APPENDIX No. 9 (Expert Reasons REF 4)

REF 4 of the „EXPERT REASONS for existence of bottled infant water as an independent category" document

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Increased sodium concentrations in drinking water increase blood pressure in neonates

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Increased sodium concentrations in drinking water increase blood pressure in neonates

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Background In a previous study, we found that increased sodium concentrations in the drinking water led to an increase in mean arterial pressure (MAP) and systolic blood pressure (SBP) in fourth- and fifth-grade school children. Milk powder formulae have a low content of sodium, almost identical to that of breast milk. However, the final sodium concentration in the milk formula depends upon the concentration of sodium in the diluting water, which varies remarkably.

Objective To evaluate changes in blood pressure during the first 2 months of life in neonates receiving low-sodium mineral water (LSMW), high-sodium tap water (HSTW), or breast milk.

Design A randomized, prospective study in a teaching hospital.

Methods Fifty-eight Jewish term infants maintained on milk formula were randomly assigned to two groups. Group 1 consisted of 25 infants whose formula was diluted with LSMW (Eden Spring Mineral Water) having a sodium concentration of 32 mg/l (1.4 mmol/l). Group 2 contained 33 infants whose formula was diluted with HSTW having a sodium concentration of 196 mg/l (8.5 mmol/l). Fifteen breastfed babies served as the control group (group 3). Weekly weight, height, head circumference, heart rate, and systolic (SBP), diastolic (DBP) and mean (MAP) blood pressures were recorded for each infant for 8 consecutive weeks after birth. After 8 weeks, group 1 reverted to a diet similar to that of group 2. At 6 months of age (week 24), a follow-up blood pressure measurement was performed in 11, 20 and seven infants in groups 1, 2 and 3, respectively. Blood pressure was measured during sleep. Urinary sodium : creatinine ratio was determined monthly during the initial 2 months.

Results Increases in weight and height were equal in all groups. Heart rate did not differ between groups during the entire study period. From the age of 6 weeks until week 8, MAP, SBP and DBP were found to be significantly greater in the group 2 (HSTW). In parallel, the urinary sodium : creatinine ratio was significantly greater in this group. At week 24, blood pressure values in group 1 increased towards those of group 2.

Conclusions Diluting milk formula with tap water containing a high concentration of sodium will result in the infant being fed a high-salt diet. To equilibrate with breast milk, formula should be diluted with low-salt water. Blood pressure in the neonate is increased by a high sodium intake via drinking water. *J Hypertens* 20:203–207 © 2002 Lippincott Williams & Wilkins.

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Introduction

The role of dietary sodium intake as a risk factor in the development of hypertension, in both animals and humans, has been extensively reported [1–8]. As the majority (> 90%) of dietary sodium originates from food [9], water as a source of sodium has been relatively ignored in most human studies on hypertension and salt intake [10,11]. The sodium content of drinking water varies widely. In industrialized countries, water supplies contain less than 20 mg/l of sodium. In contrast, in other countries, particularly in developing areas, sodium concentrations can exceed 250 mg/l [9]. Russel [12] has shown that patients maintained on a low-sodium diet with a high fluid intake containing high concentrations of sodium, would receive up to 64% of their daily sodium allowance from drinking water. In infants, the sodium consumption via drinking water has been reported to be as high as 44% [9].

All milk powder formulae contain sodium concentrations almost identical to those found in breast milk [13]. However, as these formulae are diluted in tap water, the final sodium concentration may vary widely. The aim of the present study was to assess the influ-

ence of sodium concentration in the diluting water on blood pressure during the first 2 months of life, in infants fed milk formulae either low in sodium (diluted with low-sodium mineral water (LSMW)) or high in sodium (diluted with high-sodium tap water (HSTW)).

Methods

Meir General Hospital is a university-affiliated hospital situated in the central coastal plain of Israel, subserving a mixed Jewish and Arab population of 600 000 inhabitants. Approximately 7000 births per year are recorded. The water supply to the hospital and its environs is derived from one source – the national water transporter pipe. All individuals participating in this study were enrolled from the hospital's neonatal unit. In order to avoid genetic influences (from ethnic backgrounds) only Jewish infants were recruited. Babies from families with a history of hypertension were excluded from the study.

