American Journal of Therapeutics 18, 2–8 (2011)

The Relative Bioavailability of Morphine Sulfate and Naltrexone Hydrochloride Extended Release Capsules (EMBEDA®) and an Extended Release Morphine Sulfate Capsule Formulation (KADIAN®) in Healthy Adults Under Fasting Conditions

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Morphine sulfate and naltrexone hydrochloride extended release capsules (EMBEDA®, King Pharmaceuticals®, Inc., Bristol, TN), indicated for the management of chronic, moderate to severe pain, contain extended release morphine pellets with a sequestered naltrexone core (MS-sNT). If the product is tampered with by crushing, naltrexone, a μ-opioid antagonist, is intended for release to mitigate morphine-induced subjective effects. The primary end point of this randomized 2-way crossover study in healthy fasted volunteers was evaluation of morphine bioequivalence between MS-sNT (treatment A) and morphine sulfate extended release capsules (KADIAN®, treatment B). Morphine pharmacokinetics were assessed predose to 72 hours postdose of single 100-mg doses of treatment A or B. Analysis of variance of ln-transformed ratios of least squares mean of the area under the concentration time curve (AUC) from time 0 to last measurable concentration (AUC_{0-t}) and AUC from time 0 to infinity (AUC_{inf}) and maximum serum concentration (C_{max}) for treatments A versus B were performed. Ratios and 90% confidence intervals for least squares mean for AUC_{0-t} (102.2%; 98.6–105.9%), AUC_{inf} (97.4%; 91.2–104.1%), and C_{max} (93.8%; 82.4–106.7%) indicated bioequivalence between the 2 formulations. When subjects who vomited during the 12-hour dosing interval were excluded, the confidence interval for AUC_{0-t} and AUC_{inf} fell within the 80%–125% range, but the lower limit for C_{max} was 76.9%.

Keywords: bioavailability, bioequivalence, pharmacokinetics, opioid, morphine

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This study and funding for writing and editorial support were provided by King Pharmaceuticals®, Inc, Bridgewater, NJ. Writing and editorial support for the manuscript was provided by Quintiles Medical Communications, Parsippany, NJ.

The authors have provided input into the study design, analysis and interpretation of data, writing of this manuscript, and decision to submit for publication.

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F. Johnson held stock in Alpharma Pharmaceuticals®, LLC, and is a coinventor of the EMBEDA® technology. J. Stauffer has previously owned stock in Alpharma Pharmaceuticals, LLC, and has a patent pending with Alpharma Pharmaceuticals, LLC. Opinions and discussion contained in this article do not reflect the opinion of Johns Hopkins University.

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1075-2765

INTRODUCTION

In the United States, chronic pain afflicts 9% of adults, causing personal suffering and impacting ability to work.[1,2] Opioids have frequently been prescribed for the management of moderate to severe pain, and the American Pain Society and American Academy of Pain Medicine clinical guidelines include opioid therapy as a component of comprehensive pain management plans for carefully selected and monitored patients with chronic, moderate to severe pain.[3] Immediate-release opioid formulations must be dosed frequently because of their short half-life ($T_{1/2}$).[4] Extended-release opioid formulations can provide effective around-the-clock management of chronic, moderate to severe pain, resulting in improved pain management and quality of life compared with short-acting opioids.[5] However, oral extended release opioid formulations contain an 8- to 24-hour dose amount in a single dosing unit, making them sought after by abusers wishing to gain access to the large amount of opioid all at once by tampering with the extended release characteristics of the product.[2] Hence, there is a need for extended release formulations that are less desirable for abuse relative to existing products,[6] although it is unlikely that any technology would curtail all means of abuse.[7]

Morphine sulfate and naltrexone hydrochloride extended release capsules (EMBEDA®, King Pharmaceuticals®, Inc., Bristol, TN)[8] contain extended release pellets of morphine sulfate each with a core of sequestered naltrexone (MS-sNT), a μ-opioid receptor antagonist.[9] MS-sNT is indicated for the management of chronic, moderate to severe pain.[10] When MS-sNT is taken whole (as intended), morphine is released to provide analgesia. If crushed, a common method of tampering, MS-sNT was designed to release the sequestered naltrexone to reduce morphine-induced subjective effects.[11,12] The extended release formulation of MS-sNT is based on the technology utilized in a marketed extended release morphine sulfate (ERMS) product, KADIAN® (morphine sulfate extended release) capsules (Actavis, Elizabeth LLC, NJ), which contain pellets of extended release morphine with a pharmacologically inert core[13] and provide effective analgesia in patients with chronic, moderate to severe pain when used once or twice daily.[14] It was necessary for regulatory filing purposes to establish that inclusion of sequestered naltrexone into the formulation did not impact morphine bioavailability from the MS-sNT formulation.

