Effects of Sucralose Ingestion on Fetal and Placental Weights and Umbilical-Cord Length: Experimental Study

Efectos de la Ingestión de Sucralosa sobre el Peso Fetal y Placentario y la Longitud del Cordón Umbilical: Estudio Experimental

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RODERO, A. B.; BATIGÁLIA, F.; AZOUBEL, R.; MOURA, A. A.; RODERO, L. S. & SILVEIRA JR, L. Effects of sucralose ingestion on fetal and placental weights and umbilical-cord length; experimental study. *Int. J. Morphol.*, 28(3):823-827, 2010.

SUMMARY: Sucralose is a sweetener of general use in over three thousand products (beverages, foods and medical diets), with utilization currently permitted for the general population in more than 80 countries, including for women of reproductive age. There is little information on the safe use of sucralose, and experimental studies have suggested that the administration of some sweeteners, by diverse routes, retards not only fetal and placental development but also umbilical cord size. The present study aimed to estimate the fetal and placental weights and umbilical-cord length in fetuses from rat dams, after ingestion and non-ingestion of sucralose. In the treated group (5 dams), sucralose was administered (via gavage) at the dose of 30 mg/kg/day, from the 10th to 14th day of pregnancy. In the control group (5 dams), saline solution was administered, at the same dose and by the same route. On the 20th gestation day, both groups were sacrificed for weighing of the fetuses and placentas and measurement of umbilical-cord length. Mean values of fetal weight and umbilical-cord length of the treated group were significantly lower than controls (Mann-Whitney Test, $p < 0.001$). Placental weight did not differ statistically between treated and control groups. It can be concluded from the present work that sucralose ingestion at 30 mg/kg/day, from days 10 to 14 of pregnancy, diminished fetal weight and umbilical-cord length, which suggests passage of sucralose through the placental membrane.

KEY WORDS: Sucralose; Fetus; Placenta; Umbilical cord; Weight.

INTRODUCTION

Sucralose is a sweetener of general use in more than three thousand commercial products (beverages, foods and medical diets), and is currently permissible for consumption in more than 80 countries. Discovered in 1976 (Ophardt, 2003), its utilization was extended in 1999 as a sweetener for general use in all foods, conventional beverages, dietary vitamin supplements, medical diets, as well as cooked and baked foods (Department of Health and Human Services, 1999; McNeil Nutritionals, 2006). Sucralose can be applied as a table sweetener in dry formulations, aromatizers, preservatives, seasonings, canned vegetables and in pasteurized products (Campos, 2000; Campos, 2002), and thus has been ingested by millions of persons (Pachione, 2003).

Besides being 600 times sweeter than sucrose, sucralose consumption has risen due to its lack of calories, insipidness and stability at high temperatures; in acidic medium is it non-hydrolysable even during digestion or its metabolism, and presents highly stable carbon-chlorine bonds (Berndt & Jackson, 1999; Binns, 2003). Sucralose possesses the important characteristic of not interacting with other foods, being stable in the presence of ethanol; it can be stored for more than one year while maintaining 99% of its original flavor. It also preserves its characteristics even during pasteurization, sterilization and high-temperature cooking (Godsmith & Meckel, 2001), and does not interfere in the utilization or absorption of glucose, carbohydrate metabolism or insulin secretion (Candido & Campos, 1995).

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Furthermore, clinical studies have concluded that sucralose is neither acidogenic nor cariogenic (Grotz & Mandel, 2002).

The elimination profile of sucralose in humans is similar to those found in rats, dogs and mice, although urinary excretion in rats corresponds to half of that observed in humans, while its elimination by feces is higher in rats (Roberts *et al.*, 2000; Sham, 2005). Pharmacokinetic studies have evidenced that 85% of sucralose is not absorbed, being excreted intact in feces, with absorption limits of approximately 15% of the dose consumed, by means of passive diffusion (McNeil Nutritionals, 2007).

Studies in rat dams, with the use of hydrolysis products of sucralose at high doses (270 mg/kg weight), did not reveal any evidence of maternal toxicity, although in progeny there is substantial evidence of secondary alterations in development (Grice & Goldsmith, 2000). Other works, in general toxicology, conducted on the ingestion of sucralose and its hydrolysis products in food additives did not demonstrate adverse effects to the extent of compromising human health (Grice & Goldsmith).

The present study aimed to estimate the fetal and placental weights and umbilical-cord length in fetuses of rat dams, after ingestion or non-ingestion of sucralose, at the dose of 30 mg/kg/day, from the 10th to the 14th day of pregnancy.

