Megestrol acetate in cachexia and anorexia

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Abstract: The aim is to review major clinical trials that have used megestrol acetate (MA) in the treatment of cachexia across several disease states. A review of general usage and potential side-effects are discussed. A theory that the newly approved nanocrystal formation of MA can better deliver this potent medication for treatment will also be reviewed.

Keywords: megestrol acetate, nanocrystalline particles, cachexia

Introduction

Weight loss among elderly patients is a common clinical problem. For patients with more than 4% weight loss, 2-year survival rate is less than 72%, and 3-year survival rate is less than 65% (Wallace et al 1995; Wallace and Schwartz 1997).

This manuscript will summarize the results of our studies and discuss and review the general usage of megestrol acetate (MA) in the treatment of weight loss in cachectic elderly, cancer, and HIV patients.

Involuntary weight loss in the elderly is difficult to treat. Roberts and colleagues (Roberts et al 1994, 1997; Roberts 1995, 2000) investigated the effects of aging on the mechanism of body energy regulation and thereby determined the causes of unexplained weight loss in older persons. They found that aging may be associated with a significant impairment in the ability to control food intake following overeating or undereating. Overeating and undereating are part of the normal pattern of lifetime energy regulation. Hospitalization resulting in undereating can have a devastating effect on the frail elderly (Sullivan et al 1999). These frail elderly then are thrown into a downhill spiral. Any attempt to correct undereating and poor appetite may change the course of survival.

Studies in both cancer patients and HIV patients have shown that MA can improve appetite and help patients gain weight (Tchekmedyian et al 1987, 1991; Oster et al 1994; Von Roenn 1994). MA is a synthetic derivative of a naturally occurring progestational agent, which is similar to progesterone. MA is well tolerated in patients with advanced malignant diseases and has a positive dose-response effect on appetite stimulation (Tchekmedyian et al 1987, 1991; Oster et al 1994). Loprinzi et al (1994) found the optimal dose in their study to be 800 mg/day. Loprinzi et al (1993) found that this was primarily non-fluid weight. MA has also been shown to improve body weight, sense of appetite, and performance status in patients with hormone-insensitive cancers (Feliu and Gonzalez-Baron 1992). The FDA approved in 1994 the use of MA for the treatment of anorexia, cachexia, and/or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS). MA was first produced in a tablet form, then in a concentrated oral suspension form, and most recently, in an oral suspension form developed using nanocrystal technology.

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Nanocrystal technology was designed specifically to optimize drug delivery and enhance the bioavailability of drugs that have poor solubility in water.

Mechanism of MA

The precise mechanism by which MA promotes weight gain is unclear. Proposed mechanisms and their potential side-effects are summarized in Figure 1. Reported results show that MA may act both an progestational agent as well as an anti-inflammatory/glucocorticoid agent (Bojar et al 1979; Kontula et al 1983; Loprinzi et al 1992a, 1992b; Pridjian et al 1987; Selman et al 1996, 1997; Chang 1998; Gomez et al 1998a, 1998b, 2002; Meacham et al 2003). Lapp et al (1995) have found, for example, that higher endogenous progesterone concentrations are common in late pregnancy, and those elevated concentrations result in decreased IL-6 levels, which are 40%–50% of controls. It makes sense that progesterone plays an important role in improving nutritional status and decreasing localized inflammation by

down-regulation of IL-6 production during pregnancy. MA also has been found to decrease cytokine production during the treatment of malignancy (Barak et al 1998; Mantovani 1997; Mantovani et al 1998a, 1998b).

