Cabergoline, a Hopeful Medicine for Prolactinomas and Non-tumoral Hyperprolactinemia

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Pituitary tumors are usually benign adenomas arising from the adenohypophysis and are clinically classified into two categories: functioning (hormone-secreting) and non-functioning (non-secreting) tumors. Among the functioning pituitary tumors, prolactin (PRL)-secreting tumor, prolactinoma, is the most frequently occurring adenoma. Prolactinomas affect women more often than men. For instance, the incidence is 3.38 times greater in women than in men in Japan. Most prolactinomas in women are microadenomas (<1 cm in diameter) and occur at childbearing ages, while those in men are more frequently macroadenomas and occur evenly distributed throughout their adult life span. In general, the larger the tumor, the higher the PRL level in blood. The elevated PRL level in blood (hyperprolactinemia) causes gonadal dysfunction or infertility by inhibiting the GnRH-LH/FSH-gonadal axis probably through the effect on the hypothalamus. Typical symptoms are irregular menses, amenorrhea, and galactorrhea in women and decreased libido and impotence in men. Another important issue related to hyperprolactinemia is decreased bone density or osteoporosis associated with hypogonadism. This bone complication should not be overlooked because if left untreated, it potentially increases a risk of fractures. Microadenomas rarely progress to macroadenomas; the risk of progression is only 7% (1). Tumor growth is usually directed upward into the suprasellar cistern (suprasellar extension). The tumors that are large enough to compress optic chiasm and adjacent structures produce symptoms of mass effects, including headache, decreased vision, and narrowing of visual fields, typically bitemporal hemianopsia. Furthermore, direct compression of normal pituitary tissues and, occasionally, invasion into the hypothalamus causes single or multiple pituitary hormone deficiency, i.e. hypopituitarism of the pituitary and hypothalamic origin. For these reasons, prolactinomas should be sufficiently treated at the appropriate time. The goal of treatment is to reduce or eliminate hormonal overproduction and local mass effects and to restore or preserve normal pituitary function.

Secretion of PRL by the pituitary is under tonic inhibition by dopamine, a PRL-inhibiting factor delivered from the hypothalamus. Although prolactinoma pathogenesis remains to be proved, prolactinoma retains biochemical characteristics of normal PRL cells (lactotrophs) and responds to dopamine. Dopamine receptor agonists suppress PRL secretion in prolactinoma patients as in healthy subjects. Bromocriptine was the first dopamine agonist in worldwide clinical use for treatment of hyperprolactinemia and prolactinomas (1). It can normalize elevated PRL levels in 80–90% of prolactinoma patients (1) and thereby restore normal gonadal function, cease galactorrhea, and recover visual disturbance in a majority of patients. In addition, bromocriptine shrinks 70% of prolactinomas more than 25% (1) and makes some tumors disappear. The mechanism by which dopamine agonists reduce tumor size involves a suppression of PRL synthesis and PRL gene transcription. The normalization rate of hyperprolactinemia by bromocriptine is greater than that achieved by neurosurgery, i.e. transsphenoidal tumor removal. The long-term surgical cure rate is 50–60%, although initial normalization of PRL is attained in about 70% of patients. This is the reason why dopamine agonists have been used as a first-line treatment in prolactinomas during the last two decades. By contrast, surgery remains a treatment of choice for other functioning and non-functioning pituitary tumors.

Currently available dopamine receptor agonists for hyperprolactinemia in Japan are bromocriptine and terguride. In general, these drugs are well tolerated and side effects are usually mild and transient. Common side effects are such gastrointestinal symptoms as nausea, vomiting, and constipation, and dizziness or vertigo associated with orthostatic hypotension. To minimize these side effects, bromocriptine is initially started at a low dose (1.25 mg) with a snack at bedtime and gradually increased to 2.5 mg twice or three times a day over a period of a few weeks. However, approximately 5% of patients experience side effects of sufficient severity, which limits the dose and even necessitates withdrawal of the medication. Drug intolerance is a considerable frustration for clinicians as well, if there is no alternative choice of treatment. In the August issue of this journal (2), Sabuncu et al from Turkey compared the efficacy and tolerability of a new dopaminergic agent, cabergoline, with those of bromocriptine in prolactinoma and non-tumoral (idiopathic) hyperprolactinemia.

See also 857.

They showed that cabergoline had a significantly lower incidence of adverse effects, while inhibiting elevated PRL significantly more than bromocriptine. Their results are consistent with those of Webster et al (3), who in addition, revealed that gastrointestinal symptoms were less severe and short-lived in cabergoline-treated patients. Cabergoline belongs to
the same ergot-derived dopamine receptor agonists as bromocriptine but has a longer half-life in plasma and a higher affinity to pituitary dopamine D2 receptors. This pharmacological property allows patients to take cabergoline only once or twice a week and to get maximum benefits with minimum if any adverse effects. Cabergoline would be a very promising agent for hyperprolactinemic patients intolerant to standard dopamine agonists (4–6) and hence also for clinicians in a dilemma.

An additional clinical dilemma in the treatment of prolactinomas is the fact that 5–10% of patients are resistant to medical therapy (1). However, cabergoline is reported to work well in these resistant cases as well (6–8). For example, the recent report of Colao et al is very encouraging (8). They demonstrated that cabergoline did normalize increased PRL levels in all 37 patients with resistant macro-prolactinomas and achieved a more than 80% tumor shrinkage in 30.3% of these patients during a 1 to 3-year course of treatment. Also observed was a more surprising finding that such a dramatic tumor shrinkage occurred in 92.3% of naive, previously untreated 26 patients and tumors completely disappeared on MR imaging in 61.5% of naive cases. If the treatment had been continued more than 3 years, further reduction or disappearance of the tumor mass might have occurred. Whether tumor disappearance represents an actual cure or whether cabergoline’s effects decrease during a longer-term treatment is a future issue to be solved. In any case, the remarkable effects of cabergoline on prolactinomas offer great hope to both clinicians in a dilemma and patients resistant to standard medical treatments. In Japan, cabergoline was approved as a therapeutic agent of Parkinson’s disease in 2000, but it is not available yet for hyperprolactinemia or prolactinomas. Compared with the regimen to treat prolactinomas, the treatment of Parkinson’s disease requires more frequent daily administration of cabergoline at higher doses. It is certainly a great wish to help hyperprolactinemic patients with cabergoline, in particular those intolerant or resistant patients who are eager for their children.

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References