The Science of Megestrol Acetate Delivery
Potential to Improve Outcomes in Cachexia

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Abstract

Cachexia, usually defined as the loss of >5% of an individual’s baseline bodyweight over 2–6 months, occurs with a number of diseases that includes not only AIDS and advanced cancer but also chronic heart failure, rheumatoid arthritis, chronic obstructive pulmonary disease, Crohn disease, and renal failure. Anorexia is considered a key component of the anorexia-cachexia syndrome. Progestogens, particularly megestrol acetate, are commonly used to treat anorexia-cachexia. The mechanism of action of megestrol is believed to involve stimulation of appetite by both direct and indirect pathways and antagonism of the metabolic effects of the principal catabolic cytokines. Because the bioavailability of megestrol acetate directly affects its efficacy and safety, the formulation was refined to enhance its pharmacokinetics.

Such efforts yielded megestrol acetate in a tablet form, followed by a concentrated oral suspension form, and an oral suspension form developed using nanocrystal technology. Nanocrystal technology was designed specifically to optimize drug delivery and enhance the bioavailability of drugs that have poor solubility in water. Megestrol acetate nanocrystal oral suspension is currently under review by the US FDA for the treatment of cachexia in patients with AIDS. Preclinical pharmacokinetic data suggest that the new megestrol acetate formulation has the potential to significantly shorten the time to clinical response and thus may improve outcomes in patients with anorexia-cachexia.
Progestational agents are used to treat the anorexia-cachexia syndrome and sometimes as salvage agents to treat hormone-sensitive breast cancer and cancers of the endometrium, ovary, prostate, and other organs. Because oral progesterone is poorly absorbed, the agent is usually delivered intramuscularly in an oil carrier. Megestrol acetate (Megace® 1, Par Pharmaceutical, Inc., Spring Valley, NY, USA), a synthetic progestogen currently available in tablet and suspension form, has physiologic activity similar to the natural hormone. First used in humans in 1968, megestrol acetate tablets became commercially available in the US in 1971 for the treatment of endometrial carcinoma. Since that time, megestrol acetate has been used as a component of oral contraceptive pills and in the treatment of malignant and nonmalignant conditions such as melanoma; cancers of the ovary, breast, kidney, and prostate; benign prostatic hypertrophy; and endometrial hyperplasia.​

Cachexia is a condition of starvation characterized by depletion of muscle mass and, to a lesser extent, adipose tissue. Etymologically, cachexia is derived from ‘kakos’ and ‘hexis’—Greek words meaning ‘bad condition’. Although there are various definitions of cachexia in the medical literature, it commonly refers to an involuntary loss of approximately ≥5% of an individual’s baseline bodyweight over a defined period, usually 2–6 months. Cachexia develops in approximately one half of patients with cancer, and when it does, it can substantially shorten survival time. It is often associated with other debilitating symptoms such as chronic nausea, asthenia and weakness, autonomic failure, cognitive impairment, psychologic distress, and poor/unsatisfactory quality of life. Tissue changes associated with cachexia predispose patients to other comorbidities; for example, insufficient nutrition and loss of fatty hip pads in patients with cachexia increase the risk of hip

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1 The use of trade names is for product identification purposes only and does not imply endorsement.
fractures due to falls, and compromise patients’ ability to retain body heat.[4]

The word cachexia often evokes the image of a patient with advanced cancer or a disadvantaged individual with extensive protein-calorie malnutrition in a Third World nation; however, cachexia is common in developed countries and in patients with diseases other than cancer. Cachexia is a manifestation of AIDS, chronic heart failure, rheumatoid arthritis, chronic obstructive pulmonary disease, Crohn disease, chronic renal disease, and other chronic disorders.[2,5-10]

