Combined therapy of somatostatin analogues and dopamine agonists in the treatment of pituitary tumours

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Abstract

Pituitary tumours express both somatostatin and dopamine receptors. Medical treatment with somatostatin analogues is a cornerstone of GH- and TSH-secreting tumours, while treatment with dopamine agonists is a cornerstone of prolactin-secreting tumours. Dopamine agonists have also demonstrated some efficacy in patients with GH- and TSH-secreting adenomas. Neither ACTH-secreting nor clinically non-functioning tumours have a well-established medical treatment. Nevertheless, some recent results have indicated a potential usefulness of the dopamine agonist cabergoline in patients with pituitary-dependent Cushing's disease. Combination treatment with both somatostatin analogues and dopamine agonists has been poorly investigated. Some studies conducted in small series have documented an additive effect of both drugs in patients with GH-secreting adenomas. Of mention is that none of the studies were randomised and cross-sectional so that the results should be confirmed by other well-designed studies. No data are available in other pituitary tumour histotypes. Preliminary observations in patients with clinically non-functioning adenomas are very promising.

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Introduction

The somatostatin and dopamine systems constitute two major neurotransmitter networks that share a number of structural and functional features. The various actions of somatostatin and dopamine are mediated by five specific receptor subtypes: sst₁–sst₅ and D₁–D₅ respectively. Two different isoforms of sst₂ and D₂ have been found and characterised. The different somatostatin and dopamine receptors have variable organ-, tissue- and cytospecific distribution and play different physiological roles (1, 2). Somatostatin receptors have been demonstrated to be highly expressed in pituitary adenomas, with a predominance of sst₂ and sst₅ and infrequent expression of sst₄ (3–8). The expression of sst₂ predicts a response to octreotide and lanreotide, the two somatostatin analogues most widely used in clinical practice which show high affinity for sst₂ and sst₅ and low affinity for sst₃ (9, 10).

The D₂ receptor has been clearly demonstrated in both prolactin (PRL)-secreting (5) and non-PRL-secreting pituitary tumours (6, 7–11), and its presence and intensity of expression predict a response to treatment with dopamine agonists. Moreover, D₂ has been found in thyrotrophin (TSH)- and follicle-stimulating hormone/luteinising hormone-secreting pituitary tumours, although treatment with dopamine agonists is still debated in patients bearing these tumours because of a low density of D₂ or different distribution of D₂ isoforms compared with prolactinomas (12, 13). More recently, expression of D₂ receptors has been found also in adrenocorticotrophin (ACTH)-secreting pituitary adenomas and, interestingly, the D₂ receptor expression was found to be correlated with the short-term response to cabergoline (14). Among the different dopamine agonists, cabergoline has been demonstrated to be the most effective in controlling hormonal hypersecretion and inhibiting tumour growth in pituitary tumours (12–14).

Furthermore, a functional interaction between D₂ and sst₅ receptors has recently been reported (15), suggesting a potential benefit from the combined targeting of these receptors.

The use of a combined somatostatin analogue and dopamine agonist treatment schedule seems to be of particular interest in growth hormone (GH)-secreting

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adenomas that are known to be potentially responsive to both classes of compounds (16–25). More recently, non-functioning pituitary adenomas were shown to be sensitive to a combined treatment, whereas the response rate to somatostatin analogues or dopamine agonists alone is limited. No study with combined therapy has so far been reported in PRL- and ACTH-secreting adenomas, and no rationale exists today for such an approach with the presently available somatostatin analogues.

This review focuses on literature data reporting on the results of combined somatostatin analogues (octreotide or lanreotide) plus dopamine agonists (bromocriptine or cabergoline) in patients bearing GH-secreting or clinically non-functioning pituitary tumours.

