Class: Sex hormones.

Indications: Hormone therapy in breast (**megestrol**), renal (**medroxyprogesterone**) and endometrial cancers, anorexia and cachexia (**megestrol**), †postcastration hot flashes in both women and men.

Contra-indications: Hepatic impairment.

Pharmacology

In addition to natural **progesterone**, there are several classes of synthetic progestins, e.g. derivatives of retroprogesterone, progesterone, and 17α-hydroxyprogesterone (**cyproterone**, **medroxyprogesterone acetate**, **megestrol acetate**).[1] Whereas all derivatives have a progestogenic effect on the uterus, there are differences in other biological effects (Table 7.1).

Table 7.1 Comparison of the biological effects of natural progesterone and selected synthetic progestins[1]

Progestin	*Effect*[a]		
	Androgenic	*Anti-androgenic*	*Anti-mineralocorticoid*
Progesterone	–	+	+
Cyproterone acetate	–	++	–
Megestrol acetate	+	+	–
Medroxyprogesterone	+	–	–

Key: ++ = effect present; + = weak effect; - = no effect.

a. all the above possess similar progestogenic, antigonadotrophic, anti-estrogenic and glucocorticoid effects.

Hormonal manipulation with a progestin is used in the treatment of several cancers, notably of the breast, prostate and endometrium.[2-5] Treatment is not curative but may induce remission in 15–30% of patients, occasionally for years. Tumor response and treatment toxicity need to be monitored, and treatment changed if progression occurs or undesirable effects exceed benefit.

Progestins are also used in cachexia-anorexia, although their efficacy in cachexia is debatable (see next section). Progestins may improve appetite by increasing levels of orexigenic neurotransmitters in the hypothalamus (e.g. neuropeptide Y), counteracting the anorexic effects of cytokines on the hypothalamus, or by interfering with the production of cytokines via their glucocorticoid anti-inflammatory effect.[6,7] In vitro, cytokine release from peripheral blood mononucleocytes are inhibited by both **megestrol acetate** and **medroxyprogesterone acetate** in concentrations that would be achieved by daily doses of 320–960mg and 1500–2000mg respectively.[6] The release of serotonin was also inhibited and was considered one possible mechanism by which progestins have an anti-emetic effect.[6]

Megestrol acetate is not very water-soluble and thus its bio-availability is low. Bio-availability is improved if taken with food. Several formulations have been developed in an attempt to improve bio-availability, e.g. a micronized tablet form and a concentrated oral suspension. The most recent is an oral suspension form using

nanocrystal technology, licensed for anorexia-cachexia in patients with AIDS. Compared to **megestrol acetate** oral suspension, the new Megace® ES provides a bio-equivalent dose in a smaller volume (625mg/5ml vs. 800mg/20ml), which is less viscous, and absorption less affected by fasting/food (Par Pharmaceuticals, data on file: bio-equivalence assessed as achieving similar maximum concentration and AUC).[8] Both **medroxyprogesterone acetate** and **megestrol acetate** are highly protein-bound, mainly to albumin. The majority of **megestrol acetate** is excreted unchanged in the urine. **Medroxyprogesterone acetate** is metabolized extensively in the liver, and excreted mostly as glucuronide conjugates. For pharmacokinetics, see Table 7.2.

Table 7.2 Selected pharmacokinetic data[9]

	Megestrol acetate	*Megace ES*	*Medroxyprogesterone acetate*
Bio-availability	No data	No data	1–10%
Time to peak plasma concentration	1–3h	2–3h	2–7h
Plasma halflife	13–105h (mean 30h)	~35h	38–46h

Cachexia and anorexia

Cachexia is common in cancer and other chronic diseases, impairing quality of life and increasing morbidity and mortality.[10] It is characterized by the loss of skeletal muscle and body fat. Loss of skeletal muscle is associated with impaired physical function and quality of life, whereas loss of fat (the body's main energy store) is associated with reduced survival.

In cancer, the two main mechanisms are a reduced food intake (anorexia) and abnormal host metabolism resulting from factors produced by the cancer, e.g. proteolysis-inducing factor, or by the host in response to the cancer, e.g. cytokines.[11] One outcome of this is a chronic inflammatory state, the level of which relates to the degree and rate of weight loss.[12] Cytokines such as interleukin-1 and tumor necrosis factor-α, act on the hypothalamus and skeletal muscle leading to anorexia, inefficient energy expenditure, loss of body fat and wasting of skeletal muscle. The management of cachexia requires both of these main mechanisms to be addressed, and explains why increasing nutritional intake alone is generally ineffective.[11,13-15]

Megestrol acetate is licensed to stimulate appetite and weight gain in patients with cancer or AIDS. A systematic review of 30 trials involving >4000 patients, concluded that appetite and weight was improved in patients with cancer, but was unable to comment for other groups, due to insufficient numbers. There was no difference between a low (≤800mg) and a high (>800mg) daily dose.[16,17] However, the studies in the review used body weight as a primary outcome measure, and none accurately assessed changes in body composition. In those studies that have assessed body composition, both **megestrol acetate** and **medroxyprogesterone acetate** appear to increase fat mass, but not fat-free mass, the part which includes skeletal muscle.[7,18-20] Thus it is likely that the gain in weight with progestins (and corticosteroids), rather than representing the ideal increase in skeletal muscle *and* fat, is a less helpful retention of fluid or increase in fat only. This could make

mobilizing more difficult in an already debilitated patient. In addition, the catabolic effect of progestins on skeletal muscle could further weaken the patient. Catabolism may result from the glucocorticoid effect of progestins but they also suppress the amount and function of testosterone, which is anabolic. Others have noted that progestins lead to a substantial improvement in appetite in <30% of patients, questioned the clinical relevance of the magnitude of weight gain seen (≈1kg) or have highlighted the occurrence of undesirable effects of deep vein thrombosis (5%) and male impotence (10–25%).[7,18,20-25]

