Venous Thromboembolism and Weight Changes in Veteran Patients Using Megestrol Acetate as an Appetite Stimulant

Brandon LaMarr, PharmD, BCPS; and Russell Crawford, BPharm, BCOP

These study investigators sought to answer the question whether patients treated with megestrol acetate at a local VA health care system have a greater incidence of venous thromboembolism than that seen in the general population.

Anorexia and cachexia are associated with a variety of diseases, including cancer, acquired immunodeficiency syndrome (AIDS), congestive heart failure, chronic obstructive pulmonary disease, liver disease, end-stage renal disease, and endocrine abnormalities such as hyperthyroidism, adrenal insufficiency, and diabetes mellitus.[1] Anorexia has also been shown to be associated with the aging process.[2] Loss of appetite, lean muscle mass, and adipose tissue is associated with physical weakness as well as decreases in quality of life, sense of well-being, and level of functionality.[3,4] In addition to health detriments, the visual and social effects of physical wasting can be emotionally distressing to both patients and their family or caregivers.[5]

Increased metabolic needs and decreased appetite play important roles in disease-related wasting.[6] Changing social conditions, psychiatric problems, and use of medications may also contribute to changes in appetite, weight, and nutritional status. While anorexia and cachexia may occur in any patient, they are commonly seen in patients with cancer and AIDS. Cachexia in patients with cancer can be due to decreased caloric intake (possibly due to causes such as gastrointestinal tumors or chemotherapy-induced nausea and vomiting), an increased metabolic state, or the production of proinflammatory mediators such as interleukin-1, interleukin-6, and tumor necrosis factor-α. AIDS-related cachexia can be caused by a hypermetabolic state, secondary infection, medications, or gastrointestinal disturbances.[7]

Many randomized trials have determined the safety, efficacy, and ideal dose of megestrol acetate (MA) when used for appetite stimulation. These studies have often been small and have produced inconclusive results due to the short life expectancies of the study population, as well as the many confounding variables that exist among a generally very sick and heterogeneous patient population. Uncertainty regarding the optimal dosing and possible thrombogenic effects of MA remain.

The average annual incidence of venous thromboembolism (VTE) in the general population is about 0.1%.[8] Patients with cancer are at a 4 to 7 times greater risk of VTE than patients without cancer, mainly due to thrombogenic processes associated with the disease and its treatments.[9-11] The overall prevalence of VTE in patients taking MA is unclear, as studies have focused on single diseases such as cancer or AIDS. The MA prescribing information cautions against use in patients with a history of venous thromboembolic disease, but the prevalence and degree of risk are not stated.[12] For this reason, many of the studies evaluating the efficacy of MA have excluded patients with a history of VTE.

While the risk for VTE in patients with cancer is firmly established, the risk in patients who use MA is less clear. Patients with cancer who use MA potentially share many of the same thrombogenic mechanisms, including increased levels of clotting factors as well as decreased levels of anticoagulant proteins. Oberhoff and colleagues evaluated the effects of MA on coagulation in patients with gynecologic and breast cancers and found no evidence of thrombogenic potential.[13] Contrasting this, a study by Kropsky and colleagues found a 6-fold increased incidence of deep vein thrombosis (DVT) in elderly patients who live in nursing homes and take MA.[14]

The purpose of this study was to evaluate the safety and efficacy of MA for patients in the Southern Arizona

Dr. LaMarr is a clinical inpatient pharmacist at the Southern Arizona VA Health Care System in Tucson, Arizona. **Mr. Crawford** is a clinical pharmacist in hemotology/oncology and PGY2 Oncology Residency Program Director also at the Southern Arizona VA Health Care System in Tucson, Arizona.

