Original Article

jfms Journal of Feline Medicine and Surgery

Comparing the pharmacokinetics of GS-441524 after intravenous and oral administration of remdesivir in New Zealand cats with feline infectious peritonitis

Journal of Feline Medicine and Surgery
1–9

DOI: 10.1177/1098612X251403461
journals.sagepub.com/home/jfm

This paper was handled and processed by the European Editorial Office for publication in *JFMS*

Sage

Kelsey Ann Renner[1], Benjamin Kimble[2], Ryan Cattin[1], John S Munday[3] and Sally Coggins[2]

Abstract

Objectives The aim of the study was to compare the pharmacokinetics of GS-441524 after intravenous (IV) and oral administration of compounded remdesivir (RDV) at 30 mg/kg, respectively, in cats with clinical feline infectious peritonitis (FIP) and to determine the bioavailability of GS-441524 after oral administration of compounded RDV in this population.

Methods A total of 13 client-owned cats with a clinical diagnosis of FIP were prospectively recruited. To reflect real-world use, RDV (30 mg/kg) was administered via a 20-min IV infusion or orally (rounded up to capsule size). Plasma GS-441524 concentrations were measured at eight time points over 24 h after administration. Pharmacokinetic parameters were determined by non-compartment analysis followed by bioavailability calculation.

Results Pharmacokinetic analysis of GS-441524 after administration of oral RDV achieved a mean (±SD) C_{max} of 1083.36 ± 634.19 ng/ml (coefficient of variation [CV] 59%, range 254.18–1834.73) at a mean time of 5.33 ± 3.93 h (range 2–12) with a mean elimination $t_{1/2}$ of 11.4 ± 8.00 h (range 4.58–27.01). In contrast, IV RDV administration produced a higher mean GS-441524 C_{max} of 6262.54 ± 1118.01 ng/ml (CV 18%, range 5193.40–8134.39) at a mean T_{max} 0.67 ± 0.26 h (range 0.5–1) with a mean elimination $t_{1/2}$ of 6.8 ± 5.55 h (range 3.18–17.85). The mean relative bioavailability of GS-441524 after oral RDV was 30.13%. Bioavailability (range 12–52%) and time to maximum plasma concentrations (2–12 h) were highly variable.

Conclusions and relevance The oral bioavailability of the compounded RDV used in this study is low, highly variable and appeared lower in cats with effusive disease, although this difference was not statistically significant. Given the small non-randomised sample, results should be interpreted considering the study limitations. Despite the low bioavailability, survival rates in cats treated with oral RDV are comparable to published outcome studies with injectable RDV and oral GS-441524, indicating that oral RDV is a viable treatment option when GS-441524 is not available.

Keywords: Feline infectious peritonitis; feline coronavirus; GS-441524; remdesivir; nucleotide analogue; antiviral; GS-5734

Accepted: 11 November 2025

[1]Animal Referral Centre, Auckland, New Zealand
[2]Sydney School of Veterinary Science, The University of Sydney, NSW, Australia
[3]School of Veterinary Science, Massey University, Palmerston North, New Zealand

Corresponding author:
Sally Coggins BVSc (Hons), MANZCVS (Medicine of Cats), PhD, Sydney School of Veterinary Science, The University of Sydney, NSW 2006, Australia
Email: sally.coggins@sydney.edu.au

Introduction

Feline infectious peritonitis (FIP) is a disease that affects domestic and wild cats caused by feline enteric coronavirus (FCoV).[1] In a minority of exposed cats, FIP may develop.[2–4]

The clinical presentation of FIP can be broadly divided into an effusive form, which is characterised by the presence of high protein effusions within body cavities, and the non-effusive form, characterised by granulomatous mass lesions. Both forms may demonstrate concurrent ocular or neurological involvement, and the division between clinical phenotypes is more likely to represent a disease spectrum.[1,5]

FIP carries a near 100% mortality rate without treatment.[6] Over recent years, many publications have emerged investigating the utility of the antiviral prodrug remdesivir (RDV) and its parent nucleoside GS-441524, demonstrating high survival rates (81–100%), with excellent safety profiles.[7–12]

RDV is a nucleotide prodrug that undergoes hydrolysis and dephosphorylation to the nucleoside GS-441524, then subsequent phosphorylation to the pharmacologically active GS-443902, which inhibits viral RNA synthesis.[13,14] After intravenous (IV) administration, RDV is hydrolysed within minutes, whereas the principal intermediate metabolite GS-441524 is stable in plasma, making it a more valuable target for therapeutic drug monitoring.[15,16]

Access to RDV and GS-441524 varies globally. At the time this study was completed, there was no legal source of GS-441524 in New Zealand and veterinarians were reliant on compounded RDV (Optimus Healthcare New Zealand) for treating FIP. Clinical experience demonstrated that RDV is painful on subcutaneous injection and cost-prohibitive for many cat owners. This prompted New Zealand veterinarians to prescribe compounded oral RDV as an alternative to parenteral RDV in many cases.