Wiedemann et al (1998) found that MA dosages between 160 and 480 mg activate progesterone receptors and lead to pituitary hormone secretion of a well-defined progesterone receptor ligand in a non-linear U-shape dose dependency. Our experience in randomized studies indicates that across both placebo and active treatment groups, there is a statistically significant negative correlation between the levels of pro-inflammatory cytokines, such as IL-6 and TNF, and various nutritional parameters, body mass indices, improvement in QOL, and weight gain (Yeh et al 2000a, 2000b, 2001). These findings seem to support a role for inflammatory cytokines in the idiopathic cachexia syndrome of the elderly. MA binds to glucocorticoid receptors (Kontula et al 1983) in a possible dual agonist–antagonist fashion, acting as a weak agonist, but then serving as an antagonist in blocking the binding of
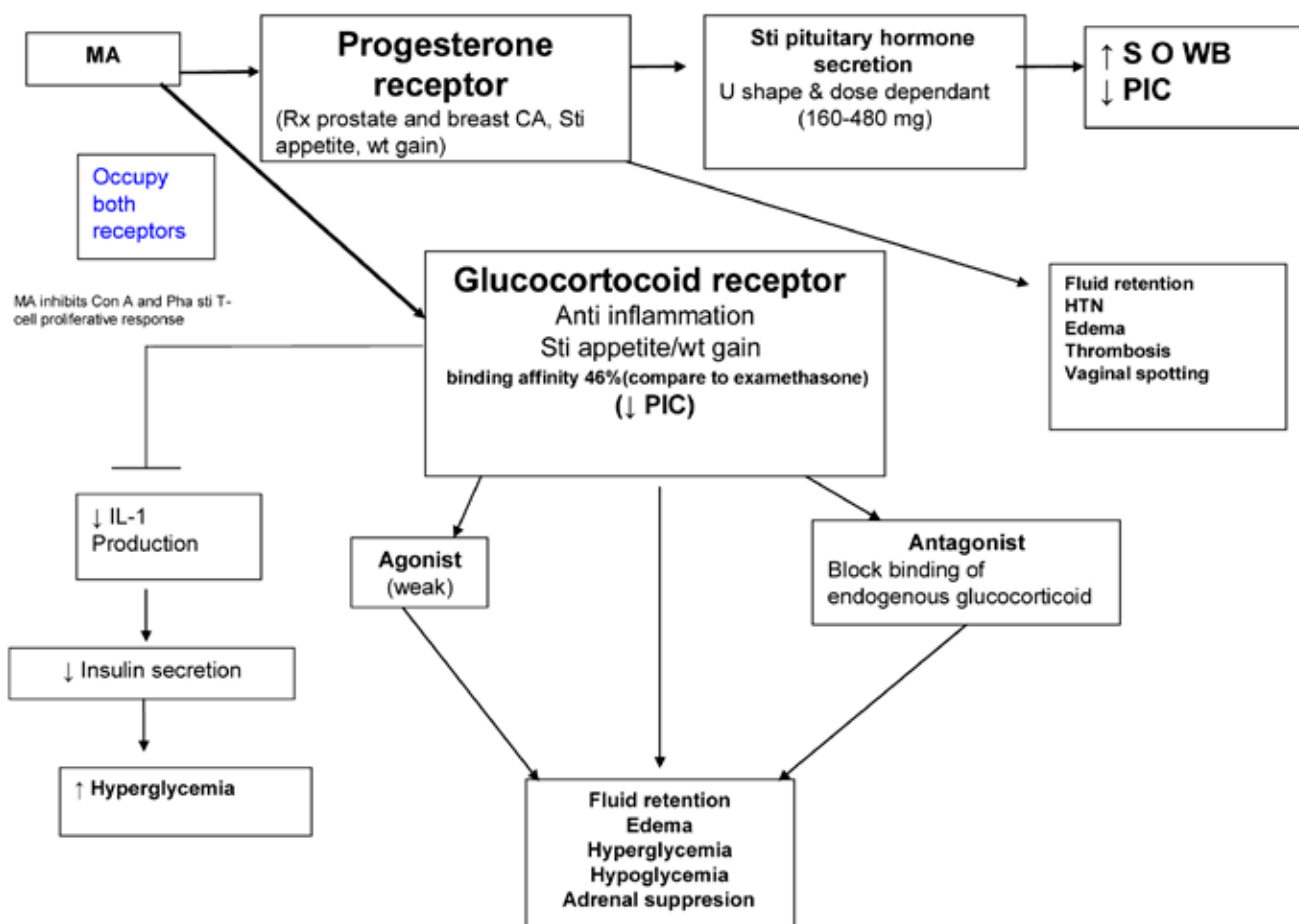