VA Health Care System (SAVAHCS). It was anticipated that data regarding the safety and efficacy of MA for appetite stimulation generated by this chart review would serve to optimize future use of MA in this veteran population. The primary objective of the study was to determine the incidence of VTE in all patients using MA for appetite stimulation. Secondary outcomes included evaluations of (1) the effects of MA on weight, including rate of response to treatment (defined by the percentage of patients maintaining or gaining weight relative to baseline) and average change in weight; (2) the effects of MA on nutritional status, including changes in prealbumin and albumin levels while on treatment; (3) effects of MA dose (low, medium, or high) on efficacy (change in weight, rate of response) in all patients and among subgroups by diagnosis (cancer, human immunodeficiency virus [HIV]-positive, and noncancer/non-HIV-positive); (4) comparison of VTE rates in all patients and among subgroups by diagnosis in patients treated with MA; and (5) effects of MA dose on VTE incidence among patients with varying doses.

It was hypothesized that patients treated with MA would have an incidence of VTE greater than the observed rate in the general population of 0.1% per year. It was also hypothesized that patients with cancer who used MA would exhibit a higher rate of VTE than those patients without cancer.

METHODS

Prior to initiating this study, full institutional review board approval was requested and obtained. A retrospective chart review was performed for patients using MA as an appetite stimulant. Electronic medication records were searched for prescriptions dispensed at SAVAHCS for MA that also contained the term *appetite* in the directions to identify patients for whom MA was dispensed and refilled at least once. This method served to ensure that an adequate trial period of at least 30 days on MA was given. Searching retrospectively beginning September 1, 2008, a chart review was performed on the most recent 100 patients treated with MA identified in the prescription record search who met the previously mentioned criteria. The reviews stopped once 100 patients were identified. Patients aged < 20 years or aged > 89 years were excluded. Patients who, on further review, were not using MA for appetite stimulation, were also excluded.

In order to define the safest and most effective doses of MA, the effects of low, medium, and high doses of MA on VTE incidence and weight maintenance were analyzed. Doses < 100 mg are rarely studied, perhaps because of their accepted lack of efficacy.[15] For this reason, doses <100 mg were categorized as *low*. Since product labeling states that doses > 400 mg have been shown to be clinically effective, this dosage range was categorized as *high*.[12] By default, the range of doses > 100 mg and < 400 mg was categorized as *medium*.

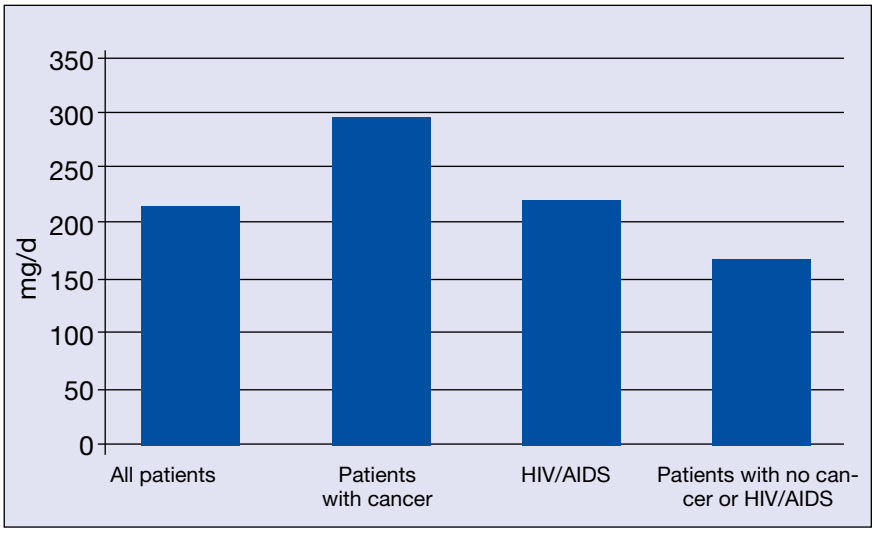

Figure 1. Average daily MA dose by diagnosis.
MA = megestrol acetate.

