

# Phototherapy-Mediated Syndrome of Inappropriate Secretion of Antidiuretic Hormone in an In Utero Selective Serotonin Reuptake Inhibitor–Exposed Newborn Infant

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**ABSTRACT.** Although selective serotonin reuptake inhibitors (SSRIs) have gained wide acceptance in the off-label treatment of mental disorders in pregnant women, there seems to be an increased risk for serotonergic adverse effects in newborn infants who are exposed to SSRIs during late pregnancy. Hyponatremia as a result of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a relatively common serious side effect of the use of SSRIs in (mostly elderly) adults. Severe hyponatremia as a result of an SIADH is proposed here as part of a neonatal serotonin toxicity syndrome in a newborn infant who was exposed prenatally to an SSRI. The definite reversal to normal serum sodium levels after fluid restriction, the lack of any alternative cause for the SIADH, and the positive temporal relation with a high score on a widely used adverse drug reaction probability scale offer solid support for the hypothesis of a causal relationship between the SIADH and the prenatal sertraline exposure in our neonate. Moreover, accumulative data on the acute enhancement of serotonergic transmission by intense illumination led us to hypothesize that phototherapy used to treat hyperbilirubinemia in the newborn infant could have been the ultimate environmental trigger for this proposed new cause of iatrogenic neonatal SIADH. The speculative role of phototherapy as a physical trigger for this drug-related adverse event should be confirmed in other cases by thorough study of the serotonin metabolism, assay of SSRI levels in cord blood, and serial measurement of plasma levels in exposed neonates. As phototherapy is used frequently in jaundiced neonates and an apparently increasing number of infants are born to mothers who take SSRIs, serotonin toxicity in neonates deserves increased attention. *Pediatrics* 2005;115:e508–e511. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-2329](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-2329); *neonate, hyponatremia, selective serotonin reuptake inhibitor, syndrome of inappropriate secretion of antidiuretic hormone, serotonin syndrome, phototherapy.*

**ABBREVIATIONS.** SSRI, selective serotonin reuptake inhibitor; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; CNS, central nervous system; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindoleacetic acid.

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Several authors have reported on neonatal serotonin toxicity syndrome after prenatal exposure to a selective serotonin reuptake inhibitor (SSRI) antidepressant.<sup>1–3</sup> Hyponatremia as a result of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a well-known side effect of SSRIs administered to adults.<sup>4,5</sup> Moreover, there is increasing evidence in the literature for the acute enhancement of cerebral serotonergic transmission by light therapy.<sup>6–8</sup> On the basis of these converging facts, we hypothesize that phototherapy could have been the ultimate physical trigger for severe hyponatremia in a neonate who was exposed in utero to an SSRI-type antidepressant drug.

## CASE REPORT

A 32-year-old insulin-dependent diabetic primipara woman used sertraline 50 mg twice daily during the last 3 weeks of pregnancy. Despite  $\beta$ -mimetic tocolysis as a result of preterm labor, a girl was born vaginally at 31 weeks of gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Because of respiratory distress, the infant was endotracheally ventilated and transferred to our neonatal department. Clinical examination of the large-for-dates infant (birth weight: 2200 g) was initially normal except for the respiratory distress. No congenital anomalies could be detected. Because of mild hyaline membrane disease (fraction of inspired oxygen  $\leq$  0.4), the infant needed respiratory support for 5 days.

Laboratory examination during the first 6 days of life revealed normal results for peripheral blood cell counts, as well as for electrolytes (sodium serum levels: 141–147 mmol/L) and renal and liver function tests. Mother and child both were group O Rhesus positive, and direct Coombs test was negative. Hypoglycemia (26 mg/dL) was noticed only once on admission, and euglycemia was maintained thereafter by dextrose-enriched parenteral nutrition. Brain ultrasound examination was normal at birth and later.

