Short Communication

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Safety of oral and intravenous mycophenolate mofetil in healthy cats

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SAGE

Jennifer E Slovak and Nicolas F Villarino

Abstract

Objectives The aim of this study was to evaluate the safety and clinical effects of intravenous (IV) and oral mycophenolate mofetil (MMF) in healthy cats.

Methods A total of 24 healthy adult cats weighing >3.5 kg were either given IV MMF (over a 2 h infusion) or oral MMF. The dosages used were as follows: 5 mg/kg IV once (n = 2), 10 mg/kg q12h IV for 1 day (n = 1), 20 mg/kg q12h IV for 1 day (n = 6) and 10 mg/kg q12h IV for 3 days (n = 5). Blood was collected from each cat at intervals of up to 12 h from the last dose for analysis purposes. Oral MMF was given at 10 mg/kg q12h for 7 days (n = 3), 15 mg/kg q12h for 7 days (n = 3) and 15 mg/kg q8h for 7 days (n = 4).

Results Side effects to MMF were minimal. There was no anorexia or vomiting noted in any of the cats during or after IV medication administration. Only 4/14 cats had diarrhea from 12–48 h after IV administration. There was hyporexia in 1/10 cats given oral MMF and no vomiting noted. In 5/10 cats given oral MMF, there was diarrhea between days 2 and 7 of the study.

Conclusions and relevance Cats tolerate MMF at an IV dose of 10 mg/kg q12h for 3 days and an oral dose ⩽15 mg/kg q12h for up to 7 days. There seems to be a dose-dependent incidence of gastrointestinal side effects. MMF may be a useful alternative immunosuppressant to be considered for use in some cats.

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Introduction

Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid. It is a selective, reversible, non-competitive inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH).[1–3] MMF is an attractive alternative immunosuppressive in veterinary medicine owing to its rapid onset, generic commercially available formulations and documented efficacy in human and canine studies.[4–8] Known side effects in human and canine patients have largely involved gastrointestinal signs such as diarrhea, inappetence and vomiting. Other less common side effects are myelosuppression and liver enzyme changes due to mycophenolate glucuronidation metabolism.[4–8] To date, there has been only one published paper describing the clinical use of MMF in cats.[9] The dose used in the published case report was extrapolated from the human and canine literature. There is currently no published paper evaluating the safety or dosing of MMF in feline patients. The lack of published data may be precluding its use in feline patients. The aim of this study was to evaluate the safety and clinical effects of MMF at various doses in healthy cats.

Materials and methods

Animal population

This study was approved by the Institutional Animal Care and Use Committee, Washington State University (ASAF # 04665-005). Twenty-four healthy adult (1–5-year-old) cats (12 spayed females and 12 neutered males), weighing 3.5–7.4 kg (median 4.6 kg) were included in this study. Twenty-one were domestic shorthairs, and three were domestic longhair cats. Cats were housed according to Washington State University Institutional Animal Care and Use Committee guidelines. All cats were freely

Department of Veterinary Clinical Sciences, Program in Individualized Medicine, College of Veterinary Medicine, Washington State University, Pullman, WA, USA

Corresponding author:
Jennifer E Slovak DVM, MS, DACVIM, Department of Veterinary Clinical Sciences, Program in Individualized Medicine, College of Veterinary Medicine, Washington State University, PO Box 646610, Pullman, WA 99164, USA
Email: jeslovak@vetmed.wsu.edu

housed as individuals or in pairs, in temperature- and humidity-controlled feline friendly enriched rooms. The cats were all adopted at completion of the study.

All enrolled cats were deemed healthy and eligible based on prestudy physical examinations, behavior assessment (friendly/socialized), and a complete blood count, serum chemistry, urinalysis and feline leukemia virus/feline immunodeficiency virus screening test (24/24 tested negative).

The study cats were acclimatized to their new environment and food for 7–10 days prior to starting the study. Only two cats were medicated and sampled in the study at any one time. Twenty-four hours prior to medication administration, the cats were sedated with an intramuscular injection of ketamine 5–8 mg/kg, acepromazine 0.01–0.03 mg/kg and butorphanol 0.2–0.4 mg/kg, and had an indwelling dual-port jugular catheter placed by a licensed veterinary technician for blood sampling.

Intravenous administration

Intravenous (IV) MMF (Cellcept) was diluted with a 5% dextrose solution, to a 6 mg/ml solution and was administered via syringe pump over 2 h. For the first two cats, a conservative MMF dose was given, 5 mg/kg of MMF administered once (n = 2). The next enrolled study cat (n = 1) received 10 mg/kg MMF q12h for 1 day, the next six cats received 20 mg/kg MMF q12h for 1 day (n = 6) and five cats received 10 mg/kg MMF q12h for 3 days (n = 5).

Oral administration

In the oral MMF administration study, MMF was administered at 10 mg/kg orally (PO) q12h for 7 days (n = 3), 15 mg/kg q12h for 7 days (n = 3) and 15 mg/kg PO q8h for 7 days (n = 4).

