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EDITORIAL

THERAPEUTIC STRATEGIES IN HYPERANDROGENISM

Hyperandrogenism is a state of increased androgen production and action. For the most part ovary and adrenal contribute to the enhanced production, even though enhanced androgen utilization at the target organ could also constitute to hyperandrogenic expression.

An androgen, namely testosterone (T), produced by the glandular or extraglandular source usually will be delivered to its target organs by a transport element represented by the circulating SHBG. Once delivered to the target organ (such as the skin) T will be subject to the action of a processing unit, namely 5 alpha reduction, resulting in formation of DHT which has twice the androgenic potency of T. Finally, the realization of androgenic biological action demands the interaction of androgen thus formed with its cytosolic receptors. Androgen readily diffuses across the cellular membrane to form the steroid receptor complex which is to be translocated to the nuclear acceptor site through which various genomic actions are exerted.

Viewed schematically, the operational characteristics of androgen hormonal action involves (i) androgen production; (ii) transport element; and (iii) the target organ. Once delivered to the target it will be subjected to (i) androgen processing, and (ii) androgen response. Therefore, the logical approach to therapeutic interventions of hyperandrogenism must be directed at either the source (production), transport (SHBG) or the target elements.

Therapeutic options targetted at source of androgen : Ovarian androgen production could be inhibited by clomiphene citrate by

its central action of balanced LH and FSH production which favours ovulation. If ovulation is not preferred, cyclical low dose estrogen-progestogen therapy (OC pills) could be employed to suppress episodic LH release. While the former approach is mandated for infertile subjects the latter approach is specifically employed when other hyperandrogenic symptoms (such as hirsutism) are to be treated.

GnRH agonists exert their therapeutic effect largely at the level of ovarian androgen production by down regulation of pituitary gonadotrophs. By rendering the subject hypogonadotrophic and hypogonadal the hyperandrogenic and estrogenic features are greatly silenced. Beyond this point if one aims at ovulation, exogenous gonadotropins could be employed as if an hypogonadotropic hypogonadal subject is induced ovulation. By contrast, if treatment of hirsutism is the concern GnRH agonist alone will do the job, and estrogen replacement will take care of the hypoestrogenic side effects. Moreover, estrogen will also have the synergestic antiandrogenic effect.

Adrenal hyperandrogenism could be effectively controlled by ACTH suppression effected by corticosteroids. Similarly hyperprolactinemia induced hyperandrogenism is taken care of by prolactin suppression. These fundemental principles of inhibition of androgen source form the clinical basis for induction of ovulation in hyperandrogenic subject employing CC, dexamethasone or bromocriptine, either alone or in various combinations.

Therapeutic options aimed at androgen transport element : Since SHBG binds the androgens, T and DHT, the circulating androgen level will be lowered by increasing the SHBG production. This forms the basis of OC pill therapy for hyperandrogenic expressions such as hirsutism. While estrogens increase the hepatic synthesis of SHBG, androgenic progestins will have the opposite action. Hence, while preferring OCs for suppressing hyperandrogenism one should be careful to select a combination with a progestogen devoid of androgenic expression (ethinodiol diacetate or desogestrel). Care also should be taken to avoid inadvertant use of corticosteroid in unindicated situations, because SHBG production will be suppressed by these steroids.

Therapeutic options foccused at androgen target inhibition : By either inhibiting 5 alpha reductase activity (processing) or by competing for the androgen receptors (response) drugs such as spironolactone could reduce androgen action on the target organs. This forms the basis for employing the antiandrogens, namely, spironolactone, cyproterone acetate and cimetidine, for peripheral antiandrogenic alleviation such as treatment of hirsutism.

Since majority of occasions a specific etiology could not be assigned for hyperandrogenemia the above therapeutic strategy appears to be quite logical and practicable. However, prompt diagnostic efforts must be made to identify an etiological factor such as an androgen producing tumor which should be treated on its merit.

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