MATERIAL AND METHOD

The project was approved by the Ethics Committee for Animal Experimentation (CEEa) of the School of Medicine at São José do Rio Preto (FAMERP), number 414707, following the instructions of COBEA (Brazilian College of Animal Experimentation) for the storage, manipulation, experimentation and sacrifice of animals. Ten pregnant rat dams were utilized, with an average weight of 244 g and age of 52 days. The animals were divided into two groups: in the treated group (5 dams); sucralose was administered (via gavage) at the dose of 30 mg/kg/day, from gestation day 10 to 14; in the control group (5 dams), saline solution was administered at the same dose and by the same route. On the 20th day of pregnancy, both groups were sacrificed (414707) for weighing of fetuses and placentas and measurement of the umbilical-cord length.

The arithmetic means and standard deviations of each variable were plotted utilizing a Microsoft Excel spreadsheet. The Mann-Whitney [U] (GraphPad InStat) test statistic was applied to the values for the measures, between the control

and treated groups, with the ordering of data from each group, adopting a 5% significance level. The test utilized was non-parametric, as a function of the means of samples, with the groups being composed of a small number of samples that were asymmetric and had large variance among the means.

RESULTS

Figure 1 presents the mean body weight values of fetuses from the two experimental groups. The treated group presented significantly diminished mean fetal body weight in relation to the control group.

Figure 2 displays the mean weights of placentas from fetuses of the two experimental groups. Mean placental weights of sucralose-treated animals were lower than controls, although without statistical significance between groups.

Figure 3 shows mean lengths of umbilical cords of fetuses from the two experimental groups. This length was significantly diminished in the treated group relative to the controls.

DISCUSSION

Studies on the use of sweeteners during gestation have been carried out in diverse countries on account of their more frequent and habitual use. It is known that the majority of sweeteners cross the placental barrier and are able to exert toxic effects on the fetus such as the toxicity of: sodium cyclamate to the fetal liver and kidneys (Arruda *et al.*, 2003; Martins *et al.*, 2005), aspartame to the fetal umbilical cord, placenta and liver (Portela *et al.*, 2007), and aspartame to the fetal exocrine pancreas, umbilical cord and placenta (Leme & Azoubel, 2006).

The thickness of the placental membrane depends on the pregnancy phase; the earlier the phase the greater the thickness and the lesser its permeability to determinate substances. During the evolution of gestation, there is a natural diminution of thickness and augmentation of permeability with greater placental diffusion. Therefore, the designation "placental barrier" is shown to be inadequate since all the molecules, of various velocities, transit bi-directionally (Guyton & Hall, 2006; Rezende, 2005; Davies & Glasser, 1968; Roby & Soares, 1993).

The transplacental passage of glucose and other sugars

* statistically significant for $p < 0,01$ ($p = 0,0079$)

Fig. 1. Means and standard deviations for body weight of fetuses from rat dams of control and treated groups.

** not statistically significant ($p = 0,0952$)

Fig. 2. Means and standard deviations for placental weights from rat dams of control and treated groups.

* statistically significant for $p < 0,01$ ($p = 0,0079$)

Fig. 3. Means and standard deviations for umbilical-cord length of fetuses of control and treated groups.

occurs by facilitated diffusion, with Glut1 (sinciotrophoblast) acting as the transporter, principally in the microvillus membrane and, to a lesser degree, in the basement membrane. Amino acids are transported against the concentration gradient (active transport), in which they activate carrier proteins present in microvilli of the placental membrane (Logic *et al.*, 2002).

In general, the ingestion of sweeteners appears to have an adverse effect on the placenta by means of interfering in its circulatory and endocrine functions, provoking alterations in permeability of its membrane, thus determining diminished placental function and fetal weight (De Matos, 2008).

Although sucralose is a disaccharide formed by a molecule of glucose associated with fructose, factors shown to be important in the permeability of the placental membrane to sucralose are related to its high solubility in water (Roberts *et al.*). In the present study, the sucralose dose administered was proportional to double the daily ingestion level tolerable to a human adult, which corresponded to 15 mg/kg/day (Godsmith & Meckel). Evidence suggests the passage of a small quantity of sucralose and/or its metabolites, through the placenta (MacNeil, 1987).