The bioavailability of oral RDV has been demonstrated to be low in dogs and humans, primarily due to extensive first-pass hepatic metabolism.[17,18] However, a recent study demonstrated that the metabolism of RDV into GS-441524 differs in cats and is hypothesised to occur in whole blood via blood esterases.[16] Bioavailability data collected by Cook et al[19] in three healthy cats treated with oral RDV revealed that plasma concentrations greater than the established EC_{50} (serotype I feline infectious peritonitis virus [FIPV] 0.03 µm, serotype II FIPV 0.18 µm) were achieved and sustained for 24 h with dosages of 25 mg/kg PO q24h. These recent data suggest that oral RDV may be more bioavailable in cats compared with other species; however, the bioavailability of oral RDV in cats with FIP has not been determined.

The first aim of this study was to compare the pharmacokinetics of GS-441524 after IV and oral administration of compounded RDV at 30 mg/kg in cats with FIP. The second aim was to determine the bioavailability of GS-441524 after oral administration of compounded RDV 30 mg/kg in cats with FIP.

Materials and methods

Animals

Client-owned cats with FIP were prospectively recruited between November 2022 and September 2023 as part of a larger study including 29 cats.[20] For inclusion, all cats had clinical and clinicopathological signs consistent with FIP, with a diagnosis achieved according to Advisory Board on Cat Diseases guidelines by a board-certified specialist.[1] Nine cats had a positive FCoV RT-PCR test on effusion, lymph node aspirates or cerebral spinal fluid (Awanui Labs/APHG; IDEXX Laboratories). Cats were excluded from the study if they weighed less than 1 kg, had already been treated with an antiviral medication or became stressed during handling. Cats were further excluded from the oral RDV arm of the study if they lacked a gag reflex or could not swallow.

RDV was sourced from a single compounding pharmacy (Optimus Healthcare). Cats were not randomly allocated to treatment groups. Cat owners chose the route of administration after a consultation with an internal medicine specialist or resident. IV RDV was recommended, but oral treatment was elected by owners with financial constraints. All cats received 30 mg/kg IV RDV or 30 mg/kg rounded up to the nearest capsule size orally. Capsules were available in 30 mg increments (30 mg, 60 mg, 90 mg and 120 mg). Physical, neurological and ophthalmic examinations were performed by an internal medicine specialist or resident before enrolment.

Jugular venipuncture using a 21 G needle and 3 ml syringe facilitated collection of 2.6 ml of blood before administration of RDV. Blood was divided equally between a 1.3 ml EDTA tube and a 1.3 ml non-additive tube for a complete blood count and serum biochemistry, as part of a broader clinical study. Once haematology was performed, the EDTA sample was centrifuged, plasma separated and stored at –80°C for use as the time zero sample.

Parenteral RDV was administered through an IV catheter in the cephalic vein over 20 mins. Anaphylaxis has been reported in humans after rapid IV administration of RDV; subsequently, slow IV infusions have been recommended.[21] This study was looking to best emulate real-world use of these drugs in the affected population of cats, therefore a 20-min constant rate infusion (CRI) was elected. Time zero for IV administration was defined as the start of the CRI. Cats that received oral RDV were given the capsule whole, followed by 1 ml of water syringed into the mouth to ensure the capsule was swallowed. Cats were fasted for at least 1 h before administration if they were eating and were offered food 1–4 h after capsule administration.

After RDV administration, additional blood samples were collected at 30 mins, then at 1, 2, 4, 8, 12, 20 and 24 h after the first dose of RDV, and placed into 0.5 ml non-additive and EDTA blood tubes. Samples were spun and separated and then stored at –80°C before being shipped on dry ice from the Animal Referral Centre, Auckland, New Zealand, to the Sydney School of Veterinary Science, The University of Sydney, Australia for GS-441524 concentration determination.

This study was approved by the Massey University Animal Ethics Committee (AEC 22/67).

The treatment regime after the first dose of RDV varied between cats. Owners chose the treatment protocol after consultation with an internal medicine specialist or resident. Cats either continued treatment with oral RDV at 30 mg/kg rounded up to the nearest capsule size or received additional doses of parenteral RDV before switching to oral RDV. No cats were solely treated with parenteral RDV. The treatment protocols and outcomes for individual cats are provided in Table S2 in the supplementary material.

The 13 cats in this study were part of a wider perspective, observational study of 29 cats. The cats in this cohort were treated with the same dose rates of oral RDV with or without prior doses of parenteral RDV.[20] See Table S2 in the supplementary material for details of all 29 cats.

Drug analysis

Plasma concentrations of GS-441524 (Assay Matrix) were quantified using high-performance liquid chromatography equipped with fluorescence detector (Nexera XR LC system; Shimadzu) employing a method previously validated.[15,22] Quantification of GS-441524 was achieved by an external calibration curve (19.53 [limit of quantification] to 10,000 ng/ml). The intra- and inter-day accuracies and precision of the quality controls were within 10% of their nominal concentrations and were in the range of 1.69–5.66% (coefficient of variation [CV]), respectively.

RDV content in the compounded capsules used in this study was quantified in a recent study by the authors.[20] Accordingly, the estimated mean quantity of RDV found within the different doses of capsules was in the range of 96–103% (see Table S3 in the supplementary material).

