Transl Clin Pharmacol. 2024 Mar;32(1):63-72
https://doi.org/10.12793/tcp.2024.32.e6
pISSN 2289-0882·eISSN 2383-5427

Translational and Clinical Pharmacology TCP

Original Article

Check for updates

Comparison of the pharmacokinetic characteristics and bioequivalence between two nanosuspension formulations of megestrol acetate in healthy Korean male subjects

Se Rin Park [1], Jun Gi Hwang [2], Sae Im Jeong [2], Young-Sim Choi [2], Hyo Jin Min [2], Hye Yun Kim [3], Bong-Hoi Choi [4,*], and Min Kyu Park [2,*]

[1]Department of Clinical Pharmacology and Therapeutics, Chungbuk National University Hospital, Cheongju 28644, Korea
[2]Department of Clinical Pharmacology and Therapeutics, Chungbuk National University College of Medicine and Hospital, Cheongju 28644, Korea
[3]Daewon Pharmaceutical Co., Ltd., Seoul 04808, Korea
[4]Department of Nuclear Medicine and Molecular Imaging, Gyeongsang National University Hospital, College of Medicine, Gyeongsang National University, Jinju 52727, Korea

OPEN ACCESS

Received: Mar 14, 2024
Revised: Mar 23, 2024
Accepted: Mar 25, 2024
Published online: Mar 26, 2024

***Correspondence to**
Bong-Hoi Choi
Department of Nuclear Medicine and Molecular Imaging, Gyeongsang National University Hospital, College of Medicine, Gyeongsang National University, 79 Gangnam-ro, Jinju 52727, Korea.
Email: bonghoi.choi@gmail.com

Min Kyu Park
Department of Clinical Pharmacology and Therapeutics, Chungbuk National University College of Medicine and Hospital, 776, 1sunhwan-ro, Seowon-gu, Cheongju 28644, Korea.
Email: mkparkdau@gmail.com

ORCID iDs
Se Rin Park
https://orcid.org/0009-0008-8886-3375
Jun Gi Hwang
https://orcid.org/0000-0002-0965-0531
Sae Im Jeong
https://orcid.org/0000-0002-5299-4305
Young-Sim Choi
https://orcid.org/0000-0003-2476-2408
Hyo Jin Min
https://orcid.org/0009-0005-2055-5083
Hye Yun Kim
https://orcid.org/0009-0007-0898-4971

ABSTRACT

Megestrol is commonly used to address appetite loss, cachexia, and significant weight loss in cancer or acquired immune deficiency syndrome patients. This study aimed to assess the pharmacokinetics and determine the bioequivalence of two orally administered megestrol acetate suspensions (625 mg/5 mL) in healthy Korean male subjects. A randomized, open-label, single-dose crossover study was conducted involving fifty-four healthy male subjects who were randomized into two sequence groups. Each subject received either a test or reference drug formulation of 625 mg/5 mL megestrol acetate with a two-week washout period between treatments. Plasma samples were collected before and up to 120 hours after administration, and their plasma drug concentrations were analyzed using validated liquid chromatography–mass spectrometry/mass spectrometry. The pharmacokinetic parameters were calculated, and bioequivalence was confirmed if the 90% confidence intervals of the geometric mean ratios were within the specified bounds of 80.00% to 125.00%. In total, fifty-two subjects completed the study, contributing to the pharmacokinetic analysis. The 90% confidence intervals for the geometric mean ratios of the test formulation compared to the reference formulation were 93.85% to 108.90% for maximum plasma concentration and 91.60% to 101.78% for area under the concentration-time curve from the point of administration to last time point of blood sampling. Throughout the study, no serious or unexpected adverse events were observed.
The pharmacokinetic profiles of both formulations of megestrol acetate (625 mg) were comparable and well tolerated in healthy Korean male adult subjects. The test formulation met regulatory criteria for bioequivalence.

Trial Registration: ClinicalTrials.gov Identifier: NCT06147908

Keywords: Bioequivalence; Pharmacokinetics; Megestrol; Appetite Stimulants

Bong-Hoi Choi
https://orcid.org/0000-0002-7131-351X
Min Kyu Park
https://orcid.org/0000-0002-9851-7555

Trial Registration
ClinicalTrials.gov Identifier: NCT06147908

Funding
This study was funded by Daewon Pharmaceutical Co., Ltd.

Conflict of Interest
- Authors: Nothing to declare
- Reviewers: Nothing to declare
- Editors: Nothing to declare

Reviewer
This article was reviewed by peer experts who are not TCP editors.

