LETTER TO THE EDITOR

MANAGEMENT OF HYPERPROLACTINAEMIA — AN ALTERNATIVE VIEWPOINT

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Dear Editor:

In their review of the management of hyperprolactinaemia, S L Tan et al (1) highlighted the fact that bromocryptine will not only lower serum prolactin levels but will, in the majority of cases, cause tumour regression. Surgery, on the other hand, was presented as an inferior alternative because of its lower success rate in producing cyclic menses, the high recurrence rate of hyperprolactinaemia and the risk of complications including panhypopituitarism. Having omitted mentioning the disadvantages of prolonged treatment with bromocryptine and the relative advantages of surgery, the authors unjustifiably conclude that "the place of surgery is increasingly limited to those patients where medical treatment has failed."

Long-term treatment with bromocryptine is not only expensive but may not be as harmless as suggestive. Although the drug has not been shown to have any serious ill effects in humans, the necessity for long-term and possibly, life-long treatment is a drawback that should not be treated lightly (2). Toxicological studies have shown that prolonged treatment can produce endometrial hyperplasia and carcinoma in rodents (3).

There are 2 dopaminergic pathways in the central nervous system: the tubero-infundibular dopaminergic system and the mesencephalic ascending system (4). The former is well-known and is the basis for the treatment of hyperprolactinaemia with a dopamine agonist such as bromocryptine. The latter is subdivided into 3 systems, namely, the nigro-striatal system, which is concerned with Parkinson's disease, and the mesolimbic and mesocortical systems, both of which have been implicated in the aetiology of schizophrenia. Essentially all antipsychotic drugs, e.g. haloperidol, chlorpromazine and thioridazine are dopamine receptor blockers (4). There are therefore hypothetical grounds for thinking that prolonged stimulation of dopamine receptors in the central nervous system with bromocryptine may lead to a disturbance (irreversible?) of the functions of these dopaminergic systems.

Cure, as opposed to control, can only be achieved by transsphenoidal microsurgery (2, 3, 5, 6). Although Serri, et al, (7) reported a 40% recurrence rate of hyperprolactinaemia 6 years following surgery, the long-term recurrence rate reported by other surgeons is much lower, being in the region of 15% to 20% (7, 8, 9). It should be pointed out that Serri's study only considered patients who were still being followed up, not the total operated group. There was selection therefore of those who were not cured, i.e., still had symptoms (6). Nevertheless, none of these patients developed a clinical or radiological recurrence. Even accepting a 40% recurrence rate as correct, surgery remains superior to bromocryptine where cessation of treatment almost invariably results in recurrence (2,5,6).

It is important to differentiate tumour regression from cure. While it is recognized that the majority of prolactinomas show clinical and radiological evidence of shrinkage with bromocryptine, most investigators report recurrence once treatment is stopped (3, 5). Similarly, the serum prolactin level eventually rises upon cessation of treatment. This is not surprising because bromocryptine therapy does not result in death of the tumour cells (3, 10, 11).

A further disadvantage of treatment of over 1 year with bromocryptine is that it causes increased vascular fibrosis in prolactinomas (3, 10). Some surgeons who have found a lower cure-rate among patients who had prolonged treatment with bromocryptine have attributed the difference to this (3, 12). Short-term preoperative treatment, on the other hand, does not seem to have the same effect, and may even facilitate surgery.

While our knowledge of the natural history of prolactin-secreting microadenomas is still fragmentary, it is clear that some may regress spontaneously (2, 10). In view of this, a case can be made for watching patients with microprolactinomas who do not wish to become pregnant and seeing if spontaneous regression occurs. In a 6-year followup of 27 patients habouring untreated microprolactinomas, tumour growth was demonstrated in 10% (13). Therefore, all patients must be followed up regularly for evidence of tumour enlargement because the opportunity to remove an enlarging microadenoma before it becomes invasive should not be missed. This is particularly important considering the very high recurrence rate of hyperprolactinaemia following surgical treatment alone for macroprolactinomas (7). It would be appropriate to mention here that tumour enlargement in all 3 patients in the series (13) mentioned was not accompanied by a rise in serum prolactin levels and serial prolactin level measurements cannot replace visual field monitoring and serial CT examinations.