GH-secreting tumours

Several groups have investigated the possible therapeutic role of a combination therapy of somatostatin analogues and dopamine agonists in the inhibition of GH and insulin-like growth factor-I (IGF-I) levels in acromegalic patients. Before octreotide was introduced, bromocriptine was the only available medical therapy for acromegaly (26). Bromocriptine was shown to suppress random growth hormone levels to $<10 \mu\text{g/l}$ in 50% of patients, but IGF-I levels normalise in only 10% of treated patients and $<20\%$ of GH-secreting tumours were reported to reduce in size (26). The subjective clinical symptoms improved in 70–90% of patients (26). Quinagolide, another dopaminergic agent, at a dose of 0.3–0.6 mg/day suppressed GH and IGF-I levels to normal in about 30% of the treated patients (16). More impressive results were obtained using cabergoline, a long-lasting $\text{D}_{2,4}$ -selective dopamine agonist. In a large series of 64 patients, treatment with cabergoline suppressed plasma IGF-I below $300 \mu\text{g/l}$ in 39% of cases and between 300 and $450 \mu\text{g/l}$ in another 28%; in GH/PRL-co-secreting adenomas ($n=16$) 50% of cases suppressed IGF-I levels below $300 \mu\text{g/l}$, and another 31% did so between 300 and $450 \mu\text{g/l}$, in contrast to only 35 and 27% respectively in pure GH-secreting adenomas (27). Additionally, tumour shrinkage was demonstrated in 13 out of 21 patients, with an $\approx 50\%$ mass reduction in five GH/PRL-co-secreting adenomas (27). Data were less impressive in our study showing that cabergoline did not normalise GH or IGF-I levels in 11 patients with GH-secreting tumours treated with 1 mg twice a week (16). Increase of the dose up to 0.5 mg/day was associated with suppressed GH and decreased tumour size (28).

Somatostatin analogues were introduced as an effective therapy for acromegaly ≈ 20 years ago. In a recent meta-analysis (29), it was reported that both depot formulations of somatostatin analogues, namely octreotide-LAR and lanreotide, are effective in 50–75% of patients with acromegaly. When given as first-line treatment, somatostatin analogues induce tumour

shrinkage by $>20\%$ in 80% of patients (29). This implies that 25 to 50% of the patients, in different series, do not fully respond to somatostatin analogues.

Combined treatment with octreotide and bromocriptine was initially observed to have an additive effect on GH and IGF-I suppression in patients with acromegaly when compared to treatment with either drug alone (16, 17, 30). The bioactivity of bromocriptine increases when administered alongside octreotide (17). *In vitro* studies highlighted that both bromocriptine and octreotide at high doses are able to inhibit cell growth from human somatotroph adenomas (18). A dose of 1 nmol/l bromocriptine decreased cell growth in 40% of somatotroph cell cultures, whereas $10 \mu\text{mol/l}$ decreased cell counts in all somatotrophs and in 92% of non-functioning adenoma cultures. Both 1 and $10 \mu\text{mol/l}$ octreotide significantly decreased cell counts in 50% of somatotroph cell cultures.

Subsequent *in vivo* studies have confirmed that the combination of somatostatin analogues and dopamine agonists is more effective than somatostatin analogues alone in reducing GH levels in patients with GH-secreting adenomas resistant to somatostatin analogues (17, 19–25).

In 51 acromegalic patients, acute co-administration of bromocriptine (2.5 mg) and octreotide (0.05 mg) had an additive suppressive effect on GH hypersecretion (19). In particular, GH levels were <2 and $5 \mu\text{g/l}$ in 32 and 56% of acromegalic patients respectively. GH levels decreased by more than 50% in 84% of patients (19). The combination of more potent dopamine agonists, such as cabergoline, with a depot preparation of somatostatin analogues, such as lanreotide, allowed us to achieve normalisation of IGF-I levels in five out of ten cases (23). Figure 1 shows the individual GH and IGF-I levels before and during different treatment schedules of these ten patients previously reported.

In contrast with these findings, Fredstorp *et al.* did not find any difference between octreotide alone and octreotide plus bromocriptine therapy in reducing GH levels in acromegalic patients (31).

In vivo and *in vitro* experiments were performed to evaluate the anti-secretive activity of somatostatin and dopamine analogues in four patients bearing mixed GH/PRL-secreting tumours, and data were correlated with the results of *in vivo* somatostatin and dopamine receptor scintigraphy and with immunohistochemical findings (32). These patients, presenting similar clinical findings and comparable peripheral hormone levels, showed different responsiveness to somatostatin and dopamine analogues. Moreover, primary tumour cell culture experiments showed that octreotide and dopamine had an inhibiting activity on GH and PRL secretion, which was positively correlated with the response observed *in vivo*. In another study, Zatelli *et al.* (33) investigated $\text{D}_{2,4}$ sst₂ and sst₅ receptor expression in 24 GH-secreting pituitary adenomas and tested the effects of somatostatin agonists selectively interacting with sst₂ (BIM-23 120)