Within 24 hours, the infant was noticed to be jittery, restless, and hyperexcitable (Fig 1). From the second day on, spontaneous tremors were also frequently observed, as well as intermittent muscular rigidity and opisthotonus. Because the preterm neonate became markedly icteric on day 3 of life (indirect serum bilirubin: 12 mg/dL) conventional phototherapy was started. Jaundice (bilirubin 18 mg/dL on day 5) progressed rapidly, and light therapy was intensified 2 days later (double halogen lamps and Ohmeda BiliBlanket; Ohmeda Medical, Laurel, MD). Blood pressure and heart rate rose progressively with mean blood pressure  $\geq$ 60 mm Hg from day 5 to day 11. Diaphoresis was noticed on days 7 and 8.

Routine laboratory assessment on day 7 showed an extremely low serum sodium concentration down to 108 mmol/L. Urine output decreased moderately from 4.8 to 3.2 mL/kg/h. Serum potassium level remained normal (4.2 mmol/L). Serum osmolality was 233 mOsm/kg, urine sodium excretion was 48 mmol/L, and urine osmolality was 558 mOsm/kg. Serum levels of creatinine and blood urea nitrogen were 0.61 mg/dL and 0.32 g/L, respec-

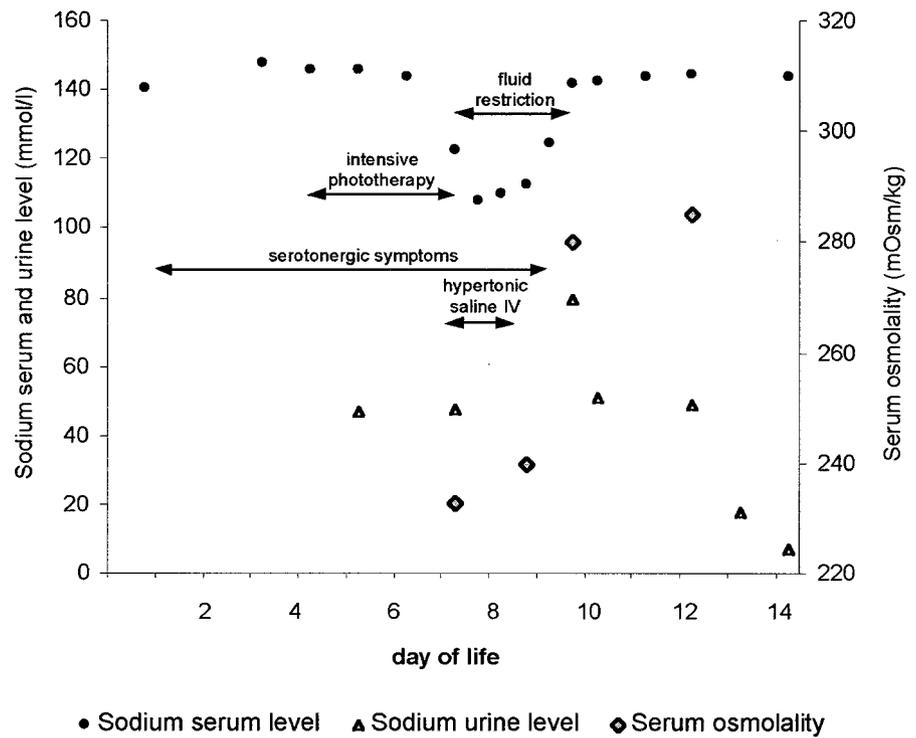


Fig 1. Time table for serotonergic symptoms, laboratory data, and therapeutic interventions in the infant.

tively. Thyroid function tests and serum cortisol level were normal.

Fluid intake was restricted from 150 to 120 mL/kg/day, and because of the extreme hyponatremia, hypertonic saline was administered temporarily. The serum sodium level gradually improved over the next 48 hours. Light therapy was switched from the intensive regimen to conventional treatment on day 8 and stopped on day 10. After day 10, the newborn became less agitated, and muscle rigidity vanished. Physical parameters such as urine volume, blood pressure, and heart rate, as well as urine sodium excretion and serum osmolality, assumed normal levels after stopping fluid restriction on day 10. Enteral feeding was started the next day, and the well-growing girl was discharged to the referring hospital after 3 weeks on full gavage feeding and in good health. An automated auditory brainstem response hearing test was normal. No serologic assessment of the serotonergic pathway was performed in this case, but sertraline and its active metabolite were assayed by liquid chromatography/tandem mass spectrometry in the infant's urine (Applied Biosystems API 2000 [Applied Biosystems, Foster City, CA]; limit of quantification is 10 µg/L). Urinary concentrations were 89 µg/L and 45 µg/L on day 5 for sertraline and desmethylsertraline, respectively. The corresponding levels were 35 µg/L and 43 µg/L on day 10.