In all, 58 newborn infants were randomly assigned to two groups. Randomization was carried out as follows: an infant whose mother refused to breastfeed and who met the above inclusion/exclusion criteria, was then randomly allocated to one of the two study groups. Infants in group 1 ($n = 25$) were fed with a formula (Materna, Maabarot, Israel) diluted with LSMW (Eden Spring Mineral Water) having a sodium concentration of 32 mg/l (1.4 mmol/l). Group 2 infants ($n = 33$) were fed with the same formula diluted with HSTW having a sodium concentration of 196 mg/l (8.5 mmol/l). Fifteen breastfed babies served as the control group (group 3). Weekly weight, height, head circumference, heart rate, and systolic (SBP), diastolic (DBP) and mean (MAP) arterial pressures were recorded during the first 8 weeks. At the completion of the initial 8-week period, group 1 infants reverted to a diet similar to that of group 2. At week 24, a follow-up measurement of blood pressure was performed in 11, 20 and seven infants in groups 1, 2 and 3, respectively.

Non-invasive monitoring of blood pressure was performed using the Dinamap 8100 Vital Signs Monitor (Critikon Inc., Tampa, Florida, USA), which detects blood pressure and pulse by the Doppler technique. Blood pressure was recorded at the infant's home during sleep after feeding, with an appropriately sized cuff on the right upper extremity, overlying the brachial artery [14].

The sodium concentrations of milk formulae and breast milk were determined using a flame photometer. The urinary sodium : creatinine ratio was determined monthly during the initial 2 months.

Statistical analysis

Differences in group means were analyzed by analysis of variance followed by Newman–Keuls multiple comparisons or Student's t test for independent samples. Stepwise multiple regression analysis was used to test the correlation between the urinary sodium : creatinine ratio and blood pressure. Significant differences were denoted by a P value < 0.05.

Results

The three groups were well matched as regards gestational age, body weight, height, head circumference, and Apgar scores (Table 1). At weeks 4 and 8, no difference between groups was noted with respect to body weight, height, and head circumference (Table 1).

The electrolyte composition of tap water in the coastal plain area of Israel (HSTW) compared with that of Eden Spring Mineral Water (LSMW) is shown in Table 2. As can be seen, the sodium concentration was markedly increased in HSTW compared with LMSW [196 and 32 mg/l (8.5 and 1.4 mmol/l), respectively]. In addition, potassium concentrations were decreased, whereas calcium concentrations were increased [2.1 and 3.5 mg/l (0.05 and 0.09 mmol/l); 36 and 26 mg/l (1.8 and 1.3 mmol/l), respectively].

The manufacturer's reported value for the concentration of sodium in infant formulae is 186 mg/l (8.1 mmol/l). The concentration in breast milk was found to be 161 mg/l (7.0 mmol/l) (Table 3). When the milk powder was diluted with either HSTW or LSMW, the sodium concentrations were found to be 382 mg/l (16.6 mmol/l) and 218 mg/l (9.5 mmol/l) – increases of 97 and 17%, respectively, over stated values. The percentage increases in sodium concentration compared with the concentration in breast milk were even greater, 128 and 35%, respectively (Table 3).

Table 1 Infant data at initiation and at weeks 4 and 8 of the study period

	Group 1 (LSMW) ($n = 25$)	Group 2 (HSTW) ($n = 33$)	Group 3 (BM) ($n = 15$)
Gestational age (weeks)	40.0 ± 1.3	40.2 ± 1.1	39.5 ± 1.6
Apgar score			
1 min	8.9 ± 0.3	8.8 ± 0.9	9.1 ± 0.6
5 min	9.5 ± 0.2	9.3 ± 0.5	9.6 ± 0.5
Body weight (kg)			
0 weeks†	3.2 ± 0.7	3.1 ± 0.6	3.2 ± 0.5
4 weeks	4.4 ± 0.6	4.3 ± 0.8	4.4 ± 0.7
8 weeks	5.6 ± 0.8	5.4 ± 0.6	5.5 ± 0.6
Height (cm)			
0 weeks	49.9 ± 2.5	49.5 ± 1.4	49.2 ± 2.2
4 weeks	54.4 ± 2.8	53.8 ± 2.6	54.1 ± 2.1
8 weeks	58.4 ± 3.1	57.8 ± 2.4	57.3 ± 1.9
Head circumference (cm)			
0 weeks	34.3 ± 1.2	34.1 ± 1.6	33.2 ± 1.4
4 weeks	37.5 ± 1.3	36.8 ± 1.8	36.2 ± 1.5
8 weeks	39.7 ± 1.5	39.3 ± 1.2	39.3 ± 1.6

Results are expressed as mean ± SD. LMSW, low-salt mineral water; HSTW, high-salt tap water; BM, breast milk.
†Weeks after birth.