Figure 1 Serum GH levels (top) and serum IGF-I levels (bottom) in ten patients with resistant acromegaly. Data are derived from ref. 22. The patients were initially treated with subcutaneous octreotide (OCT; Sandostatina, Novartis, Italy) at a starting dose of 0.3 mg/day over three doses, increased up to 0.6 mg/day after 1 month, to achieve normalisation of GH and IGF-I levels. After 6 months, quinagolide (CV; kindly provided by Novartis, Italy) was added for 3 months at a dose of 0.3 mg twice daily, because GH and IGF-I were not suppressed. Due to the unresponsiveness to the combination scheme intramuscular lanreotide (LAN; Ipstyl, Ipsen, Milan, Italy) treatment was initiated, after 15–30 days wash-out from OCT+CV treatment, at a dose of 30 mg at 14-day intervals for 3 months and then at 10-day intervals in all patients. After a 6-month treatment, cabergoline (CAB; Dostinex, Pharmacia&Upjohn, Italy) was added at a dose of 1.5 mg per week (0.5 mg three times a week) for the first month and then at a dose of 3.5 mg per week (0.5 mg daily) for another 2 months. At the end of the study five of ten patients achieved control of GH and/or IGF-I levels. Normal GH levels are in the grey area (≤ 2.5 µg/litre) while normal IGF-I levels for age and gender are marked by an asterisk.

and sst₅ (BIM-23 206) on GH secretion in primary culture. GH secretion was inhibited by BIM-23 120 in all samples, while it was reduced by BIM-23 206 only in adenomas not expressing D₂. These results suggest that adenomas expressing D₂ are less likely respond to the clinically available somatostatin analogues in terms of inhibition of GH secretion (33).

In summary, a few studies reported an additive effect of dopamine agonists (mainly cabergoline) to that of

somatostatin analogues on suppressing GH and IGF-I levels. Though experimental data support these clinical observations, the combined treatment with depot somatostatin analogues plus dopamine agonists is not routinely applied to patients partially responsive to somatostatin analogues. A recruitment bias of previous studies is the inclusion of most patients with concomitant hyperprolactinaemia. More recently, Cozzi *et al.* (24) reported that the addition of cabergoline, using the minimal effective and the maximal tolerated dose (range 1–3.5 mg/week), significantly decreased GH and IGF-I levels after 6 months (Fig. 2); in this study, results were not dependent on PRL status (serum levels or immunohistochemistry). The combined treatment decreased GH to < 2.5 µg/l in 21% of 19 patients and normalised IGF-I for age in 42% of patients (24).

Therefore, randomised, prospective, controlled studies are required to confirm the beneficial effect of a combined treatment of somatostatin analogues plus dopamine agonists in acromegaly.

Non-functioning pituitary adenomas

Clinically non-functioning adenomas (NFA) represent a very heterogeneous group of pituitary tumours, accounting for 25% of all pituitary adenomas (34).

Presently, there is no established role for pharmacotherapy in NFA. There is a rationale for both dopamine agonists and somatostatin analogues in the treatment of NFA in accordance with *in vitro* and *in vivo* evidence of dopamine and somatostatin receptor expression in this adenoma histotype (7, 35–42). However, the results of bromocriptine, quinagolide (36–40) and octreotide treatment (43–46) were disappointing in almost all studies, except for some case reports.

The majority of studies on dopamine agonists in these tumours were performed with bromocriptine, which inhibited hormone secretion *in vitro* and *in vivo* in a consistent percentage of cases but inhibited *in vitro* tumoural cell growth and reduced *in vivo* tumoural mass only in a minority of patients (7, 36, 37, 47). In particular, bromocriptine sporadically induced tumour shrinkage only by using high doses of drug. A few studies have investigated the efficacy of quinagolide in the treatment of these tumours. Quinagolide induced a short-term inhibition of gonadotrophins and/or α -subunit secretion in 80%, tumour shrinkage in 20% and tumour stabilisation in 60% of cases (48). The higher efficacy of quinagolide compared to bromocriptine in reducing pituitary tumour mass in a 39-year-old woman was also demonstrated (39). On the other hand, pituitary tumour uptake at scintigraphy with radio-labelled dopamine analogue, [¹²³I]-methoxybenzamide, was predictive of hormone inhibition and tumour shrinkage in patients with clinically non-functioning pituitary tumours (49). Moreover, cabergoline treatment

Figure 2 Serum GH levels (top) and serum IGF-I levels (bottom) in 19 patients with resistant acromegaly. Data are derived from ref. 23. The patients were receiving somatostatin analogue therapy and without any change in dose or schedule of somatostatin analogue treatment, cabergoline (CAB; Pharmacia) was started at 0.25 mg during evening meal twice a week for 2 weeks. The dose was then progressively up-titrated, adding 0.25 mg every week until the dose of 0.25 mg four times weekly was reached or side-effects occurred. This dose was administered for 1 month.

