The Effect of Metoclopramide Administration on Electrolyte Status and Activity of Renin-Angiotensin-Aldosterone System in Premature Infants

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ABSTRACT. The present study has been carried out to define whether endogenous dopamine contributes to the regulation of renal sodium handling and the function of the renin-angiotensin-aldosterone system in low birth weight premature infants. Twelve premature infants with mean birth weight of 1420 g and mean gestational age of 29.2 wk were given metoclopramide (MTC) in a dose of 0.1 mg/kg/day to treat delayed gastric emptying, regurgitation, and abdominal distension at the age of 17–23 days. Infants were kept on either a low (2–3 mEq/kg/day) or high (4–7 mEq/kg/day) sodium diet to modulate activity of RAAS. Prior to and after a 3-day period of MTC administration, blood samples were taken, and in six male infants 24-h urine collections were made to determine plasma and urine electrolytes, plasma renin activity, plasma aldosterone concentration, and urinary aldosterone excretion. We demonstrated that plasma sodium and potassium concentrations and plasma renin activity were not altered by MTC. On the other hand, in response to MTC, there was a significant increase in urinary sodium excretion (1.8 ± 0.3 *versus* 2.3 ± 0.3 mEq/kg/day) and a decrease in potassium excretion (1.2 ± 0.2 *versus* 0.8 ± 0.1 mEq/kg/day); plasma aldosterone concentration and urinary aldosterone excretion decreased significantly from initial values of 2101 ± 274 pg/ml and 2.91 ± 0.52 μg/day to 1500 ± 207 pg/ml ($p < 0.01$) and 2.21 ± 0.43 μg/day ($p < 0.01$), respectively, after MTC. These alterations were independent of the pretreatment hormone levels. We conclude that in low birth weight premature infants endogenous dopamine has no influence on plasma renin activity and enhances rather than inhibits aldosterone production and renal tubular sodium reabsorption. (*Pediatr Res* 19: 912–915, 1985)

Abbreviations

DA, dopamine
RAAS, renin-angiotensin-aldosterone system
PRA, plasma renin activity
pAldo, plasma aldosterone concentration
UAE, urinary aldosterone excretion
MTC, metoclopramide

In recent years several lines of evidence have suggested a role of DA in the regulation of renal sodium excretion and the involvement of dopaminergic mechanisms in the control of the

RAAS system. Urinary DA excretion has been demonstrated to correlate positively with sodium intake and urinary sodium excretion (1–4), and a dose-dependent increase in urinary sodium excretion has been reported after DA administration (5–7) suggesting a natriuretic role for DA. Moreover, DA has been shown to increase renin release (8–10), to inhibit angiotensin-induced aldosterone production (11–13), and to enhance the renal response to aldosterone (14).

Very few data are available on the interactions among dopaminergic mechanisms, sodium homeostasis, and the RAAS during the neonatal period. It has been observed, however, that DA given to sick premature infants in a dose of 0.5–4.0 μg/min/kg increased sodium and water diuresis (15) and enhanced PRA, but did not cause significant alteration in pAldo (16). In an attempt to define the relationship between endogenous DA, renal sodium excretion, and the function of RAAS, the present study was designed to assess alterations in electrolyte status, PRA, pAldo, and UAE in premature infants who were given MTC, a specific DA antagonist.

MATERIALS AND METHODS

Twelve premature infants with a mean birth weight of 1420 g (range 990–1700 g) and mean gestational age of 29.2 wk (range 28–31 wk) were selected for the study. They were given MTC in a dose of 0.1 mg/kg/day to treat delayed gastric emptying, regurgitation, and abdominal distension at a mean postnatal age of 20.5 days (range 17–23 days), as suggested by Sankaran *et al.* (17). Eight of the 12 infants were kept on high sodium (4–7 mEq/kg/day); four infants were on a low (2–3 mEq/kg/day) sodium diet to modulate activity of the RAAS. During the course of the study four infants on high sodium were given Penicillin G and Kanamycin in a dose of 100,000 U/kg/day and 10 mg/kg/day, respectively, for a period of 6 days.