Pharmacokinetic analysis

The kinetic indices of GS-441524 after IV or oral compounded RDV were analysed via a non-compartment model using PK Solver add-in for Microsoft Excel.[23] The terminal elimination constant (λ_z) was calculated as the absolute value of the negative slope of the terminal elimination phase in a plot of the natural logarithm (ln) of drug concentration vs time. The elimination half-life ($t_{1/2}$) was then estimated as $\ln(2)/\lambda_z$. The area under the concentration–time curve (AUC_{0-t}), the area under the first moment curve ($AUMC_{0-t}$) and area under the plasma concentration–time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) were calculated to the last quantifiable concentration using the linear trapezoidal method. The mean residence time (MRT) was calculated as AUMC/AUC.

As this study was conducted in FIP-affected cats, a crossover design was not feasible or ethical. Consequently, individual IV and oral AUCs could not be compared within the same animals. To estimate bioavailability (F%) of GS-441524 after administration of oral remdesivir, each cat's oral AUC was compared with the mean AUC achieved in the IV group. All cats in the IV group received 30 mg/kg; however, the oral dose rate varied slightly because of capsule rounding. As such, the second part of the equation below adjusts for these differences by dividing the IV dose rate by the exact oral dose rate administered to each individual cat in the oral group:

$$F\% = \left[\left(AUC_{ORAL(indiv)} / AUC_{IV(mean)} \right) \times \left(Dose_{IV(mg/kg)} / Dose_{ORAL(mg/kg)} \right) \right] \times 100 \quad (1)$$

Statistical analysis

Graphs were generated using R 4.4.0 and ggplot2 package version 3.5.1. Unless stated otherwise, error bars on charts correspond to 95% confidence intervals given by two-sided *t*-tests on log-transformed data (assuming log-normally distributed data).

Results

Animal results

A total of 13 client-owned cats (one female entire, two female spayed, two male entire and eight male castrated) were recruited. Eight cats had effusive FIP and five cats had non-effusive FIP. The median age was 9 months (range 2 months to 7.5 years). Breeds included Tonkinese (n = 2), Burmese (n = 2), domestic shorthair (n = 4), domestic longhair (n = 2), Ragdoll (n = 1), British Shorthair (n = 1) and Birman (n = 1). None of the cats that received oral or IV RDV were observed to experience adverse effects. See Table S2 in the supplementary material for more details on the individual cats.

Pharmacokinetics of GS-441524 after IV and oral remdesivir

Non-compartmental analysis The first dose pharmacokinetics of GS-441524 after IV and oral administration of RDV at 30 mg/kg, respectively, are reported in Table 1. Notably, the C_{max} of plasma GS-441524 concentrations when RDV was administered IV CRI was six-fold higher than per os (PO) (6262.54 ng/ml and 1083.36 ng/ml, respectively). In contrast, the T_{max} of plasma GS-441524 when RDV was administered orally was 10-fold longer than IV CRI (5.33 and 0.67 h, respectively). It should be noted that significant variation was observed in the oral

Table 1 Non-compartmental analysis of GS-441524 after intravenous (IV) (n = 6 cats) and oral (n = 6 cats) administration of compounded remdesivir

Administration route		λz (1/h)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/ml)	AUC_{0-24} (ng/ml*h)	$AUC_{0-\infty}$ (ng/ml*h)	$MRT_{0-\infty}$,obs (h)	Oral dose (mg/kg)	Relative bioavailability (F%)
IV	Mean ± SD	0.14 ± 0.06	6.8 ± 5.55	0.67 ± 0.26	6262.5 ± 1118	36,142.2 ± 11,623.2	41,925.1 ± 15,080.1	8.84 ± 5.57	N/A	N/A
	CV(%)	45.57	81.7	38.7	17.85	32.16	36.0	63.04	N/A	N/A
	Median (range)	0.15 (0.04–0.22)	4.8 (3.18–17.9)	0.5 (0.5–1)	5903.1 (5193.4–8134.4)	36,833.3 (23,270.1–50,203.6)	45,872.6 (23,814.1–60,727.6)	6.86	N/A	N/A
Oral	Mean ± SD	0.08 ± 0.04	11.4 ± 8	5.33 ± 3.93	1083.4 ± 643.1	11,478.9 ± 7036.5	14,670.38 ± 7672.5	18.94 ± 10.25	37 ± 8.83	30.13 ± 17.69
	CV(%)	52.45	70.1	73.7	59.37	61.3	52.30	54.15	23.87	58.72
	Median (range)	0.07 (0.03–0.15)	9.91 (4.58–27)	4 (2–12)	1232.1 (254.18–1834.7)	9727.76 (4323.85–21,408.1)	12,641.03 (5935.44–24,700.20)	15.97 (9.29–38.68)	33.5 (33–55)	27.06 (11.66–51.98)

F% = relative oral bioavailability, calculated per cat using $AUC_{0-\infty}$ values: $F\% = [(AUC_{ORAL}[individual]/AUC_{IV}[mean]) \times (Dose_{IV}/Dose_{ORAL})] \times 100$. Bioavailability calculations for each individual cat using both $AUC_{0-\infty}$ and AUC_{0-24} can be found in Table S1 in the supplementary material

λ_z = terminal elimination rate constant (1/h); AUC_{0-24} = area under the plasma-concentration time curve over 24 h; $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time zero extrapolated to infinity; C_{max} = peak plasma concentration; CV(%) = coefficient of variation; $MRT_{0-\infty}$,obs = mean residence time from time zero to infinity (observed); N/A – not applicable; $t_{1/2}$ = elimination half-life; T_{max} = time to reach peak plasma concentration

T_{max} (range 2–12 h). The mean elimination $t_{1/2}$ of plasma GS-441524 after the administration of oral RDV was also longer (10.03 h, range 4.41–20.96) when compared with IV CRI (6.8 h, range 3.18–17.85). The pharmacokinetic analysis of the individual cats can be found in Table S1 in the supplementary material.

