Drug treatment of hyperprolactinemia

Traitement médical de l’hyperprolactinémie

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Résumé

Le traitement médical de l’hyperprolactinémie fait appel aux agonistes dopaminergiques (DA) : bromocriptine, lisuride, quinagolide, cabergoline. Dans plus de 80 % des cas, une prolactinémie normale et des cycles ovulatoires sont obtenus sous DA. En cas de résistance, il faut changer de DA. La tolérance est parfois médiocre, en particulier avec la bromocriptine qui semble moins bien tolérée que le quinagolide et surtout la cabergoline. En cas d’intolérance à un DA, il ne faut pas hésiter à changer d’agoniste. Sous DA, en cas de macroprolactinomine, la surveillance IRM sera faite après trois mois de traitement pour vérifier la diminution tumorale puis après un an, puis tous les ans pendant cinq ans et une fois tous les cinq ans lorsque le volume de l’adénome est stable. En cas de microprolactinomine, un contrôle est inutile sous traitement. Une IRM peut être faite après un an puis cinq ans. Une fois la normalisation de la prolactine obtenue, on peut essayer d’arrêter le traitement. En effet, lorsque le traitement, en particulier par cabergoline, a été prolongé, la réascension de la prolactinémie et le retour des symptômes de l’adénome hypophysaire et, si nécessaire, donner un traitement par stéroïde sexuel de façon à assurer une imprégnation en stéroïde sexuel satisfaisante et éviter une ostéoporose. En cas de macroprolactinomine, le traitement de première intention est le traitement médicamenteux par les DA. Actuellement, il n’existe pas d’argument pour penser qu’un traitement préalable par les DA avant la chirurgie modifie les résultats du geste chirurgical. En cas de microprolactinomine, le traitement médicamenteux par les DA constitue une bonne option thérapeutique en première intention mais la chirurgie est aussi possible. On peut interrompre le traitement DA après la ménopause en cas de microprolactinomine.

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Abstract

Medical treatment of hyperprolactinemia is based upon use of dopamine agonists (DA): bromocriptine, lisuride, quinagolide and cabergoline. In over 80% of cases, these drugs induce normal prolactinemia and ovulatory cycles. In resistant cases, the DA should be changed. Tolerance may occasionally be poor, particularly with bromocriptine, which appears less well-tolerated than quinagolide and than cabergoline above all. In the event of intolerance to a given DA, another should be tried. In patients with macroprolactinoma treated with DA, MRI monitoring should be carried out after 3 months of treatment to verify tumor size reduction, then after 1 year, yearly for the next 5 years and once every 5 years if adenoma size is stable. In cases of microprolactinoma, control under treatment is pointless. MRI may be performed after 1 year and then after 5 years. Once normal prolactin levels have been achieved, attempts may be made to stop the treatment. When a prolonged treatment is interrupted, especially with cabergoline, progressive increase in serum prolactin and return of hyperprolactinemia symptoms are seen in only around 20–30% of cases, particularly when residual adenoma exists after prolonged treatment. Nevertheless, prolactin levels should continue to be monitored after discontinuation of DA, possibly with MRI monitoring, since prolactin levels may rise again after a number of months or years. When normal prolactin levels have been achieved with DA, another solution consists in reducing the dose or dosing frequency of DA in steps to the lowest effective dose consistent with maintenance of normal prolactin levels and stable adenoma size. For drug-induced hyperprolactinemia, where the causative medication cannot be withdrawn, it is often pointless and possibly even dangerous to administer a DA. It is

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therefore necessary to check for absence of pituitary adenoma and where necessary, begin treatment with sex steroids so as to ensure satisfactory impregnation with sex steroids and avoid osteoporosis. For macroprolactinoma, the first-line treatment is drug therapy with DA. At present, there is no evidence to suggest that prior treatment with DA can modify the outcome of surgery. With microprolactinoma, DA treatment offers a good first-line therapeutic option but surgery may also be useful. DAs for microprolactinoma may be withdrawn after menopause.

1. Introduction

Medical treatment for hyperprolactinemia is based upon use of dopamine agonists (DA): bromocriptine (Parlodel®), lisuride (Dopergine®), quinagolide (Norprolac®) and cabergoline (Dostinex®).

In more than 80% of cases, these drugs induce normal serum prolactin levels and ovulatory cycles [9,23,33,39]. Once normal prolactin levels have been achieved (particularly where these are very low), the tendency is to reduce the dosage (or the rate of administration for cabergoline) in order to obtain the lowest dose consistent with normal prolactin levels to be maintained [39].