Table 2 Electrolyte composition of high-salt tap water (HSTW) and low-sodium mineral water (LSMW)

	HSTW		LSMW	
	(mg/l)	(mmol/l)	(mg/l)	(mmol/l)
Na^+	196	8.5	32	1.4
K^+	2.1	0.05	3.5	0.09
Ca^{2+}	36	1.8	26	1.3
Cl	110	3.1	24	0.68
HCO_3	186	3.05	198	3.25

Table 4 Blood pressure values at 8 and 24 weeks, and urinary sodium : creatinine ratio at 8 weeks

	Group 1	Group 2	Group 3
8 weeks			
SBP (mmHg)	85.6 ± 7.9	90.9 ± 7.7*	83.3 ± 6.5
DBP (mmHg)	48.9 ± 6.9	60.0 ± 5.7*	46.5 ± 8.7
MAP (mmHg)	60.7 ± 6.4	69.6 ± 6.6*	59.1 ± 7.5
Urinary Na^+ : Cr	1.2 ± 0.21	2.6 ± 0.30*	1.1 ± 0.25
24 weeks			
SBP (mmHg)	93.2 ± 6.3	95.1 ± 6.0†	88.3 ± 4.4
DBP (mmHg)	57.3 ± 6.9	63.2 ± 7.4†	53.8 ± 7.4
MAP (mmHg)	68.9 ± 5.5	71.4 ± 8.6†	63.1 ± 8.2

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; urinary Na^+ : Cr, urinary sodium : creatinine ratio. $P < 0.05$ compared with: *groups 1 and 3; †group 3.

Heart rate did not differ between the study groups during the entire study period. From the 6th week, SBP, DBP, and MAP were found to be significantly greater in group 2 (HSTW) than in groups 1 (LSMW) and 3 (breastfed) (Table 4). In parallel, the urinary sodium : creatinine ratio was significantly greater in group 2 than in groups 1 and 3, and was correlated with SBP, DBP, and MAP (Table 4, Fig. 1). At week 24, average blood pressure values in group 1 increased towards those of group 2 (Table 4, Fig. 2).

Discussion

An excess intake of salt is an established risk factor for the development of hypertension in animal models [2,5]. Adult blood pressure in hypertension-prone rats is significantly influenced by salt intake in the pre-weaning period. In man, epidemiological studies tend to substantiate the causative role of salt in the pathogenesis of hypertension [1,4,7,8]. The average salt consumption of different cultures correlates with the prevalence of hypertension in those cultures. In primitive societies typically characterized by a very low salt intake, blood pressure is maintained within the normal range throughout life [8].

Studies assessing the influence of sodium intake on blood pressure during the neonatal period are relatively scarce. One trial in newborn infants exposed to less dietary sodium from birth found lower SBP at 5–6 months of age, in addition to an attenuation of the rate of increase of blood pressure with age [15]. In contrast, Lucas and Morley [16] found no difference in blood pressure in a study of 400 premature infants fed either a low- or higher-salt diet and followed up to 8 years of age. Similarly, one other study reported no difference in blood pressure at age 8 years in children who were fed either a low- (1.9 mmol/l) or high- (9.3 mmol/l) salt diet between 3 and 8 months of age [17].

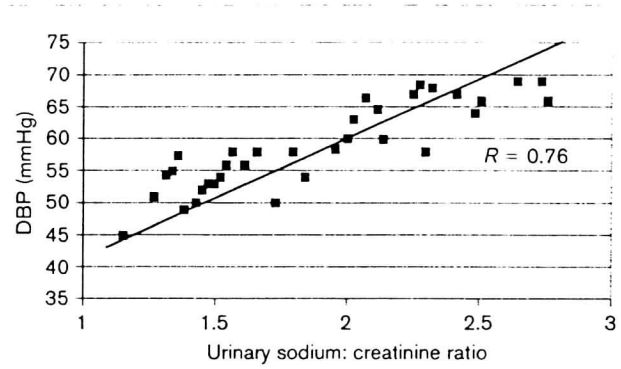
Human milk is a low-sodium food, averaging about 7 mmol/l. Its sodium content falls within the range (4–8 mmol/l) calculated to be a more than adequate daily metabolic requirement during rapid growth in the first year of life [13]. Although manufacturers' stated values of sodium in milk formulae approximate those of breast milk, the definitive sodium concentration in the prepared formula is dependent on the concentration of sodium in the diluting water. Diluting formulae with tap water containing a high sodium concentration will result in the infant being fed a high-salt diet. This was indeed shown to be the case in our study. Tap-water sodium concentration in our region is far in excess of that recommended by the World Health Organization [9]. Accordingly, infants in the HSTW group imbibed a formula 128% richer in sodium than breast milk. As the weight and height gain were equivalent among the three groups, their caloric intake must have been equal. Both breast milk and formulae contain a constant 281.4–285.6 kJ/100 ml. The fluid intake was, therefore, of similar magnitude among the groups, the only significant difference being its sodium content.