When graphed individually on a linear scale (ng/ml) over time, considerable intercat variability was observed (Figure 1), as quantified by the large CV, expressed as a percentage when comparing AUC_{IV} vs AUC_{ORAL} (32.16% and 54.15%, respectively).

A notable outlier was observed with cat 13 (Figure 1b). This cat exhibited a prolonged $t_{1/2}$, delayed T_{max} and persistently elevated GS-441524 plasma concentrations. The data from cat 13 were excluded from the bioavailability calculation to prevent skewing the results because of significant variability.

Bioavailability The mean percent bioavailability (F%) of plasma GS-441524 when RDV was administered orally relative to intravenously CRI was low. The mean F% based on $AUC_{0-\infty}$ was 30% ± 17.69%, while the corresponding mean F% using AUC_{0-24} was 27% ± 18.35 (Table 1). Individual cat values for F% are provided in Table S1 in the supplementary material. Interestingly, when comparing the bioavailability of effusive and non-effusive cats that received oral RDV, the mean bioavailability of the non-effusive cats (41.7% ± 16.2%) was higher than effusive cats (18.7% ± 10.7%), but did not achieve statistical significance ($P = 0.20$, exact Mann–Whitney U-test). Figure 2a shows the mean plasma GS-441524 concentrations achieved with the IV and oral groups. Figure 2b demonstrates the difference observed between effusive and non-effusive cats at a target RDV dose of 30 mg/kg PO.

Discussion

In this study, we present pharmacokinetic data comparing IV CRI and oral administration of compounded RDV in two independent groups of cats clinically affected with FIP.

After IV CRI administration of RDV, a monophosphate prodrug, we observed near-complete systemic delivery of the parent nucleoside GS-441524. In this study, 30 mg/kg IV CRI RDV yielded a GS-441524 AUC of 36,142.2 ng*h/ml. Based on the molar weight of RDV (602.6 g/mol) and GS-441524 (291.3 g/mol), a 30 mg/kg dose of RDV is molar-equivalent to 14.5 mg/kg of GS-441524. Murphy et al[24] reported an AUC of 12,759 ng*h/ml after IV administration of 5 mg/kg GS-441524 in healthy cats (ie, approximately one-third the dose given and one-third the AUC achieved). Similarly, another study reported an AUC of 18,167 ng*h/ml after RDV 15 mg/kg IV (equivalent to 7.3 mg/kg GS-441524) in FIP-affected cats,[22] representing half the dose given in the

