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RESEARCH LETTER

The use of a glucose spray device to control progression towards hypoglycaemia

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Introduction

Hypoglycaemia is a condition that occurs when plasma glucose concentration is low enough (≤70 mg/dl–3.9 mmol/l) to cause symptoms causing impairment of brain function [1]. Since the brain relies on glucose for energy supply, a decrease in glucose blood levels cause both neuroglycopenic and adrenergic symptoms. The American Diabetes Association guidelines indicate for treatment of hypoglycaemia consumption of carbohydrates containing glucose such as sucrose or sweetened beverages without suggesting a precise quantity [2]. However, overtreatment of hypoglycaemia may lead to rebound hyperglycemia and weight gain [3]. To reduce these side effects, subjects should be able to correct early signs of hypoglycaemia with a practical and easy tool able to deliver the exact amount of glucose. Such a tool has been missing to date.

The aim of our study was to investigate the effect of the administering of small amounts of glucose through a glucose spray device (GRS) on blood glucose in healthy subjects.

Subjects and methods

Subjects

Ten healthy subjects were studied. They were selected on the basis of young age (18–30) and body mass index (BMI kg/m^2) within normal range (18.5–25 kg/m^2). Subjects were males and females, mean age 25 ± 3 years and BMI between 18.8 and 25 kg/m^2. None was on drugs or medications known to alter glucose metabolism.

The protocol was carried out according to the Helsinki Declaration, approved by the Ethical Committee of the University Campus Bio-Medico (Rome). A written informed consent was obtained.

Subjects were asked to use a glucose spray device throughout a typical day. The glucose spray device, Glucose Rapid Spray™—Generex Pharmaceuticals Inc. (Toronto, Canada) consists of a 19 ml bottle containing 10 g glucose solution with the addition of artificial flavors and excipient (orange or raspberry) to facilitate buccal absorption and delivering by spray puffing glucose in quantity as small as 0.5 g.

Glucose puffs were administered after a minimum of 4 h fasting. Subjects were asked to spray ten oral puffs three times a day (in the early morning, afternoon and evening) and write in a log how they felt in relation to hunger using a visual analog scale [4].

In three subjects insulin levels after ten oral puffs in the morning were measured to find out whether stimulation of insulin secretion from beta cells occurred.

The continuous glucose monitoring system (CGMS) was applied to record changes in glucose levels.

Laboratory analysis

Insulin levels were assessed by chemiluminescence using the Liaison® system (Diasorin).

24 h changes in blood glucose were recorded using CGSM (® System Gold™—Medtronic). Statistical analysis was performed using Graph Pad 5.0 prism software.

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Results

Table 1 shows the characteristics of subjects studied and their metabolic responses to GRS administration. No hypoglycaemic episodes were recorded.

There was a mean glycaemic increase of 2.9 ± 1.2 mg/dl 5 min after GRS administration, with a rise of 3.1 ± 1.3 mg/dl after 10 min and 4.1 ± 1.4 mg/dl after 15 min ($P < 0.01$), with a mean glycaemic increase of about 5% after 15 min. Insulin levels measured before and after GRS administration did not significantly change from baseline being the mean increase of 0.6 ± 0.2 μ IU/ml). All subjects reported in their logs beneficial effects on hunger reduction in their logs, following increases in blood glucose levels of approximately 5.0 ± 0.9 mg/dl. It should be noted that subjects were not aware of changes in blood glucose as a real time measurement for glucose was not available.

Discussion

We have demonstrated that glucose administration by the GRS in small quantity of ~0.5 g is able to increase blood glucose of approximately 5 mg in our study population probably without stimulating endogenous insulin release (as shown in three subjects).

There are very few studies comparing our results with, apart from one where use of buccal glucose spray was compared with liquid sugars and dextrose tablets [5]. These authors observed no increase in blood glucose following buccal glucose spray, unlike those detected with liquid sugars and dextrose tablets. What may have weakened their results is that the amount of dextrose, fructose and saccharose used in that study was different. Furthermore the authors suggest that their results might be due to the different rates of absorption of glucose between the intestinal and the oral mucosa route. However, several studies have shown the oral mucosa as a valid alternative route for glucose and drug administration, since this area is highly vascularized and therefore enables glucose to quickly enter systemic circulation bypassing gastrointestinal tract and liver metabolism [6]. One study showed the inefficacy of glucose administered through the buccal cavity compared to a swallowed dose for the treatment of hypoglycaemia [7]. However, other investigators [8] have suggested the existence of some specialised mechanism on dorsal surface of the tongue and on stratified cell layer of oral mucosa cells which provide transportation of D-glucose across the buccal mucosa. According to Oyama et al. [9] there might be an expression of GLUT1, GLUT2 and GLUT3 on epithelial cells of human oral mucosa. Most recently a study in children has shown that sublingual absorption of glucose shows a bioavailability comparable to that of intravenous route, which may account for the increase in glucose through this route [10].

This preliminary study has limitations such as the small sample size, the lack of a control group and that subjects were young and healthy, hence not representative of the overall population. Further studies are needed in insulin resistant, overweight and obese subjects to see if the same glycaemic and insulinemic responses would be observed. If confirmed, GRS might prove to be a useful tool also for those subjects who report postprandial hypoglycaemia which often is due to high carbohydrate intake [1].

Table 1 Clinical and laboratory parameters of normal weight subjects participating in continuous glucose monitoring following oral glucose spray device (GSD) administration

Subjects	*n* 10
M/F (*n*)	4/6
Age—years (min–max)	25 ± 3 (21–28)
Body weight—Kg (min–max)	62.6 ± 8.4 (48.6–74.5)
BMI—kg/m^2 (min–max)	21.6 ± 2.4 (18.6–25)
Glycaemia during 24 h—mg/dl	88.2 ± 5.4
Minimum values during 24 h—mg/dl	69.3 ± 7.9
Maximum values during 24 h—mg/dl	148.7 ± 19.1
Glycaemic increase after GRS administration—mg/dl	5.0 ± 0.9
Insulin levels—μ IU/ml	4.2 ± 0.9
Insulin increase after GSD administration—μ IU/ml	0.6 ± 0.2
HOMA-IR [fasting serum glucose (mmol/l) × fasting serum insulin (μ IU/ml)/22.5]	0.92 ± 0.07

Values are mean ± SD

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