Growth Hormone & IGF Research 25 (2015) 53–56

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Potential risks of glucagon stimulation test in elderly people ☆

Ana Beatriz Winter Tavares [a,*], Ignácio Antônio Seixas-da-Silva [a], Diego H.S. Silvestre [a], Carlos Montes Paixão Júnior [b], Mario Vaisman [a], Flávia Lucia Conceição [a]

[a] Division of Endocrinology, Department of Internal Medicine, Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[b] Division of Geriatric Medicine, Department of Internal Medicine, Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 15 October 2014
Received in revised form 24 November 2014
Accepted 24 November 2014
Available online 29 November 2014

Keywords:
Glucagon
Pituitary gland
Aged

ABSTRACT

The glucagon stimulation test (GST) is a reliable measure for assessing growth hormone (GH) and adrenocorticotropic hormone (ACTH) secretion. The GST is considered to be a safe test, with few mild side effects, especially in adults and in the elderly in whom underlying co-morbidities may be present.

Objective: To describe the side effects of the GST in elderly people.

Design and setting: The study was performed with patients of the geriatric ambulatory of our hospital who were recruited to voluntarily participate in a research study concerning the GH and ACTH axis in the elderly people. Forty-two subjects ($n = 5$ males and 37 females) aged 67–88 years, without hypothalamic–pituitary disease, were submitted to the GST. The GST was performed by intramuscular injection of 1 mg of glucagon. Blood samples were collected at baseline, and 90, 120, 150, and 180 min after glucagon injection for GH and cortisol measurements.

Results: During the test, 9 subjects (21.4%) had side effects, which included: nausea (14.2%), indisposition (11.9%), hypotension (9.5%), vomiting (7.1%), sweating (4.7%), and dizziness (2.3%). There were four cases of severe symptomatic hypotension, with inaudible blood pressure in two cases. In one case of severe hypotension, the subject suffered two episodes of generalized tonic seizures. Patients who had side effects at GST had statistically higher peak of cortisol (28.9 ± 6.67 μg/dL) and a statistical trend to higher GH peak (8.74 ± 5.96 μg/L). In the group of patients who did not have side effects, the mean cortisol and GH peak were 19.05 ± 5.36 μg/dL and 5.32 ± 3.52 μg/L, respectively.

Conclusion: Although the GST is a reliable alternative test to the ITT, it should be cautiously used in the elderly because this population may have co-morbidities including vascular and cardiac diseases that could be potentiated with side effects of the test, such as severe hypotension.

1. Introduction

The efficient diagnostic assessment of growth hormone (GH) secretion depends on provocative tests. The insulin tolerance test (ITT) is considered to be the gold standard test for assessing GH reserve and has been recommended by several consensus guidelines [1–3], despite concerns regarding its safety, reproducibility, and specificity [4]. However, ITT is not recommended in elderly patients because of the cardiovascular risks consequent to hypoglycemia [4].

The glucagon stimulation test (GST) is an alternative and reliable test for assessing GH secretion that has been used more frequently after the withdrawal of the GH-releasing hormone (GHRH), and the use of the GHRH plus arginine test was interrupted [4]. The GST is simple to perform and can be used in patients of different ages because of its few contraindications. Moreover, the GST is considered to be a safe test, with few mild side effects, such as nausea, vomiting, sweating, and headache [5,6], which is an important positive point of the test, primarily in adults and in the elderly in whom underlying co-morbidities may be present.

There are no studies regarding the GST exclusively in subjects over 70 years of age. Our previous study using the GST [7] did not demonstrate severe side effects in middle-aged men. Several studies included subjects older than 70 years of age [5,8,9], without severe side effects. We performed the GST in 42 subjects over 67 years old without hypothalamic–pituitary disease (40 subjects older than 70 years of age) to assess their GH and cortisol release as part of a research protocol concerning the GH and ACTH axis. The present report aimed to describe and discuss the non-expected side effects of this test in the elderly.

2. Subjects and methods

Forty-two subjects ($n = 5$ males and 37 females), aged 67–88 years, were recruited from the geriatric ambulatory unit of our hospital to

☆ Registration number: NCT02240043.

* Corresponding author at: Rua Barão de Lucena, 135/202, Botafogo, Rio de Janeiro, RJ, CEP 22260-020, Brazil. Tel.: +55 21 22463158.
E-mail address: anabeatrizwinter@yahoo.com.br (A.B.W. Tavares).

http://dx.doi.org/10.1016/j.ghir.2014.11.002
1096-6374/

voluntarily participate in a research study concerning the GH and ACTH axis in the elderly, which included the realization of the GST as the first phase of the study. Subsequently, the subjects were submitted to a protocol for evaluating sarcopenia.

The GST was the chosen test to assess both ACTH and GH release because of its few known contraindications and mild side effects. Moreover, we aimed to evaluate the GST *per se* in the elderly because the test had never been used in this population.

The elderly had common morbidities peculiar to their age, such as systemic arterial hypertension, diabetes mellitus, Parkinson's disease, initial stages of senile dementia, and osteoporosis. The exclusion criteria were pituitary disease, severe acute disease, terminal renal chronic disease, active malignant cancer, the presence of any other disease that could interfere with the somatotrophic axis evaluation, and the contraindications for glucagon administration (pheochromocytoma, insulinoma and malnourishment).