Figure 1 Summary of proposed megestrol acetate (MA) mechanism for weight gain and potential side-effects.
Abbreviations: CA, cancer; Con A, concanavalin A; HTN, hypertension; MA, megestrol acetate; Pha, phytohemagglutinin; PIC, pro-inflammatory cytokine; Rx: treatment; S O WB, sense of well being; Sti, stimulation; wt, weight.

more potent endogenous glucocorticoids (Kontula et al 1983; Mann et al 1997). Structural similarities between MA and glucocorticoids have been invoked to explain glucocorticoid-like activity and increased peripheral resistance to insulin after treatment with the drug (van Veelen et al 1984, 1985; Loprinzi et al 1992b; Herkert et al 2001).

The dual action of MA may be the possible explanation for the unresolved inconsistencies of megestrol acetate's neuroendocrine-progesterone effects and its potential reported side-effects such as hyperglycemia, hypoglycemia, venous thromboembolism, secondary adrenal suppression, and adrenal insufficiency (Selman et al 1996, 1997; Koller et al 1999; Herkert et al 2001; Oberhoff 2001; McKone et al 2002; Bennett 2003; Kropsky et al 2003; Thomas 2004). Reuben and colleagues reported that all patients had cortisol suppression after 9 weeks on MA (70% with MA>400 mg/day) (Reuben et al 2005). The suppression of the adrenal axis was at the level of the hypothalamus/pituitary (Kontula et al 1983). Effects on cortisol are reversed in 2–4 weeks once off MA (Meacham et al 2003). MA also inhibits CON-A and PHA stimulated T-cell proliferative response (Kontula et al 1983), making patients with long-term usage of MA vulnerable to infection and malignancy. Short-term (12 weeks) use of the drug appears to be safe (Yeh et al 2000b; Pascual Lopez et al 2004; Simmons et al 2004; Reuben et al 2005).

Review of clinical trials

MA appears to be one of the more potent appetite stimulants of currently used drugs (Loprinzi et al 1999; Mwamburi et al 2004; Jatoi et al 2002, 2004; Tomiska et al 2003). Jatoi found that eicosapentaenoic acid (EPA) supplement, either alone or in combination with MA, is no better than MA alone (Jatoi et al 2002, 2004). MA provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone (Jatoi et al 2002), and combination therapy did not appear to confer additional benefit (Jatoi et al 2002). Pascual Lopez et al (2004) did relevant database searches for randomized controlled trials of MA to treat anorexia–cachexia in patients with cancer, AIDS, or other conditions. Data were extracted by two independent reviewers, and meta-analyses were performed where possible; 26 studies were included (n=3887). Compared with placebo, MA increased appetite in oncology patients (Pascual Lopez et al 2004), led to weight gain (RR=1.88 [95% CI 1.43–2.47]) and improved quality of life (HRQOL) (RR=1.52 [95% CI 1.00–2.30]). In AIDS patients, it increased weight (RR=2.16 [95% CI 1.45–3.21]). There were no appreciable differences between

lower (<800 mg/day) and higher (>800 mg/day) doses of MA (Pascual Lopez et al 2004). They found the main side-effect of MA was lower limb edema (RR=1.67 [CI 1.22–2.28]) (Pascual Lopez et al 2004) . Berenstein and Ortiz (2005) also found MA improved appetite and weight gain in patients with cancer in their Cochrane Database System Review.

MA usage, dosing, and duration

Our experience with MA has shown that its use in treating cachexia in the elderly improves quality of life and weight gain (Yeh et al 2000b, 2001).

We found that MA improved appetite (Yeh et al 2000b) and had a tendency to improve weight gain. Furthermore, it improves quality of life (Yeh et al 2000a, 2000b). During the study, reduction of pro-inflammatory cytokine levels was associated with improved quality of life, as well as increased appetite, lean muscle mass, and overall weight (Yeh et al 2000b, 2001).