Author Contributions
Conceptualization: Park SR, Park MK, Hwang JG, Jeong SI, Choi YS; Data curation: Park SR; Formal analysis: Park SR, Park MK, Hwang JG, Jeong SI, Min HJ; Funding acquisition: Kim HY; Investigation: Park MK, Hwang JG, Jeong SI; Project administration: Park SR, Park MK, Hwang JG, Jeong SI, Kim HY; Resources: Park SR, Park MK, Hwang JG, Jeong SI, Choi YS; Supervision: Park MK, Hwang JG, Choi BH; Validation: Park SR, Park MK, Hwang JG, Choi BH; Visualization: Park SR; Writing - original draft: Park SR, Hwang JG; Writing - review & editing: Park SR, Park MK, Hwang JG, Jeong SI, Choi YS, Min HJ, Kim HY, Choi BH.

INTRODUCTION

Cachexia refers to a phenomenon in which despite the intake of sufficient calories, there is a decrease in body weight, loss of appetite, or an imbalance in effects. The metabolic changes triggered by cancer cachexia, such as autophagy, elevated energy expenditure, nutrient sequestration by tumors, and proteolysis, collectively result in reduced oxidative capacity of cardiac muscle, disrupted mitochondrial homeostasis, and muscle atrophy, ultimately culminating in weight loss [1]. Cancer cachexia is multifactorial and cannot be fully reversed by nutritional support. It stems from both reduced food intake and metabolic abnormalities, which appear to be influenced by factors originating from the tumor and the host [2]. The incidence of cachexia symptoms, including loss of appetite and weight loss, in cancer patients varies depending on the underlying disease. These symptoms have been reported in approximately 14% to 85% or more of patients [3-5]. Some studies have indicated that approximately 77% of cancer patients with appetite loss report experiencing distress associated with this symptom [6]. Additionally, cachexia causes weight loss, negatively affects patient quality of life, and may reduce a patient's capacity to respond to chemotherapy [7]. Death normally occurs when weight loss is approximately 30% due to severe cachexia [8].

Megestrol acetate is a synthetic derivative (17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione) of a naturally occurring progestational agent that is similar to progesterone [9]. Megestrol acetate is a progestogen widely used in the palliative treatment of endometrial carcinoma and breast cancer, and in clinical use, appetite improvement and weight gain have been observed [10]. Some studies have indicated that approximately 95% of cancer patients report improved appetite [11]. The precise mechanism by which megestrol acetate induces weight gain is unclear [12]; however, the following mechanisms have been predicted: i) Megestrol acetate can increase neuropeptide Y (NPY) levels, and the orexigenic effects of orexigenic peptides, such as NPY, are mediated through neuronal nitric oxide synthase, which activates adenosine monophosphate kinase, resulting in a decrease in malonyl coenzyme A and increased food intake [13]. ii) Megestrol acetate inhibits calcium (Ca^{2+}) channel currents. The inhibition of calcium channel currents by megestrol acetate may promote appetite by reducing the activity of ventromedial nucleus neurons involved in satiety mechanisms [14]. iii) The action of megestrol acetate includes the inhibition of inflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor alpha, and interferon gamma, leading to a reduction in cytokine secretion and a potential amelioration of cancer cachexia [12,15].

Megestrol acetate can cause glucocorticoid-related side effects, including adrenal insufficiency [16]. Additionally, patients may experience adverse reactions such as rash, menstrual irregularities, hyperglycemia, diarrhea, headache, dizziness, lactate dehydrogenase elevation, nausea, abdominal pain, dyspnea, cough, and thrombosis. However, it has been reported that the incidence of thromboembolic phenomena is less than 5%, and no serious unexpected adverse events (AEs) have been reported in studies using megestrol acetate oral suspension at doses up to 1,200 mg/day [17-19].

Megestrol acetate is a Biopharmaceutics Classification System (BCS) class II drug with low aqueous solubility (2 μg/mL) and high membrane permeability [20]. BCS Class II drugs may exhibit incomplete and variable absorption when administered orally, depending on gastrointestinal conditions [20]. It has also been difficult to optimize the dosage of megestrol acetate due to its pharmacokinetic characteristics, which are similar to those of other BCS

Class II drugs. These characteristics include reduced bioavailability and susceptibility to food intake when taken orally [21]. Although megestrol acetate has increased bioavailability when administered after a high-fat meal [22], in clinical use, it is usually administered under fasting conditions because it is used in patients with cachexia. This has led to improvements in formulation by using a new formulation with higher absorption rates. Several studies have shown that compared to tablets, suspensions of nanoparticles enhance the bioavailability of BCS Class II compounds, such as megestrol. They also aid in the oral absorption of the drug, reducing the effects of food [23-25].

