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EDITORIAL

Intragastric injection of botulinum toxin for the treatment of obesity. Where are we?

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Abstract

Obesity has reached epidemic proportions particularly in western countries. Most non-surgical treatments of this condition are disappointing. Since 2005, several studies evaluating the effect of Botulinum Toxin type A (BT-A) in gastric antrum by means of endoscopy for the treatment of obesity have been published. This treatment modality was based on the observation that gastric injection of BT-A in laparatomized rats induced a significant reduction of food intake and body weight. Nowadays, 6 studies have been published yielding conflicting results. Differences in selection of patients, doses of BT-A, method of administration of the toxin and instruments of evaluation of some parameters among these studies may be the cause of divergent results. We discuss herein some important features of these studies pointing out on differences among them. At the same time, based on the knowledge of physiological characteristics of normal and abnormal gastric function related with feeding, we discuss the probable causes of failure observed in these trials. Finally, we give some guidelines concerning the way that future research in this field may follow, not without calling attention to disadvantages of this treatment.

Key words: Botulinum toxin; Obesity; Gastric emptying; Gastric motility; Gastroparesis

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INTRODUCTION

The prevalence of obesity has increased in western countries in the last few decades, reaching epidemic proportions[1]. It affects more than 30% of general population in the US. In this country, the costs attributed to obesity amounts to 100 billion dollars per year[2] and the number of deaths attributed to obesity is approximately 280 000 annually[3]. Obesity increases the risk of morbidity and mortality, since some disorders such as diabetes, arterial hypertension, cardiovascular and cerebral illnesses, as well as hepatobiliary disorders, are particularly frequent in obese individuals[2].

The dietetic, pharmacological and behavioral treatments have demonstrated to have limited effect and duration[4]. The intragastric balloon applied by endoscopy has equally given partial and transitory results[5]. Surgical treatments (gastric banding and gastric by-pass), even if they are the most effective in some patients, particularly those with morbid obesity, are invasive procedures and may have complications, some of them fatal[6]. In view of the above, the search for new methods for weight reduction is completely justified.

In the year 2000, Gui *et al* published a pioneering study in which they show that intra-muscular injections of Botulínum Toxin type A (BT-A) in the gastric wall of laparatomized normal-weight rats significantly reduced their food intake and body weight[7]. Subsequently, such findings were confirmed in 2005, by Coskun *et al* in obese rats. This group also observed a significant delay of gastric emptying in rats that had received BT-A[8]; therefore, they attributed body weight reduction to an effect of early satiety probably induced by the pharmacologically induced gastroparesis.

BOTULINUM TOXIN

Botulínum Toxin is produced by the bacterium *Clostridium botulinum*. There are several serotypes from A to G. When this toxin is ingested by the human being it can produce a form of food poisoning known as botulism. The BT-A

has a powerful inhibiting effect of long duration on the muscular contractions of smooth and striated muscles[9]. This pharmacological property has been used in the treatment of some digestive illnesses characterized by muscular spasm, particularly achalasia and anal fissure[10,11]. BT-A binds with high affinity to cholinergic nerve endings and selectively inhibits their activity. Acetylcholine is considered the most important stimulating agent both in intrinsic (myenteric) and extrinsic (vagal) nervous systems[12].

SATIETY AND GASTRIC MOTILITY

Additionally, the mechanisms that induce the gastric satiety are complex and they are related to the motor function of the stomach as well as to endocrine and paracrine effects acting in interrelated form. It is known that several mechanisms are involved in the induction of satiety such as distension and accommodation of the stomach, as well as hormones such as cholecystokinin (CCK), glucagon-like peptide (GLP-1), bombesin, liberating-gastrin peptide and somatostatin. It has also been observed that ghrelin, which is a peptide produced in the stomach, has orexigenic effect that probably controls the appetite at a central hypothalamic level. Other factors also intervene for the control of appetite as glycemia and some hormones such as insulin, leptin and enterostatin. It has been observed, for example, that duodenal infusion of fat induces a delay of gastric emptying and sensation of satiety[13]. Additionally, gastric banding increases the cholecystokinin plasma levels[14], the Roux-en Y gastric by-pass inhibits basal and postprandial ghrelin plasma levels and increases peptide YY (PYY) concentrations[15]. The jejunoileal by-pass increases cholecystokinin, motilin, GLP-1 and PYY[16], delays gastric emptying and reduces hunger sensation. As cholecystokinin, ghrelin and PYY also influence the gastrointestinal motility, it may be possible that a mechanism related to modifications of the gastric emptying is responsible for the early satiety and reduction of body weight observed in these operated patients.

