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THE INFLUENCE OF ORAL CONTRACEPTIVES ON DIURNAL URINE REGULATION

Hypothesis / aims of study

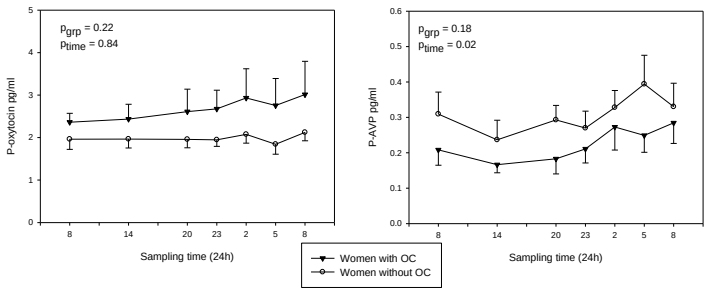
Sex hormones have a pronounced effect on arginine vasopressin (AVP), and therefore on the diurnal water homeostasis. The structural resemblance of oxytocin to AVP has likewise led to speculations of a possible additive antidiuretic effect of oxytocin (1). Prostaglandin E2 (PGE-2) counteracts the effect of AVP on water reabsorption and will be elevated when the concentration of estrogen is above normal range (2). In consequence of these relationships, it seems reasonable to assume that the endpoint, the diurnal urine production, would be influenced by the concentration of sex-hormones. Since the ethinyl estradiol of oral contraceptives (OC) is much more potent than the endogenous estrogens, ingestion of OC can, therefore, be expected to exaggerate diurnal variations in urine flow. This study therefore aims to elucidate the influence of oral contraceptives (OC) on diurnal urine regulation. We hypothesized that: 1) combined oral contraceptives decrease AVP concentration and diminish the circadian profile of AVP. 2) The high content of ethinyl estradiol in the pills increases the level of oxytocin and will lead to an oxytocin-induced antidiuresis. In addition we determined renal prostaglandins to clarify whether they were involved in the diurnal urine regulation in females taking oral contraceptives.

Study design, materials and methods

Fifteen healthy non-smoking natural cycling women in mid-follicular phase and 11 healthy non-smoking long-term OC (20 µg estradiol) users underwent in-patient circadian studies measuring the diurnal rhythm of AVP, oxytocin, plasma sodium and plasma osmolality, urine volume and excretion of free water, sodium, aquaporin-2 (AQP-2) and PGE-2. Blood-samples were taken at 8:00, 14:00, 20:00, 23:00, 2:00, 5:00, and 8:00 h. Blood pressures (mean arterial blood pressure (MAP)) were monitored by cuff every hour with an automatic ambulatory blood pressure monitor. Urine was collected every three hours from 8 00 to 23 00 hours. During admission a total fluid intake of 30 ml/kg body weight /24 h of tap water, distributed equally during the day was allowed. Meals with known contents of sodium (3 mmol/kg/24 h) and calories were served at 8:00, 12:00, and 18:00 h. To detect effects in p-AVP of approximately 0.20 or greater, the sample size was estimated to 10 participants in each group. A=0.05 and β=0.2. To compare the evolution over time for the two groups, we used a mixed model with time, group and their interaction as fixed effects and subject as random effect. When appropriate the data were log-transformed to fit the statistical model. The log transformed data are presented as geometric mean with normal 95% confidence intervals. Non-detectable values were set to equal half the detection level. Results were considered significant at $p<0.05$.

Results

We found a circadian rhythm in P-AVP in both groups (p=0.02), but no difference between the groups (p= 0.18) Quantifying the day-to-night difference, a nocturnal increase of approximately 34% (95%-conf. interval: 14-56%) from mean day time values was found for AVP in both groups (p<0.001). No circadian rhythm was found in oxytocin (p=0.83) and there was no difference between the two groups.



Participants taking oral contraceptives had significantly lower plasma osmolality; (Δosm 3.05 ± 0.29 mosm/kg, p=0.04) and likewise a lower plasma sodium; (ΔNa^+: 0.91 ± 0.09 mmol/l, p=0.05). Packed cell volume was on the other hand similar between the groups (p=0.54). We were able to demonstrate a circadian rhythm with a night time decrease in diuresis (1.08 ± 0.04, p<0.001), urine osmolality (109 ± 9 mosm/kg, p=0.02) and excretion of PGE-2 (0.77 ± 0.03 pg/h/kg, p<0.001). We found no difference between the groups in any of these parameters. We found a significant nighttime decrease in MAP of approximately 13 % in both groups (p<0.001). MAP was significantly higher in the women using oral contraceptives (4.7 ± 0.4 mmHg, p=0.02). We found a significant positive correlation between AQP-2 and urine osmolality (r=0.5315, p<0.001) and reabsorption of free water (r=0.4790, p<0.001), but no correlation between AQP-2 excretion and secretion of AVP or oxytocin. There was a negative correlation between 24 h diuresis and AVP (r=-0.2520, p=0.01). A similar correlation with oxytocin was not significant.

Interpretation of results

The influence of oral contraceptives on the diurnal urine production is not easy predictable. Our study confirms the finding of a circadian rhythm in AVP in natural cycling women in mid-follicular phase, but furthermore we were able to demonstrate a preserved circadian rhythm in women taking oral contraceptives. We were on the other hand not able to demonstrate that combined oral contraceptives decrease the overall concentration of AVP. We demonstrated likewise that ingestion of oral contraceptives decreased both plasma sodium and plasma osmolality. This reflects a shift to a lower osmotic threshold for AVP

release, which is a well-known phenomenon (3). Neither this resetting nor the elevated mean blood pressure in the OC-group was, however, related to changes in urine production or urine osmolality. We observed no diurnal variation in the concentration of oxytocin and likewise no difference between the two groups. AVP correlated negatively with diuresis whereas oxytocin does not seem to be involved in antidiuresis under normal physiological conditions. PGE-2 counteracts the effects of AVP on water reabsorption (2). In the present study urinary PGE-2 excretion revealed a distinct diurnal rhythm in excretion, but was unchanged between the two groups indicating that high exogenous ethinyl-estradiol and progestin at least in combination has no influence on the excretion, and it appears that PGE-2 plays no independent role in the diurnal urine regulation, when women ingest OC´s.

Concluding message

This study is to the best of our knowledge the first to describe the diurnal rhythm in the regulation of the female urine production under influence of oral contraceptives. Natural cycling women in low-estrogen states and women taking combined oral contraceptives have been examined. We observed small differences between the groups, but altogether, our investigations show that the diurnal urine production remained unchanged in spite of the use of OC`s.

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Was informed consent obtained from the patients?	**Yes**