Anorexia is a key component of cachexia, and accumulating data suggest that the anorexia-cachexia syndrome is a cytokine-derived process manifested by loss of appetite and cytokine-driven hypercatabolism.[11] Megestrol acetate is commonly used to treat anorexia-cachexia and is the only FDA-approved treatment of cancer- and AIDS-related anorexia-cachexia syndrome. Other less common interventions include dronabinol, glucocorticoids, anabolic steroids, antiserotonergic drugs, and prokinetic medications.[12] Until recently, the mechanism of action of megestrol acetate in anorexia-cachexia was poorly understood, but it is now believed that megestrol acetate acts by stimulating appetite, by both direct and indirect mechanisms, and by antagonizing the metabolic effects of the main or most relevant catabolic cytokines (figure 1). Since the efficacy and safety of megestrol acetate is directly linked to the drug’s bioavailability,[13] this article reviews the science of megestrol acetate delivery and describes recent advances in the therapeutic area, focusing on the numerous metabolic effects of physiologic levels of progesterone and the specific effects of pharmacologic amounts of the hormone on processes associated with cachexia.

1. Progesterone Physiology

1.1 Secretion

Progesterone is a naturally occurring steroid hormone secreted by the ovary, testes, placenta, and adrenal gland.[14] In menstruating women, endogenous progesterone is secreted from the ovarian follicle just before ovulation and thereafter from the corpus luteum, with concentrations peaking approximately 7 days after ovulation. If a fertilized ovum does not implant, progesterone concentrations fall to basal levels immediately prior to menstruation.[14] Progesterone has a variety of physiologic activities in the reproductive tract, mammary gland, and central nervous system that are beyond the scope of this article.

2. Pharmacodynamics of Megestrol Acetate

2.1 General Characteristics

Megestrol acetate is a synthetic derivative of naturally occurring progesterone, chemically designated 17α-(acetox-y)-6-methylpregna-4,6-diene-3,20-dione (figure 2).[15] A white,
crystalline solid, megestrol acetate is delivered in both tablet and suspension form. The suspension is generally preferred over the tablet because it has significantly greater bioavailability as well as a lower cost, which tends to improve adherence.\cite{12}

Considerable evidence demonstrates the efficacy of megestrol acetate in the treatment of cachexia, the key characteristics of which are decreased appetite and low bodyweight.\cite{16,17} Megestrol acetate significantly increases both appetite and bodyweight. In doses ranging from 160 to 1600 mg/day, megestrol acetate has been shown to stimulate appetite, increase caloric intake, induce a sense of wellbeing, and produce weight gain (for details see review in Drugs\cite{18}). Weight gain occurs predominantly in the form of fat, which is potentially beneficial because the caloric stores in fatty tissue provide more kilocalories per gram than similar amounts of either protein or carbohydrate (i.e. 9.0 kcal vs 4.0 kcal and 4.0 kcal, respectively). Fat also helps stabilize core body temperatures and protects bony tissue; for example, the fat pads in the hips can help protect debilitated patients from hip fractures secondary to falls.

The benefits of megestrol acetate are dose related. Although dosages up to 1600 mg/day of megestrol acetate have been used, the drug’s effects on anorexia-cachexia tend to plateau at 800 mg/day.\cite{18} Thus, current recommendations are that treatment be titrated from 160 mg/day (40 mg four times daily) up to 800 mg/day according to clinical response.\cite{18-20}

### 2.2 Anticytokine Properties of Megestrol Acetate in Cachexia

The principal cytokines involved in cachexia include tumor necrosis factor (TNF-\(\alpha\)), interleukin (IL)-1, IL-6, and interferon (IFN)-\(\gamma\).\cite{12} TNF-\(\alpha\) is believed to work through numerous mechanisms to produce much of the severe cachexia that occurs in patients with chronic infections and cancer.\cite{21} At low concentrations (\(\leq 1\) U/mL) in C2C12 myotubes in cell culture, TNF-\(\alpha\) has been shown to exert a clearly catabolic effect, decreasing both total and myofibrillar protein content.\cite{22} Additional data suggest TNF-\(\alpha\) and other inflammatory cytokines contribute to muscle wasting through inhibition of myogenic differentiation via an NF-\(\kappa B\)-dependent pathway.\cite{23} TNF-\(\alpha\) also increases levels of mitochondrial uncoupling proteins, thus providing an energy sink,\cite{24,25} and it inhibits lipoprotein lipase activity and directly stimulates lipolysis.\cite{26}

