Editorial: Megestrol Acetate Use for Weight Gain Should Be Carefully Considered

Megestrol acetate (MA) is a progestational agent with a powerful effect on appetite. It was initially used as a contraceptive agent; however, the common side effect of weight gain led to its current use as an orexigenic agent. Administration of MA results in substantial increases in appetite and body weight in patients with HIV-associated wasting and in those with cancer (1). MA is currently Food and Drug Administration (FDA) approved for HIV-associated weight loss. In addition, both in healthy, community-dwelling older individuals (2) and elderly people residing in long-term care facilities (3), the use of MA results in a robust increase in body weight. The use of orexigenic agents such as MA in these settings is appropriate because involuntary weight loss has been associated with increased mortality. Indeed, MA has a greater effect on body weight and appetite than other orexigenic agents such as dronabinol and eicospentaenoic acid. However, in older people and patients with cancer or renal failure, fat is the principal or the only constituent of weight gain (4), with little accrual of skeletal muscle or other components of fat-free mass. Among the many side effects of the use of MA, suppression of testosterone and estrogen production is prominent. Before the common use of other effective anabolic suppressive treatments (flutamide, bicalutamide) in men with prostate cancer, MA was commonly used in this setting. Indeed, in older men, use of MA results in near-castrate levels of testosterone. MA has also been used to suppress estrogen levels in women with breast cancer (5).

The study published this month in *JCEM* (6) examined the combined effects of testosterone and MA on the composition of weight gain in patients with HIV-associated wasting. This study demonstrates, once again, that MA has a substantial effect on appetite and body weight, with fat gain the principal component of the increase in body weight. However, fat-free mass was also increased along with total body weight in this trial, similar to a previous examination of the effect of MA on weight gain in patients with HIV-associated weight loss. Mulligan *et al.* (6) showed that testosterone was suppressed, and testosterone replacement had no effect on the composition of the weight gain; furthermore, MA administration resulted in decreased libido. This suppressive effect of MA on testosterone production and in blocking the effects of testosterone on lean body mass accrual should be carefully considered before using MA in this patient population. Loss of lean mass in HIV patients is strongly linked to low androgen levels (7).

Engelson *et al.* (8) termed MA a drug with “anabolic” properties. Lambert *et al.* (2) examined the effects of testosterone and resistance exercise on the composition of weight gain stimulated by the use of MA in elderly men. Similar to the study by Mulligan *et al.* (6), the use of testosterone with MA produced no greater effects than use of MA alone. Lambert *et al.* (2) observed a significant increase in body weight and a 5% decrease in skeletal muscle mass within 3 months of MA use. Testosterone replacement had no effect on muscle accrual in MA-treated elderly men, suggesting that MA competes with testosterone for binding to the androgen receptor (9). Only exercise with MA had a significant effect on muscle mass.

These studies also call into question the use of MA to treat cachexia. Cachexia is a pathological state of loss of skeletal muscle and fat and occurs in the presence of underlying illness. Genes associated with muscle protein degradation are selectively targeted in the cachectic state with a resultant rapid loss of skeletal muscle (10). Because of the anabolic properties of MA, its use is very unlikely to result in the preservation or an increase in muscle mass during conditions associated with cachexia. However, by stimulating appetite, MA can preserve or increase fat mass during cachexia. We do not know whether MA-induced gains in fat mass affect mortality. It is also unclear whether changing the trajectory of weight loss during these conditions has any effect on mortality.

Involuntary weight loss is associated with increased mortality among patients with HIV-associated wasting (11), cancer (12), and in elderly men and women (13), and MA has been demonstrated to increase appetite and body weight in these conditions. However, use of MA is associated with a number of side effects. MA-induced suppression of testosterone results in loss of libido and impotence as well as hyperprolactinemia. MA suppresses estrogen in women (5) and has glucocorticoid-like effects that result in secondary adrenal suppression and low cortisol levels (14). There is no evidence that stimulating appetite and increasing body weight in patients with involuntary weight loss affects mortality. No data exist to indicate that the composition of weight gain is important in affecting the outcome of these patients. However, restoration of appetite in an anorexic patient can have an important palliative effect, even if no other benefit is seen (15).

A number of unanswered questions concerning the effects of MA remain. Its use must be carefully considered and carefully managed. If an improvement in appetite and a gain in fat mass are desirable goals in the management of cachexia or involuntary weight loss, MA remains one of the most potent orexigenic agents currently available. Its use must be weighed against the potential for adrenal suppression and suppression of androgen production. Because of its anabolic properties, the anabolic effects of MA are not ameliorated by testosterone administration.

Abbreviation: MA, Megestrol acetate.

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