The objective of this bioequivalence study was to compare, under fasting conditions, the single-dose relative morphine bioavailability of MS-sNT 100-mg capsules (treatment A) and ERMS 100-mg capsules (treatment B) in healthy volunteers.

MATERIALS AND METHODS

Ethics

The study was conducted in compliance with the principles and requirements described in Good Clinical Practice (US Code of Federal Regulations 21 CFR Parts 50 and 312), International Conference on Harmonisation guidelines regarding Good Clinical Practice,[15] and the Declaration of Helsinki.[16] The independent Institutional Review Board at Celerion (formerly MDS Pharma Services) reviewed and approved informed consent forms and all protocols before initiation of the study in accordance with the US Code of Federal Regulations (21 CFR Part 56). All participants were informed of procedures to be performed and potential hazards and provided signed informed consent before study entry.

Study design

This was an open-label, randomized, single-dose, 2-sequence, crossover design (Sponsor study number ALO-01-07-101) under fasting conditions (Fig. 1).

Subjects

Requirements for study participation included the following: the participants should be healthy adult volunteers (male or female) aged 19–45 years; men should weigh ≥60 kg and women should weigh ≥52 kg and be within 15% of ideal weight; they should have clinically normal laboratory profiles, vital signs, and electrocardiograms; and women of childbearing age should use acceptable forms of birth control. Subjects were excluded from participation if they had a significant health condition; any history of or current alcohol

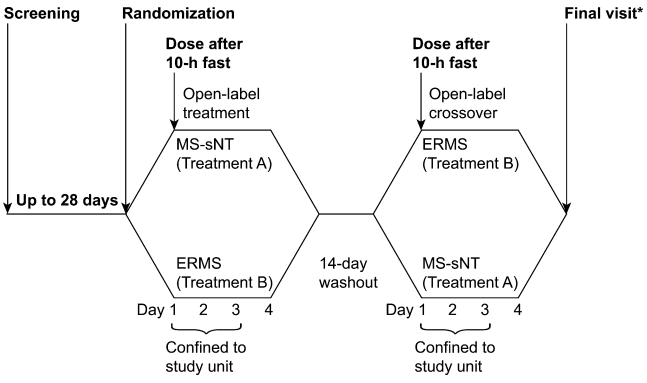

FIGURE 1. Study design. *The final visit was conducted at the end of period 2 (day 4) or before early termination.

or drug abuse; hypersensitivity to naltrexone, naloxone, or other opioid antagonist; hypersensitivity to morphine or any other opioid; or were women who were pregnant, lactating, or who had received any hormone replacement therapy within 3 months of dosing. The following medications or foods were prohibited: hepatic-enzyme–inducing drugs (eg, ketoconazole, cimetidine) within 3 months of study entry; drugs or substances known to strongly inhibit cytochrome P450 enzymes within 10 days of study entry; medications including over-the-counter products and herbal supplements within 7 days before the first dose, during the time of sample collection, or during the 14-day washout period between drug administrations; oral or transdermal estrogen and/or progestin-containing contraceptives or hormone replacement therapy 3 months before dosing and throughout the study; hormonal contraceptive injections or implants (eg, levonorgestrel, medroxyprogesterone) 6 months before dosing and throughout the study; grapefruit 10 days before dosing and throughout the study; alcohol 48 hours before dosing and throughout the period of sample collection; xanthines 24 hours before dosing and throughout the period of sample collection; red meat, organ meat, red wine, and beets 3 days preceding screening until stool for occult blood sampling was collected. At check-in, each subject was screened for alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opiates. A determination of serum alanine transaminase, serum aspartate transaminase, and serum amylase was also performed at each check-in.

