The effects of salmon calcitonin on prolactin secretion in women with pathologic hyperprolactinemia

Miyase BAYRAKTAR, Aydan USMAN

Department of Endocrinology, Hacettepe University School of Medicine, Ankara, TURKEY

Data exist that suggest calcitonin may be an important intrapituitary regulator of prolactin release. The present study was designed to determine whether exogenously used salmon calcitonin has an effect on prolactin release in patients with pathological hyperprolactinemia. Saline (2 ml) or salmon calcitonin (100 MRC units) was injected intravenously to women with pathologic hyperprolactinemia on separate days in random order. Following salmon calcitonin or saline administration, venous samples were obtained every 30 minutes for 5 hours for prolactin, calcium and salmon calcitonin levels. Serum calcium levels did not change significantly across time with infusion of either saline or salmon calcitonin. Salmon calcitonin levels were undetectable initially and rose to 6.06±0.61 ng/ml at 30 minutes after salmon calcitonin infusion and remained undetectable following saline administration. A mean 43.9% reduction in prolactin levels was observed 5 hours after salmon calcitonin infusion. No change in prolactin levels was achieved following saline infusion. At all times, the prolactin levels were significantly lower following an infusion of salmon calcitonin as compared to saline. These findings suggest that exogenously administered salmon calcitonin suppress prolactin secretion in individuals with pathologic hyperprolactinemia in a manner similar to what it does in normal individuals presumably by acting directly on pituitary lactotrophs. [Turk J Med Res 1995, 13(5):177-179]

Key Words: Calcitonin, Hyperprolactinemia, Prolactin, Calcium

In addition to the well-known hypocalcemic action of calcitonin (CT), it is also known to inhibit the secretion of several hormones including insulin, TSH and growth hormone in men (1-3). The mechanism by which CT suppresses these hormones is not completely known. The presence of immunoreactive salmon calcitonin (sCT) and specific bindings sites for it have been demonstrated in several areas of the human brain, particularly in the posterior hypothalamus, median eminence and pituitary gland (4,5).

Data suggesting a potential neuroendocrine role for sCT has been accumulating for several years. Both in vitro and in vivo studies suggest that parenterals as well as centrally administered sCT can alter prolactin (PRL) secretion.

In the present study, the effects of intravenously administered sCT on PRL secretion in women with pathological hyperprolactinemia was investigated.

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Correspondence: Miyase BAYRAKTAR
Department of Endocrinology
Hacettepe University School of Medicine,
Ankara, TURKEY

MATERIALS AND METHODS

Ten women with established chronic hyperprolactinemia participated in this study. Their mean age was 37±2 years (ranging from 32-48). Four had persistent hyperprolactinemia despite a prior sphenoidal surgical procedure and resection of a PRL secreting adenoma. Of the remaining 6 patients, 3 were diagnosed as having a. PRL secreting pituitary adenoma on the basis of the following criteria: prolactin level >200 ng/ml and the presence of a pituitary adenoma demonstrated by computed tomography. The other three patients had a diagnosis of idiopathic persistent hyperprolactinemia. Their serum PRL levels were less than 100 ng/ml but above 30 ng/ml. The computed tomography scans of these 3 were normal. None of the patients had been using a PRL lowering medication for at least 1 month before the initiation of the study. All 10 gave informed written consent for the studies performed.

The study was performed on two different days at least seven days apart. After an overnight fast at 8-9 a.m., an intravenous cannula was inserted into both antecubital veins of the patient. Either sCT (100 MRC units) or saline (2 ml) was injected by intravenous push and blood samples were obtained at -15, 0, 30, 60, 120, 180, 240 and 300 minutes after the bolus in-

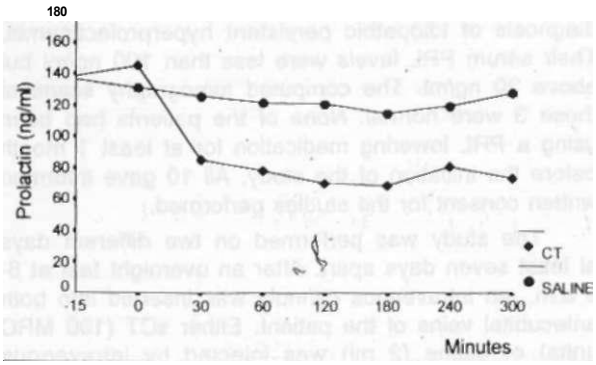
fusion from the opposite side. The patient remained in a supine position throughout the study interval.

The plasma of each sample was collected by centrifugation at 4°C and stored at -20 °C until being assayed. PRL levels were measured using a commercially available radioimmunoassay kit (Kodak Clinicla Diagnostics, Amersham UK). The inter and intraassay coefficient of variations for this assay were 2.4-4.3% and 4.6-5.8% respectively. Plasma sCT was measured by RIA using a Salmon Calcitonin Kit (Diagnostic System Laboratories, Inc. USA). Plasma calcium and phosphorus levels were measured by atomic absorption spectroscopy.

All results are expressed as mean ± SEM. The data were analyzed using two way analysis of variance and a paired T - test. A p value <0.05 was considered to be significant.