### DISCUSSION

SSRIs inhibit serotonin (5-hydroxytryptamine [5-HT]) reuptake at the presynaptic junction, which leads to increased 5-HT concentrations at the synaptic cleft and enhanced serotonergic neurotransmission. SSRIs readily cross the placental barrier and expose the infant to altered 5-HT levels during early development.<sup>9</sup> Maternal doses are usually predictive for their umbilical cord concentration. In a pilot study on SSRIs in cord and maternal serum, it was shown that the median cord-maternal concentration ratio for sertraline was 0.67.<sup>10</sup> In studies that have evaluated the safety of SSRIs during pregnancy, neither an increase of major anomalies nor higher rates of miscarriage or stillbirth have been reported. This lack of teratogenic risk may have led to increasing off-label prescription of SSRIs to pregnant wom-

en.<sup>11,12</sup> However, prospective studies have found higher rates of premature delivery and lower birth weight in infants who are exposed to SSRIs in utero.<sup>13</sup>

The most prominent symptoms observed in our SSRI-exposed infant included tremor, restlessness, intermittent rigidity, tachycardia, and diaphoresis, which altogether resemble the symptoms of central nervous system (CNS) serotonergic overstimulation in adults. In a prospective, controlled, follow-up study, Laine et al<sup>2</sup> showed that infants who are exposed to SSRIs during late pregnancy are more likely to experience serotonergic adverse effects. The severity of these symptoms was inversely related to cord blood 5-hydroxyindoleacetic acid levels (5-HIAA). It is known that lowered 5-HIAA level in serum or cerebrospinal fluid is an accurate indicator of SSRI-induced increase in CNS serotonin activity.<sup>14</sup> In addition, a significant positive relationship was found between the serotonergic symptom score and the SSRI blood concentrations in drug-exposed infants of Laine's study.<sup>2</sup> As medication levels decreased in exposed infants' plasma, symptoms quickly disappeared, prompting the conclusion that the symptoms were attributable to serotonin overstimulation rather than to SSRI discontinuation syndrome. Other recently published controlled studies showed that in utero exposure to SSRIs late in pregnancy led to disruption in a wide range of neurobehavioral outcomes for the offspring.<sup>3,15</sup> This does not exclude that the neonatal SSRI discontinuation syndrome exists separately. However, it is highly important to distinguish both entities through serial measurement of serum SSRI levels postnatally, as inadvertent use of SSRIs to counteract withdrawal signs may potentially increase toxicity.<sup>1,2</sup>

In our patient, the abrupt and severe hyponatremia in combination with decreased serum osmolality, high sodium excretion, and high urine osmolality in the presence of normal renal, adrenal, and thyroid function was consistent with SIADH. SIADH-mediated hyponatremia is a relatively common serious side effect of the use of SSRIs in (mostly elderly) adults, with an incidence as high as 25%.<sup>4,5</sup> The definite reversal to normal serum sodium levels after fluid restriction, the lack of any alternative cause for the SIADH, and the positive temporal relation with a total score of 7 on the Naranjo adverse drug reaction probability scale<sup>16</sup> offer solid support for the hypothesis of a causal relationship between the SIADH and the prenatal sertraline exposure in our neonate. Serotonin-mediated effects on several 5-HT receptors have been shown to induce cerebral antidiuretic hormone release in anesthetized rats, which favors the explanation that SIADH is a direct central serotonergic stimulus.<sup>17</sup> Moreover, the SIADH observed in the newborn is a strong argument in favor of the existence of a genuine neonatal serotonin toxicity syndrome after prenatal exposure to SSRIs.