Treatments

Subjects (n = 36) were housed at the study center at least 10 hours before dosing for an overnight fast and were randomized to receive a single MS-sNT capsule (treatment A, 100 mg of morphine sulfate extended release/4 mg of sequestered naltrexone hydrochloride) or ERMS capsule (treatment B, 100 mg of morphine sulfate extended release) with 240 mL of water. Treatment sequences were AB and BA, which were randomized before study initiation and assigned based on the order of enrollment. Food was not permitted between 10 hours before dosing and 4 hours postdosing; smoking was prohibited from 1 hour before to 4 hours postdosing.

Blood samples (1 × 5 mL) for serum morphine determination were taken predose and at selected times postdose through 72 hours. Serum was prepared and stored at −20 ± 10°C until analysis. Subjects were housed at the study site through the 48-hour blood draw and returned to the study site for the 72-hour sampling. After a 14-day washout, subjects returned to the study center and were administered the alternate treatment under the same schedule.

Physical examination, including vital signs, laboratory profiles, and electrocardiograms were repeated on the final visit at the end of period 2 or at early termination.

Outcome measures

Morphine and its major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G),[17] were analyzed using validated liquid chromatography coupled to tandem mass spectrometry methods. The analytical range of the assay used for morphine was 0.75–75 nmol/L with inter- and intra-assay coefficients of variation (CVs) of 6.8% and 5.3%. The analytical range was 21.66–2166 nmol/mL for M3G (inter- and intraassay CV: 2.8% and 2.2%) and 2.17–217 nmol/mL for M6G (inter- and intraassay CV: 7.2% and 3.8%).

Area under the concentration time curve (AUC) from time 0 to last measurable concentration (AUC_{0-t}) and AUC from time 0 to infinity (AUC_{inf}) were estimated by the linear trapezoidal method; maximum serum concentration (C_{max}) over a specified time span and time of maximum serum concentration (T_{max}) were determined by the direct observation of the data.

Statistics

Descriptive statistics included calculation of arithmetic means, geometric means, standard deviation, CV, and minimum, median, and maximum values. Analysis of variance was performed on ln-transformed pharmacokinetic parameters and included formulation group, sequence, period nested within group, and subject nested within group*sequence as a random effect. Analysis of variance included calculation of least squares mean (LSM), differences between formulation LSM and standard error associated with the differences. Ratios of ln-transformed LSM values for AUC_{0-t}, AUC_{inf}, and C_{max} were expressed as a percentage relative to the reference formulation (ERMS); therefore, comparison of interest was treatment A versus treatment B.

The primary end point was bioequivalence. Bioequivalence is considered established if 90% confidence intervals (CIs) for the ln-transformed ratios of AUC and C_{max} fall within the 80%–125% range.[18,19] For bioequivalence studies involving modified-release products, data from those subjects who experience vomiting during the dosing interval can be removed.[19] Therefore, analysis was also performed after removing data from those patients who vomited during the 12-hour dosing interval.

RESULTS

Study subjects, disposition, and demographics

Of 36 subjects who enrolled, 34 completed the study per the protocol. One subject withdrew due to a family emergency; the other subject did not report for check-in for period 2. Both had received MS-sNT (treatment A) in period 1. Participants (25 men and 11 women) ranged in age from 19 to 45 years (mean, 26 years), and most were white (32 of 36 or 88.9%). Mean (standard deviation) height was 175.4 (8.9) cm, and mean weight was 74.2 (6.7) kg.

Pharmacokinetic profiles of morphine and its major metabolites

Similar serum morphine concentration–time profiles were observed for MS-sNT and ERMS (Fig. 2A). Overall, morphine exposure was similar (Table 1). Although the rate of absorption appeared to be faster for MS-sNT versus ERMS (median T_{max} 7.5 versus 10.0 hours), given the variability of both treatments, the overall difference in T_{max} may not be clinically relevant. Similar results were observed for morphine metabolites M3G and M6G (Table 1). Concentration–time curves for M3G and M6G were also similar for MS-sNT and ERMS (Fig. 2B, C).