This clinical trial was conducted to compare the bioequivalence between a test and reference drug with the same dosage and formulation.

METHODS

Subjects

This study targeted healthy adult male subjects aged 19 to 55 years with a body weight of 50 kg or more and a body mass index (BMI) between 18.0 and 30.0 kg/m^2. Subjects underwent a medical history assessment, physical examinations, clinical laboratory tests, 12-lead electrocardiography, a medication history assessment, a vital sign assessment, and other evaluations to determine eligibility for participation based on the inclusion/exclusion criteria.

This study was conducted at the Clinical Trial Center of Chungbuk National University Hospital in accordance with the protocol approved by the Ministry of Food and Drug Safety and the Institutional Review Board (IRB) of Chungbuk National University Hospital (IRB No. 2022-04-030). Additionally, this study adhered to the principles of the Helsinki Declaration, Korean Good Clinical Practice, and applicable laws and regulations. Prior to performing any study-related procedures, the subjects provided written informed consent during the screening period (ClinicalTrials.gov identifier: NCT06147908).

Study design

The study was a randomized, open-label, two-way, single-dose oral crossover trial in healthy subjects (**Fig. 1**).

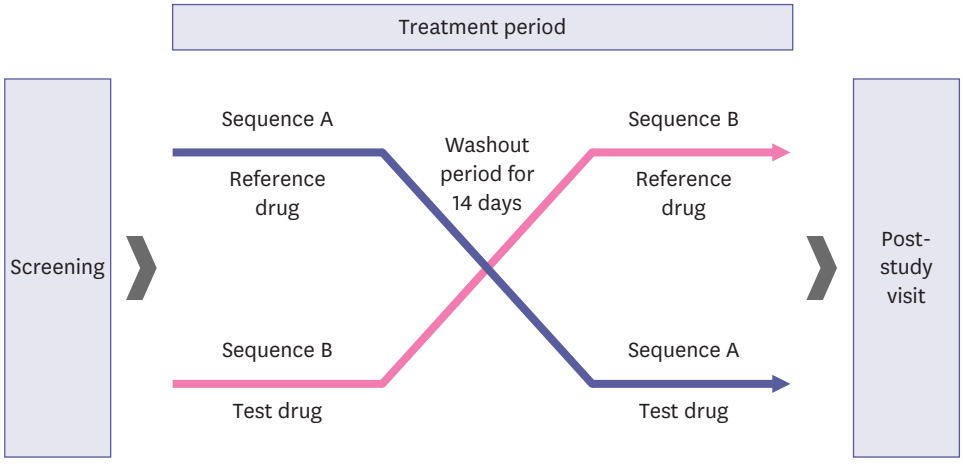

Figure 1. Study design.

https://doi.org/10.12793/tcp.2024.32.e6

Subjects were admitted to the clinical trial center on day -1 and randomly assigned in 1:1 ratio to the two sequence arms (Sequence A: reference-test, Sequence B: test-reference). Fifty-four subjects were administered a single oral dose of either the reference or test investigational drug in a fasting state on day 1. Immediately thereafter, they were instructed to drink 10 mL of water twice, for a total of 20 mL of water consumed. This study utilized the Megace F suspension (Boryung Pharmaceuticals, Seoul, Korea) as the reference drug and the Daewon Megestrol ES suspension (Daewon Pharmaceutical, Seoul, Korea) as the test drug, both of which were administered at a dose of 625 mg/5 mL. Subjects were hospitalized until 24 hours postdose and then returned for outpatient visits until 120 hours postdose for pharmacokinetic blood sampling and safety testing. The washout period between each dose was two weeks.

PK evaluation

Blood samples for single-dose pharmacokinetic evaluation were obtained at predose, 10, 20, 30 and 45 minutes and 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 and 120 hours after administration. At each time point, approximately 6 mL of blood was collected into a K2 ethylene diamine tetraacetic acid tube and centrifuged at 4°C and 3,000 rpm for 10 minutes. The plasma was then aliquoted into polypropylene tubes and stored at approximately −80°C until analysis.

Plasma concentrations of megestrol acetate were determined using liquid chromatography (SHIMADZU LC-40, SCIEX, Mundelein, IL, USA) with tandem mass spectrometry (TQ5500+(2), SCIEX) in positive ion mode in accordance with the Ministry of Food and Drug Safety bioanalytical method validation guidelines.