Before and after a 3-day period of MTC administration, blood samples were taken, and in the six male infants 24-h urine collections were made to determine plasma electrolyte concentration, PRA, pAldo and urinary electrolyte excretion, and UAE.

Blood samples were immediately placed in tubes in ice water containing EDTA (for PRA) or heparin (for pAldo). Plasma was separated in a refrigerated centrifuge and stored at −20° C until assayed. Urine specimens were pooled and stored at −20° C until analysis.

PRA, pAldo, and UAE was determined by radioimmunoassay according to the methods of Haber *et al.* (18) and Vetter *et al.* (19) using SORIN-CEA-IRE RIA kits. Sodium and potassium concentrations in plasma and urine were measured by flame photometry.

Statistical analyses were performed by calculating the coefficient of correlation regression equations and Student's paired *t*

test. Approval of the local ethical committee and informed parental consent were obtained for all studies.

RESULTS

As shown in Table 1 no significant change was observed in plasma sodium or potassium concentrations after MTC administration, although tendencies for a fall in plasma sodium and to rise in plasma potassium were seen.

Urinary sodium excretion increased significantly from the pretreatment level of 1.8 ± 0.3 to 2.3 ± 0.3 mEq/kg/day ($p < 0.05$) after MTC, and there was a moderate, but significant, reduction in urinary potassium excretion from 1.2 ± 0.2 to 0.8 ± 0.1 mEq/kg/day ($p < 0.05$).

When plasma and urinary electrolyte values of infants on high and low sodium intakes were studied separately, it was observed that infants on low sodium were hyponatremic and tended to increase their sodium excretion more in response to MTC than those on the high sodium intake. Due to the small numbers of cases, however, statistical significance was not reached for this observation.

Figure 1 demonstrates that PRA remained unaltered by MTC (39.4 ± 5.9 versus 42.0 ± 11 ng/ml/h), whereas in response to MTC treatment, there was a significant decrease in pAldo with mean levels falling from 2101 ± 274 to 1500 ± 207 pg/ml ($p < 0.01$). Similarly, the UAE responded to MTC with a significant fall from 2.91 ± 0.52 to 2.21 ± 0.43 μg/day ($p < 0.01$). It is also evident in Figure 1 that PRA, pAldo, and UAE tended to be higher in infants on low sodium than in those on high sodium intake. Basal hormone levels, however, had no apparent influence on the response pattern induced by MTC.

Figure 2 shows a significant positive correlation between UAE and urinary K/Na ratio suggesting that the high rate of sodium excretion is mainly due to suppressed aldosterone production.

DISCUSSION

Contrary to the general view, the results of the present study show that the administration of MTC, a specific DA antagonist, to premature infants results in an increase of urinary sodium excretion suggesting that endogenous DA may enhance renal tubular sodium reabsorption in this early period of life. The MTC-induced natriuresis was associated with a significant fall of pAldo and UAE and there was a significant positive correlation between UAE and urinary K/Na ratio. It is likely, therefore, that the higher rate of urinary sodium excretion results from the decreased aldosterone production. Additionally, inhibiting a di-

rect action of DA on renal tubular sodium reabsorption may be a complementary factor (20).

