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Non- nutritive sweeteners in breast milk: Perspective on potential implications of recent findings

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We recently determined that nonnutritive (NNS) sweeteners ingested by lactating mothers are passed to their infants in breast milk (Sylvetsky et al., 2015). Three NNS including sucralose, acesulfame-K (ace-K), and saccharin were found in the breast milk of 65% of twenty lactating women who had been enrolled in the study, irrespective of their history of NNS usage. While most of the mothers reported NNS intake during the day prior to collection of the breast milk sample, NNS were also found in samples from women who were not aware of consuming NNS. The findings that NNS are present in breast milk raises several issues regarding infant exposure to these nonnutritive compounds and highlights the need for future research studying the potential short- and long-term effects of exposure to NNS early in life.

Pharmacokinetic studies of sucralose in adult humans and animals indicated that the majority of ingested sucralose is eliminated in feces with less than 40% absorbed from the intestine (Grice and Goldsmith, 2000). Abou-Donia et al. (2008) demonstrated in rodents that the absorption of ingested sucralose from the gut is reduced by the efflux transporter P-glycoprotein (P-gp). P-gp serves as a barrier and extrudes sucralose back into the intestinal lumen for excretion in the feces (Abu-Qare et al, 2003). Although generally described as ‘non-metabolized’ and thus excreted in its intact form, a substantial fraction of sucralose is in fact metabolized in the intestine by two isozymes of cytochrome P450, specifically CYP3A4 and CYP2D6. These transporters and metabolizing enzymes play a role in the pharmacokinetics of numerous substances (e.g. medications) and are immature in neonates and infants (Alcorn and McNamara, 2002; Lam and Koren, 2014; Lacroix et al., 1997). P-gp expression is low at birth (Lam and Koren, 2014), and CYP3A4 levels in one-month old infants only reach 30-40% of those for adults (Lacroix et al., 1997). Assuming that sucralose also induces these transporters and enzymes in humans, its absorption may be greater and its excretion delayed relative to the pharmacokinetics observed in adult safety studies, as

sucralose can partition through bilipid layers of the gut (Grice and Goldsmith, 2000; Schiffman and Rother, 2013).

Furthermore, because P-gp is also expressed at the blood brain barrier as well as the intestine (Abu-Qare et al, 2003), low expression of P-gp in neonates would hypothetically allow more sucralose to pass into the central nervous system than in adults. In rodents, the penetration of sucralose into the nutrient-sensing areas of the hypothalamus has been shown to produce inaccurate signals regarding extracellular brain glucose levels (Ren et al., 2009). If a similar mechanism exists in humans, this might affect appetite regulation in infants. The pharmacokinetics of all three NNS reported in breast milk, sucralose, ace-K and saccharin, may also be affected by immature clearance mechanisms in infants (Alcorn and McNamara, 2002; Rhodin et al., 2009), as they undergo urinary excretion. Neonates have glomerular filtration rates as low as 20 ml/min/1.73 m² at birth, which rise only gradually to reach adult rates (typically above 90 ml/min/1.73m²) at about 18 months of age (Alcorn and McNamara, 2002; Rhodin et al., 2009). NNS may therefore display an increased half-life in newborns and infants during the first years of life, reiterating the need for further testing before adult safety data are extrapolated to infants. Beyond exposure through breast milk, this is also important for older infants and toddlers, because intake levels may approach or exceed the acceptable daily intake (ADI) due to their considerably lower body weight compared to adults.

A second issue relates to whether NNS occur at concentrations that are sufficient to intensify the perceived sweetness of natural breast milk. Sylvestsky et al (2015) indicated that sucralose levels in breast milk are, in fact, higher than the taste threshold for sweetness of sucralose. The maximum concentration of sucralose in breast milk reported by Sylvestsky et al (2015) was 0.034 µg/ml (0.0855 mM) and the minimum level measured was 0.01 µg/ml (0.0251 mM). The mean taste detection threshold for sucralose in adults is 0.00877 mM and average sweetness recognition threshold is 0.013 mM (Schiffman et al., 2008). Thus, the maximum concentration of sucralose in breast milk is approximately 7-fold higher than the level at which sweetness is typically first recognized. The maximum concentration of ace-K found in breast milk was 2.22 µg/ml (0.011 mM) while its sweetness recognition threshold is 0.161 mM. The maximum concentration of saccharin found in breast milk was 1.42 µg/ml (0.00775 mM) while the sweetness recognition threshold of Na saccharin is 0.0497 mM. Although neither ace-K nor saccharin by themselves reach the sweetness threshold, the intensity of sweetener mixtures is often additive or even synergistic with NNS and natural sweeteners. Synergistic sweetener combinations, especially those with ace-K, are sweeter than expected given the intensity of the components (Schiffman et al., 1995). Thus, sucralose levels in breast milk may be further amplified by the presence of additional NNS or natural sweeteners in breast milk. It should also be pointed out that NNS concentrations in breast milk may reach higher concentrations than reported in this pilot study, since breast milk samples were obtained at random times, and not at time points when peak concentrations are expected to occur.

