher in the CKD cats when compared to the other two groups (**$P < 0.05$). Albumin levels were significantly lower in the CKD cats and cats with liver disease when compared to the healthy geriatric cats (#$P < 0.05$).

Table 2.

Pharmacokinetic parameters of subcutaneous ondansetron in healthy geriatric cats, cats with CKD, and cats with liver disease

	Geriatric			CKD			Liver		
Pharmacokinetic parameter	**Median**	**Range**	**Mean ± SD**	**Median**	**Range**	**Mean ± SD**	**Median**	**Range**	**Mean ± SD**
AUC (ng/mL·h)	295.4*,#	147.0–449.5	301.4 ± 105.3	437.7#	228.8–719.6	415.2 ± 132.2	504.3*	151.9–1230.5	587.0 ± 337.2
Clearance/F (L/h/kg)	1.14**	0.76–1.70	1.16 ± 0.28	0.89	0.58–1.50	0.97 ± 0.46	0.69**	0.23–1.88	0.79 ± 0.46

AUC was significantly greater in the cats with liver disease (*$P < 0.05$) and CKD (#$P < 0.05$) when compared to healthy geriatric cats. The CL/F was significantly lower in the cats with liver disease when compared to the healthy geriatric cats (**$P < 0.05$).

J Vet Pharmacol Ther. Author manuscript; available in PMC 2020 January 31.

Table 3.

Age-matched subset analysis of pharmacokinetic parameters of subcutaneous ondansetron in healthy geriatric cats, cats with CKD, and cats with liver disease

	Geriatric			CKD			Liver		
Pharmacokinetic parameter	**Median**	**Range**	**Mean ± SD**	**Median**	**Range**	**Mean ± SD**	**Median**	**Range**	**Mean ± SD**
AUC (ng/mL·h)	334.1	186.7–449.5	321.8 ± 112.4	437.7	228.8–719.6	416.1 ± 158.4			
	296.0*	147.0–449.2	304.2 ± 97.4				468.6*	151.9–1230.5	613.5 ± 355.7
Clearance/F (L/h/kg)	1.04	0.76–1.50	1.06 ± 0.26	0.89	0.58–1.20	0.92 ± 0.19			
	1.12**	0.75–1.70	1.12 ± 0.29				0.71**	0.23–1.88	0.79 ± 0.49

AUC was significantly greater in cats with liver disease when compared healthy geriatric cats (*$P < 0.007$). The CL/F was significantly lower in the cats with liver disease when compared to the healthy geriatric cats (**$P < 0.004$).