The single-dose pharmacokinetic parameters of megestrol acetate were determined using a noncompartmental method with Phoenix WinNonlin® Version 8.3.5 (Certara, Princeton, NJ, USA). The pharmacokinetic parameters of megestrol acetate, such as the maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were directly derived from observed individual plasma concentration–time profiles. The terminal elimination half-life ($t_{1/2}$) was calculated as the natural logarithm of 2 divided by λ_z, the terminal elimination rate constant estimated during the linear decline phase of the natural logarithm-transformed individual plasma concentrations. The areas under the concentration–time curve from the point of administration to last time point of blood sampling (AUC_t) and the areas under the concentration–time curve from the point of administration to infinity (AUC_{inf}) were calculated using the linear trapezoidal method (linear trapezoidal linear interpolation). The apparent clearance and volume of distribution were calculated as the administered dose divided by the AUC.

Safety evaluation

Safety was evaluated based on AEs, physical examinations, 12-lead electrocardiograms, vital signs and clinical laboratory tests, including urinalysis. Documentation of all AEs involved recording signs and symptoms and coded with system organ classes and preferred terms according to the Medical Dictionary for Regulatory Activities version 25.0. AEs were graded as mild, moderate or severe, and their causality was assessed to determine if they were related to megestrol acetate. An adverse drug reaction (ADR) was defined as an AE that could not be ruled out as being unrelated to megestrol acetate.

https://doi.org/10.12793/tcp.2024.32.e6

Statistical analysis

Safety analysis were conducted on subjects who received at least one dose of the study drug, whereas pharmacokinetic analyses were performed on subjects who completed the entire study schedule.

For statistical analysis, SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA) was utilized. All descriptive statistics summarized continuous variables as the mean and standard deviation, and the categorical variables as the frequency and percentage. The bioavailability of megestrol acetate was assessed through the geometric mean ratios (GMRs) and the 2-sided 90% confidence intervals (CIs) of the PK parameters (log-transformed C_{max} and AUC_t) using Phoenix WinNonlin® Version 8.3.5 (Certara). According to the regulations, bioequivalence was established if the 90% CI of the GMR was between 80.00% and 125.00%. The incidence rates of AEs and ADRs were compared among the treatment groups using Fisher's exact test.

RESULTS

Demographics

Within a period of up to four weeks prior to the first dose administration, a total of eighty-five volunteers were screened, and demographic information for the fifty-four enrolled subjects in this study is presented in **Table 1**. Among the fifty-four enrolled subjects, twenty-seven were allocated to sequence group A (reference-test), and twenty-seven were allocated to sequence group B (test-reference). No statistically significant differences observed with in the sequence groups regarding demographic information (age, height, weight, BMI). Furthermore, none of the subjects had a history of clinically significant concurrent medication use or medical conditions prior to dosing. A total of fifty-two subjects completed the clinical trial.

Pharmacokinetics

The lower and upper limits of quantitation for megestrol acetate were 2 and 4000 ng/mL (coefficient of correlation (r) ≥ 0.9987), respectively, and the accuracy ranged from 99.4 to 106.6% (the coefficient of variation ranged from 1.7 to 3.6%) at concentrations of 6, 160, 1,600, and 3,200 ng/mL megestrol acetate. There were no samples that underwent reanalysis for exceeding the upper limit.

A graph of the mean concentration versus time after a single dose of 625 mg/5 mL megestrol acetate is shown in **Fig. 2**, which shows a similar time-concentration pattern for administration of the reference and test drugs. The pharmacokinetic parameters for both formulations of megestrol acetate are presented in **Table 2**. Both drugs were observed to have a T_{max} of 1.5 hours (median), with C_{max} and AUC_t (mean ± SD) values of 911.19 ± 274.20 ng/mL and 10,056.30 ± 3,163.78 h*ng/mL for the reference drug and 925.95 ± 283.41 ng/mL and 9,868.35 ± 3,674.01 h*ng/mL for the test drug, respectively. The GMR and 90% CI of the test

Table 1. Demographics of the subjects who enrolled in the study

Demographics	Sequence A (n = 27)	Sequence B (n = 27)	Total (n = 54)	*p*-value
Age (yr)	24.26 ± 3.38 (19.00–33.00)	23.52 ± 4.47 (19.00–41.00)	23.89 ± 3.94 (19.00–41.00)	0.1504*
Height (cm)	174.23 ± 4.52 (166.90–182.80)	173.43 ± 5.52 (163.50–182.10)	173.83 ± 5.01 (163.50–182.80)	0.5585†
Weight (kg)	70.93 ± 7.05 (53.50–85.60)	69.71 ± 8.12 (57.00–87.60)	70.32 ± 7.56 (53.50–87.60)	0.5590†
BMI (kg/m^2)	23.38 ± 2.26 (18.00–27.20)	23.17 ± 2.47 (18.50–29.30)	23.28 ± 2.35 (18.00–29.30)	0.7533†

