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A comparison of single-dose effects of short acting somatostatin analogs: octreotide vs pasireotide in patients with acromegaly

Porównanie skuteczności jednorazowego podania krótkodziałających analogów somatostatyny: oktreotydu i pasireotydu u pacjentów z akromegalią

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Słowa kluczowe

akromegalia, pasireotyd, krótkodziałające analogi somatostatyny

S u m m a r y

Introduction. Acromegaly is a rare endocrine disorder caused in most cases by growth hormone secreting pituitary adenoma. The aim of acromegaly treatment is biochemical normalization of GH and IGF-1 concentrations leading to mortality risk reduction to the level expected in the general population. First-line medical treatment includes first generation long acting somatostatin analogs: octreotide LAR and lanreotide autogel. Recently, pasireotide – a second generation somatostatin analog has been widely investigated in acromegalic patients.

Aim. The aim of this study was to compare the single-dose effects of short acting somatostatin analogs: octreotide and pasireotide in patients with active acromegaly.

Material and methods. 13 patients with active acromegaly were enrolled in the study. All patients had short acting octreotide and pasireotide administered on two following days and GH and IGF-1 concentrations measured before and after drug administration. Nadir GH concentrations were compared.

Results. Nadir GH value in octreotide test was reached 60 minutes after drug administration, while in pasireotide test – 180 minutes after drug administration. Median nadir GH was 3.25 ug/L (1.99-4.11) vs 1.84 ug/L (0.97-2.03) respectively, p = 0.002.

Conclusions. Short acting pasireotide is more effective than short acting octreotide in supression of GH release in patients with active acromegaly.

S t r e s z c z e n i e

Wstęp. Akromegalia jest rzadką chorobą powodowaną najczęściej przez gruczolak przysadki wydzielający autonomicznie hormon wzrostu. Celem leczenia akromegalii jest normalizacja stężeń GH i IGF-1 prowadząca do zmniejszenia śmiertelności do poziomu opisywanego w populacji ogólnej. Lekami z wyboru w akromegalii są długodziałające analogi somatostatyny pierwszej generacji: oktreotyd LAR oraz lanreotyd autogel. W ostatnim czasie pojawiły się doniesienia mówiące o większej skuteczności pasireotydu w porównaniu z oktreotydem u pacjentów z akromegalią.

Cel pracy. Celem pracy było porównanie skuteczności jednorazowego podania krótkodziałających analogów somatostatyny: oktreotydu i pasireotydu u pacjentów z czynną akromegalią.

Materiał i metody. Do badania włączono 13 pacjentów z czynną akromegalią. U wszystkich pacjentów w dwóch kolejnych dniach podano podskórnie krótkodziałający oktreotyd oraz krótkodziałający pasireotyd. Oznaczono stężenie GH i IGF-1 przed podaniem oraz po podaniu obu leków.

Wyniki. Najniższe stężenia GH osiągnięto w 60. minucie po podaniu oktreotydu oraz w 180. minucie po podaniu pasireotydu. Wynosiły one średnio 3,25 ug/l (1,99-4,11) po podaniu oktreotydu oraz 1,84 ug/l (0,97-2,03) po podaniu pasireotydu. Różnica jest istotna statystycznie (p = 0,002).

Wnioski. Krótkodziałający pasireotyd okazał się skuteczniejszy niż krótkodziałający oktreotyd w obniżaniu stężenia GH u pacjentów z czynną akromegalią.

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INTRODUCTION

Acromegaly is a rare and severe disease. In over 90% of cases it is caused by excessive secretion of growth hormone (GH) by pituitary adenoma resulting in elevated serum insulin-like growth factor-1 (IGF-1) (1). This leads to doubling of the mortality rate and reduction in life expectancy by about 10 years among acromegalic patients compared to general popula-

tion (1, 2). The main goals of treatment are biochemical normalization, symptoms relief, reduction of tumor volume, maintenance of pituitary function and finally mortality risk reduction.

According to Endocrine Society Clinical Practice Guidelines the first-line therapy is transsphenoidal surgery followed by medical treatment in patients with active disease postoperatively. The medical treatment of choice are somatostatin receptor ligands (3).

Somatostatin receptors are present on the surface of GH-secreting pituitary adenomas, 90% of which are sst2 and sst5 (two from all 5 subtypes of somatostatin receptors). Due to their anti-proliferative effect somatostatin receptor ligands reduce not only the secretion of GH but also tumor volume. There are two equally effective long-acting preparations of first generation available: octreotide LAR and lanreotide autogel (4). They bind selectively to sst2 and to lesser extend to sst5 receptors. Recently, the use of pasireotide – a second generation somatostatin analogue with higher affinity to sst5 receptors has been widely investigated in acromegalic patients.