Clinical evaluation and monitoring

Clinical evaluation and monitoring of the cats occurred during the 2 h IV infusion of MMF and for up to 4 h post-infusion or for up to 1 h post-oral administration of MMF. In addition, each cat received a daily physical examination and measurement of body weight during the entire study. The litter boxes were evaluated twice daily for loose stool.

A follow-up complete blood count and serum chemistry was performed on all study cats within 12 h of its last MMF dose (IV or PO). The blood was submitted for analysis to the Washington State University Veterinary Teaching Hospital clinical pathology laboratory. All cats' jugular sampling catheters were removed immediately postsubmission of the follow-up bloodwork (within 12 h of final sampling).

Analysis and reporting

Data are reported as median (range).

Results

Clinical signs and findings

Four of 24 cats had heart murmurs, discovered on initial evaluation. Three of the cats' murmurs were deemed innocent, with no significant structural abnormalities on echocardiogram and thus remained in the study. The fourth cat was diagnosed with early and mild hypertrophic cardiomyopathy that required no therapy, and also remained in the study. One of 24 cats developed a superficial corneal ulcer from a scratch, postdrug administration that subsequently healed with topical antibiotic therapy four times daily for 1 week.

There were no vomiting or drug administration reactions in any of the cats enrolled in the study. Eleven of 24 cats had weight loss from the first day of enrollment, to the last day on which MMF was administered (median 0.2 kg, range 0.1–0.4 kg). At discharge (7–10 days later), all cats maintained or gained in body weight. There were 4/14 cats that had isolated, self-resolving loose stools within 48 h of IV MMF administration and 4/10 cats that had isolated self-resolving loose stool during oral MMF administration and one of which was also hyporexic (Table 1). The loose stools resolved in all affected cats within 24 h of stopping MMF.

Clinical pathology

Serum alanine transferase values were normal in all cats post MMF administration. Table 2 shows the significant clinical pathology data of the 24 study cats. There was a decrease in red blood cell (RBC) percentage detected in 19/24 cats post-MMF administration, and 19/24 cats had evidence of thrombocytopenia post-MMF administration. Of note, total white blood cell (WBC) concentrations were normal or slightly elevated in all study cats post-MMF administration.

Discussion

To our knowledge, this is the first report of the short-term safety of IV and oral MMF administration in healthy cats. In this study, no serious adverse clinical effects were noted during IV or oral MMF administration. The diarrhea observed was self-limiting (MMF was discontinued) and no therapy was instituted. The one cat that developed hyporexia responded within 24 h of discontinued MMF and the administration of maropitant (Cerenia) and a dose of mirtazapine. The side effects that were seen in the cats followed a dose-dependent trend and the changes noted were reversible. To date, there is only one published paper describing the use of MMF in two cats with immune-mediated hemolytic anemia in which no reaction to MMF was noted; however, MMF was administered orally at 10 mg/kg q12h, not IV.[9]

Diarrhea was the most frequent adverse drug event in this study. Four of 14 cats (29%) of the IV

Table 1 Adverse events in cats treated with different dosage regimens of mycophenolate mofetil (MMF; n = 24)

Clinical signs	IV MMF 5 mg/kg once (n = 2)	IV MMF 10 mg/kg q12h × 1 day (n = 1)	IV MMF 20 mg/kg q12h × 1 day (n = 6)	IV MMF 10 mg/kg q12h × 3 days (n = 5)
Anorexia	0	0	0	0
Vomiting	0	0	0	0
Diarrhea	0	1	2	1
Hyporexia	0	0	0	0
		Oral MMF 10 mg/kg q12h × 1 week (n = 3)	Oral MMF 15 mg/kg q12h × 1 week (n = 3)	Oral MMF 15 mg/kg q8h × 1 week (n = 4)
Anorexia		0	0	0
Vomiting		0	0	0
Diarrhea		0	1	4
Hyporexia		0	0	1

IV = intravenous

patient population had an isolated episode of loose stool following medication administration. In the cats that had an episode of diarrhea, there was variability when it occurred. Two of four cats had a loose stool within 12 h of drug administration, one had an episode at 24 h and the last at 48 h. We suspect that the diarrhea seen in two cats at 12 h was likely the result of the MMF administration; however, we are skeptical of the later onset of loose stool for the remaining two cats. In all cases, the diarrhea was self-limiting and did not require any additional medical intervention. The frequency of diarrhea seems to be dose dependent. All the cats treated orally with 15 mg/kg of MMF q8h had diarrhea. In contrast, only one of the cats treated with a lower daily dose showed signs of diarrhea. Dose-related gastrointestinal side effects have been reported in human and canine patients.[3,5–7] The exact cause of the gastrointestinal side effects remains unknown, but it has been suggested that enterohepatic recycling of the active drug mycophenolic acid (MPA) and/or the accumulation of one of MMF metabolites (MPA acyl glucuronide) may contribute to this side effect.[2,3]

Although 19/24 cats had a lower packed cell volume at conclusion of the study, this was to be expected, as blood was collected for pharmacokinetic/pharmacodynamic evaluation. All cats had no more than a total of 9 ml/kg of blood sampled (range 5–9 ml/kg). Additionally, as dual-port sampling catheters were used, periodic flushing with heparinized sodium chloride solution of both ports occurred and may have diluted the total blood volume and measured RBC percentage. Total WBC values were not below the reference interval (RI) in any of the cats. In fact, five cats had total WBC counts above the RI, but this may be a result of stress or excitation at the time of blood sampling. There did not seem to be a dose-dependent trend when evaluating the RBC percentages or the total WBC count.