The subjects had fasted for 12 h before the test, which started between 7:30 and 8:00 am. All of the subjects were asymptomatic at the beginning of the test, with normal blood pressure values (i.e., above 110/70 mm Hg, not higher than 160/110 mm Hg). Blood pressure was not checked during the test if the patient was asymptomatic. The GST was performed by intramuscular injection of 1 mg of glucagon (Glucagen® Hypokit, Novo Nordisk A/S, Denmark). The blood samples were collected at baseline and after 90, 120, 150 and 180 min of glucagon injection for GH and cortisol measurements. The subjects were recumbent during the test, and a cannula was maintained in a vein in the arm or forearm with a saline solution slowly infused to avoid multiple punctures.

The research ethics committee of Hospital Universitário Clementino Fraga Filho approved the protocol. All of the patients provided their written informed consent.

3. Statistical methods

A descriptive analysis of the side effects of the GST was realized; the results are expressed as percentages.

The Mann–Whitney test was realized to evaluate if cortisol and GH peaks at GST were different among patients who had side effects and those who did not have side effects.

A p value < 0.05 was considered statistically significant.

4. Results

The GST was performed in 42 subjects between 67 and 88 years (77.1 ± 5.2 years). Nine subjects (21.4%) had side effects during the test, which included nausea, dizziness, vomiting, sweating, malaise and severe symptomatic hypotension (Table 1). In all of these cases, capillary blood glucose levels were taken at the onset of the symptoms, and no one had hypoglycemia (capillary glycemia ranged from 84 mg% to 197 mg% in symptomatic subjects during the test).

The subjects who presented side effects did not have different co-morbidities from the rest of the group. Eight subjects who exhibited side effects had slight systemic arterial hypertension (all of the subjects who had side effects were using at most two classes of antihypertensive medications); four subjects had known dyslipidemia and used statins; one patient was diabetic and used only metformin (this patient had nausea and dizziness) (Table 2). The four patients who had symptomatic hypotension were using the following classes of anti-hypertensive medications: angiotensin-converting enzyme inhibitor associated with thiazide diuretic ($n = 2$ patients), angiotensin antagonist receptor ($n = 1$ patient), and calcium-channel blocker ($n = 1$ patient). These anti-hypertensive agents were the same agents used by the majority of subjects in the study.

The co-morbidities in subjects who did not present side effects at the GST were as follows: hypertension, diabetes mellitus, dyslipidemia, chronic coronary disease, chronic atrial fibrillation, primary hypothyroidism, senile dementia, osteoporosis, asthma, and Parkinson's disease.

The majority of subjects took their usual medications before the GST, except for hypoglycemic agents, which they were instructed not to use before the test.

Side effects occurred between 55 min and 90 min in two subjects, between 90 min and 120 min in three subjects, and between 120 min and 150 min in four subjects.

In 4 cases of hypotension, the subjects were symptomatic and blood pressure was inaudible in two cases. The intravascular volume expansion with saline solution was performed in all cases. One case of inaudible blood pressure (69-year-old female), was accompanied by filiform pulses and decreased level of consciousness, without recovery of blood pressure levels after volume expansion, followed by generalized tonic seizures (two episodes). This patient was admitted to the emergency room of our hospital for observation and was released after normal complementary examinations. The other case of inaudible blood pressure (82-year-old female) was accompanied by malaise, nauseas and dizziness. Although there was recovery of blood pressure after intravenous hydration, dizziness remained for 5 h, which prevented her from standing during this period. The blood pressure levels in the other 2 patients were 80/40 mm Hg and 70/40 mm Hg; both cases were accompanied by malaise, and one case was also associated with nausea and sweating. In all patients with hypotension, an electrocardiogram was conducted and did not reveal an acute ischemic episode. Although no cases of hypotension were accompanied by vomiting, two cases of severe hypotension were accompanied by nausea, which could explain a likely vagal stimulation. No patient with nausea and hypotension received metoclopramide before the hypotensive episode.

All of the patients with nausea and vomiting received metoclopramide intravenously. In one patient who had nausea and vomiting, this medication did not resolve the vomiting after 10 min; the patient became very anxious and felt ill. In this patient, ondansetron was intravenously administered, with cessation of the vomiting.

Although the aim of this study was not to show the results of cortisol and GH on GST, among patients with side effects at GST only 1 patient had GH peak <3 μg/L and the 9 patients had a cortisol peak >18 μg/dL. Among patients who did not have side effects during the GST ($n = 33$ patients), 10 patients had GH peak below 3 μg/L. The mean GH and cortisol peak at GST in the subjects who had side effects were 8.74 ± 5.96 μg/L and 28.9 ± 6.67 μg/dL, respectively. In the group of patients who did not have side effects, the mean GH and cortisol peak were 5.32 ± 3.52 μg/L and 19.05 ± 5.36 μg/dL, respectively. The cortisol peak at GST in the patients who had side effects was statistically higher than in patients who did not have side effects ($p < 0.05$). The GH peak at GST showed a statistical trend to be higher in the group of patients who had side effects ($p = 0.097$).

5. Discussion

The GST has become a suitable alternative test when ITT is contraindicated because it is capable of assessing both GH and ACTH release. However, the test is still not largely used in adults and has not been previously studied exclusively in normal controls over the age of 70 years.

Table 1
Side effects during the GST in this study population.

Side effects	Percentage (n)
Nausea	14.2% [6]
Malaise	11.9% [5]
Severe symptomatic hypotension[a]	9.5% [4]
Vomiting	7.1% [3]
Sweating	4.7% [2]
Dizziness	2.3% [1]

[a] One patient had severe symptomatic hypotension followed by seizures.