has recently been demonstrated to induce tumour shrinkage: 7 out of 13 patients had tumour shrinkage above 10% of the initial volume and four patients achieved an increasing distance of the tumour from the optic chiasm because of shrinkage (50). Additionally, two out of nine patients with visual field defects before therapy showed improvements in visual acuity during cabergoline treatment (50). These data suggested improved effectiveness of cabergoline over bromocriptine in the treatment of this category of pituitary tumours as well (50). Another recent study demonstrated that 1 year of cabergoline treatment at the dose of 3 mg/week induced more than 25% tumour shrinkage in 56% of patients with clinically non-functioning tumours (51). In this study, tumour shrinkage by cabergoline treatment was accompanied by a significant correlation with D_2 receptor expression (51). Some degree of tumour shrinkage was also noted during cabergoline treatment; greater tumour shrinkage was observed in patients with expression of mRNA D_2 receptors on their tumour membrane surfaces (Fig. 3).

Somatostatin analogues represent another category of drugs used in the medical treatment of NFA. Their utilisation in NFA was justified by the evidence of sst receptor expression in these tumours. The reduction in tumour volume during octreotide treatment has been reported in a few NFA-bearing patients. Liuzzi *et al.* (52) reported tumour reduction in 15% of 20 patients and Plockinger *et al.* (44) reported in 50% of four patients. Warnet *et al.* (46) reported a tumour mass decrease in two NFA patients who undergone short-term octreotide treatment.

The presence of both somatostatin and dopamine receptors in NFA suggests the possibility of treating these tumours with somatostatin and dopamine agonists (37–40, 44, 45, 52–55). As already mentioned, a functional interaction between D_2 and sst₅ receptors has recently been reported (15), supporting a potential benefit from combined use of these two categories of compounds. In a recent study, the effect of combination therapy with octreotide and cabergoline was investigated

Figure 3 Exemplary cases of tumour mass change after 1 year of cabergoline treatment and comparison with the expression of dopamine receptor in the tumour as evaluated at the RT-PCR study. DR, dopamine receptor; D_{2i}, D₂ receptor isoforms (D_{2short} and D_{2long}); MW, molecular weight. Case 1 represents a case not responsive to cabergoline with a maximal diameter reduction of 0% and a tumour volume increase of 4% of baseline; the RT-PCR shows no expression of any dopamine receptor in the tumour. Case 3 represents a case responsive to cabergoline with a maximal diameter reduction of 36% and a tumour volume decrease of 52% of baseline; the RT-PCR shows the expression of D_{2long}, D_{2short} and D₄ in the tumour. Data drawn from Ref. 51 with permission of the Endocrine Society.

in ten patients with NFA (55). Tumour shrinkage > 10% has been reported in six out of ten patients. However, markedly high doses of octreotide and cabergoline, accounting for 200 µg × 3/day and 0.5 mg/day respectively, had been employed. Recent studies on patients with NFA treated with somatostatin analogues have shown a rapid improvement of the visual field in most cases (56, 57).

On the basis of these data, combined therapy can be an efficacious and safe schema in the treatment of NFA, since it enables induction of remnant tumour shrinkage in most of the patients who previously undergone surgery, together with a marked improvement in visual function. Unfortunately, to date, no studies have been reported using modern somatostatin analogues in combination with cabergoline to respond to this hypothesis.

Conclusion

Pituitary tumours express both somatostatin and dopamine receptors with a pattern that differs according to different tumour histotypes. Treatment with dopamine agonists is characteristically effective in PRL-secreting tumours, but GH-, TSH-, ACTH-secreting tumours and NFA may also show some degree of efficacy. Treatment with somatostatin analogues is effective particularly in GH-secreting tumours, but also in TSH-secreting tumours and (much less) in NFA. The combination treatment with both drug classes has been shown in a few studies of clinical relevance in GH-secreting adenomas and NFA. Further studies with

the new selective analogues and the new chimeric compounds will further enlarge the possibility to treat pituitary tumours using a medical approach.

In particular, the use of the so-called universal ligand, SOM230, which is able to bind with high affinity to the sst₁₋₃ and sst₅, either alone or in combination with cabergoline or other selective D₂ agonists, would probably be of use in treating more patients with resistant pituitary and (potentially) neuroendocrine tumours. The preliminary data of SOM230 in acromegaly (58) and Cushing's disease (59) are very promising, but further studies are needed to clarify the role of this new drug (alone or in combination with dopaminergic drugs) in the algorithm of therapy of pituitary adenomas.

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