Interestingly, the total platelet counts for the cats was quite variable. These data are worth noting but should be cautiously scrutinized. Traditional causes for thrombocytopenia are decreased production, destruction or loss/consumption. Feline platelets are notorious for aggregating and are often falsely lowered on automated instruments; therefore, a blood smear should always be evaluated.[10] The total recorded platelet counts were lower post-IV MMF administration in 10/14 cats and 9/10 cats post-oral MMF. Many cats had platelet aggregates identified and large platelets noted on their blood smears. Although MMF can cause dose-dependent myelosuppression in humans, there is interpatient variability reported in the literature.[8] As MMF is a selective non-competitive inhibitor of IMPDH, which largely inhibits T- and B-cell production, we do not suspect MMF as a primary cause for lack of platelet production for this finding.[2,11] More likely, the thrombocytopenia was due to loss/consumption, possibly from the gastrointestinal tract. It is important to note that no cats had any indication of clinical thrombocytopenia or bleeding as a result of their decreased platelet numbers. On subsequent blood smears prior to discharge, platelet numbers were deemed adequate.

One limitation of this study is the low numbers of cats enrolled, which may affect the likelihood or manifestation of clinical signs if there is excessive interpatient variability in response to MMF. However, to date, there are no published studies of the pharmacology of MMF in vivo in cats. Another factor to consider is the relatively short treatment period of administered MMF. In choosing the length of treatment for the cats, we tried to mimic the approximate amount of time that we would administer IV MMF in hospital (approximately 3 days before being transitioned to oral medications), and 1 week of oral administration of MMF was chosen to see if there were any acute side effects, as seen in humans and dogs.[4–6,8,11]

Table 2 Effect of different dosage regimens of mycophenolate mofetil (MMF) on percentage of red blood cells (RBC%) and platelets in cats (n = 24)

Cat and dosage	RBC% pre-MMF	RBC% post-MMF	Platelet (200–500 $\times 10^3$/μl) pre-MMF	Platelet (200–500 $\times 10^3$ /μl) post-MMF
5 mg/kg IV once				
1	33	23	144,000	109,000
2	30	32	51,000 (large platelets)	211,000
10 mg/kg IV q12h				
3	51	46	140,000 (many aggregates)	15,000 (large platelets)
20 mg/kg IV q12h				
4	43	30	175,000	299,000
5	44	36	339,000	167,000
6	40	36	330,000	61,000 (large platelets, many aggregates)
7	39	36	493,000	35,000 (platelet aggregates)
8	39	32	367,000	541,000
9	37	37	96,000 (many platelet aggregates)	485,000
10 mg/kg IV q12 × 3 days				
10	40	29	372,000	91,000 (large platelets, aggregates)
11	33	30	494,000	105,000 (large platelets, aggregates)
12	35	35	590,000	72,000 (large platelets)
13	32	30	145,000 (platelet aggregates)	81,000
14	34	32	482,000	186,000 (large platelets)
10 mg/kg PO q12h × 1 week				
15	48	32	212,000	187,000 (large platelets, aggregates)
16	33	32	390,000	222,000
17	39	34	380,000	161,000 (large platelets)
15 mg/kg PO q12h × 1 week				
18	29	32	301,000 (platelet aggregates)	84,000
19	36	31	468,000 (large platelets)	90,000 (platelet aggregates)
20	39	34	250,000	43,000 (large platelets, many aggregates)
15 mg/kg PO q8h × 1 week				
21	39	27	382,000	92,000 (large platelets)
22	36	31	304,000 (platelet aggregates)	163,000
23	26	26	190,000 (platelet aggregates)	207,000
24	29	28	219,000	96,000

Conclusions

This study suggests that cats can tolerate MMF IV at 10 mg/kg q12h for 3 days, and they can tolerate an oral dose of ⩽15 mg/kg q12h for up to 1 week. Our results suggest that there is a dose-dependent incidence of gastrointestinal side effects. Future studies should be undertaken to identify the lowest effective dosage regimen of MMF for use in cats, especially as the immunosuppressive effect of MMF is dose dependent. Additionally, further research into individualized therapy and effectiveness of MMF in cats should be explored as there is variability of the side effects among the treated cats. As a result of this study, MMF may be a useful and reasonable alternative or adjunctive immunosuppressant in certain feline patients with immune-mediated diseases.

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