AIM

The aim of this study was to compare the effects of short acting pasireotide and octreotide on GH release in acromegalic patients.

MATERIAL AND METHODS

Thirteen adult male and female patients with active acromegaly (GH > 1.0 ug/L and/or elevated IGF-1 for age- and sex-matched controls) were enrolled in the study. There were 4 men and 9 women with an average age of 45 years ± 12 in the group. There were 2 *de novo* patients with acromegaly and 11 acromegalic patients who have already been treated with long acting somatostatin analogs alone or with dopamine agonists. The median time of treatment was 5 years (2.5-12.5). Eight patients underwent a transsphenoidal surgery, 2 patients had inoperable tumors and 1 had been prepared for operation with octreotide LAR. Three patients were treated with long acting somatostatin analogs alone and 8 with long acting somatostatin analogs and dopamine agonists. There were no patients treated with radiotherapy. Table 1 shows the characteristics of the patients.

All patients had both short acting octreotide and short acting pasireotide tests performed on two following days. On the first day short acting octreotide 100 μg was administered subcutaneously. On the next day short acting pasireotide 60 mg was administered subcutaneously. On both days blood samples for GH were collected just before and 60, 120 and 180 minutes after drug administration and for IGF-1 at time points 0' and 180'.

The statistical analysis was performed using STAT software. The assumption of normality of all data was investigated by Shapiro-Wilk test. When the data did not represent a random sample from normal distribution, p-values from Wilcoxon's signed-rank tests were reported (GH concentrations). By normal distribution p-values from paired t-tests were reported (IGF-1 concentration).

RESULTS

The median baseline serum GH concentration was 5.05 μg/L (IQR: 3.97-11.8) before octreotide administration and 7.89 μg/L (3.75-21.0) before pasireotide administration. The average baseline serum IGF-1 concentration was 675.98 ng/mL ± 187.93 before octreotide administration and 662.28 ng/mL ± 185.34 before pasireotide administration. The differences in baseline GH and IGF-1 concentrations were statistically insignificant ($p = 0.34$ and $p = 0.23$). In octreotide test most patients (61.54%) reached the nadir GH value 60 minutes after drug administration, whereas in

Table 1. The characteristics of the enrolled patients.

	Age	Sex	GH [ug/L] baseline	IGF-1 [ng/mL] baseline	Treatment duration [years]	Surgical treatment	Pharmacological treatment
1	30	M	11.8	810.2	0.5	0	Octreotide LAR
2	55	F	3.36	477.9	14	1	Octreotide LAR
3	38	F	4.21	678	5	1	Lanreotide autogel + cabergoline
4	58	F	18.6	627.3	0	0	*De novo*
5	47	F	3.97	732.8	17	1	Octreotide LAR + bromocriptine
6	43	F	59.3	882.1	0	0	*De novo*
7	67	F	4.15	681.7	0	Inoperable	Octreotide LAR + bromocriptine
8	44	F	5.05	626.4	3	1	Lanreotide autogel + bromocriptine
9	28	F	7.49	577.9	2	1	Octreotide LAR
10	34	M	5.82	905.8	11	1	Octreotide LAR + cabergoline
11	55	M	0.78	306.7	15	1	Lanreotide autogel + cabergoline
12	56	F	2.48	507.2	10	1	Lanreotide autogel + bromocriptine
13	35	M	27.2	973.8	5	Inoperable	Octreotide LAR + bromocriptine

pasireotide test 84.61% of patients reached the nadir GH 180 minutes after drug administration. We compared nadir GH concentrations after octreotide vs pasireotide administration. Median nadir GH in octreotide test was 3.25 ug/L (1.99-4.11) vs 1.84 ug/L (0.97-2.03) (p = 0.002). Figure 1 presents nadir GH values in both tests. In all patients nadir GH after pasireotide administration was lower than nadir GH after octreotide administration. Nadir GH values after octreotide administration were lower than 2.5 ug/L in 6 patients (46.15%) and lower than 1 ug/L in 2 patients (15.38%) compared to 10 patients (76.92%) and 4 patients (30.77%) after pasireotide administration respectively.

In our study short acting octreotide was well tolerated, while in pasireotide test 5 patients (38.46%) reported nausea and weakness lasting up to 2 hours after drug administration. Serious adverse events were not reported.