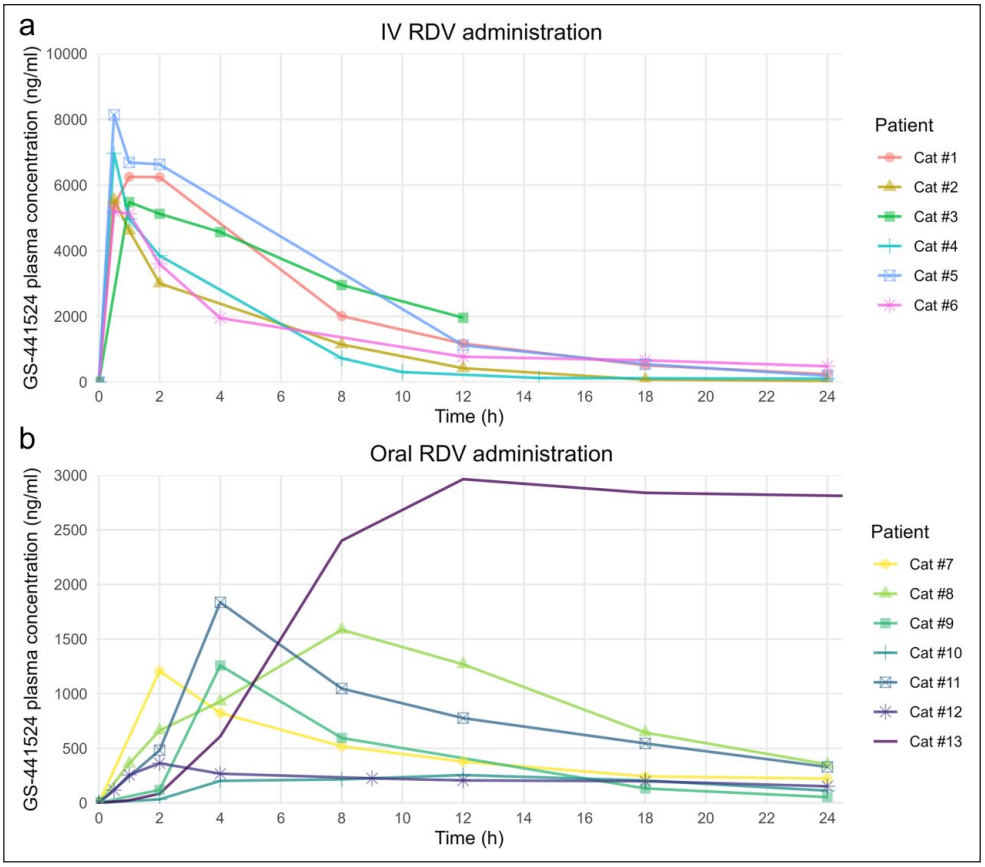

Figure 1 (a) GS-441524 plasma concentrations in six cats after first-dose administration of intravenous remdesivir (RDV) at 30 mg/kg and (b) GS-441524 plasma concentrations in seven cats after first-dose administration of oral RDV, targeting 30 mg/kg (median achieved dose 33.5 mg/kg, range 33–55)

present study and half the AUC achieved. These findings scale proportionately, supporting linear pharmacokinetics of plasma GS-441524 after IV RDV administration at doses in the range of 5–14.5 mg/kg, despite RDV being administered as a 20-min CRI in the present study.

In contrast, the bioavailability of GS-441524 after oral RDV in this population was low (mean F% 30%) and highly variable between cats (range 12–52%). Given how rapidly RDV hydrolyses into GS-441524 in vivo,[8,15,22] one issue may lie with absorption of RDV from the gastrointestinal tract. Disease-associated factors impacting gastrointestinal tract absorption might explain this (eg, hypotension, dehydration, gastrointestinal hypoperfusion or dysmotility), as many cats in this study were inappetent and clinically unwell at presentation. The T_{max} of GS-441524 after oral RDV administration was highly variable between cats (range 2–12 h). This intercat variability makes it challenging to reliably predict the timing of peak concentrations. Although therapeutic drug monitoring does not necessarily rely on C_{max} and could instead focus on a consistent time point or duration above a target concentration, the consistent finding of wide intra- and intercat variability across studies in the absence of a defined pharmacodynamic target for GS-441524 in FIP complicates this approach. Without a consistent T_{max} or clear pharmacodynamic correlate, single time point measurements may not accurately reflect drug exposure or reliably guide clinical decision-making.

The oral bioavailability of RDV in our study differs markedly from the 120% reported by Cook et al.[19] Although both studies are limited by low sample sizes and high intercat variability, this major discrepancy also likely reflects differing study aims, methodologies and study populations. Our study aim was to assess GS-441524 exposure after oral RDV relative to IV RDV in sick FIP-affected cats, while Cook et al[19] looked to develop a reference model in specific pathogen-free (SPF) cats, to allow comparison of new antiviral formulations against historical GS-441524 AUC control. As such, the F% of 120% reported in the paper by Cook et al[19] compares the GS-441524 exposure from oral RDV in three SPF cats against historical IV GS-441524 exposure in two different SPF cats (Murphy et al[24]). The formula used to calculate F% was not reported. Interestingly, when we apply the F% formula used in this study to the GS-441524 AUCs reported in the paper by Cook et al[19]