Values are represented as the arithmetic mean ± standard deviation (range).
Sequence A = Reference-Test; Sequence B = Test-Reference, Reference = Megace F suspension; Test = Daewon Megestrol ES suspension.
*Wilcoxon's rank-sum test; †Independent t test.

https://doi.org/10.12793/tcp.2024.32.e6

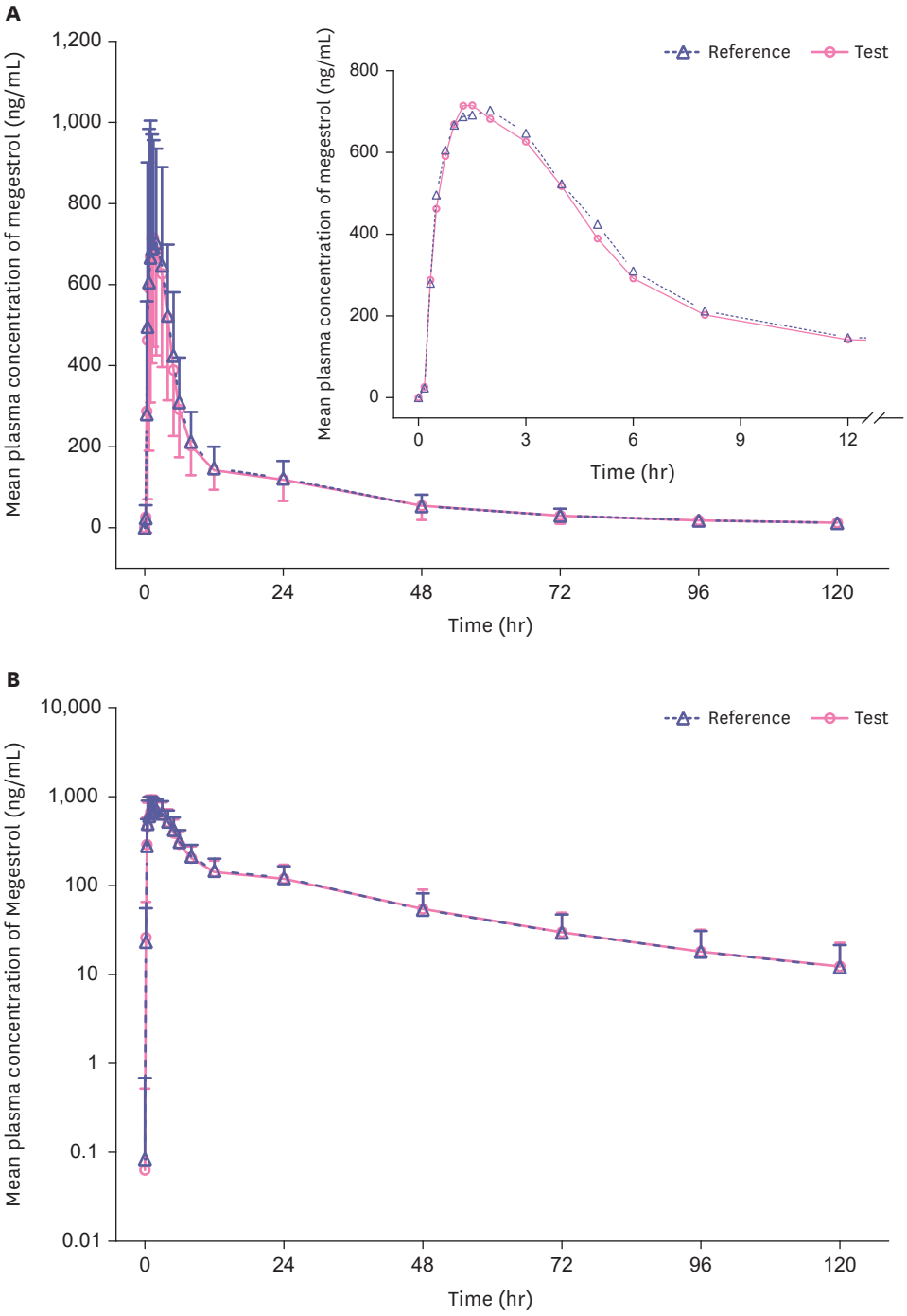

Figure 2. Mean (standard deviation) plasma concentration-time profiles of megestrol acetate after oral administration of a single dose. (A) Megestrol acetate (linear scale), inserted graph shown the megestrol acetate (linear scale) during initial 12 hours, (B) Megestrol acetate (semilog scale).

