Tolvaptan Did Not Reduce Hospital Stay for Hyponatremia

Written by Brian Hoyle

Michael J. Koren, MD, Jacksonville Center for Clinical Research, Jacksonville, Florida, USA, reported a prospective clinical trial that evaluated the effect of the selective, competitive vasopressin 2 antagonist tolvaptan in the treatment of hyponatremia [Koren MJ et al. ICE ENDO 2014 (poster LBSA-0737)].

Hyponatremia is the most common clinically encountered serum electrolyte abnormality, occurring in 7% to 8% of elderly, ambulatory patients and 15% to 20% of hospitalized patients [Huda MS et al. *Postgrad Med J* 2006]. If left untreated, a subnormal (< 130 mEq/L) serum sodium concentration can led to seizure, reduced alertness, diminished pain sensitivity, and death, especially if the decline occurs rapidly.

The present study evaluated the influence of tolvaptan on medically necessary hospital length of stay (LOS) and time to improvement of neurocognitive (NC) symptoms of hyponatremia caused by water retention. The study was terminated early when only 124 of a planned 400 patients had been randomized into the study at 2 years.

Patients hospitalized with symptoms of mild to moderate dilutional hyponatremia were randomized to tolvaptan (15 to 60 mg) with fluid replacement as needed (n = 66) or placebo with < 1.5 L fluid daily (fluid restriction; n = 58). Patients were stratified by Clinical Global Impression–Severity (CGI-S) scores of 3 to 4 and 5 to 6 (of a maximum score of 7), a measure of NC symptoms.

Fifty-three (80.3%) and 48 (82.8%) of the tolvaptan and fluid-restricted patients, respectively, completed the trial. The rate of study discontinuation was similar in the tolvaptan and fluid-restricted arms (19.7% and 17.2%, respectively), mostly due to adverse events (AEs; 6.1% and 5.2%, respectively) or investigator decision (9.1% and 10.3%, respectively). The baseline demographics of both groups were similar (Table 1).

The primary end point of LOS was not significantly different between patients receiving tolvaptan (estimated mean, 3.5 days; range, 3.0 to 4.5 days) and fluid-restricted patients (estimated

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Table 1. Baseline Demographics

	Tolvaptan (n = 66)	Fluid Restriction (n = 58)	Total (n = 124)
Age (mean, y)	65.7	67.7	66.7
Male, %	56.1	41.4	49.2
Race, %			
Caucasian	66.7	70.7	68.5
Black	16.7	20.7	18.5
Asian	6.1	5.2	5.6
Etiology, %			
SIADH	57.6	63.7	60.4
CHF	28.8	17.2	23.3
Cirrhosis	12.1	6.8	9.7
Undefined	1.5	12.3	6.6

SIADH=syndrome of inappropriate antidiuretic hormone; CHF=chronic heart failure.

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.