RESULTS

Flushing and transient nausea occurred in seven patients after sCT administration. There were no adverse reactions to the normal saline infusions. No significant change in plasma calcium and phosphorous levels were obtained in the 10 patients throughout the study period (Data not shown). Plasma sCT levels were undetectable at the beginning of each study and throughout the saline study. In response to sCT infusion, the plasma sCT levels rose to a peak value of 6.06±0.61 ng/ml at 30 minutes and remained stable during the rest of the study period. Basal serum PRL levels before the sCT and saline administration studies were similar (145.17±35.42 ng/ml vs. 131.08±26.82 ng/ml respectively, p=NS). A marked reduction in PRL levels was seen after sCT administration but not after the saline infusion (Figure 1). The reduction in PRL levels was most marked at the 30 minute time point. The PRL level declined from a value of 145.17±35.42 ng/ml prior to sCT to a value of 84.58±16.78 ng/ml 30 minutes after sCT injection. Five hours after the sCT injection, the PRL level was still reduced by 43.9% on mean.



Figüre 1. Mean PRL levels after sCT and saline injection.

DISCUSSION

In the present study, an intravenous injection of sCT markedly inhibited PRL secretion in 10 patients with pathologic hyperprolactinemia. The effect was most prominent at 30 minutes, but persisted for at least 5 hours.

Several investigators have been described an inhibitory effect of sCT on PRL release in healthy subjects, in individuals with impaired renal function and in pyschotic patients on neuroleptic drugs (6-8). Using human, porcine, eel calcitonin, a similar inhibitory effect on PRL secretion has not been seen in either normal subjects or patients with prolactinemia (9-11). The reason for the failure of these calcitonins to inhibit PRL secretion in these reports may have been due to the structural difference that exists between sCT and other forms of calcitonins. In this regard, sCT Is reported to be more potent than human calcitonin using several different assay endpoints.

The mechanism by which sCT imparls PRL secretion is not clear. Shah et al (12,13) reported that sCT inhibits both basal and TRH stimulated PRL release. It also reduces basal and TRH stimulated PRL mRNA levels in cultured lactotrophs. This suggests that the inhibitory affect of sCT occurs at the level of the lactotraph. The regulation of PRL in pathological hyperprolactinemia is different than taht which occurs in normals. Thus, it was important to demonstrate that sCT could suppress PRL secretion in individuals with pathological hyperprolactinemia.

Because sCT affects the secretion of PRL in both tumor or normal cells, its site of action is most likely at the level of the lactotroph. Recently, a structural homology between sCT and calcitonin gene related peptide (CGRP) has been reported. Specific bindings sites for CGRP are known to be present within the pituitary. Moreover, CGRP inhibits PRL secretion (14). Thus, it is likely that sCT by interacting with CGRP receptors within the pituitary, probably at the level of the lactotroph, inhibits PRL secretion.

As a result of this action of sCT to reduce PRL secretion in individuals with pathological hyperprolactinemia, it may be interesting that it be used as an adjunct to dopaminergic therapy in the clinical management of individuals with hyperprolactinemia, especially in those who are either resistant to dopaminergic agents or do not tolerate dopaminergic agents well.

Patolojik hiperprolaktinemili kadınlarda Prolaktin sekresyonuna salmon kalsitoninin etkisi

Salmon kalsitoninin hipofiz içinde Prolaktin salınmasında önemli düzenleyicilerden biri olduğuyla ilgili veriler giderek artmaktadır. Bu çalışmada patolojik hiperprolaktinemisi olan hastalarda prolaktin salınımı üzerinde salmon kalsitoninin etkileri

araştırıldı. Farklı günlerde patolojik hiperprolaktinemisi olan kadınlara salmun kalsitonin veya plasebo olarak saline (2 ml) intravenoz yolla verildi. İnjeksiyonu takiben 5 saat süreyle her 30 dakikada bir prolaktin, kalsiyum ve calcitonin ölçümleri için kan alındı. Serum kalsiyum seviyeleri saline veya salmon kalsitonin kullanımından sonra değişmedi. Salmon kalsitonin seviyeleri başlangıçta ölçülemeyecek düzeydeydi. Salmon kalsitonin injeksiyonundan 30 dakika sonra 6.06±0.61 ng/ml'ye yükseldi. Saline kullanımından sonra değişmedi. Prolaktin seviyelerinde saline kullanımından sonra önemli bir değişiklik olmazken salmon kalsitonin veriliminden sonraki 5. saatte başlangıç seviyesinin %43.9 kadar altına düştü. Salmon kalsitonin verilimini takiben ölçülen tüm. prolaktin düzeyleri saline veriliminden sonra elde edilenlerle karşılaştırıldığında belirgin olarak daha düşüktüler. Bu bulgular salmon kalsitonin verilmesinin patolojik prolaktinemisi olan hastalarda normal kişilerdekine benzer şekilde, muhtemelen pituiter laktotrop hücreler üzerinde etki ederek prolaktin sekresyonunu baskılayabileceğin! desteklemektedir. [Türk J Med Res 1995(5): 177-179]

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