Strangely the authors do not advise evaluation of the patient's visual fields or acuity, the importance of which cannot be over-emphasized in the management of pituitary lesions. Plain X-rays of the pituitary fossa do not provide any information regarding the extent, if any, of suprasellar extension.

Further, the authors advise that CT scanning should be restricted to patients with serum prolactin levels of over 100ng/ml or patients with moderate elevation of serum prolactin levels but abnormal plain skull X-rays. Such a policy is dangerous if bromocryptine therapy is contemplated. ("almost all patients with increased prolactin secretion should be treated") CT scanning not only documents the presence or absence of a pituitary adenoma and its extent but also discloses any pathology of the hypothalamus or the pituitary stalk. Either of these can cause a mild elevation of serum prolactin levels by interference with production or transportation of prolactin inhibitory factor. Thus, restricting CT scanning to those with very high prolactin levels or plain X-ray abnormalities will result in hypothalamic and para-pituitary tumours being missed. It is recognized that tumors such as tuberculum and diaphragma sella meningiomas, intrasellar and suprasellar craniopharyngiomas, and non-secretory pituitary adenomas are best removed when small because surgical removal of large tumours in this region may be associated with a higher morbidity and mortality. Further, these tumours can easily be missed if visual field defects are not detected early and CT scans are needlessly restricted. What is more, CT scanning is especially important in patients treated with bromocryptine for infertility for should such patients develop visual or hypothalamic disturbance during pregnancy, there will be no baseline to guide management particularly in those cases where reinstitution of bromocryptine thereapy has failed to give a beneficial result.

What are the risks of transsphenoidal microsurgery? In an effort to answer this question, (14) 8 neurosurgeons with considerable transsphenoidal experience reported an operative mortality of only 0.4% in a total of 4876 transsphenoidal operations. It is significant that none of these surgeons lost a patient with a microadenoma. The non-endocrine complication rate was 2.3%. Based on a review of several reported series, the risk of permanent diabetes insipidus and iatrogenic hypopituitarism is estimated to be less than 2% (15).

In view of these considerations, I would propose the following alternative approach to the patient with hyperprolactinaemia:

If the initial prolactin level is not markedly elevated, ie., less than 100ng/ml, it should be repeated to rule out transient, physiological variations. Hypothyroidism and drug ingestion should be excluded and visual fields and acuity determined. When persistent hyperprolactinaemia (>25ng/ml) is demonstrated, a CT scan and X-ray of the pituitary fossa should be performed, even in the absence of any signs of a sellar mass lesion. The CT scan should include the standard axial sections followed by contrast-enhanced coronal sections, and sagittal reconstructioins if indicated.

Bromocryptine therapy should be recommended to the hyperprolactinaemic patient presenting with infertility provided the CT scan shows either no definite

lesion, or only a pituitary microadenoma. I would recommend transsphenoidal microsurgery by a competent neurosurgeon if the patient is unable to tolerate the side effects of the drug. The success rate in normalizing the prolactin level without compromising pituitary function will depend on the surgeon's experience and skill. The patient who is single or who has no immediate desire to be pregnant need not be treated. The place of long-term bromocryptine in the prevention of osteoporosis is still controversial and it must be remembered spontaneous resolution can occur. The patient must be followed up over several years, though, as it is not possible to tell which microadenoma will eventually develop into a macroadenoma.

A neurosurgeon must be consulted should the CT scan show any lesion other than a microadenoma. In fact, it would be advisable for an endocrinologist or gynaecologist to follow up all patients with a CT-demonstrable microadenoma jointly with a neurosurgeon so that any occurrence of tumour expansion can be detected and treated early. Pituitary macroadenomas should primarily be treated by surgery.

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