Progestins are much more expensive than **dexamethasone** or **prednisone**. **Megestrol acetate** 800mg/day and **dexamethasone** 3mg/day are comparable with regard to appetite stimulation and non-fluid weight gain, although the latter was not accurately assessed.[26] In this study a high proportion of patients discontinued **dexamethasone** (36%) or **megestrol acetate** (25%) because of undesirable effects. **Dexamethasone** was more likely to cause cushingoid changes, myopathy, heartburn and peptic ulcers; **megestrol acetate** was associated with increased thrombo-embolism.[26] **Dexamethasone** is a fluorinated corticosteroid, a class which are more prone to cause muscle catabolism.[27] Thus, ideally, the use of **dexamethasone** should be limited to short-term use only.

If long-term use of a corticosteroid is contemplated, a switch to the non-fluorinated **prednisone** 10–20mg/day should be considered.[7] However, for patients expected to live months rather than weeks, progestins may be more appropriate. Caution is still required as long-term progestins can also cause cushingoid changes (25% of patients after 3 months in one study),[28] muscle catabolism and adrenal suppression, and additional corticosteroid replacement therapy would be a reasonable precaution in patients with serious infections or undergoing surgery (see p.000).[7,29,30] Adrenal suppression is secondary to a central glucocorticoid effect on the hypothalamus and is dose-related; maximal suppression seen with daily doses of **megestrol acetate** 200mg and **medroxyprogesterone acetate** 1000mg.[28]

The combination of a progestin and an NSAID has been investigated.[31,32] **Megestrol acetate** 160mg t.i.d. in combination with **ibuprofen** 400mg t.i.d. resulted in improved quality of life and weight gain. However, this was probably caused by fluid retention, because total body water increased *even though there was no clinical edema*.[31] The combination of **medroxyprogesterone** 500mg b.i.d. and **celecoxib** 200mg b.i.d. also stabilized weight and improved systemic symptoms.[32] Because the NSAID probably provided benefit by reducing the chronic inflammatory response (CRP levels were reduced), others have used **indomethacin** alone.[33]

In conclusion, progestins and corticosteroids (see p.000) are useful *appetite stimulants* which can increase calorie intake and as such may be indicated in selected patients for anorexia. Progestins may be a more appropriate choice for long-term use than corticosteroids, but significant undesirable effects can occur. Starting doses should be low and titrated to the lowest effective dose. Both progestins and corticosteroids are best *not* regarded as *'anticachexia' agents*; any weight gain is likely to be due to an increase in fat and fluid retention, and the catabolism of skeletal muscle *increased*, particularly in inactive people.

Cautions

Undiagnosed vaginal bleeding, breast cancer, active thrombophlebitis, past thrombo-embolic disorder, cerebral vascular disease, and women with significant liver disease. May reduce serum levels of **indinavir**.[9]

Undesirable effects
For full list, see manufacturer's PI.
Frequency not stated: hyperglycemia, depression, insomnia, fatigue, thrombo-embolism, hypertension, edema/fluid retention, nausea, vomiting, constipation, Cushingoid changes, bone mineral density loss, reduced libido, impotence, altered menstruation, breast tenderness, urticaria, acne.
Rare (<0.1%): jaundice, alopecia, hirsutism.

Dose and use
Appetite stimulation
- start with **megestrol acetate** 80–160mg PO q.a.m.
- if initial response poor, consider doubling the dose after 2 weeks[34,35]
- maximum dose generally 800mg PO daily.

Medroxyprogesterone acetate 500mg PO q.a.m.–b.i.d. is an alternative in countries where higher strength tablets are available (e.g. 100mg, 250mg and 500mg; not USA).

Hot flashes after surgical or chemical castration
Medroxyprogesterone acetate 5–20mg b.i.d.–q.i.d. or **megestrol acetate** 40mg q.a.m.[36] The effect manifests after 2–4 weeks.

Supply
Megestrol acetate (generic)
Tablets 20mg, 40mg, 28 days @ 160mg q.a.m. = $60.
Oral suspension 40mg/ml, 28 days @ 160mg q.a.m. = $62.

Megace® (Bristol-Myers Squibb)
Tablets 20mg, 40mg, 28 days @ 160mg q.a.m. = $138.
Oral suspension 40mg/ml, 28 days @ 160mg q.a.m. = $71.

Megace® ES (Par Pharmaceutical)
Oral suspension 125mg/ml, 28 days @ 125mg q.a.m. (bio-equivalent to megestrol acetate oral suspension 160mg) = $20.

Medroxyprogesterone acetate (generic)
Tablets 2.5mg, 5mg, 10mg, 28 days @ 5mg b.i.d. = $17.

Provera® (Pharmacia)
Tablets 2.5mg, 5mg, 10mg, 28 days @ 5mg b.i.d. = $58.

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