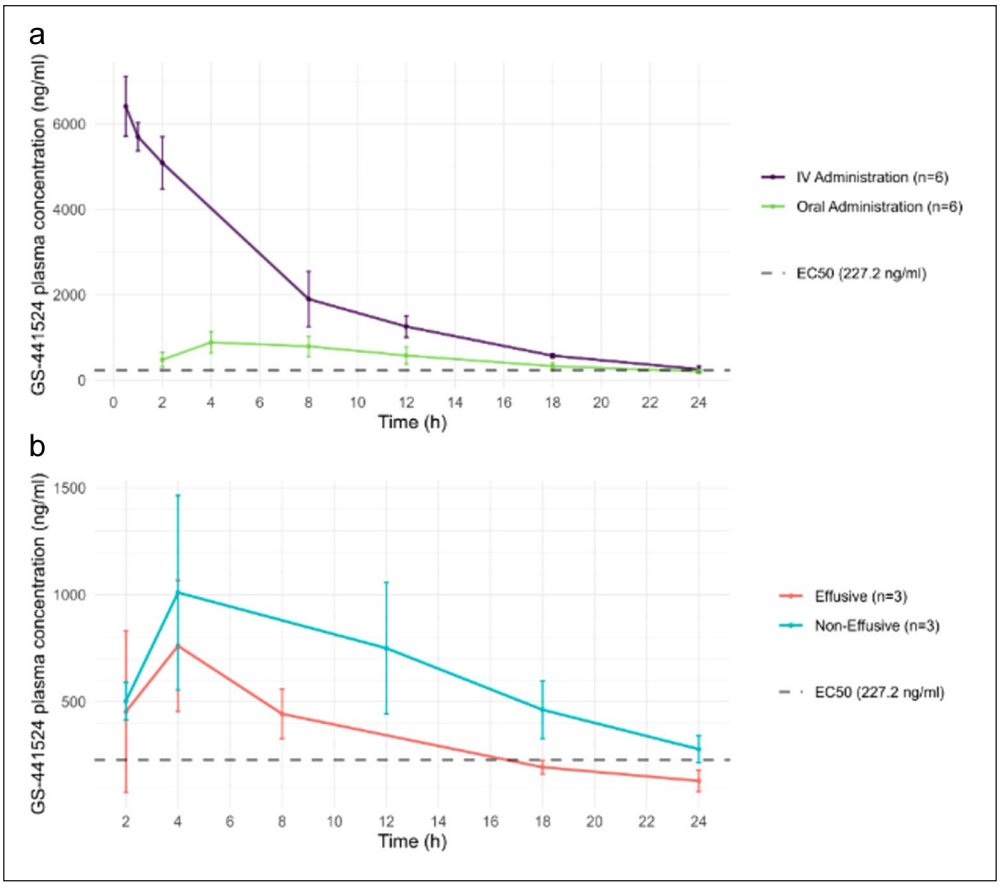

Figure 2 (a) Mean concentration of GS-441524 (ng/ml) over time (h) after remdesivir administration. Error bars indicate one standard error. (b) Mean concentration over time of effusive vs non-effusive cats that received a target remdesivir dose of 30 mg/kg PO. Error bars indicate one standard error. The horizontal dashed line represents the EC_{50} (227.2 ng/ml), as described by Murphy et al[24]

for oral vs IV RDV, the resulting bioavailability was approximately 68%. This remaining discrepancy is likely attributable to the fact that neither study employed a crossover design (which was unethical in our clinical population). It is now known that significant inter- and intra-individual variability exists in nucleoside analogue pharmacokinetics in cats,[22] which limits the accuracy of any cross-study comparisons. The potential impact of systemic illness on gastrointestinal absorption of antivirals also warrants further investigation. Formulations of oral RDV administered also differed: Cook et al[19] used self-packed gelatin capsules containing powdered RDV from MedKoo Biosciences (likely free base), whereas our study used compounded capsules from a commercial veterinary pharmacy. The excipient profile and physicochemical characteristics of these formulations may differ, which could have a significant impact on absorption from the gut and bioavailability, and were not reported. Taken together, differences in comparator selection, formulation and analytical approach likely account for the divergent results.

The RDV content of the compounded capsules was 96–103% of the expected amount, confirming that compounding error or drug degradation within the capsules before administration was not a major factor in the observed variability.

Notably, in the current study, apparent bioavailability was higher in cats with non-effusive disease (mean 41.7% ± 16.2%) compared with those with effusive disease (18.7% ± 10.7%). It has been demonstrated that GS-441524 enters body cavity effusions after administration of parenteral RDV and oral GS-441524.[22] A possible explanation is that the lower plasma concentrations observed in effusive cases do not reflect poor bioavailability but rather result from expansion of the volume of distribution, with drug sequestered into the effusion as a 'third space' compartment, which may lead to underestimation of apparent bioavailability. Another alternative hypothesis for the lower plasma concentrations observed in effusive cases is enhanced uptake and utilisation of GS-441524 at sites of active viral replication. Effusive cats are often more severely systemically affected and

may carry higher viral loads, potentially driving more rapid intracellular conversion of GS-441524 to its active triphosphate form intracellularly. This could result in lower measurable plasma concentrations, despite adequate systemic exposure, with higher drug concentrations achieved at the intended sites of action within cells. These observations highlight the need for further studies investigating the metabolism, distribution and pharmacodynamics in FIP-affected cats.

Interestingly, the survival rates of cats treated with oral RDV were similar to cats treated with IV CRI RDV and oral GS-441524 in other studies, despite the low reported bioavailability.[7–9] Thus, the relationship of GS-441524 plasma concentrations (an intermediate metabolite of RDV) with respect to treatment effectiveness remains unclear. The intracellular concentration of the active nucleotide triphosphate (GS-443902) within macrophages is responsible for the antiviral effects of RDV and GS-441524. In cats, the concentration of GS-443902 after a single dose of GS-441524 (5 mg/kg) produced concentrations in peripheral blood mononuclear cells (a proxy for tissue macrophages) that exceeded the EC_{50} by eight- to 20-fold, out to 72 h.[24] In these cats, plasma GS-441524 concentrations were zero at 72 h, yet the antiviral effect was still occurring at an intracellular level. In humans, plasma RDV and GS-441524 concentrations may not accurately reflect the intracellular GS-443902 exposure,[25] concluding that whole-body physiologically based pharmacokinetic modelling is a more accurate and informative surrogate for estimating active drug levels in target tissues,[25] and signalling a potential disconnect between plasma concentrations and intracellular antiviral activity in humans. A final explanation for the positive clinical outcomes, despite low F% of GS-441524 in this cohort, may be that all administered doses resulted in supratherapeutic systemic exposures, saturating intracellular targets and placing the response on the plateau of the dose–response curve. These observations suggest that although plasma GS-441524 concentrations may provide some insight into drug exposure, their utility for predicting clinical outcomes or guiding therapeutic drug monitoring remains unclear and requires further investigation.