Increasing prealbumin correlated with reduction in TNFR-p55 and TNFR-p75 (Yeh et al 2000b, 2001). There was no difference in adverse effects between two groups (Yeh et al 2000b). Increasing weight/fat free mass correlated with reduction in sIL-2r and TNFR-p75 (Yeh et al 2001). Improving appetite correlated with quality of life improvement, weight gain, and nutritional indicator changes (Yeh et al 2000a, 2000b, 2001). Reduction in one pro-inflammatory cytokine was highly correlated with reduction in the other cytokine levels (Yeh et al 2001). The factors that could predict survival among the subjects were higher prealbumin, albumin, and weight gain (Yeh et al 2000b, 2001, 2004). Elevated IL-6, CRP, TNFR-p55 and TNFR-p75 were associated with decreased survival (Yeh et al 2000b, 2001, 2004). However, no significant differences in survival were noted between the MA-treated and the placebo groups (p=0.72), as estimated by the Kaplan-Meier method (Yeh et al 2000a, 2000b, 2001, 2004).

In our experience, most patients had improved appetite by 6 weeks with MA treatment, although the weight gain was not yet significant at that time (Yeh et al 2001, 2000b). A course of treatment with MA for 12 weeks is probably enough to improve the appetite that will result in eventual weight gain. By 6 months, the MA group had significant weight gain. Most of the treated patients gained weight, and there was a trend for this weight gain to be in the form of fat. Increased fat mass has been noted in patients with cancer and AIDS following treatment with MA (Von Roenn et al 1988; Loprinzi et al 1993; Von Roenn 1994; Von Roenn and Knopf 1996). Dulloo and colleagues (Dulloo et al 1997; Dulloo 1998,

1997) found that replenishment of fat stores was the initial event following feeding of volunteers previously subjected to semi starvation and reported that this observation could be generalized to recovery from other forms of refeeding after weight loss. They attributed the preferential gain in fat to reduced thermogenesis and changes in energy partitioning during recovery from starvation. The initial gain in fat mass was related to the pre-starvation fat mass (patients with a higher initial fat mass gained more fat during recovery). Gaining fat may be the first step toward recovering from cachexia–starvation. No patients in this study had fat mass increases that were sufficient to make them obese or to take them beyond the normal range for fat mass. Several studies reported that inclusion of resistance exercise training led to gains–maintenance in lean body mass and better functional improvement results (Strawford et al 1998, 1999).

Old formulation MA oral suspension (Megace® OS, Bristol-Myers Squibb, Princeton, NJ, USA) is best given at a dosage of 480–800 mg with a maximum daily dose of 800 mg and taken with meals (Pascual Lopez et al 2004; Berenstein and Ortiz 2005). Newer MA nanocrystal oral suspension (Megace® ES) employs a nanocrystal strategy that increases the surface area and, therefore, the absorption and bioavailability of the drug. It can be given at a dosage of 625 mg (5 mL) daily in the fed or unfed state.

Most patients treated with conventional MA suspension had improved appetite by 6 weeks, although weight gain was not yet significant at that time. A course of treatment with MA for 12 weeks is probably enough to improve the appetite for eventual weight gain (Yeh et al 2000b). Lambert and co-workers found that despite significant weight gain, MA appears to have an anti-anabolic effect on muscle size even when combined with testosterone replacement. Resistance exercise attenuated this reduction in muscle mass. When MA is combined with testosterone and resistance exercise, resistance exercise had an anabolic effect on muscle mass (Lambert et al 2002). Thus, patients should also receive strength and a local, muscular, endurance-training program to improve their functional status. If there is no improvement in appetite by week eight, we suggest discontinuing the usage of MA because of the potential secondary adrenal suppression and adrenal insufficiency.