Bioequivalence assessments for morphine and metabolites are summarized in Table 2. Ninety percent CI limits for ln-transformed pharmacokinetic parameters for the ratio of MS-sNT to reference ERMS (n = 34) for AUC_{0-t}, AUC_{inf}, and C_{max} fell between the 80% and 125% range required for establishing bioequivalence. When subjects who experienced emesis within 12 hours were excluded (n = 23 remaining subjects), the CI limits for AUC_{0-t} and AUC_{inf} were also within the 80%–125% boundary; C_{max} values when all subjects were included and when subjects who vomited were excluded were similar (0.018 and 0.017 μmol/L, respectively); however, the CI for ln-transformed C_{max} had a lower limit of 76.9%. For M3G and M6G, the 90% CI limits for ln-transformed ratios for C_{max}, AUC_{0-t}, and AUC_{inf} were between 80% and 125% in all subjects and in the sample excluding those who experienced emesis (Table 2).

Overall incidence of adverse events (AEs) judged possibly, probably, or definitely related to treatment was similar for the 2 treatments: 30 subjects (83.3%) with MS-sNT, 28 subjects (82.4%) with ERMS.

The most frequently reported AEs (nausea, headache, dizziness, vomiting) with both treatments in healthy volunteers under fasting conditions were those that typically occur with opioid therapy (Table 3). Most AEs were mild and resolved with or without treatment. Moderate AEs, 15 with MS-sNT and 26 with ERMS, included nausea, vomiting, headache, somnolence, generalized pruritus, dizziness, irritability, fatigue, and decreased oxygen saturation; all resolved during the study. There were no serious AEs.

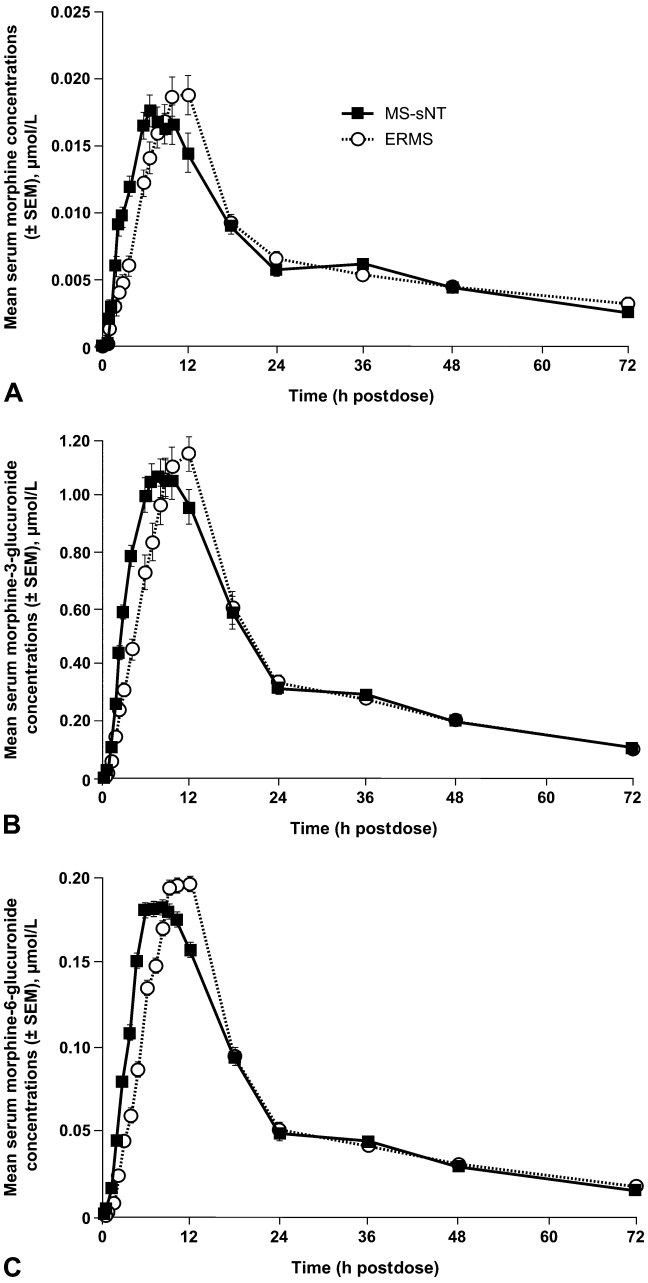

FIGURE 2. Mean (SEM) serum morphine (A), morphine-3-glucuronide (B), and morphine-6-glucuronide (C) concentrations.

