Table 2. Serum Sodium Levels at Baseline and Before Discharge

	Tolvaptan Mean (SD)	Fluid Restriction n (%)	Total n (%)
Baseline	125.5 ± 4.8	126.1 (3.7)	125.8 (4.3)
Predischarge	133.1 ± 5.0	130.6 (4.7)	131.9 (5.0)
Change from baseline	7.6 ± 5.9	4.6 (4.6)	6.1 (5.5)

Table 3. Serum Sodium Levels at Discharge

Serum Sodium at Discharge (mEq/L)	Tolvaptan (n = 60) n (%)	Fluid Restriction (n = 54) n (%)	Total (n = 114) n (%)
≥135	25 (41.7)	8 (14.8)	33 (28.9)
< 135	35 (58.3)	46 (85.2)	81 (71.1)
≤130	14 (23.3)	23 (42.6)	37 (32.5)
≤125	6 (10.0)	7 (13.0)	13 (11.4)

mean, 4.0 days; range, 3.5 to 5.0 days; p = .95). The baseline CGI-S was 3.88 and 3.64 in the tolvaptan and fluid-restricted arms, and at 48 hours it was reduced to 2.65 and 2.73, respectively. The secondary end point of improvement in NC symptoms measured by CGI-S showed a nominal improvement with tolvaptan compared with fluid restriction (between-group difference, −0.30; 95% CI, 0.70 to 0.11; p = .1460).

The mean serum sodium levels at baseline and before discharge were similar in both arms (Table 2).

At discharge, serum sodium had normalized in 25 of 60 (41.7%) and 8 of 54 (14.8%) of patients in the tolvaptan and fluid restriction arms, respectively. The majority (71.1%) of patients were discharged with hyponatremia despite clinical intervention to correct sodium levels. Of these, 32.5% of the total patients were moderately hyponatremic and 11.4% were severely hyponatremic (Table 3).

The incidence of treatment-emergent AEs was higher in the tolvaptan arm (87.9%) than in the fluid restriction group (80.0%), as was the incidence of serious AEs (27.3% and 16.4%, respectively).

The findings that a majority of patients were discharged with moderate or severe hyponatremia suggests that hyponatremia influences, but does not prevent, hospital discharge. Study limitations included difficulty in accurately defining the LOS because the discharge decision was typically not made by the physician treating the hyponatremia and the relatively small sample size.

Neonatal Exposure to BPA Affects Puberty Onset in Rats

Written by Maria Vinall

Bisphenol A (BPA) is an industrial chemical used to make polycarbonate—a hard, clear plastic used in many consumer products. It is also found in epoxy resins, which act as a protective lining inside some metal-based food and beverage cans. Endocrine-disrupting effects of low BPA doses in the microgram range are a matter of controversy. In a late-breaking presentation, Jean-Pierre Bourguignon, MD, PhD, University of Liège, Liège, Belgium, reported that injection of a very low dose (25 ng/kg/day) of BPA into neonatal rats delayed puberty, slowed down gonadotropin-releasing hormone (GnRH) secretion, and changed hypothalamic RNA expression. Opposing effects, including early puberty, were observed with a high dose (5 mg/kg/day).

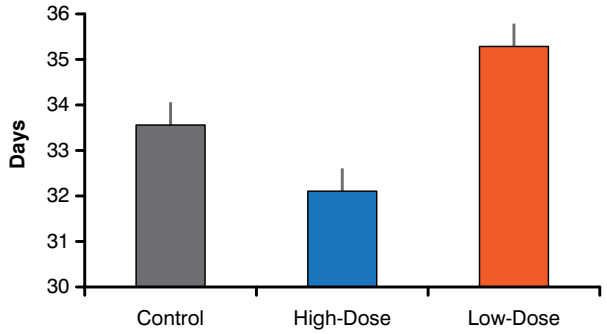
A related study reported on the effects of neonatal exposure to diethylstilbestrol (DES) on pubertal timing in female rats, showing that age at vaginal opening (VO) was advanced after exposure to 10 µg/kg/day of DES and delayed after 1 µg/kg/day, given subcutaneously [Franssen D et al. *Reprod Toxicol* 2014]. There were also consistent changes in maturation of pulsatile GnRH secretion.

In the current study, newborn female rats were exposed to vehicle (corn oil) or BPA, injected subcutaneously from postnatal day (PND) 1 to 5 or from PND 1 to 15. VO and estrous cyclicity were followed. The GnRH interpulse was studied ex vivo with hypothalamic explants obtained at PND 15, 20, or 25. Gene expression in the retrochiasmatic hypothalamus was assessed by whole-exome RNA sequencing on PND 20 (3 samples per condition).

The age at VO after neonatal exposure to 25 ng/kg/day of BPA for 15 days was 35.3 ± 0.7 days, compared with 32.1 ± 0.6 days at 5 mg/kg/day. In animals receiving vehicle (control), VO was 33.5 ± 0.5 days. Thus, the high dose advanced, and the low dose delayed, the age at VO compared with the control (Figure 1). The difference in pubertal timing between the 2 doses was significant (p < .05).

