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IN UTERO-EXPOSURE TO SACCHARIN: A THREAT?

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SUMMARY

In-utero or immediate post-utero exposure of rats to saccharin results in an increased incidence of bladder tumors when compared to post-weaning exposure only. We studied 6 human mother-infant pairs following maternal intake of saccharin close to delivery. High performance liquid chromatography revealed the presence of saccharin in all 6 newborn cord sera as well as their mothers' sera and urine. This constitutes the first report of placental transfer of saccharin in humans. Despite the relative weakness in carcinogenicity of saccharin, this in-utero exposure, coupled with ex-utero exposure, may possibly contribute to an increased incidence of neoplasms.

INTRODUCTION

Saccharin has been replaced in some soft drinks by aspartame, but remains the main artificial sweetener in toothpastes, gums, etc. In rats, saccharin causes bladder tumors when given orally in high doses [1] and enhances the carcinogenic effects of other cancer-producing compounds [6]. Two recent human studies of potential carcinogenic effects of saccharin seemed reassuring [8,9]. Two findings, however, were of concern: a dose-response relation to cancer in women who never smoked nor had a hazardous occupation, and an increased risk of cancer in heavy smokers using saccharin in comparison with those who do not. Hence, saccharin may be a weak carcinogen in humans.

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In the United States, children currently consume more saccharin per unit of body weight than adults [10]. Studies [2,12] in rats showed that animals exposed to saccharin from fetal life until death developed an increased incidence in bladder tumors as adults compared to those exposed after weaning only. This raises concern about a possible in-utero exposure of the human fetus superimposed to consumption after birth.

Saccharin crosses the placenta in Rhesus monkeys [11]. In the fetuses of this species saccharin distributed to all tissues except the CNS following acute administration and there did not appear to be a difference in saccharin concentration in the various tissues save for the CNS. Although the membrane structure of the placenta is similar in humans and Rhesus monkeys, the latter have 2 placentas per fetus. The effects of such an arrangement on transport mechanisms are not known. The placental transfer of saccharin in man has not yet been established.

SUBJECTS AND METHODS

Six pregnant women, age 19—40, who consumed saccharin in their diets during the last month of pregnancy were included in the study after written informed consent was obtained. Five were diabetics (4 in class B and 1 in class A). Four had primary Cesarean section (2 for fetal distress and 2 for failure to progress). All neonates were born at, or close to, term (36—42 weeks). Five were Black and I Hispanic. The daily saccharin consumption was estimated using their history of intake of 'diet' drinks and food sweeteners. Their daily intake during the last month of pregnancy ranged from 25 to 100 mg. Maternal blood (5 ml) and urine samples (20 ml) were collected within 2 h. Cord blood samples (5 ml) were obtained.

The saccharin concentrations were determined by high performance liquid chromatography as previously described by Bekersky and Colburn [4] with sensitivity of 20 ng/ml.

RESULTS AND DISCUSSION

The results are listed in Table 1. Saccharin was identified in all samples of urine and blood. While 3 neonates displayed only trace concentrations (less than 50 ng/ml), the serum concentration in the other 3 neonates ranged from 110 to 160 ng/ml. Two infants had higher serum saccharin levels than their mothers.

To our knowledge, this is the first study to demonstrate the placental transfer of saccharin in humans.

The concentrations in cord blood samples in cases 4 and 6 were higher than the matching maternal concentrations. While these maternal samples were collected at 0.5 h and 2 h after delivery, retropolation from previously obtained data in non-pregnant female volunteers [7] still leads to lower saccharin concentrations in these mothers at the time of birth than in their

TABLE 1

MATERNAL AND NEONATE SERUM SACCHARIN LEVELS WITH TABULATION OF MATERNAL INTAKE AND OUTPUT, AND NEWBORN CHARACTERISTICS (BIRTH WEIGHT AND GESTATIONAL AGE)

Case	Mother				Neonate		
	Daily consumption (mg) by history	Urinary saccharin (μg/mg creatinine)	Blood sampling (ng/ml) rel. to delivery	Serum saccharin (ng/ml)	Serum saccharin (ng/ml)	Birth weight (g)	Gestational age (weeks)
1[a]	25	15.3	1/2 after	80	20—50	3750	39
2	100	17.0	2 before	146	20—50	3925	41
3[a]	75	112.0	1/2 before	263	110	3700	41
4[b]	100	13.0	2 after	20—50	159	3050	40
5[a]	100	6.8	1/2 after	74	20—50	2850	36
6[a]	55	17.2	1/2 after	74	160	3515	42

[a]Insulin dependent diabetes, <10 years duration.
[b]Gestational diabetes, not insulin dependent.

offsprings. The reason for higher serum saccharin levels in these infants than in their mothers requires further investigation.

Saccharin, therefore, crosses the human placenta. In view of the results of increased incidence of bladder neoplasms in rats exposed to saccharin from fetal life, and the present confirmation of its placental transfer in humans, speculation may be made of a potential increased carcinogenic risk in humans who have both in-utero and ex-utero exposure to saccharin. This could possibly explain the apparent discrepancies in the population studies (summarized in Ref. 3) regarding the association of saccharin consumption and bladder neoplasms. The effect of in-utero exposure to saccharin was not evaluated in these studies. On the other hand, extensive consumption of saccharin was not a fact of life until 1959–1960 when the FDA allowed the use of saccharin in a variety of dietetic foods. In the rodent studies, the latent period before apparition of the tumors was at least 18 months. The twenty-five years which have elapsed since the FDA approval might not be sufficient latent period in humans to test the rodent findings through epidemiologic studies. However, as speculated by Carlborg [5], the saccharin dose-response curve in one rodent study may be sufficiently steep implying that the cancer risk in humans at the usually ingested doses is sufficiently small, may be despite in utero exposure.

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