There was 1 clinically significant change in laboratory results in 1 subject who experienced elevated eosinophils at 72 hours postdose of MS-sNT and on recheck 2 weeks later. This subject had seasonal allergies, had been taking loratadine, and was following up with her usual physician. There were no other

Table 1. Summary of pharmacokinetic assessments of morphine, M3G, and M6G.

Assessment (n = 34)	MS-sNT (A)	ERMS (B)
Morphine		
C_{max} (μmol/L), geometric mean (CV%)	0.018 (36.8)	0.020 (45.7)
T_{max} (h), median (range)	7.50 (2.50–18.0)	10.0 (6.00–24.0)
$T_{1/2}$ (h), arithmetic mean (CV%)	28.8 (39.9)	33.8 (34.6)
AUC_{0-t} (μmol·h/L), geometric mean (CV%)	0.466 (25.3)	0.457 (25.8)
AUC_{inf} (μmol·h/L), geometric mean (CV%)	0.576 (24.1)	0.586 (29.9)
M3G		
C_{max} (μmol/L), geometric mean (CV%)	1.143 (25.7)	1.208 (34.4)
T_{max} (h), median (range)	8.00 (6.00–18.0)	12.0 (6.00–12.0)
$T_{1/2}$ (h), arithmetic mean (CV%)	26.5 (35.8)	28.6 (31.9)
AUC_{0-t} (μmol·h/L), geometric mean (CV%)	26.6 (16.5)	26.0 (17.9)
AUC_{inf} (μmol·h/L), geometric mean (CV%)	30.9 (18.5)	30.5 (18.0)
M6G		
C_{max} (μmol/L), geometric mean (CV%)	0.203 (24.0)	0.208 (33.9)
T_{max} (h), median (range)	8.00 (4.00–18.0)	10.0 (6.00–12.0)
$T_{1/2}$ (h), arithmetic mean (CV%)	26.9 (34.3)	29.5 (38.1)
AUC_{0-t} (μmol·h/L), geometric mean (CV%)	4.35 (15.8)	4.24 (16.5)
AUC_{inf} (μmol·h/L), geometric mean (CV%)	5.07 (18.0)	5.01 (18.8)

Table 2. Comparison of LSM ratios for morphine and metabolites in serum after MS-sNT (A) and ERMS (B) treatments.

		90% CI limits (%)		
	Ratio LSM (A/B) %	Lower	Upper	CV%
Morphine				
Including all subjects who completed				
C_{max}, n = 34	93.8	82.4	106.7	32.2
AUC_{0-t}, n = 34	102.2	98.6	105.9	8.6
AUC_{inf}, n = 30	97.4	91.2	104.1	13.9
Excluding subjects who vomited within the 12-h dosing interval				
C_{max}, n = 23	88.6	76.9	102.1	27.4
AUC_{0-t}, n = 23	103.6	99.5	107.8	7.6
AUC_{inf}, n = 21	99.6	94.3	105.1	9.6
M3G				
Including all subjects who completed				
C_{max}, n = 34	94.9	86.0	104.8	24.4
AUC_{0-t}, n = 34	102.3	99.3	105.3	7.1
AUC_{inf}, n = 32	101.5	97.5	105.8	9.1
Excluding subjects who vomited within the 12-h dosing interval				
C_{max}, n = 23	94.5	83.3	107.1	24.1
AUC_{0-t}, n = 23	103.7	99.6	108.1	7.8
AUC_{inf}, n = 22	105.2	100.1	110.6	8.8
M6G				
Including all subjects who completed				
C_{max}, n = 34	97.8	88.3	108.4	25.2
AUC_{0-t}, n = 34	102.5	99.6	105.4	6.9
AUC_{inf}, n = 31	100.0	95.7	104.5	9.9
Excluding subjects who vomited within the 12-h dosing interval				
C_{max}, n = 23	94.6	83.8	106.9	23.4
AUC_{0-t}, n = 23	103.1	99.2	107.2	7.3
AUC_{inf}, n = 22	101.8	97.4	106.4	8.1

Table 3. Most frequently reported AEs [≥10% (4 or more) subjects]; N = 36.