Common clinical practice has been to stop MA without tapering the dose because of its long half-life and storage in adipose tissue (Loprinzi 1996; Loprinzi et al 1992a, 1992c). No untoward clinical sequelae have been seen in most patients (Tchekmedyian et al 1987, 1991; Oster et al 1994; Pascual Lopez et al 2004; Simmons et al 2004). The deposition of

MA in fat stores may allow for a naturally occurring slow tapering of glucocorticoid activity after discontinuation of therapy. Patients who require more than 12 weeks of treatment should have their morning free cortisol levels checked at 12 weeks and biweekly thereafter. A patient with adrenal suppression, ascertained by an abnormal adrenocorticotropic hormone (ACTH) stimulation test, but with no symptoms of adrenal insufficiency, should be monitored for fever, nausea and vomiting, hypotension, dehydration, clouded sensorium, pain in the abdomen, joints, and muscles, hypoglycemia, and acidosis. Upon withdrawal of the drug, biochemical suppression of cortisol alone is not sufficient to warrant adrenal hormone replacement therapy. This is because adrenal suppression is not equivalent to adrenal insufficiency.

If, on the other hand, patients have already developed a Cushingoid appearance, abrupt discontinuation of MA could precipitate an Addisonian crisis. This can be prevented by supportive steroid therapy starting at a dosage of prednisone of 7.5 mg/day that is tapered at a rate of 2.5 mg/day every 2–3 weeks for patients who have recently been treated with a course of MA and have an abnormal ACTH level. It appears reasonable to recommend that stress doses of prednisone be given during a period of acute illness or prior to surgery to prevent possible complications due to adrenal suppression. Fasting blood sugar level should be checked to monitor hyperglycemia or hypoglycemia.

MA nanocrystal oral suspension

The problem with MA oral suspension is its poorly solubility and absorption in a fasting state (Femia and Goyette 2005). A recent study revealed that conventional MA suspension is best absorbed in the fed state. Its serum concentration and effect is many times higher when given in a fed rather than under fasting conditions (Alakhov et al 2004; Femia and Goyette 2005). Newer MA nanocrystal oral suspension (Megace ES) can be given at a dosage of 625 mg (5 mL) daily without meals.

MA oral suspension median t_{max} was 5 hours (Graham et al 1994). There was a significant plasma concentration difference in fed versus fasting study beagle dogs (Femia and Goyette 2005). A significant relationship was observed between weight gain and the percentage of the 24-hour administration interval, during which plasma concentrations of MA exceeded 300 ng/mL (Graham et al 1994). This may be the best explanation for the results in our clinical study, in which one third of the sickest study patients did not respond to MA oral suspension. These non-responders were exactly the study patients who were too weak and anorexic to eat

and who took the study medication in the fasting state) (Yeh et al 2000b).

MA nanocrystalline particles significantly increased surface area per unit mass (Femia and Goyette 2005). MA nanocrystalline particles increase the rate of absorption and decrease absorption variability when the drug is taken with food (Alakhov et al 2004; Femia and Goyette 2005). MA nanocrystal oral suspension (Megace ES) can be given at a dosage of 625 mg (5 mL) daily without meals. Preclinical pharmacokinetic data suggest that the new MA formulation has the potential to significantly shorten the time to clinical response and thus may improve outcomes in patients with anorexia–cachexia (Femia and Goyette 2005). Clinical studies in cancer, geriatric and HIV patients might be conducted to demonstrate the benefit of the neww formulation.

Conclusion

The etiology of the wasting syndrome is multifactorial. Patients with documented involuntary weight loss should be screened for possible reversible causes and should also be checked for untreated hyperthyroidism, depression, poor dentition, uncontrolled diabetes mellitus, severe dysphagia, or malabsorption. They should receive aggressive nutritional support (food supplements [1.5–2 g/kg of protein daily, 25–35 cal/kg daily], for a total of 2500 cal/day, dietitian consultations, and assistance with feeding).

If other treatable etiologies are ruled out, MA should be considered for use as an appetite stimulant. Because all other anabolic agents such as growth hormone depend on adequate energy intake for optimal effect, the role of nutritional support and appetite stimulants remains fundamental. Patients will typically improve their appetite within the first few weeks after starting the drug. Weight gain, often in the form of fat, may take longer. Resistance exercise traing coupled with the weight gain may lead to improved lean muscle mass. A typical treatment duration may be 12 weeks. Patients should be monitored for signs and symptoms of adrenal suppression. The newer MA nanocrystal oral suspension (Megace ES) can be given in a smaller volume and depends less on a patient taking it in the fed state to achieve a clinical benefit.

Acknowledgments

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