The involvement of DA in the control of renal sodium handling is far from clear. On the basis of the apparent parallelism between urinary sodium and DA excretion, a natriuretic effect
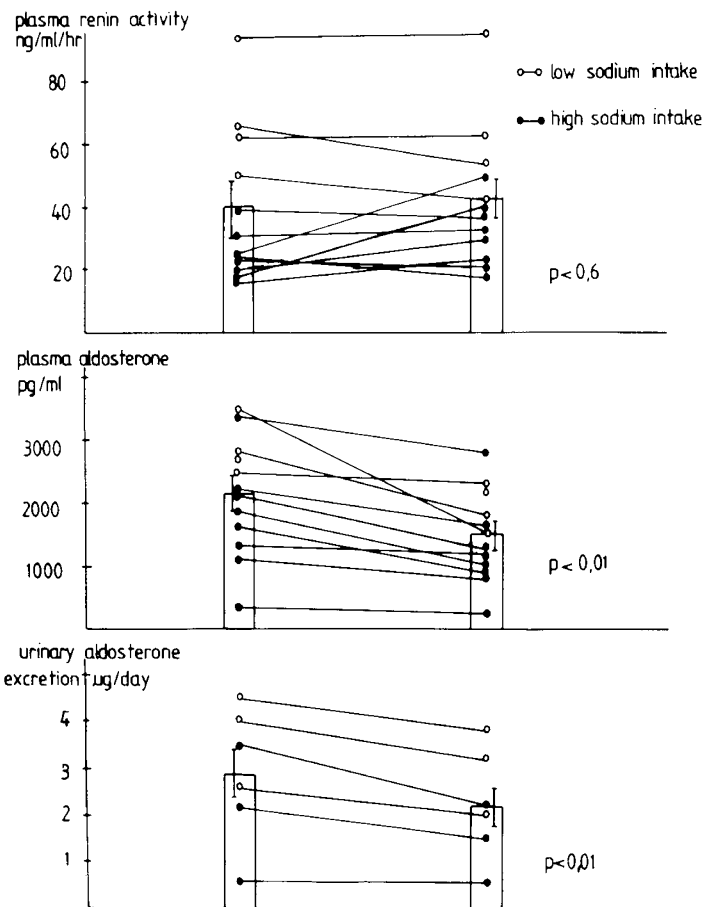

Fig. 1. Effect of metoclopramide treatment on plasma renin activity, plasma aldosterone concentration, and urinary aldosterone excretion in premature infants. The *symbols* represent values obtained before and after metoclopramide administration, respectively.

Table 1. *Effect of metoclopramide treatment on plasma level and urinary excretion of sodium and potassium in premature infants on high and low sodium diet (mean ± SE)*

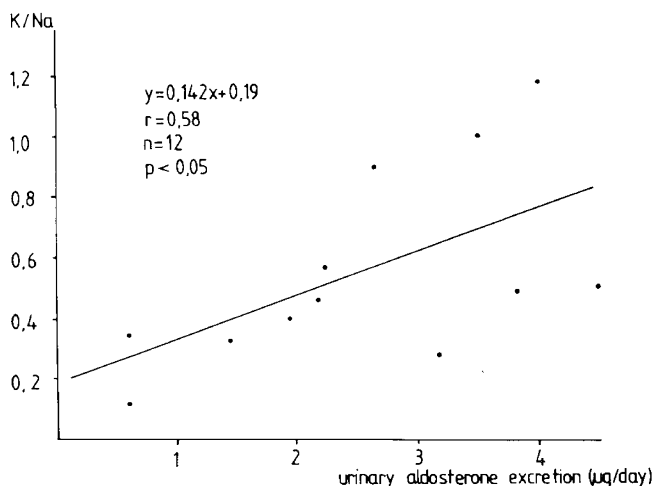|	Plasma concentration (mEq/liter)		Urinary excretion (mEq/kg/day)	
	Sodium	Potassium	Sodium	Potassium
Before metoclopramide				
High sodium	139.0 ± 2.9	5.0 ± 0.30	2.6 ± 0.5	1.4 ± 0.3
	$n = 8$	$n = 8$	$n = 3$	$n = 3$
Low sodium	130.7 ± 1.3	5.6 ± 0.2	0.9 ± 0.1	1.0 ± 0.2
	$n = 4$	$n = 4$	$n = 3$	$n = 3$
Total	136.0 ± 2.5	5.1 ± 0.2	1.8 ± 0.3	1.2 ± 0.2
	$n = 12$	$n = 12$	$n = 6$	$n = 6$
After metoclopramide				
High sodium	136.9 ± 2.7	5.2 ± 0.3	$2.8 \pm 0.4*$	1.0 ± 0.3
	$n = 8$	$n = 8$	$n = 3$	$n = 3$
Low sodium	128.8 ± 2.4	5.5 ± 0.2	1.8 ± 0.1	$0.7 \pm 0.1*$
	$n = 4$	$n = 4$	$n = 3$	$n = 3$
Total	134.1 ± 2.2	5.3 ± 0.2	2.3 ± 0.3	0.8 ± 0.1
	$n = 12$	$n = 12$	$n = 6$	$n = 6$

$* p < 0.05$.