drug compared to the reference drug for C_{max} and AUC_t of megestrol acetate were calculated as 101.09% (93.85–108.90%) for C_{max} and 96.56% (91.60–101.78%) for AUC_t, respectively (**Table 3**).

https://doi.org/10.12793/tcp.2024.32.e6

Table 2. Summary of the PK parameters of plasma megestrol acetate after oral administration of a single dose

PK parameters (units)	Test (n = 52)	Reference (n = 52)
C_{max} (ng/mL)	925.95 ± 283.41 (30.61)	911.19 ± 274.20 (30.09)
AUC_t (hr·ng/mL)	9,868.35 ± 3,674.01 (37.23)	10,056.30 ± 3,163.78 (31.46)
AUC_{inf} (hr·ng/mL)	10,484.34 ± 4,196.91 (40.03)	10,750.65 ± 3,863.77 (35.94)
T_{max}* (hr)	1.50 [0.33–5.00]	1.50 [0.50–6.00]
$t_{1/2}$ (hr)	31.74 ± 9.70 (30.55)	34.52 ± 13.80 (39.97)

Values are represented as the arithmetic mean ± standard deviation (CV%).
PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_t, area under the plasma concentration-time curve from the point of administration to the last time point of blood sampling; AUC_{inf}, area under the plasma concentration-time curve from the point of administration to infinity; T_{max}, time to peak plasma concentration; $t_{1/2}$, terminal half-life.
*Median [minimum - maximum].

Table 3. Geometric mean ratio [90% CI] of C_{max} and AUC_t of megestrol

PK parameters (units)	Geometric mean ratio (Test/Reference)	
	Point estimate	90% CI
C_{max} (ng/mL)	101.09	93.85–108.90
AUC_t (hr·ng/mL)	96.56	91.60–101.78

CI, confidence interval; C_{max}, maximum plasma concentration; AUC_t, area under the plasma concentration-time curve from the point of administration to the last time point of blood sampling; PK, pharmacokinetic.

Table 4. Summary of adverse drug reactions by system organ class and preferred term

System organ class/ Preferred term	Test (n = 53)		Reference (n = 53)		*p*-value
	No. of subject (%)	No. of case	No. of subject (%)	No. of case	
Total	1 (1.89)	1	2 (3.77)	2	1.0000*
Gastrointestinal disorders					
Abdominal pain upper	1 (1.89)	1	0 (0.00)	0	
Diarrhea	0 (0.00)	0	1 (1.89)	1	
Nervous system disorders					
Headache	0 (0.00)	0	1 (1.89)	1	

*Fisher's exact test.

Safety

Treatment-emergent AEs were reported in 7 of the seven subjects who received at least one dose of megestrol acetate during the study. Five of the seven AEs occurred in the reference drug group, and two occurred in the test drug group. Of the 7 AEs, 3 were identified as ADRs (upper abdominal pain, diarrhea, headache) occurring in three subjects. However, these reactions were not statistically significant when comparing the incidence of AEs between the two products (**Table 4**). All ADRs were judged to be mild in severity, and subjects recovered without further action. No SAEs occurred. Two concomitant medications were reported in one subject receiving an investigational drug; the reported concomitant medication was administered to treat an AE not related to the investigational drug after all pharmacokinetic blood sampling had been completed. Otherwise, there were no clinically significant findings in 12-lead electrocardiograms or vital signs.

DISCUSSION

The aim of this study was to compare and evaluate the safety and pharmacokinetic characteristics of two megestrol acetate suspensions (625 mg/5 mL).

Consequently, considering the GMR and 90% Cis of the investigational drug compared to the control for C_{max} and AUC_t, both parameters met the bioequivalence criteria (80.00 to 125.00%). The lack of pharmacokinetic differences between the two formulations suggests

https://doi.org/10.12793/tcp.2024.32.e6

equivalent efficacy and clinical interchangeability. Moreover, the ADRs that were observed in this clinical trial were abdominal pain, diarrhea, and headache, all of which are known adverse reactions according to previous studies of megestrol acetate. Throughout the study, all adverse reactions were mild and resolved without intervention, and no serious or unexpected adverse reactions were observed. There were no significant differences observed between the two formulations regarding safety. Therefore, the bioequivalence of the investigational drug was confirmed.

The investigational drug in this study was a megestrol acetate nanomolecular suspension. A suspension is a dispersed system in which insoluble solid particles are dispersed in a liquid medium, and nanosuspensions have been defined as drugs with particle sizes ranging from 10–1,000 nm [26]. Nanosuspensions can enhance the absorption rate of drugs, thereby enabling a reduction in drug dosage [25,26]. When treating cancer or acquired immune deficiency syndrome (AIDS) patients for cachexia with megestrol acetate tablets, a maximum dose of 800 mg/day is administered [20]. In contrast, when utilizing the nanosuspension formulation for the same indication, a daily dose of 625 mg/5 mL is administered [19].