STATISTICS

Statistical analyses on the secondary endpoints assessed the effects of dose on efficacy and VTE within diagnosis categories as well as on comparisons of VTE incidence among diagnoses. The chi-squared test was used for the efficacy analyses and compared the percentages of patients who maintained or gained weight at different dose levels with the different diagnoses. A one-way analysis of variance was performed comparing the average changes in weight at different dose levels with the different diagnoses as well as the incidences of VTE among the different diagnoses.

RESULTS

A total of 145 charts were reviewed with 45 charts excluded. Reasons for exclusion included MA use for hot flashes (37 charts), aged > 89 years (4 charts), gynecologic issues (3 charts), and lack of any data relating to studied endpoints (1 chart). Nine charts

Table 1. Demographic data	
Treatment courses (N)	111
Average age	70 years
Male	96%
Patients with cancer	37%
Patients with HIV/AIDS	4%
Patients with no cancer or HIV/AIDS	59%

Table 2. Incidence of VTE		
Subgroup	VTEs (N)	Incidence
All patients	3	2.7%
Patients with cancer	3	7.3%
Patients on high-dose MA	2	5.9%
Patients on low-dose MA	1	1.7%

MA = megestrol acetate; VTE = venous thromboembolism.

Table 3. Rates of response to treatment				
	All patients	Patients with cancer	Patients with HIV/AIDS	Patients with no cancer or HIV/AIDS
Patients on high-dose MA	73%	71%	100%	73%
Patients on medium-dose MA	59%	50%	N/A	64%
Patients on low-dose MA	65%	58%	100%	66%

MA = megestrol acetate.

documented more than 1 treatment course with MA in the same patient with 2 charts documenting 3 separate MA courses. Each course was analyzed independently. In total, 111 treatment courses with MA for appetite stimulation were included in the analysis.

Demographic data for the study population is presented in Table 1. The distribution of patients by MA dosing category was as follows: 34 patients (31%) received high doses, 19 patients (17%) received medium doses, and 58 patients (52%) received low doses.

In all patients, the average daily dose of MA was 216 mg/d. MA doses were in the range of 20 mg/d to 800 mg/d. Patients with cancer received the highest average MA daily doses; those without either cancer or HIV/AIDS received the lowest average MA doses (Figure 1).

Out of 111 total treatment courses with MA, 3 VTEs occurred (Table 2). This resulted in a total overall incidence of VTE of 2.7%. All VTEs occurred in patients with cancer leading to an incidence of VTE of 7.3% in this subgroup. VTE occurred in 2 patients on high-dose MA and 1 patient on low-dose MA resulting in an incidence of 5.9% for the high-dose group and 1.7% for the low-dose group. No VTE occurred in patients with a prior history of VTE.

Ninety-nine patients had >1 weight recorded while on MA. Sixty-six (67%) of these patients responded to treatment. The average change in weight was an increase of 1.3 kg (range: - 14.0 kg to + 18.0 kg). When patients who continued to lose weight while on MA were excluded, the average change in weight was an increase of 4.0 kg.

While not statistically significant, high-MA doses resulted in higher rates of response and more positive weight changes than did lower doses in all subgroups (Tables 3 and 4). When those patients who lost weight while on MA were excluded from analysis, these effects became even more dramatic (Table 5).

Albumin and prealbumin levels were not frequently measured in this group. More than 1 albumin level was recorded in 37 patients while on MA. Prealbumin levels were recorded more than 1 time during MA treatment in 16 patients. There was insufficient data to perform analyses on these endpoints.

DISCUSSION

The rate of VTE observed in the SAVAHCS population using MA for appetite stimulation was higher than that of the population in general. Since all VTE events occurred in patients with cancer, it is not possible to compare the incidence of VTE with different diagnoses. The observed rate of VTE in patients with cancer using MA was also high when compared with literature estimates.