In 5–10% of cases, resistance to bromocriptine requires use of an alternative DA (with varying success rates regarding normalization of serum prolactin). Many patients resistant to bromocriptine are sensitive to quinagolide and particularly to cabergoline [2,5–7,13,15,17,34,38,43,44]. Normalization of PRL can take a number of months or years under cabergoline in patients with “resistant” adenomas; in some patients with macroprolactinoma, dissociation of therapeutic effect may occur, with significant reduction in tumor size despite poor laboratory results. In such cases, the minimum aim of treatment is to achieve normal cycles (and stabilization of tumor size), irrespective of PRL. Where no DA are effective, surgery may be contemplated; even if normal prolactin levels are not achieved (as seen especially in macroadenoma and/or invasive adenoma), this approach can nevertheless reduce tumor size and serum prolactin levels. A DA may subsequently be reintroduced in the hope of achieving satisfactory therapeutic objectives starting from a lower post-surgical prolactin level.

Tolerability of DA is occasionally poor (e.g. faintness, nausea, orthostatic hypotension), particularly with bromocriptine, which appears less well-tolerated than quinagolide, which is itself less well tolerated than cabergoline [5–7,13,15,17,34,38,43,44]. Where gastrointestinal intolerance occurs with a given DA, another should be tried, starting at a low dose and gradually up-titrating until normal prolactin levels are achieved. If the doses required to ensure normal PRL are poorly tolerated, the dosage may be reduced with the objective of achieving normal cycles, regardless of PRL level.

2. What neuroradiological follow-up is required with drug therapy?

Neuroradiological follow-up must obviously allow for specific situations. Experience has nevertheless shown that changes in tumor size are generally so gradual (usually taking several months, but in rare cases more than 2 years), that the vast majority of microadenomas do not progress beyond microadenomas (particularly if treated using DA) and that once achieved, tumor size reductions remain stable, especially if DA therapy is continued. Neuroradiological follow-up must thus allow for all of the above factors.

Thus, for macroprolactinoma an initial MRI may be performed after 3 months of treatment, then after 1 year of treatment, yearly for 5 years, and then once every 5 years where stable tumor size is achieved (provided PRL is controlled annually).

For microprolactinoma, most experts regard control during treatment as pointless, with very few recommending initial MRI after 1 year then 5-yearly.

3. If treatment with cabergoline is better tolerated and more effective than the other DA, why not prescribe it as first-line therapy?

Everything effectively seems to point towards prescription of cabergoline as first-line therapy in hyperprolactinemia. However, first-line use of this drug is debated on account of the following two factors: treatment costs (a mean daily dose of 5 mg of bromocriptine costs around €15–18 per month, a mean daily dose of 75 μg of quinagolide costs around €30 per month and a weekly dose of 0.5 mg of cabergoline costs €21 per month) and a wish by patients to become pregnant in the short term, which requires crossover to bromocriptine for the sake of safety, due to lack of adequate epidemiological data concerning the absence of teratogenic effects of cabergoline.

4. Can treatment with DA be discontinued or must it be continued for life?

There are no arguments suggesting any drawbacks of long-term DA therapy (bromocriptine has been prescribed since the 1970s and many women have been on this treatment for more than 20 years).

However, the current tendency is to attempt withdrawal of treatment in patients showing long-term (several years) normalization of prolactin levels, particularly in the light of our experience with cabergoline treatment. After prolonged treatment with bromocriptine, withdrawal results in an increase in PRL and return of hyperprolactinemia symptoms in only around 20–30% of patients [26,36], although after prolonged treatment with cabergoline, this reversal is seen in around two-thirds of patients [11]. Persistence of residual adenoma under treatment constitutes a risk factor for post-withdrawal
relapse [11]. It is therefore reasonable to suspend DA treatment from time to time (once every 2 years?) in order to check whether the patient still needs it. However, attention is required where long-term treatment with cabergoline has been prescribed due to the extremely long half-life of the drug, since prolactin levels can sometimes take months or even years to increase again: extremely long-term (several years) monitoring of PRL is therefore essential before concluding on definitive cure of prolactinoma through drug treatment.

Where normal prolactin levels have been achieved (and where reduction in macroadenoma size is stable), another solution to determine whether attempts to withdraw treatment are warranted consists in gradually reducing the dosage of DA in steps (6 monthly? yearly?) in order to achieve the lowest effective dose ensuring normal PRL levels and maintenance of stable adenoma size [9,12,39].

5. What should be done about drug-induced hyperprolactinemia symptoms?

The presence of hyperprolactinemia in patients on neuroleptics is not necessarily synonymous with clinical signs: in most cases, hyperprolactinemia seen in women on neuroleptics is without consequence [28,40] and the question of therapeutic intervention should be considered more for secondary symptoms of hyperprolactinemia (oligomenorrhea or amenorrhea, vaginal dryness, sexual dysfunction or osteoporosis).

In the event of such symptoms, rather than prescribing a DA (which is generally ineffective), it makes more sense to withdraw the causative medication. However, this may on occasion be difficult or even dangerous, particularly in psychotic patients being treated with neuroleptics (thankfully new-generation or “atypical” neuroleptics appear to be associated with less hyperprolactinemia than conventional neuroleptics [16,32,46]).