Furthermore, nanosuspensions have the following advantages: First, patients who are unconscious or critically ill generally cannot take tablet medications orally [27]. The liquid formulation of the nanosuspension is convenient for patients who have difficulty taking tablets, such as those with missing teeth or swallowing disorders, and can be administered via a gastrostomy tube [28,29]. Nanosuspensions can also be formulated for various routes of administration, including oral, nonoral (e.g., pulmonary, topical), allowing for versatile delivery options. Additionally, solidification enables the conversion of various formulations, such as powders, tablets or capsules [26]. Third, nanosuspensions enhance the stability and solubility, thereby reducing variability in bioavailability due to dietary influences [26,30]. Thus, the use of nanosuspensions with increased solubility and reduced dietary impact in this study is advantageous for real clinical applications.

Furthermore, the investigational drug utilized in this study was a viscous nanosuspension. Such formulations pose challenges in precise dosing and may result in interindividual variances in drug absorption times due to viscosity. To address these issues, previous studies have administered the drug with water [23]. In this study, the subjects were instructed to ingest the investigational drug with water. Furthermore, residual drug in the container was minimized by rinsing with 20 mL of water (twice, 10 mL each). Therefore, in comparative pharmacokinetic studies of suspension formulations, careful attention should be given to the method of administration to ensure precise dosing.

There were several limitations to this study. The results were based on single-dose administration in fasting healthy adult males, not in patients with the indicated conditions. In real-world application to patients, administration is possible for patients of both sexes and is expected to occur over a prolonged period rather than as a single dose considering the pathophysiology of cachexia. Furthermore, while actual patients may be on various concomitant medications, this study was conducted under restricted concomitant medication conditions, thus not reflecting potential drug interactions. Megestrol is a medication used for appetite stimulation and weight gain; however, due to the comparative pharmacokinetic evaluation nature of this study, efficacy assessment was not possible because single-dose administration and postdosing weight measurements were not conducted.

In conclusion, the pharmacokinetic profiles both formulations of megestrol acetate (625 mg) were comparable and well tolerated in healthy subjects. The test formulation of megestrol acetate met the regulatory criteria for bioequivalence, indicating its suitability for clinical use.

ACKNOWLEDGMENTS

The authors certify that this manuscript represents valid work and that neither this manuscript nor 1 with substantially similar content has been published or is being considered for publication elsewhere. The biospecimens and data used for this study were provided by the Biobank of Korea-Chungbuk National University Hospital (CBNUH), a member of the Korea Biobank Network. All materials derived from the National Biobank of Korea-CBNUH were obtained (with informed consent) under Institutional Review Board (IRB)-approved protocols.