Table 4. Change in weight (kg)				
	All patients[a]	Patients with cancer[b]	Patients with HIV/AIDS	Patients with no cancer or HIV/AIDS[c]
Patients on high-dose MA (≥ 400 mg/d)	2.1 (n = 30)	0.76 (n = 17)	4.0 (n = 2)	3.9 (n = 11)
Patients on medium-dose MA (100-399 mg/d)	1.5 (n = 17)	-0.5 (n = 6)	N/A	2.6 (n = 11)
Patients on low-dose MA (< 100 mg/d)	0.7 (n = 52)	-1.66 (n = 12)	0.5 (n = 2)	1.5 (n = 38)

[a]*P* = .48; [b]*P* = .60; [c]*P* = .35.
MA = megestrol acetate.

Table 5. Change in weight (kg) in treatment responders				
	All patients[a]	Patients with cancer[b]	Patients with HIV/AIDS	Patients with no cancer or HIV/AIDS[c]
Patients on high-dose MA	5.4	5.1	4	6.1
Patients on medium-dose MA	5.0	3.0	N/A	5.9
Patients on low-dose MA	2.9	1.9	0.5	3.4

[a]*P* = .02; [b]*P* = .05; [c]*P* = .12.
MA = megestrol acetate.

While the design of this study did not allow for differentiation between the thrombogenic effects of MA and those of cancer and its treatments, the very high rate of VTE in these patients suggests that treatment with MA may be contributory.

The incidence of VTE in patients taking high-dose MA was nearly 3 times higher than that of patients taking low doses. This may be due to greater thrombogenic potential in patients taking high-dose MA. An alternative explanation for this result is that it echoes the higher VTE rates in cancer patients, since patients with cancer represented the group using the highest doses of MA.

The results of this study suggest that higher doses of MA were more effective. This observation is supported by previous studies. Von Roenn and colleagues performed a double-blind, randomized, placebo-controlled trial assessing the safety and efficacy of MA in patients with AIDS and cachexia.[16] The study enrolled 271 patients and assessed weight gain, body composition, caloric intake, sense of well-being, appetite, and adverse effects (AEs) for placebo and MA doses of 100 mg, 400 mg, and 800 mg, respectively. MA use increased patient weight in a dose-dependent manner ($P < .001$). Patients in the 800-mg group had significantly ($P < .001$) greater final weight gain compared with baseline than did patients in the placebo group. Lean body mass also increased in a dose-dependent manner. However, differences in lean body mass were only statistically significant ($P < .001$) between the placebo and 800-mg groups. A statistically significant ($P < .001$) trend was observed correlating increased patient well-being scores with increased MA doses. Patients treated with 800 mg of MA also had significantly ($P = .001$) greater caloric intake than those treated with placebo. No statistically significant differences were found among the 4 groups in terms of AEs; 1 patient experienced DVT.

In 1999, Parnes and colleagues performed a randomized dose-finding study for MA in cancer patients with cachexia.[17] A total of 381 patients receiving MA doses of 125 mg, 625 mg, or 1,250 mg corresponding to low-, medium-, and high-dose groups, respectively, were followed. The study showed similar effects between the medium- and high-dose groups throughout the study. Patients in the medium- and high-dose groups were not significantly more likely to have a higher maximum percentage weight gain, but were statistically less likely to lose weight. The medium- and high-dose groups were statistically more likely to cause edema when compared with the low-dose group. VTE occurred in 9 patients with no differences between the 3 groups.

Maltoni and colleagues performed a meta-analysis evaluating the efficacy of high-dose progestins (MA and medroxyprogesterone acetate)

in cancer patients with anorexia-cachexia.[18] Fifteen studies qualified for analysis, which included 2,102 patients. Analysis of weight gain included 11 of the 15 studies and showed that patients on a high-dose progestin treatment were more than twice as likely to gain weight as were those patients on placebo (OR = 2.66; 95% CI, 1.80%-3.92%).

When analysis was performed on just the patients who responded to MA, significant (P = .02) positive trends of weight gain were observed. These results support previously published studies that showed an increasing dose-response relationship in patients treated with MA. However, there was also a large portion of the study sample that did not respond to MA for unknown reasons. Identification of factors that lead to response to treatment with medium- or high-dose MA for appetite stimulation is a potential area of further research. Until these factors are known, it may be prudent to try alternative appetite stimulants in patients not exhibiting a response to treatment with MA after receiving an adequate trial.