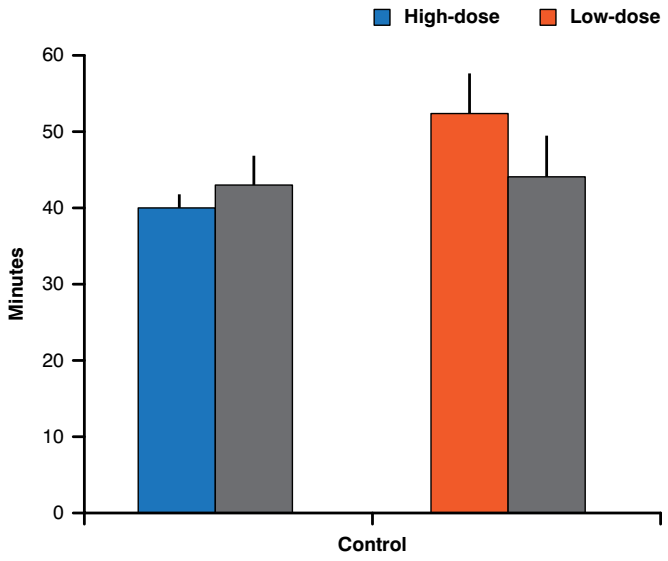
Late VO came after exposure to 25 ng/kg/day of BPA and was preceded at PND 20 by a significant increase in GnRH interpulse interval (52.5 ± 0.8 min vs 44.6 ± 0.7 min in controls). Early VO after exposure to 5 mg/kg/day, however, was preceded by a significant decrease in GnRH interpulse interval (40.3 ± 0.1 min vs 42.8 ± 0.4 min; Figure 2). After BPA exposure from PND 1 to 5, comparable dose-related changes in GnRH secretion were observed.

Figure 1. Median Age at Vaginal Opening After High and Low Doses of BPA



BPA=bisphenol A.

Figure 2. GnRH Interpulse Interval After Exposure to High and Low Doses of BPA



BPA=bisphenol A; GnRH=gonadotropin-releasing hormone.

RNA expression of 10 genes showed significant opposing changes in the high- versus low-dose groups at PND 20. The dose of 25 ng/kg affected expression of 14 genes, while 5 mg/kg modified the expression of 472 genes versus controls. A significant difference in levels of RNA expression was observed for 1407 genes when the 2 BPA dose conditions were compared.

Neonatal exposure to a very low dose of BPA delayed pubertal onset, slowed GnRH secretion, and changed hypothalamic RNA expression. Changed hypothalamic RNA expression confirmed the neuroendocrine effects of the 2 BPA doses, with opposing changes of similar genes in relation to BPA dose and with alteration of distinct genes by each dose.

While these data add to the large body of evidence in animal models concerning the effects of BPA on the female reproductive tract [Caserta et al. *Reprod Biol Endocrinol* 2014], the influence of BPA on the pathogenesis of premature puberty in girls has not been confirmed. Some have found a correlation between pubertal stages and BPA serum or urinary levels [Qiao et al. *Wei Sheng Yan Jiu* 2010; Durmaz et al. *J Clin Res Pediatr Endocrinol* 2014], while others have found conflicting data [Wolff et al. *Environ Res* 2008; Yum et al. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2013] perhaps due to confounding variables, such as body mass index and race [Wolff et al. *Environ Health Perspect* 2007]. More studies need to be conducted in humans.

ALN Reduces Bone Turnover in Perimenopausal Women With Low BMD

Written by Emma Hitt Nichols, PhD

Alendronate plus cholecalciferol treatment improved bone mineral density (BMD) at the lumbar spine and reduced bone turnover in perimenopausal women with low BMD. Aliya Khan, MD, McMaster University, Hamilton, Ontario, Canada, presented data in a poster from the Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of Alendronate (ALN) on Bone Mineral Density (BMD) and Bone Turnover in Perimenopausal Women With Low BMD [ICE/ENDO 2014. Poster LBSA-0269].

Menopause-associated bone loss begins during perimenopause, ~2 years before the last menstrual period. The purpose of this study was to determine if treatment with alendronate (ALN), an antiresorptive agent, can prevent bone loss in women who are perimenopausal and have low BMD. This is the first study to evaluate the efficacy of an antiresorptive agent on maintaining BMD in perimenopausal women.

In this double-blind trial, women aged 40 to 55 years with reduced bone density (T-score < –1.0) of the lumbar spine, total hip, or femoral neck were randomly assigned to receive 70 mg of ALN plus 2800 IU of cholecalciferol (vitamin D3) once weekly or placebo for 1 year. In addition, all patients received 500 mg of calcium carbonate once daily. Patients were eligible if they had at least 5 menstrual periods per year and had follicle-stimulating hormone (FSH) levels > 20 IU/L but < 40 IU/L on 2 independent occasions. Patients were excluded if they had