REFERENCES

1. Setiawan T, Sari IN, Wijaya YT, Julianto NM, Muhammad JA, Lee H, et al. Cancer cachexia: molecular mechanisms and treatment strategies. J Hematol Oncol 2023;16:54-54. PUBMED | CROSSREF
2. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab 2012;16:153-166. PUBMED | CROSSREF
3. Takahashi S, Matsumoto K, Ohba K, Nakano Y, Miyazawa Y, Kawaguchi T. The incidence and management of cancer-related anorexia during treatment with vascular endothelial growth factor receptor-tyrosine kinase inhibitors. Cancer Manag Res 2023;15:1033-1046. PUBMED | CROSSREF
4. Mariean CR, Tiucă OM, Mariean A, Cotoi OS. Cancer cachexia: new insights and future directions. Cancers (Basel) 2023;15:5590. PUBMED | CROSSREF
5. Bruera E. Clinical management of anorexia and cachexia in patients with advanced cancer. Oncology 1992;49 Suppl 2:35-42. PUBMED | CROSSREF
6. Chang VT, Xia Q, Kasimis B. The functional assessment of anorexia/cachexia therapy (FAACT) appetite scale in veteran cancer patients. J Support Oncol 2005;3:377-382. PUBMED
7. Amano K, Baracos VE, Morita T, Miura T, Mori N, Tatara R, et al. The impact of cachexia on dietary intakes, symptoms, and quality of life in advanced cancer. JCSM Rapid Commun 2022;5:162-170. CROSSREF
8. Tisdale MJ. Cachexia in cancer patients. Nat Rev Cancer 2002;2:862-871. PUBMED | CROSSREF
9. Yeh SS, Lovitt S, Schuster MW. Usage of megestrol acetate in the treatment of anorexia-cachexia syndrome in the elderly. J Nutr Health Aging 2009;13:448-454. PUBMED | CROSSREF
10. Evans WJ. Editorial: megestrol acetate use for weight gain should be carefully considered. J Clin Endocrinol Metab 2007;92:420-421. PUBMED | CROSSREF
11. Tomíska M, Tomisková M, Salajka F, Adam Z, Vorlícek J. Palliative treatment of cancer anorexia with oral suspension of megestrol acetate. Neoplasma 2003;50:227-233. PUBMED
12. Yeh SS, Schuster MW. Megestrol acetate in cachexia and anorexia. Int J Nanomedicine 2006;1:411-416. PUBMED | CROSSREF
13. Morley JE, Farr SA. Cachexia and neuropeptide Y. Nutrition 2008;24:815-819. PUBMED | CROSSREF
14. Costa AM, Spence KT, Plata-Salamán CR, ffrench-Mullen JM. Residual Ca2+ channel current modulation by megestrol acetate via a G-protein alpha s-subunit in rat hypothalamic neurones. J Physiol 1995;487:291-303. PUBMED | CROSSREF
15. Argilés JM, Anguera A, Stemmler B. A new look at an old drug for the treatment of cancer cachexia: megestrol acetate. Clin Nutr 2013;32:319-324. PUBMED | CROSSREF
16. Chidakel AR, Zweig SB, Schlosser JR, Homel P, Schappert JW, Fleckman AM. High prevalence of adrenal suppression during acute illness in hospitalized patients receiving megestrol acetate. J Endocrinol Invest 2006;29:136-140. PUBMED | CROSSREF
17. Tuca A, Jimenez-Fonseca P, Gascón P. Clinical evaluation and optimal management of cancer cachexia. Crit Rev Oncol Hematol 2013;88:625-636. PUBMED | CROSSREF

18. Boccanfuso JA, Hutton M, McAllister B. The effects of megestrol acetate on nutritional parameters in a dialysis population. J Ren Nutr 2000;10:36-43. PUBMED | CROSSREF
19. Food and Drug Administration (FDA). MEGACE® ES (megestrol acetate) oral suspension full prescribing information. White Oak (MD): FDA; 2018.
20. Halder S, Suzuki H, Seto Y, Sato H, Onoue S. Megestrol acetate-loaded self-micellizing solid dispersion system for improved oral absorption and reduced food effect. J Drug Deliv Sci Technol 2019;49:586-593. CROSSREF
21. Li Y, Song CK, Kim MK, Lim H, Shen Q, Lee DH, et al. Nanomemulsion of megestrol acetate for improved oral bioavailability and reduced food effect. Arch Pharm Res 2015;38:1850-1856. PUBMED | CROSSREF
22. Guk J, Son H, Chae DW, Park K. Quantitative assessment of food effect on the pharmacokinetics of nanocrystallized megestrol acetate. Basic Clin Pharmacol Toxicol 2017;120:270-277. PUBMED | CROSSREF
23. Jang K, Yoon S, Kim SE, Cho JY, Yoon SH, Lim KS, et al. Novel nanocrystal formulation of megestrol acetate has improved bioavailability compared with the conventional micronized formulation in the fasting state. Drug Des Devel Ther 2014;8:851-858. PUBMED | CROSSREF
24. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res 2020;24:3. PUBMED | CROSSREF
25. Bandarkar F, Masocha W, Nada A. Pharmacodynamic/pharmacokinetic correlation of optimized ibuprofen nanosuspensions having enhanced anti-inflammatory and antinociceptive activity. J Pharm Pharmacol 2022;74:387-396. PUBMED | CROSSREF
26. Yadollahi R, Vasilev K, Simovic S. Nanosuspension technologies for delivery of poorly soluble drugs. J Nanomater 2015;2015:1-13. CROSSREF
27. Harnett A, Byrne S, O'Connor J, Lyons D, Sahm LJ. Adult patients with difficulty swallowing oral dosage forms: a systematic review of the quantitative literature. Pharmacy (Basel) 2023;11:167. PUBMED | CROSSREF
28. Klang MG. Developing guidance for feeding tube administration of oral medications. JPEN J Parenter Enteral Nutr 2023;47:519-540. PUBMED | CROSSREF
29. Arora K, Vats V, Verma PK. A review on pharmaceutical suspension and its advancement. Ann Clin Case Rep 2022;7:2321.
30. Pınar SG, Oktay AN, Karaküçük AE, Çelebi N. Formulation strategies of nanosuspensions for various administration routes. Pharmaceutics 2023;15:1520. PUBMED | CROSSREF