This study was limited in that its retrospective nature did not permit conclusions to be attributed to direct causes and effects. Additionally, in order to allow an adequate trial of MA, patient selection may have created a preference for patients in whom MA was more effective thereby introducing a sampling bias. The study population consisted mostly of elderly males, which limited the generalizability of the results. The study also attempted to compare safety and efficacy of MA between patient populations with different disease processes (eg, cancer vs AIDS), which created a potentially heterogeneous population in terms of disease. While the study was designed to analyze different disease populations independently, overall results must be understood in the proper context. Additionally, the design of this study did not allow for differentiation between the thrombogenic effects of cancer and its treatments and any potential thrombogenic effects of MA. The study also did not allow for differentiation between the type of weight that was gained (ie, lean body mass, adipose tissue, or edema).

In conclusion, higher doses of MA seem to generate more weight gain and higher rates of response to treatment. The VTE rates in patients with cancer using MA as an appetite stimulant were considerable. While MA seems to be effective for appetite stimulation, a thorough risk assessment for VTE should be performed in patients with cancer prior to initiating treatment with MA for appetite stimulation.

Acknowledgment

This manuscript was prepared and research was conducted with resources and the use of facilities at the Southern Arizona VA Health Care System in Tucson, Arizona.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Quadrant HealthCom Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

REFERENCES

1. Thomas DR. Anorexia: Aetiology, epidemiology, and management in older people. *Drugs Aging.* 2009;26(7):557-570.
2. Serra Prat M, Fernández X, Ribó L, Palomera E, Papiol M, Serra P. Loss of appetite in elderly people in the community and its relationship with functional capacity. *Med Clin (Barc).* 2008;130(14):531-533.
3. Keys A, Brozek J, Henschel A, Mickelesen O, Taylor HL. *The Biology of Human Starvation (Volumes 1 and 2).* Minneapolis, MN: University of Minnesota Press; 1950.
4. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer.* 1998;34(4):503-509.
5. Poole K, Froggatt K. Loss of weight and loss of appetite in advanced cancer: A problem for the patient, the carer, or the health professional? *Palliat Med.* 2002;16(6):499-506.
6. Argilés JM, Alvarez B, López-Soriano FJ. The metabolic basis of cancer cachexia. *Med Res Rev.* 1997;17(5):477-498.
7. Grunfeld C. What causes wasting in AIDS? *N Engl J Med.* 1995;333(2):123-124.
8. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol.* 2008;28(3):370-372.
9. Blom JW, Vanderschoot JP, Oostindiër MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: Results of a record linkage study. *J Thromb Haemost.* 2006;4(3):529-535.
10. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293(6):715-722.
11. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. *Arch Intern Med.* 2000;160(6):809-815.
12. Megace [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2012.
13. Oberhoff C, Hoffmann O, Winkler UH, Schindler AE. Hemostatic effects of high-dose megestrol acetate therapy in patients with advanced gynecological cancer. *Gynecol Endocrinol.* 2001;15(5):341-348.
14. Kropsky B, Shi Y, Cherniack EP. Incidence of deep-venous thrombosis in nursing home residents using megestrol acetate. *J Am Med Dir Assoc.* 2003;4(5):255-256.
15. Berenstein G, Ortiz Z. Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev.* 2005;(2):CD004310.
16. Von Roenn JH, Armstrong D, Kotler DP, et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med.* 1994;121(6):393-399.
17. Parnes HL, Conaway M, Aisner J, et al. Megestrol acetate for the treatment of cachexia in patients with advanced lung or colorectal cancers. *Cancer Ther.* 1999;2:75-82.
18. Maltoni M, Nanni O, Scarpi E, Rossi D, Serra P, Amadori D. High-dose progestins for the treatment of cancer anorexia-cachexia syndrome: A systematic review of randomised clinical trials. *Ann Oncol.* 2001;12(3):289-300.