AE	Number (%) of subjects with AEs		
	MS-sNT, 100 mg (A)	ERMS, 100 mg (B)	Total (%)
Nausea	16 (44.4)	15 (44.1)	20 (55.6)
Headache	13 (36.1)	12 (35.3)	18 (50.0)
Dizziness	16 (44.4)	10 (29.4)	18 (50.0)
Vomiting	11 (30.6)	13 (38.2)	17 (47.2)
Pruritus, generalized	10 (27.8)	9 (26.5)	15 (41.7)
Dysuria	5 (13.9)	3 (8.8)	7 (19.4)
Somnolence	3 (8.3)	5 (14.7)	6 (16.7)
Dry mouth	3 (8.3)	3 (8.8)	5 (13.9)
Feeling hot	3 (8.3)	1 (2.9)	4 (11.1)

clinically significant changes in laboratory values, physical findings, or vital signs.

DISCUSSION

This study compared the relative bioavailability of ERMS (100 mg) to MS-sNT (100 mg) as assessed by serum morphine and its glucuronidated metabolites. Based on the results including all subjects who completed the study, MS-sNT (100 mg) and ERMS (100 mg) were bioequivalent under fasting conditions for all 3 analytes evaluated. Median T_{max} for morphine was numerically decreased by 2.5 hours for MS-sNT relative to ERMS (Table 1). Morphine T_{max} values for the in vivo extended release profiles for ERMS and MS-sNT typically vary from 6 to 16 hours postdose with a few occasional values outside of these boundaries. Given the variability in the extended release profiles for these 2 morphine products, which are formulated in a similar fashion, a T_{max} difference of 2.5 hours within this approximate range of individual values is not considered clinically relevant in terms of safety and efficacy of MS-sNT relative to ERMS. Excluding subjects who experienced emesis within the 12-hour dosing interval from the analysis reduced the number of subjects by approximately one-third with the potential for increased variability, especially for single-point measurements. However, the CIs of ratios of LSMs of ln-transformed AUC_{0-t} and AUC_{inf} remained within the 80%–125% range, indicating comparable bioavailability.

The pharmacokinetic profiles of the major metabolites M3G and M6G were similar to the parent compound for both MS-sNT and ERMS. Serum samples were not analyzed for naltrexone or its major metabolite 6-β-naltrexol in this study. A subsequent clinical study in the clinical development program for MS-sNT specifically addressed the potential exposure to naltrexone after MS-sNT was administered intact as directed or after ingestion of crushed pellets to simulate ingestion of the tampered product. Results from this study are reported separately.[12]

This single-dose study established bioequivalence between MS-sNT and ERMS in healthy adult volunteers under fasting conditions. In this clinical trial, the study design and conduct and minimum age of study participants followed the guideline recommendations for establishing bioequivalence.[19] As with most single-dose bioequivalence trials, the study population was composed of healthy individuals rather than those with chronic, moderate to severe pain for whom the product is intended. The age, sex, and race of study participants in this single-dose trial, in which there were twice as many men as women and most participants were white and aged ≤45 years, may not be representative of a patient population with chronic, moderate to severe pain. Steady-state bioavailability was assessed in another study in patients with chronic pain due to osteoarthritis of the hip or knee. Under steady-state conditions, morphine exposure (AUC_{0-12}) was similar for MS-sNT and ERMS (95% CI, 0.82–1.07 for ERMS/MS-sNT). Analgesic efficacy, based on pain intensity scores, and safety profiles were similar for MS-sNT and ERMS.[10]

The results of this study, conducted to assess the impact of the sequestered naltrexone on morphine pharmacokinetics, established that inclusion of sequestered naltrexone in the formulation did not affect morphine bioavailability when compared with the existing product with an inert core. Both products had a similar safety profile, with the most frequent AEs typical of opioid treatment.

CONCLUSIONS

MS-sNT (EMBEDA®) and ERMS (KADIAN®), a marketed ERMS formulation, are bioequivalent under fasting conditions when all subjects are included in the analyses. The disposition of serum morphine and that of its major metabolites (M3G and M6G) was similar between the 2 treatments.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Paul F. Cavanaugh, Jr, and Donald Manning to this project.

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