Also the patterns of the gastric motility are well known. The fundus and proximal portion of the gastric body relax during the prandial and postprandial period; therefore, the intra gastric pressure is not modified in a significant form at the beginning of food ingestion. This phenomenon is known as "gastric accommodation", a term which was introduced almost 100 years ago[17]. It consists of a receptive relaxation induced by the bolus deglutition and an adaptive relaxation influenced by the increase of the intragastric pressure due to food accumulation into the stomach. The impairment of the gastric accommodation seems to be initially responsible for the sensation of fullness and satiety[18]. Meanwhile, gastric antrum muscles contract in concentric form by means of rings of distal displacement impelling the gastric content to the duodenum. Nevertheless, the pylorus in postprandial period contracts preventing the early passage of solid meals to the duodenum. Thus, meals are returned to the gastric body in repeated form[19]. The speed with which the stomach empties depends on the nature of meals (the solids retain more time than the liquids), of the osmolarity (the isosmotic meals retain less time than the hypo-osmotic and hyper-osmotic) and of the chemical composition (the fats retain the most time). The hormonal mediators previously mentioned are produced by means of chemical and mechanic stimuli triggered by meals in the stomach and the proximal intestine and their main function is regulation of the gastrointestinal motility.

GASTROPARESIS

Gastroparesis is a gastric disorder characterized by a delay in the gastric emptying. The etiology is very diverse. The typical clinical manifestations are eructation, early satiety and sensation of gastric fullness, epigastric discomfort, nausea and vomiting and reduction of body weight[20]. It has been found that the patients with anorexia nervosa have a significant delay of gastric emptying compared to normal individuals or those with bulimia[21].

CLINICAL STUDIES OF BT-A FOR TREATMENT OF OBESITY

In accordance with all mentioned above, the clinical use of the BT-A injected into the gastric antrum in obese patients for inducing gastric emptying delay and body weight reduction seemed logical.

This idea was reinforced from the report of Rollnik *et al*, of a patient in whom the injection of BT-A in the gastric antrum by endoscopy was associated with a reduction of 9 kg of body weight and 32.5% of the caloric daily intake 4 mo after treatment[22].

In the last two years, 6 studies evaluating this novel treatment have been published[23-28]. Three were open pilot and 3 were randomized double blind controlled trials (one of them performed by our group[23]) of which in only one, beneficial effect of BT-A on body weight reduction was observed[27]. Nevertheless, important differences among these studies deserve to be discussed in detail (Table 1).

The dose of BT-A

The dose of BT-A used in all the studies was highly variable. It ranged from 100 UI to 300 UI. However, in the study in which the maximum dose was used no effect on body weight reduction was observed. Perhaps more important than the dose of BT-A was the method of application.

Method of application of BT-A

In all the studies, BT-A was administered by means of endoscopic antral injections in a number of punctures that ranged from 8 to 24 in circular disposition. Probably, it was expected that the more the punctures performed the more intra muscular diffusion of the toxin might have been obtained. Nevertheless, this factor was not crucial since in the study in which the greatest number of punctures was done, (24 punctures) the results were negative.

It is important to point out that BT-A were injected both into the antrum and the gastric fundus in the only study in which positive results were obtained (in the rest of the studies only antral injections were done). If we remember, the gastric fundus does not have a propulsive

Table 1 Description of the results of 6 studies in which intragastric injection of Botulinum Toxin type A was administered to obese patients for treatment of obesity

Reference	*n*	Design	Dose (UI)	Follow-up (wk)	Results
Garcia-Compean[23]	12	Pilot	100 antrum	12	Reduction of body weight: No Gastric emptying: Negative
Albani[24]	8	Pilot	100 antrum	16	Reduction of body weight: No
Cardoso[25]	12	Pilot	200/300 antrum	12	Early satiety: Yes Reduction of body weight: No Gastric emptying: Negative
Gui[26]	14	RCT[1]	133/200 *vs* saline antrum	8	Early satiety: Yes Reduction of body weight: No Gastric emptying: Negative
Foschi[27]	24	RCT[1]	200 *vs* saline antrum + fundus	8	Early satiety: Yes Reduction of weight: Yes Gastric emptying: Positive Max. gastric capacity for liquids: Positive
Mittermaier[28]	10	RCT	200 *vs* saline /antrum	24	Early satiety: No Reduction of weight: No

[1]RCT: Randomized controlled trials.

effect as the antrum, injections in this place to cause gastric emptying delay would not seem to have justification. Notwithstanding, the existence of other mechanisms related to satiety that might have origin in the fundus must be considered as we will discuss later.

Early satiety

Of 4 studies in which early satiety was evaluated after therapy, a positive effect was observed in 3 (two of them were randomized double blind controlled trials). However, only in 1 of these 3 studies a significant body weight reduction was observed. This incongruousness between early satiety and absence of weight reduction observed in some studies may be due to the difficulties of measuring a subjective parameter like this, or perhaps the intensity of the early satiety was not enough to produce significant body weight loss.