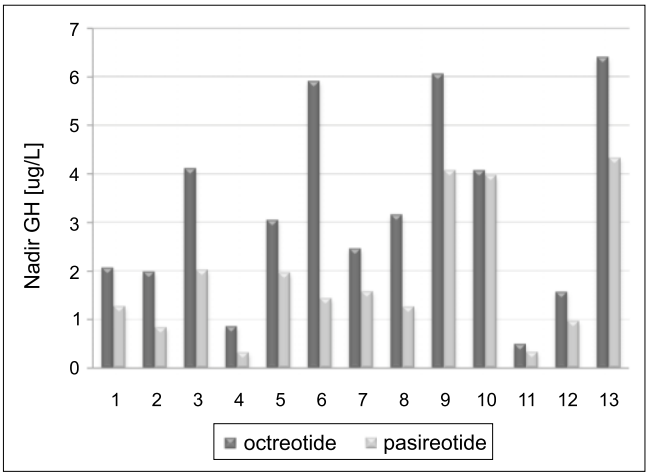

Fig. 1. Nadir GH values octreotide vs pasireotide.

DISCUSSION

We have observed better response to short acting pasireotide vs short acting octreotide expressed as lower values of nadir GH concentration in all enrolled patients (in both *de novo* patients and previously treated and uncontrolled patients). The suppression of GH release is stronger after pasireotide administration.

Not much has been published regarding short acting somatostatin analogs use in acromegaly. Van der Hoek et al. have already compared acute effects of octreotide and pasireotide (5). They have presented three different patterns of response to pasireotide, related to sst receptors distribution on tumor cells: equal effectiveness in lowering GH concentration of both analogs, better effectiveness of pasireotide than octreotide or better effectiveness of octreotide. It shows the pivotal meaning of molecular mechanisms responsible for pasireotide effects.

It is already known that there are five somatostatin receptors expressed in the adult human pituitary gland (sst1, sst2, sst3, sst4, sst5). Sst2 receptors are found in 95% of GH-secreting pituitary adenomas whereas sst5 receptors are expressed in 85% (6). Other receptors are less common. First generation somatostatin analogs bind mainly to sst2 receptors, while a second generation analog – pasireotide has the ability to bind to four of the five types of sst receptors (sst1, sst2, sst3 and sst5). Pasireotide's affinity for sst5 is 39-fold higher than octreotide's and for sst2 is 2,6-fold lower than octreotide's, but 2-fold higher in comparison to endogenous somatostatin (7-9). Due to its specific receptors affinity pasireotide seems to be promising in patients resistant to first generation somatostatin analogs. In our study we had no data on the receptors' pattern on the tumor cells, so the efficacy of the analogs administered cannot be assessed regarding its receptors affinity. However, due to the fact that the majority of enrolled patients were previously treated with first generation long acting somatostatin analogs without reaching the biochemical control of disease, we may presume the high expression of sst5 on their tumor cells.

The fact that nadir GH levels were reached in our study in various time points after octreotide and pasireotide administration is the evidence of different pharmacokinetics of the investigated analogs. As already indicated short acting octreotide reaches its peak concentration 40 minutes after the injection and has a mean t1/2 of 1.7 hours (1, 8). That is why we observed the lowest GH levels 60 minutes after octreotide administration and no statistic significance between GH level before and 180 minutes after octreotide injection was reported. Pasireotide has much longer half-life (t1/2 = 7-11 hours), more stable biochemical structure and reaches its peak concentration after 0.25-0.5 hours after the injection, which causes more sustained working profile (8, 9).

There are much more data published regarding long acting somatostatin analogs. As already known both first generation analogs seem to be equally effective in acromegaly (10). Although there was no head to head well-designed trial comparing the efficacy of octreotide LAR and lanreotide autogel, it has been shown that 20 to 70% (depending on population and study protocol) of patients treated with octreotide long acting release or lanreotide depot do not achieve biochemical control of acromegaly (10-12). Colao et al. have shown several possible reasons for octreotide and/or lanreotide resistance pointing the expression of sst2 and sst5 receptors on tumor surface, somatostatin receptor genes mutations and clinical predictors such as age, gender, initial GH and IGF-1 serum concentration and tumor mass (7).

Long acting pasireotide has already been investigated in acromegaly. Gadelha et al. have compared the effectiveness of pasireotide LAR to octreotide LAR in acromegalic patients (13). They have shown that after 24 weeks of treatment pasireotide LAR had led to normalization of serum IGF-1 and GH levels in 15 to 20% of patients uncontrolled during octreotide treatment.

The status of pasireotide in acromegaly treatment still remains unclear. It seems to be more effective than

octreotide. However, further investigation is required to define the groups of patients who would benefit the most from pasireotide therapy.

CONCLUSIONS

1. Pasireotide was more effective in supressing GH release than octreotide in patients with active acromegaly.
2. Molecular mechanism is probably responsible for differences in effectiveness of pasireotide and octreotide. The analogs have different receptors affinity. Octreotide binds mainly to sst2 receptors, while pasireotide binds to multiple somatostatin receptors, predominant sst5.
3. Pasireotide may be a good alternative in acromegalic patients resistant to octreotide.

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