Both IL-6 and IL-1 interact with other cytokines in the development of cachexia. In nude mice transplanted with human cachexia-inducing tumors, administration of a monoclonal antibody to IL-6 either essentially abrogated weight loss or resulted in a net weight gain.\cite{27} Binding of IL-1 to its receptors induces a variety of effects within the central nervous system and liver, including anorexia, acute-phase protein synthesis, and downregulation of hepatic production of albumin and other ‘housekeeping’ proteins. Some of the anorexigenic effects of IL-1 are due to the ability of the cytokine to stimulate leptin release, an effect that is blocked by administration of soluble IL-1 receptor.\cite{28}

Megestrol acetate appears to have direct anticytokine properties. The drug significantly antagonizes the effects of cytokines such as TNF\(\alpha\), IL-6, and IL-1. In patients with cancer, megestrol acetate has been shown to significantly reduce serum levels of IL-1\(\alpha\) and \(\beta\) and reduce IL-6 production in peripheral blood mononuclear cells.\cite{29,30} In humans, anti-IL-6 monoclonal antibody therapy has been shown to decrease the incidence of cancer-related anorexia/cachexia.\cite{31} Experimentally, in Naval Medical Research Institute (NMRI) mice, megestrol acetate has been shown to prevent the weight loss induced by TNF-\(\alpha\) and a cachexia-inducing tumor (MAC-16).\cite{32} In patients with advanced metastatic cancer, the drug has been shown to reverse anorexia and weight loss associated with IFN\(\alpha\)- and IL-2-based therapies.\cite{33}

### 2.3 Orexigenic Effects of Megestrol Acetate in Cachexia

The mechanisms of anorexia-cachexia are complex. The disorder appears to be associated with disruption in a number of neurohumoral orexigenic signaling pathways including hypothalamic neuropeptides and possibly melanocortin signaling. Physiologically, low plasma levels of leptin, a hormone of adipocyte origin associated with loss of body fat, increase orexigenic signals within the hypothalamus, decrease neurohormonal anorexigenic signals, and suppress energy expenditures.\cite{11,12,34-36} Cytokines may contribute to the anorexia component of the anorexia-cachexia syndrome by stimulating the expression and release of leptin or mimicking the hypothalamic effects of excess leptin on orexigenic neuropeptides such as neuropeptide Y, galanin, opioids, melanin-concentrating hormone, orexin, and agouti-related peptide.\cite{12} In addition, a disruption in energetics leads to an imbalance in energy intake and expenditure.

Megestrol acetate has significant orexigenic properties. Although the precise mechanism of action of megestrol acetate has not been fully elucidated, the drug is believed to alter levels of central neurotransmitters involved in appetite regulation (e.g. neuropeptide Y). This effect may be mediated by modulation of calcium channels in the satiety center of the ventromedial hypothalamus or directly through increased levels of neuropeptide Y. Neuropeptide Y is a 36-amino-acid peptide present in significant amounts in the hypothalamus and other areas of the brain.\cite{36} Acting directly, through a variety of interconnected pathways,
neuropeptide Y stimulates release of other orexigenic neuropeptides and may itself be intrinsically orexigenic.\(^{12}\)

Alterations in endogenous opioid-mediated receptors and response mechanisms have also been implicated in the pathogenesis of anorexia-cachexia.\(^{37}\) Megestrol acetate has been reported to stabilize declining cerebrospinal fluid levels of \(\beta\)-endorphin in the elderly, as well as to increase plasma and cerebrospinal fluid levels of the appetite-stimulatory neuropeptide Y.\(^{38,39}\) A direct sex hormone effect may also be operative in megestrol acetate-induced appetite stimulation. Whereas estrogen has been shown to decrease food intake in animal models, prostaglandin agents such as megestrol acetate antagonize this effect.\(^{40}\)