Fig. 2. The relationship of UAE to urinary K/Na ratio in premature infants treated with metoclopramide.

of DA seemed likely (1–4). Several studies, however, questioned a role for DA as a physiological natriuretic hormone, since changes in urinary sodium and DA excretion could be dissociated (3, 21, 22).

Further, the renal response to DA appears to be influenced by age. Pelayo and Jose (23) reported an age-dependent increase in DA-induced natriuresis in puppies. On the other hand Tulassay *et al.* (15) demonstrated that therapeutic DA administration to sick premature infants produced a significant increase of sodium and water diuresis. No differences were noted, however, in the natriuretic response to DA in infants of various gestational and postnatal ages (15).

There is considerable evidence of an interrelationship between DA and the function of RAAS. It has been reported that DA given at a low rate has no apparent influence of PRA (24, 25), whereas DA infused at higher rates stimulated renin release (8, 10, 24). The mechanism(s) by which DA increases renin release is uncertain. It may act either directly through dopaminergic and β-adrenergic stimulation or indirectly, as a result of a direct DA-induced natriuresis (8, 10).

In this regard DA administration to sick preterm neonates was found to be associated with a significant elevation of PRA (16). However, studies of DA blockade with MTC demonstrated variable effects on PRA: in response to MTC, PRA has been reported to remain unchanged (6, 12) to decrease (27) or to increase (28). When a rise occurred in PRA after MTC, the response was delayed and strongly influenced by the pretreatment PRA level. The greater PRA increment was seen in subjects on a low sodium diet with high prevailing PRA levels (28). In the present study MTC treatment of premature infants, either on a low or high sodium intake, failed to induce significant alterations in PRA, suggesting that endogenous DA is not involved directly in the control of renin release at any level of RAAS activity.

Concerning the role of DA in the regulation of aldosterone secretion, it has been suggested that DA might have a tonic inhibitory effect on angiotensin II-induced aldosterone production (12). In support of this notion it has been demonstrated that administration of DA or the DA agonist bromocriptine produced a significant suppression of the aldosterone response to angiotensin II, diuretics, and posture (13, 29–31). Moreover, MTC has been found to cause a rise in aldosterone secretion without changes in the known regulators of aldosterone production such as PRA, ACTH, electrolytes, and blood pressure (12, 32–34). Furthermore, the MTC-induced increment in plasma aldosterone concentration could be attenuated by simultaneous administration of DA (26, 33).

The general concept of dopaminergic inhibition of aldosterone secretion has been questioned (35) because of recent studies in

rats, rabbits, and dogs which failed to demonstrate an increased aldosterone secretion after MTC (36, 37). These observations lend support to the view that the inhibitory effect of DA on aldosterone production is species specific. Nevertheless its consistency in humans and nonhuman primates has been adequately substantiated. However, there is evidence that MTC produces its effect on aldosterone production by nondopaminergic mechanisms as well (35).

During the neonatal period there are limited data on the dopaminergic control of aldosterone secretion. In a previous study we observed unaltered plasma aldosterone levels in DA-treated premature infants despite significant increases of PRA. The finding has been interpreted to indicate either that the angiotensin II-induced aldosterone production is overridden by the inhibitory effect of DA, or that, in the absence of DA inhibition, the immature adrenals are unresponsive to further stimulation by the renin-angiotensin system (16). The present results suggest that in low birth weight premature infants endogenous DA is enhancing rather than inhibiting aldosterone production. This assumption is consistent with several recent studies in various animal species in which an effect of MTC on aldosterone could not be demonstrated (36, 37).

In conclusion, the present study on MTC-treated premature infants suggests that, in this early period of life, endogenous DA has no apparent influence on PRA but, enhances aldosterone secretion by the immature adrenals. The MTC-induced fall in pAldo and UAE seems to be independent of the pretreatment hormone levels and may contribute to the increased urinary sodium excretion seen in premature infants treated with this drug.

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