In the present work, it was verified that the mean body weight of fetuses from the group treated with sucralose was significantly lower than that of controls (Fig. 1), which permits us to infer that there was effective passage of sucralose through the placental membrane. Several studies utilizing other sweeteners found similar results, showing that the placenta is permeable to the majority of sweeteners, which provoke diminutions in fetal and placental weights and in umbilical-cord length, with toxic effects in tissues and organs (Arruda *et al.*; Martins *et al.*; De Mattos *et al.*, 2006; Portela *et al.*; De Matos).

The administration of sucralose from the 10th to 14th day of pregnancy, associated with a probable disruption of the placental flow, brought about alterations in development, with reductions in placental (Fig. 2) and fetal weight. Diminutions of both fetal growth and intra-uterine space produced a reduction in fetal movements and umbilical-cord length (Moessinger *et al.*, 1982).

Results similar to those of the present study were found in recent works with sweeteners, demonstrating that the length of the umbilical cord is used as an indicator fetal movement, since its length is influenced by normal fetal movement and by the presence of adequate space in the uterine cavity (Arruda *et al.*; Martins *et al.*; De Mattos; Portela *et al.*). The shrinkage of intra-uterine space or lessening of fetal movements brings loss of fetal elasticity and consequently reduction of body size, as well as umbilical-cord length (De Matos; Martins & Azoubel, 2006). However, the reduced size of umbilical cord has been shown to be associated with diverse intra-uterine exposures and conditions that can diminish uterine development and fetal activities including oligohydramnios, membrane rupture and structural anomalies of the uterus (Miller *et al.*, 1981; Miller *et al.*, 1982; Fujinaga *et al.*, 1990), placental detachment, the labor of prolonged partum and fetal stress (Sornes, 1989).

Thus, in the present study, the diminution of placental and fetal weights may have occurred via retardation of placental development, with consequent lessening of intra-uterine fetal growth due to diminution of the uterine cavity, reaffirmed by diminution of the umbilical-cord length. It is known that the umbilical cord grows in proportion to the application of tensile forces, which depend on fetal movement and the space available during development. Such diminution occurred, in the present work, through the restriction of fetal movements, which, in turn, lessened the fetal development (Moessinger *et al.*).

In conclusion, the ingestion of the sweetener sucralose at the dose of 30 mg/kg/day, administered via gavage to rat dams from day 10 to 14 of pregnancy, causes reductions in fetal weight and umbilical-cord length, which suggests the passage of sucralose through the placental membrane.

RODERO, A. B.; BATIGÁLIA, F.; AZOUBEL, R.; MOURA, A. A.; RODERO, L. S. & SILVEIRA JR, L. Efectos de la ingestión de sucralosa sobre el peso fetal y placentario y la longitud del cordón umbilical: estudio experimental. *Int. J. Morphol.*, 28(3):823-827, 2010.

RESUMEN: La sucralosa es un edulcorante de uso general en más de tres mil productos (bebidas, alimentos y dietas médicas), con permisos de utilización para la población general en más de 80 países, entre ellos mujeres en edad reproductiva. Hay poca información sobre el uso seguro de la sucralosa, y los estudios experimentales han sugerido que la administración de algunos edulcorantes, por diversas vías, no sólo retrasa el desarrollo del feto y la placenta, sino también el tamaño del cordón umbilical. Este estudio tuvo como objetivo estimar el peso fetal y placentario y la longitud del cordón umbilical de los fetos de ratas madres después de la ingestión y la no ingestión de sucralosa. En el grupo tratado (5 crías), la sucralosa se administró (a través de sonda) en una dosis de 30 mg/kg/día, desde el día 10 hasta 14 de la preñez. En el grupo control (5 crías), se administró solución salina, con la misma dosis y por la misma vía. En el día 20 de la gestación, ambos grupos fueron sacrificados, para determinar el peso de los fetos y de las placentas y la medición de la longitud del cordón umbilical. Los valores medios del peso fetal y la longitud del cordón umbilical en el grupo tratado fueron significativamente más bajos que los controles (U de Mann-Whitney, $p < 0.001$). El peso de la placenta no difirió estadísticamente entre los grupos tratados y los controles. Se puede concluir de este trabajo que el consumo de sucralosa en 30 mg/kg/día, desde el día 10 al 14 de la preñez, disminuye el peso fetal y la longitud del cordón umbilical, lo que sugiere el paso de la sucralosa través de la membrana placentaria.

PALABRAS CLAVE: Sucralosa; Feto; Placenta; Cordón umbilical; Peso.

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- Received: 10-06-2010
Accepted: 12-07-2010