3. Tolerability of Megestrol Acetate

Megestrol acetate is generally well tolerated, with mild adverse effects that rarely lead to drug discontinuation.\(^{12}\) However, megestrol acetate can induce thromboembolic phenomena in patients with risk factors for venous thromboembolic disease.\(^{12}\) This appears to be partly a result of the drug’s ability to increase availability of thrombin receptors on smooth muscle cell membrane and thus markedly potentiate the procoagulant effects of thrombin.\(^{41}\) A hormone-induced decrease in tissue factor pathway inhibitor may also play a role in the development of venous thromboembolic disease.\(^{42}\) In addition, progestogens may increase venous distensibility and capacitance, resulting in reduced blood flow and stasis,\(^{43}\) and are likely to induce breakthrough endometrial bleeding.\(^{12}\)

Nonprogestational effects of megestrol acetate may account for sporadic case reports of Addison disease and exacerbation of glucose intolerance, which appear to be manifestations of the steroid’s intrinsic activity at corticosteroid and glucocorticoid hormone receptors. In this setting, Addison disease results from receptor ligation with either stimulation or blockade, and exacerbations of glucose intolerance is a function of the ability of megestrol acetate to stimulate gluconeogenesis or insulin secretion, or both. In a study of patients treated with megestrol acetate 160–800 mg/day, Loprinzi et al.\(^{44}\) found that the drug reversibly inhibited the hypothalamic-pituitary-adrenal axis and decreased serum cortisol concentrations. This effect is generally asymptomatic and patients do not acquire Cushingoid symptoms while receiving megestrol acetate. Furthermore, Addisonian crisis requiring abrupt discontinuation of therapy has not been reported despite the widespread use of megestrol acetate for decades. In addition to its glucocorticoid effect, megestrol acetate significantly suppresses plasma levels of estradiol. Wermers et al.\(^{45}\) have reported two cases of osteoporosis and multiple vertebral fractures associated with high-dose megestrol acetate therapy and speculate a causative relationship.

As previously noted, discontinuation of megestrol acetate is seldom required; however, a few precautions are indicated. For example, in patients with a history of thromboembolic disease or heart disease or a serious risk of fluid retention, megestrol acetate should be administered only after a thoughtful risk-benefit assessment.\(^{46}\)

4. Pharmacokinetics of Megestrol Acetate

4.1 General Characteristics

Megestrol acetate is absorbed rapidly from the gastrointestinal tract. However, studies in patients given the oral suspension demonstrate considerable variability in the rate and degree of absorption\(^{47}\) a factor that may be more significant in patients receiving the tablet formulation. In some patients, absorption is slower, with the more sustained plasma drug levels seen in a 1-compartment model. In others, absorption is rapid, with a 2-compartment-like elimination curve.\(^{43,47}\) Megestrol acetate is completely metabolized in the liver to free steroids and the metabolites are conjugated with glucuronic acid. Metabolites account for only 5–8% of the administered dose, which is considered negligible.\(^{15}\) The major route of drug elimination in humans is renal.\(^{15}\)

The effects of megestrol acetate on weight gain appear to be a function of at least four factors: (i) duration of administration; (ii) patient morbidities; (iii) concomitant medications; and (iv) pharmacokinetic effects, particularly those related to bioavailability. Studies in patients with cancer have shown that weight gain continues with longer duration of therapy.\(^{48,49}\) In patients with AIDS, absorption of megestrol acetate shows significant interpatient variability,\(^{47}\) possibly owing to comorbidities such as enteropathy, achlorhydria, and other disorders that alter gastrointestinal tract physiology. Concomitant medications affect megestrol acetate pharmacodynamics; for example, drugs such as azoles affect the rate or extent of megestrol acetate metabolism and thus alter efficacy. According to Graham et al.\(^{47}\) the area under the plasma concentration-time curve (AUC) of megestrol acetate was not directly correlated with weight gain; instead, a significant relationship was observed between weight gain and the percentage of the 24-hour administration interval that plasma megestrol acetate levels exceeded 300 ng/mL. That is, at least during the early stages of megestrol acetate therapy, weight gain requires plasma megestrol acetate concentrations >300 ng/mL for ≥40% of a 24-hour administration interval. Alterations in the formulation of megestrol acetate have produced three formulations of drug, a progres-
sion associated with increased bioavailability and thus improved efficacy in the treatment of anorexia-cachexia.