It is not yet known if amplification of the sweetness of breast milk by NNS might affect future food preferences and choices in humans. Rodent studies showed that dietary exposure of mothers to ace-K during lactation enhanced preferences for sweet solutions in their

breast-fed offspring in adulthood (Zhang et al., 2011). In rodents, NNS were also found to induce body weight gain along with metabolic derangements including impairment of glucose homeostasis (Swithers, 2013). In humans, early feeding experiences are known to be one of the major determinants of later food choices and intake in children (Mennella, 2014). For example, children who were fed sugar water during infancy on a routine basis were shown to prefer sweeter liquids than children who were seldom exposed. Thus, it is possible that exposure to NNS through breast milk may potentially affect food choices and body weight.

The third issue concerns the concomitant use of medications with NNS by lactating mothers. If sucralose is in fact determined to induce P-gp and CYP enzymes in humans, drugs that inhibit the efflux transporter P-gp or metabolic enzymes CYP3A4 or CYP2D6 in the gut may counteract P-gp/CYP absorption barrier and increase the amount of sucralose that reaches the bloodstream and likely breast milk. Many commonly used drugs are inhibitors of P-gp, CYP3A4, and/or CYP2D6. Examples of medications that affect these transporter and enzyme systems are antibiotics (e.g. erythromycin, clarithromycin) and antidepressants (e.g. selective serotonin reuptake inhibitors) (Balayssac et al., 2005, Flockhart, 2007). Further, inhibitors of CYP2D6 may potentially elevate the amount of intact sucralose in breast milk since this CYP isozyme is found in normal breast tissue (Iskan et al, 2001). Drugs can also interfere with excretion of saccharin in the kidney. The co-existence of saccharin in plasma with drugs that are substrates of organic ion transporters called OATs (e.g., anti-HIV therapeutics, antitumor drugs, antibiotics, antihypertensives, and anti-inflammatory agents) can interfere with saccharin excretion (Schiffman, 2012). It is therefore necessary to test whether NNS may affect circulating concentrations of medications.

Finally, sucralose, saccharin, and ace-K were found to exert numerous biological effects in adult humans and animal models at levels approved by regulatory agencies worldwide. One biologically plausible mechanism that may explain the epidemiological associations between NNS consumption, obesity, and metabolic complications, is the influence of NNS on intestinal microbiota. Abou-Donia et al (2008) and Schiffman and Rother (2013) showed that sucralose exposure at concentrations consistent with human consumption reduced the number of beneficial bacteria in the gut by 50% or more. Suez et al (2014) demonstrated that sucralose, saccharin, and aspartame-containing products alter the normal balance of bacteria in the human gut. Suez et al. (2014) also showed that 11 weeks exposure to saccharin resulted in glucose intolerance in rodents, thus establishing a causal relationship between NNS exposure, alterations in gut microbiota and glucose metabolism. In fact, NNS were also found to up-regulate microbial pathways promoting energy storage and increased efficiency of nutrient uptake by the host. Given these compelling data in rodents and the preliminary yet consistent data in humans, it is critical to study the extent to which exposure to NNS through breast milk may alter infant gut microbiota. This is particularly important because early life exposures including antibiotics (Nylund et al., 2014) and infant feeding practices (Doré and Blottière, 2015) are known to exert persistent effects on human gut microbiota. Due to the importance of the gut microbiome in immune function, metabolism, inflammation, and obesity (Rosenbaum et al, 2015; Tilg and Kaser, 2011), understanding the influence of NNS on the gut microbiome needs to be considered when making recommendations for their use, particularly amongst lactating mothers.

In summary, there are currently inadequate human data on the consequences of early life exposure to NNS through breast milk. Because the effects of prolonged infant exposure to sucralose, ace-K, and saccharin on their current and future health are not well understood, we encourage caution in concluding that NNS are appropriate for consumption by lactating mothers.

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