In this case, DA may be tried, but unfortunately they are generally ineffective [37] and can result in risk of psychiatric decompensation. Routine verification should be performed by C-T scan or MRI to rule out associated pituitary adenoma, with potential amplification of PRL hypersecretion, although this condition may be cured by straightforward surgery (however, prolactin levels are not necessarily a reliable indicator since serum prolactin levels of up to 400 ng/ml have been seen in patients on neuroleptics [37]). If treatment with a DA is initiated, the therapeutic goal in these patients is not normalization of PRL at all costs but rather restoration of spontaneous cycles (or induction of cycles by progestin prescribed for a period of 10 days each month), which indicate satisfactory estrogen impregnation.

If this cannot be achieved (particularly since contraception may be essential), it is often necessary, particularly in women with amenorrhea due to estrogen deficiency at risk of developing early osteoporosis, to initiate estrogen–progestin replacement therapy or contraceptives (although this approach does not resolve galactorrhea, where present) or to suggest that the psychiatrist replace the patient’s current neuroleptic with an atypical neuroleptic known to be less hyperprolactinemic.

6. While there is some uncertainty concerning the value of drug therapy as first-line treatment in microprolactinoma because of the good results obtained with surgery (cure rate of 85%), there is no doubt in cases of macroprolactinoma with prolactin tumors (generally with prolactin levels well above 150–200 ng/ml)

In effect, in these macroprolactinomas, surgical results are frequently disappointing (with postoperative persistence of hyperprolactinemia in more than 60% of cases, since complete tumor excision is rarely achieved) [9,21,33]. Above all, treatment with DA results not only in normalization of serum prolactin levels but in some 70% cases, dramatic tumoral shrinkage is frequently seen (with rapid resolution of visual problems caused by tumor compression of the optic chiasm) [4,9,33]. If prolactinoma is discovered in children or prepubertal adolescents, in most cases, first-line drug therapy restores gonadotropic function thanks to normalization of serum prolactin levels, leading to satisfactory pubertal development [8,14].

7. In cases of macroprolactinoma under drug treatment with DA, should high doses be used from the outset or do low doses have the same effect?

There is as yet no data supporting the unequivocal recommendation of either approach. However, gradually increasing dose after initiation of treatment ensures better compliance by limiting the initial side-effects.

8. Can initial treatment with DA decrease the outcome of subsequent surgical treatment?

After an initial sensational article describing surgical difficulties following initial therapy with DA [29] resulting in a lower success rate for surgery, as well as studies demonstrating fibrous remodeling of adenomas on histopathological examination [30], the idea has taken root that prior treatment with DA should not be initiated where surgery is envisaged. In fact, a number of controlled prospective studies in which surgeons were unaware whether their patients had previously received DA demonstrated no effect of previous medical treatment either on the “fibrous” nature of adenomas or on the success rate of surgery in the event of microprolactinoma [3,19,20,25,45]. At most, it may be more difficult for surgeons during operations to distinguish adenomas whose images have disappeared from MRI scans following prior treatment with DA. In the case of macroadenoma, treatment with bromocriptine, if given for more than 6–12 weeks, can result in development of fibrosis in some patients, thereby limiting the quality of excision [3,19,20,25,45], but surgical treatment for macroprolactinoma is very rarely adopted these days.

9. Should microprolactinoma be treated after the menopause?

Treatment with DA may be discontinued after menopause in microprolactinoma for two reasons: 1) there is no evidence of harmful effects of hyperprolactinemia on the health other than...
on gonadotrophic function (and thus on ovarian function with problems of infertility and estrogen deficiency and which are therefore only relevant during the childbearing years). In particular, there are no convincing epidemiological arguments in favor of an association between hyperprolactinemia and breast cancer. The majority of studies have found either no association, or at most a non-significant positive association, between post-menopausal breast cancer and serum prolactin [10]. Only one recent study reports an association with borderline significance [41]. Post-menopausal hyperprolactinemia thus appears not to expose patients to risk of breast cancer. 2) The second reason is the spontaneous gradual normalization commonly seen in PRL levels after menopause (44% of cases in one study [27]). Hormone replacement therapy for menopause is not contraindicated. Treatment can be resumed in the event of troublesome galactorrhea.

10. Are there any indications for drug treatment of macroprolactinemia?

In principle, macroprolactinemia should not be treated with DA if it is asymptomatic (in other words, if it is discovered by chance and the patient has no menstrual disorders or galactorrhea) or if the menstrual disorders are due to another cause [22, 31, 42], such as polycystic ovarian disease, the high prevalence of which among the general population is well known [1, 18], since drug treatment is effective in such cases and can even delay investigation for other causes of gonadic or sexual disorders, or lead to infertility [24]. However, authentic prolactinomas are accompanied by authentic hyperprolactinemia as well as macroprolactinemia [35]. In this event, treatment should naturally not be stopped on discovery of macroprolactinemia but drugs should be given as for all cases of hyperprolactinemia: return of normal cycles and/or normal fertility provides practical evidence of the role played by hyperprolactinemia in the patient’s presenting symptoms.

French version

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Références


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