4.2 Megestrol Acetate Tablets

Megestrol acetate was formulated as a tablet requiring administration four times daily. In humans, the rate of excretion of radiolabeled megestrol acetate 4–90mg given in tablet form was 56.5–78.4% (mean 66.4%) in urine and 7.7–30.3% (mean 19.8%) in feces within 10 days of administration. The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). At least part of the radioactivity not found in the urine and feces may have been excreted by respiration as labeled carbon dioxide or held in fat storage.

Absorption of megestrol acetate 160 mg/day (40mg tablets given four times daily) varied among 23 healthy male volunteers. Peak plasma drug concentrations (Cmax) after the first 40mg dose ranged from 10 to 56 ng/mL (mean 27.6 ng/mL), and the times to Cmax (tmax) ranged from 1 to 3 hours (mean 2.2 hours). Plasma elimination half-life ranged from 13 to 104.9 hours (mean 34.2 hours). Steady-state plasma drug concentrations with a megestrol acetate 40mg four times daily regimen have not been established.

4.3 Megestrol Acetate Oral Suspension

To obviate the need for administration of multiple tablets, a megestrol acetate preparation was formulated as a concentrated oral suspension. Plasma steady-state pharmacokinetics of megestrol acetate oral suspension were evaluated in 10 adult male patients with AIDS and cachexia manifesting as involuntary weight loss >10% from baseline. Patients received oral megestrol acetate 800mg once daily for 21 days, and plasma concentrations were measured up to 48 hours after the last dose on day 21. Data analysis showed that mean ± 1 SD Cmax was 828 ± 513 ng/mL, and mean AUC0-24h was 11 250 ± 7305 ng·hr/mL, results similar to those reported in the megestrol acetate oral suspension (40 mg/mL) package insert (Cmax 753 ± 539 ng/mL and AUC 10 476 ± 7788 ng·hr/mL). The median tmax was 5 hours. All patients reported an increase in appetite, and 8 of 10 patients gained weight by the end of 3 weeks of treatment. These data underscore the clinical significance of the pharmacokinetic profile of megestrol acetate. The two patients who did not gain weight had the lowest Cmax, trough plasma concentration (Cmin), and AUC in the study. A statistically significant relationship was observed between weight gain and the percentage of the 24-hour administration interval that plasma concentrations of megestrol acetate exceeded 300 ng/mL. No correlation could be made between weight gain and AUC, and investigators suggested that early weight gain can be anticipated when plasma megestrol acetate concentrations exceed 300 ng/mL for at least 40% (10 hours) of a 24-hour administration interval.

In another study, megestrol acetate oral suspension 750mg was administered once daily for 14 days in 24 asymptomatic HIV-seropositive men. On pharmacokinetic evaluation, the mean Cmax was found to be 490 ± 238 ng/mL and the mean AUC was 6779 ± 3048 ng·hr/mL. The mean Cmin was 202 ± 101 ng/mL, with a median tmax of 3 hours. The mean percentage of fluctuation was 107% ± 40%.

The relative bioavailability of megestrol acetate 40mg tablets or oral suspension and the effect of food on the bioavailability of the oral megestrol acetate suspension have not been evaluated.

5. Megestrol Acetate Nanocrystal Oral Suspension

Megestrol acetate nanocrystal oral suspension was designed to optimize drug delivery and enhance the performance of drugs with poor water solubility. This megestrol acetate formulation is currently under review by the US FDA for the treatment of cachexia in patients with AIDS. Compared with micronized drug particles, nanocrystalline particles produced with nanocrystal technology have significantly increased surface area per unit mass. The manufacturing process uses a conventional high-energy medial milling technique to process a mixture of megestrol acetate, water, and stabilizers, creating a colloidal dispersion of megestrol acetate