Because this probable SSRI-related adverse effect has not been reported in newborns before, we carefully checked for potential chemical or physical triggers in the history of our case. First, as SSRIs are known to inhibit a number of cytochrome P450 isoenzymes, we excluded any known drug-to-drug interaction.<sup>18</sup> Second, in search of a possible implication of phototherapy to which our patient was subjected before the SIADH became obvious, we read about the hitherto unreported occurrence of a typical acute serotonin syndrome in 2 SSRI-treated adult patients with seasonal affective disorder after the introduction of phototherapy.<sup>19</sup> The serotonergic symptoms resolved completely after light therapy was discontinued. The important role of serotonin in the mechanism of light treatment in seasonal affective disorder is demonstrated by the finding that the therapy's beneficial effect can be reversed by lower-

ing the serotonin precursor tryptophan.<sup>6-8</sup> In a placebo-controlled trial, Benedetti et al<sup>20</sup> showed a significant enhancing effect of light treatment on the antidepressant properties of an SSRI drug (citalopram) in adults with a major depressive disorder. It is interesting that Lambert et al<sup>18</sup> showed prospectively in 101 volunteers that turnover of serotonin in the brain was lowest during winter and directly related to the prevailing duration of bright sunlight. Furthermore, brain serotonin turnover adjusted promptly to acute changes in luminosity. Before this, Zammarchi et al<sup>21</sup> showed that free tryptophan serum levels decrease significantly in jaundiced newborn infants after 24 hours of phototherapy. In light of recent scientific knowledge, this tryptophan drop points toward an increase of brain serotonin turnover through enhanced take up of the serotonin precursor free tryptophan at the blood-brain barrier (Fig 2). Because these convergent observations clearly demonstrate the involvement of the CNS serotonergic system in the mechanism of action of light, we conclude that intensive phototherapy, started 2 days before the onset of severe hyponatremia, may have been the ultimate trigger for acute serotonin toxicity in our newborn.

This is the first report of SIADH-mediated severe hyponatremia associated with in utero SSRI exposure in a newborn infant. The speculative role of phototherapy as an external trigger for this drug-related adverse event should be confirmed in other cases by thorough study of the serotonin metabolism (tryptophan, 5-HT, and 5-HIAA), assay of SSRI levels in cord blood, and serial measurement of plasma levels in exposed neonates. As phototherapy is used frequently in jaundiced neonates and an apparently increasing number of infants are born to mothers who take SSRIs, serotonin toxicity in neonates deserves increased attention. Our observations may also help to elucidate further the enigmatic link between light and mood.

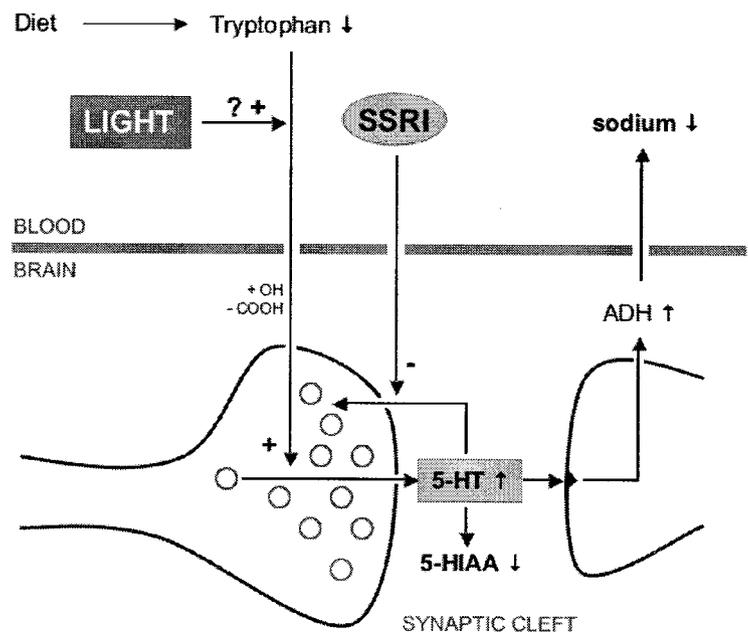


Fig 2. Hypothetical interaction of an SSRI-type drug and "light" at the synaptic cleft leading to serotonin toxicity and SIADH-mediated hyponatremia. ADH indicates antidiuretic hormone.

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