Gastric emptying

In only 1 of 5 studies in which gastric emptying after therapy was evaluated a significant delay was observed. Notwithstanding, diverse methods were used for measuring this parameter: octanoic acid breath test, gastric emptying scintigraphy for solids and liquids labeled with Technetium 99 and Indium 111, respectively. It is well known that results of these procedures can be affected by several factors (type of test meals, chemical composition and osmolarity of the test meals, quantity of liquid, *etc*.). For this reason these procedures must be carefully standardized in every laboratory. In regards to the above mentioned, presently highly sensitive and specific procedures for measuring gastric emptying are not available[29].

HOW TO EXPLAIN THE DIFFERENCES OF RESULTS BETWEEN THE ONLY POSITIVE AND THE 5 NEGATIVE STUDIES?

In the only positive study performed by the Italian group, 8 injections of BT-A were done in the gastric fundus in addition to the injections in gastric antrum. Conversely in the other studies, injections in the antrum were only done. In this positive study a significant modification of all the evaluated parameters were observed after treatment: presence of early satiety, a delay in gastric emptying, a reduction of the maximal gastric capacity for liquids and more importantly: a significant reduction of body weight. As authors of this study pointed out, gastric fundus is the principal source of ghrelin[30] and it also has sensory activity that regulates the total gastric capacity[31]. Ghrelin is a 28 amino acids peptide produced by the stomach with orexigenic effect acting on the arquatte nucleus of the hypothalamus. Ghrelin plasma levels increase during periods of fasting and reduce after a meal, in other words, this peptide seems to have a regulatory effect of hunger. However, published studies have shown that ghrelin expression in gastric mucosa, measured by histochemistry, increased one year after gastric banding in obese patients who maintained body weight loss; this would discard the physio-pathogenic role of ghrelin in body weight loss of these patients[32]. Similarly, in another study, high ghrelin plasma levels did not predict a minor loss of body weight in patients with gastric banding compared to patients with normal plasma ghrelin levels[33]. Conversely, Roux-en Y gastric by-pass inhibits basal and postprandial ghrelin plasma levels[15]. Additionally, ghrelin increases gastric emptying and stimulates gastric motility during fasting[34]. For all the above mentioned, it is difficult to clarify the role of ghrelin in body weight reduction of the patients in the positive study, particularly when plasma levels of this peptide were not measured.

The reduction of the maximal capacity for liquids after BT-A treatment may be explained by impairment of the gastric fundus accommodation inducing early satiety. Nevertheless, the test of gastric maximal capacity for liquids has poor reproducibility for measuring gastric accommodation. Recently, a novel scintigraphic method for simultaneously assessing gastric accommodation and emptying has been developed using dual-isotopes,

either (^{99}m)Tc-pertechnetate intravenously and (111) In-diethylenetriaminepentaacertic acid in a liquid nutrient drink or an (111) In-oxine-labeled egg sandwich meal. Emptying and accommodation were measured using single positron emission computer tomography (SPECT) every 20 min and up to 240 min[35].

On the other side, the mean delay of gastric emptying observed in patients after BT-A, although significant, was short. Therefore, it makes it difficult to attribute early satiety and body weight reduction to this mechanism.

Finally, treated and untreated patients were given reductive diets of 1200 kcal/day. This may explain the reason why non treated patients also had a significant body weight reduction. Therefore, it is very probable that in treated patients a combined effect of reductive diet and toxin was observed.

FUTURE OF BT-A IN THE TREATMENT OF OBESITY

In the context of all the above discussed, the following question arises: What is the future of the endoscopic gastric injections of BT-A for the treatment of obesity?

In our opinion the method of antral injections has a very uncertain future. If we take into account that this drug is expensive (100 UI cost about 350 Euros or $530 dollars), the performance of a study on a major scale is very difficult to achieve given the present circumstances.

Notwithstanding, it remains to be clarified if BT-A injections in the gastric fundus have better results in body weight reduction in obese patients. Perhaps the mechanism of action would be more difficult to explain. Modifications of gastric accommodation inducing early satiety may be an attractive hypothesis. Nevertheless, the measurement of this parameter in future studies by means of reliable tests will be the obstacle to overcome.

If gastric injections of BT-A demonstrate to be effective for the treatment of obese patients in the future, there is another disadvantage that must be considered: the limited duration of its effect (3 mo-6 mo). Therefore, for long-term administration by repeated administration of this drug, the cost-benefit relation has to be taken into account.

In medical science, it is frequent to find an agent that works and less frequent to know how it works. Consequently, we considerably learn from the test error method.

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