Table I. Pharmacokinetic parameters of megestrol acetate in beagle dogs. Four megestrol acetate formulations were given by gavage tube to male beagle dogs (n = 3 per formulation) in fed or fasted state. All data are presented as mean (CV%).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nanocrystal formulation #1</th>
<th>Nanocrystal formulation #2</th>
<th>Oral suspension (BMS)</th>
<th>Oral suspension (Par)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fed</td>
<td>fasted</td>
<td>fed</td>
<td>fasted</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>3777.3</td>
<td>2209.7</td>
<td>2875.8</td>
<td>1563.0</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>1.67</td>
<td>0.8</td>
<td>3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>AUC0-24h (ng·hr/mL)</td>
<td>48 543.6</td>
<td>37 774.2</td>
<td>36 687.9</td>
<td>21 857.7</td>
</tr>
<tr>
<td>AUC0-24h (ng·hr/mL)</td>
<td>61 734.9</td>
<td>49 408.9</td>
<td>42 787.7</td>
<td>27 863.6</td>
</tr>
</tbody>
</table>

AUC = area under the plasma concentration-time curve; BMS = Bristol-Myers Squibb; Cmax = peak plasma concentration; CV = coefficient of variation; Par = Par Pharmaceutical, Inc.; tmax = median time to Cmax.
to obtain a mean particle size of <200nm. During milling, aggregation of the nanocrystalline particles is prevented by stabilizing the mixture with hydroxypropyl methylcellulose and docusate sodium. Since the absorption of megestrol acetate is dissolution-rate limited, the nanocrystalline particles increase the rate of absorption and decrease absorption variability when the drug is taken with food.

5.1 Preclinical Pharmacokinetics

A study was conducted in 12 male beagle dogs to determine the pharmacokinetic characteristics of megestrol acetate when administered as a 10 mg/kg suspension or colloidal dispersion by oral gavage.[51] The assay was calibrated over the range of 1–512 ng/mL. The following four formulations were evaluated at a dose of 10 mg/kg: (i) nanocrystal formulation #1; (ii) nanocrystal formulation #2; (iii) megestrol acetate oral suspension manufactured by Bristol-Myers Squibb; and (iv) megestrol acetate nanocrystal oral suspension manufactured by Par Pharmaceutical, Inc. Each product was available in a concentration of 40 mg/mL, so all study treatments were administered in equal volumes by oral gavage to a group of three dogs, first under fasted conditions and then under fed conditions, after a 14-day washout. Before administration on day 1, all dogs were fasted 12–16 hours. On day 14, the dogs were fed a high-fat meal approximately 1 hour before administration, and on days 1 and 14, blood samples were collected pre-administration and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours after administration to determine plasma megestrol acetate concentrations and calculate pharmacokinetic parameters.

In the fasted state, the nanocrystal formulations of megestrol acetate produced 4- to 6-fold higher $C_{\text{max}}$ values >2 hours earlier than the two currently available suspensions (table I). As reflected in the AUC, exposure to the drug was 2- to 4-fold higher with the nanocrystal formulations than with the suspensions, and variability was lower, particularly with nanocrystal formulation #2. Administration after a high-fat meal markedly increased bioavailability; peak concentrations were 5- to 7-fold higher and occurred earlier, and AUC values were 2- to 3-fold higher (figure 3).

### 6. Conclusions

Progestational agents have long been used in the treatment of the anorexia-cachexia syndrome, a component of numerous diseases including AIDS, cancer, chronic heart failure, rheumatoid arthritis, chronic obstructive pulmonary disease, Crohn disease, and chronic renal disease. Megestrol acetate, the preferred progestational agent for the treatment of anorexia-cachexia, has been shown to be effective in stabilizing weight loss or even producing weight gain. However, the tablet and oral suspension formulations of the drug are accompanied by pharmacokinetic characteristics that may have limited optimal use.
The improved bioavailability of megestrol acetate nanocrystal oral suspension has the potential to address unmet needs in the treatment of anorexia-cachexia. By rapidly increasing plasma megestrol acetate concentrations, this formulation may have the potential to produce a more rapid clinical response and significantly improve outcomes in patients with this common and potentially deadly disorder.

Acknowledgments

Robert A. Femia is the Executive Vice President, Scientific and Regulatory Affairs for Par Pharmaceutical, Inc.

Dr. Goyette is not an employee, shareholder, or retained consultant of Par Pharmaceutical, Inc. There is no conflict of interest.

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