Table 3 Sodium concentration of breast milk and formulae diluted with either high-salt tap water (HSTW) or low-salt mineral water (LSMW)

	Na^+		Na^+ imbibed†			
	(mg/l)	(mmol/l)	(mg/l)	(mmol/l)	Change from stated (%)	Change cf BM (%)
Breast milk			161	7.0		
Infant formula‡	186	8.1	186	8.1	0	11.5
HSTW	196	8.5	382	16.6	105	137
LSMW	32	1.4	218	9.5	17	35.4

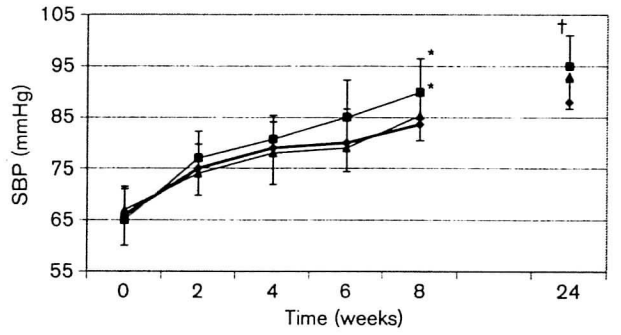
†Definitive sodium concentration imbibed by infant. ‡Manufacturer's stated sodium concentration.
BM, breast milk.

Fig. 1



Correlation (R) between diastolic blood pressure (DBP) and urinary sodium : creatinine ratio in a group of infants receiving milk formula diluted with high-salt tap water. Similar graphs were obtained for correlations between systolic blood pressure and mean arterial pressure and the urinary sodium : creatinine ratio.

Fig. 2



Systolic blood pressure (SBP) plotted against time. Similar graphs were obtained for diastolic blood pressure and mean arterial pressure. ■, high-salt tap water (HSTW); ▲, low-salt mineral water (LSMW); ◆, breast milk. * $P < 0.05$, HSTW compared with LSMW and breast milk; † $P < 0.05$, HSTW compared with breast milk.

This was also reflected by the urinary sodium : creatinine ratio which, in group 2, was more than double that found in groups 1 and 3. Although the determination of sodium intake by only one urine sample has the potential of being an inaccurate estimate, we have previously shown that the ratio correlates well with 24 h urinary sodium measurements [18].

As a consequence of being fed a high-salt diet, in comparison with LMSW and breastfed babies those in the HSTW group exhibited a progressive increase in MAP, SBP, and DBP from week 4 that attained significance at weeks 6–8 of the study period. When group 1 infants reverted to a high-salt intake after 8 weeks, their blood pressure values increased towards those observed in group 2.

Lever *et al.* [19] hypothesized that, in the early stages of hypertension, blood pressure is increased by a process related more to potassium than to sodium. This hypothesis was supported by the findings of Geleijnse *et al.* [20] in a study of a cohort of children aged 5–17 years, in whom an increase in SBP was shown to be inversely related to dietary potassium and the dietary sodium:potassium ratio. In our study, however, the urinary excretion of either potassium or calcium did not differ between groups, and there was no correlation between the urinary excretion of these cations and blood pressure.

Our data demonstrating an increase in blood pressure in neonates receiving a high-salt diet extend our previously published work in which we reported an increase in blood pressure in fourth- and fifth-grade school children exposed to a high sodium concentration in their drinking water [18]. It is interesting to note that, in Dahl salt-sensitive rats, exposure to a high-sodium diet is particularly detrimental when begun very early in life, at the time of weaning. In these animals, a brief period of a high-salt diet in early life leads to permanent hypertension, despite later maintenance on a low-salt diet [8]. On the basis of our findings, the establishment and maintenance of diets containing less sodium as the norm for infants and children would probably reduce the prevalence of essential hypertension in generations to come.

Of importance, our data show unequivocally that diluting milk formulae with tap water containing a high sodium content will result in the infant being fed a high-salt diet. To achieve equivalence to breast milk, formulae should be diluted with low-salt mineral water.

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