One notable outlier in our study was cat 13, which exhibited a prolonged elimination $t_{1/2}$, delayed T_{max} and persistently elevated GS-441524 plasma concentrations. This cat was hypotensive, dehydrated and azotaemic (creatinine 431 µmol/l) at the time of dosing and was euthanased 2 days later because of clinical deterioration. Exposure of GS-441524 after administration of RDV CRI IV was 7.9-fold higher in humans with renal impairment than those with normal renal function.[26] Renal hypoperfusion or impaired clearance may explain the elevated GS-441524 levels in this cat.

These 13 cats were part of a larger cohort of 29 treated with oral and/or IV RDV, achieving a 6-month survival rate of 86%,[20] comparable to outcomes reported with GS-441524 or parenteral RDV alone. This supports the hypothesis that plasma GS-441524 concentrations may not reliably predict treatment success. Despite apparently low GS-441524 bioavailability determined in plasma after oral RDV administration, clinical outcomes support oral RDV as a treatment option for FIP when access to compounded GS-441524 or molnupiravir is unavailable.

In this study of 13 cats, 4/6 cats that received IV CRI RDV before oral dosing died, whereas all cats treated with oral RDV alone survived. Although the sample size is small, this likely reflects clinician bias to recommend IV therapy for more critically ill patients rather than low effectiveness of the IV route itself. This treatment approach is supported by the pharmacokinetic profile of IV CRI RDV, which demonstrated higher and more consistent plasma drug exposure with less intercat variability compared with oral administration. For this reason, parenteral RDV remains the preferred route of administration for initial treatment of cats with severe FIP.

Conducting this study in sick, client-owned cats with FIP imposed several unavoidable design limitations. The primary limitation of this study is the small sample size. Although substantial variability in oral RDV bioavailability was observed, the study was underpowered to identify covariates associated with this variability. The mean bioavailability in the oral group, however, was notably lower in cats with effusion compared with those without effusion. It would be valuable to analyse a larger data set to determine if this finding is repeatable and may become statistically significant with larger numbers of treated cats. Another notable limitation was the administration of RDV via a 20-min CRI for the IV group, implemented to minimise risk of anaphylaxis. This slower delivery may have altered T_{max} and reduced the peak plasma concentrations and overall AUC of GS-441524, potentially leading to an overestimation of oral bioavailability. In addition, bioavailability was determined by comparing AUCs from separate cohorts of cats rather than using a crossover design. Such design, however, is not ethical in FIP-affected cats. This study accurately reflects real-world use of RDV in clinical practice. Although future studies in healthy cats using bolus IV administration could refine bioavailability estimates, pharmacokinetic modelling based on existing data may offer a more ethical and clinically relevant approach to understanding RDV disposition. Finally, the treatment groups were not randomised, and no cat received IV RDV exclusively. As all cats transitioned to oral RDV for the final 10 weeks of the 12-week treatment course, outcomes associated with IV vs oral administration cannot be directly compared.

Conclusions

This study provides important pharmacokinetic data on the use of compounded IV and oral RDV in cats with

FIP, demonstrating near-complete systemic conversion to GS-441524 after IV administration, with low and variable bioavailability after oral dosing. Despite the observed variability and generally low plasma concentrations of GS-441524 after oral RDV, clinical outcomes remained favourable, suggesting that plasma GS-441524 may not be a reliable surrogate for treatment efficacy. The potential pharmacodynamic and pharmacokinetic impacts of disease severity, effusion-associated drug sequestration and intracellular drug dynamics highlights the complexity of interpreting plasma concentrations in FIP-affected cats. Although IV RDV resulted in more consistent plasma exposure, the higher mortality in IV-treated cats likely reflects a bias towards using IV therapy in more critical cases rather than a treatment route of administration associated risk. Taken together, these findings support the use of IV RDV as an induction therapy in severely affected cats and supports oral RDV as a viable treatment option when other formulations are not legally available. Further studies with larger, randomised cohorts are needed to confirm these findings, better understand the determinants of oral RDV bioavailability and refine the role of therapeutic drug monitoring in this setting.

Supplementary material The following files are available as supplementary material:

Table S1. Treatment protocols, outcomes of individual cats and non-compartmental analysis of GS-441524 after IV (n = 6 cats) and PO (n = 6 cats) administration of remdesivir 30mg/kg in individual cats.

Table S2. Cats included in the study, includes signalment, FIP form, treatment, relapse and survival data.

Table S3. Amount of RDV (mg) in the 60 mg, 90 mg and 120 mg compounded RDV from Optimus Healthcare, New Zealand.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding This research was supported by Healthy Pets New Zealand.

Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iD Kelsey Ann Renner https://orcid.org/0000-0002-5680-4257
Sally Coggins https://orcid.org/0000-0001-8683-5014

References

1 Tasker S, Addie DD, Egberink H, et al. **Feline infectious peritonitis: European Advisory Board on Cat Diseases guidelines.** *Viruses* 2023; 15. DOI: 10.3390/v15091847.
2 Foley JE, Poland A, Carlson J, et al. **Risk factors for feline infectious peritonitis among cats in multiple-cat environments with endemic feline enteric coronavirus.** *J Am Vet Med Assoc* 1997; 210: 1313–1318.
3 Addie DD and Jarrett O. **A study of naturally occurring feline coronavirus infections in kittens.** *Vet Rec* 1992; 130: 133–137.
4 Thayer V, Gogolski S, Felten S, et al. **2022 AAFP/EveryCat feline infectious peritonitis diagnosis guidelines.** *J Feline Med Surg* 2022; 24: 905–933.
5 Pedersen NC. **An update on feline infectious peritonitis: virology and immunopathogenesis.** *Vet J* 2014; 201: 123–132.
6 Pedersen NC. **A review of feline infectious peritonitis virus infection: 1963–2008.** *J Feline Med Surg* 2009; 11: 225–258.
7 Taylor SS, Coggins S, Barker EN, et al. **Retrospective study and outcome of 307 cats with feline infectious peritonitis treated with legally sourced veterinary compounded preparations of remdesivir and GS-441524 (2020–2022).** *J Feline Med Surg* 2023; 25. DOI: 10.1177/1098612X231194460.
8 Coggins SJ, Norris JM, Malik R, et al. **Outcomes of treatment of cats with feline infectious peritonitis using parenterally administered remdesivir, with or without transition to orally administered GS-441524.** *J Vet Intern Med* 2023; 37: 1772–1783.
9 Green J, Syme H and Tayler S. **Thirty-two cats with effusive or non-effusive feline infectious peritonitis treated with a combination of remdesivir and GS-441524.** *J Vet Intern Med* 2023; 37: 1784–1793.
10 Krentz D, Zenger K, Alberer M, et al. **Curing cats with feline infectious peritonitis with an oral multi-component drug containing GS-441524.** *Viruses* 2021; 13. DOI: 10.3390/v13112228.
11 Zwicklbauer K, Krentz D, Bergmann M, et al. **Long-term follow-up of cats in complete remission after treatment of feline infectious peritonitis with oral GS-441524.** *J Feline Med Surg* 2023; 25. DOI: 10.1177/1098612X231183250.
12 Jones S, Novicoff W, Nadeau J, et al. **Unlicensed GS-441524-like antiviral therapy can be effective for at-home treatment of feline infectious peritonitis.** *Animals (Basel)* 2021; 11. DOI: 10.3390/ani11082257.
13 Warren TK, Jordan R, Lo MK, et al. **Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys.** *Nature* 2016; 531: 381–385.
14 Sheahan TP, Sims AC, Graham RL, et al. **Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses.** *Sci Transl Med* 2017; 9. DOI: 10.1126/scitranslmed.aal3653.

15 Kimble B, Coggins SJ, Norris JM, et al. **Quantification of GS-441524 concentration in feline plasma using high performance liquid chromatography with fluorescence detection.** *Vet Q* 2023; 43: 1–9.
16 Coggins SJ, Kimble B, Malik R, et al. **Assessing in vitro stability of remdesivir (GS-5734) and conversion to GS-441524 in feline plasma and whole blood.** *Vet Q* 2024; 44: 1–9.
17 Yan VC, Pham C-D, Yan MJ, et al. **Pharmacokinetics of orally administered GS-441524 in dogs.** *bioRxiv* [Preprint]. Posted online 31 May 2021. DOI: 10.1101/2021.02.04.429674.
18 Xie J and Wang Z. **Can remdesivir and its parent nucleoside GS-441524 be potential oral drugs? An in vitro and in vivo DMPK assessment.** *Acta Pharm Sin B* 2021; 11: 1607–1616.
19 Cook S, Wittenburg L, Yan VC, et al. **An optimized bioassay for screening combined anticoronaviral compounds for efficacy against feline infectious peritonitis virus with pharmacokinetic analyses of GS-441524, remdesivir, and molnupiravir in cats.** *Viruses* 2022; 14. DOI: 10.3390/v14112429.
20 Renner K, Cattin R, Kimble B, et al. **Efficacy of oral remdesivir in treating feline infectious peritonitis: a prospective observational study of 29 cats.** *J Feline Med Surg* 2025; 27. DOI: 10.1177/1098612X251335189.
21 Hopkins BJ and Prokesch BC. **Anaphylaxis due to remdesivir.** *Antimicrob Agents Chemother* 2021; 65. DOI: 0.1128/AAC.00233-21.
22 Coggins SJ, Govendir M, Norris JM, et al. **Pharmacokinetics of GS-441524 following intravenous remdesivir in six cats and results of therapeutic drug monitoring during treatment of feline infectious peritonitis: 22 cases (2021–2024)**. *J Small Anim Pract* 2025; 66: 495–506.
23 Zhang Y, Huo M, Zhou J, et al. **PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel.** *Comput Methods Programs Biomed* 2010; 99: 306–314.
24 Murphy BG, Perron M, Murakami E, et al. **The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies.** *Vet Microbiol* 2018; 219: 226–233.
25 Fan J, Yang Y, Grimstein M, et al. **Whole body PBPK modeling of remdesivir and its metabolites to aid in estimating active metabolite exposure in the lung and liver in patients with organ dysfunction.** *Clin Pharmacol Ther* 2022; 111: 624–634.
26 Velkury Ltd. **Remdesivir 100 mg powder for injection data sheet v4.0 22 January 2025**. https://www.medsafe.govt.nz/other/siteinfo.asp (accessed 27 March 2024).