

## SHORT REPORT

## Neonatal paroxetine withdrawal syndrome

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**Abstract**

**Four term neonates presented with symptoms such as jitteriness and necrotising enterocolitis after paroxetine exposure in utero.**

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Keywords: neonates; paroxetine; withdrawal; serotonin reuptake inhibitors; necrotising enterocolitis

Use of serotonin reuptake inhibitors (SSRIs) during pregnancy has become common. Neonatal withdrawal symptoms characterised by poor adaptation after pregnancy exposure to selective SSRIs have been reported for fluoxetine.<sup>1,2</sup> However, little is known about paroxetine withdrawal in neonates. According to the after marketing study on the database of spontaneous adverse drug reaction reports of SSRIs, the reporting rate of withdrawal reaction was 10 times higher with paroxetine (0.3 per thousand) than with sertraline and fluvoxamine (0.03), and 100 times higher than with fluoxetine (0.002).<sup>3</sup> In this report, we describe four patients with neonatal complications which were consistent with neonatal SSRI (paroxetine) withdrawal syndrome.

**Patient 1**

This boy was born at 38 weeks gestation (birth weight 1.9 kg) to a 39 year old woman who had used paroxetine 10 mg/day and had smoked throughout her pregnancy (10 cigarettes a day). Apgar scores were 9 at one and five minutes. Soon after birth, the infant started vomiting on feeding, with frequent episodes of jitteriness. However, tachypnoea and respiratory difficulties were not noted. Although overall muscle tone was increased, deep tendon reflexes were normal. Intravenous fluid was started and continued for 24 hours. The infant tolerated feeding relatively well thereafter. Heart rate was initially about 100–110 beats/min with one episode of bradycardia (88 beats/min) without changes in colour or respiratory rate. Jitteriness gradually resolved over several days.

**Patient 2**

This child was born at 37 weeks gestation (birth weight 2.6 kg) to a 37 year old woman who used paroxetine and desipramine (150 mg/day) throughout pregnancy. The dose of

paroxetine was 60 mg/day from early pregnancy to week 35; from 35 weeks to delivery, she took 120 mg/day as a result of a dispensing error. She became tremulous, and the previous dose of paroxetine was reinstated after delivery. In the neonatal period, the breast fed infant had persistent hypothermia, jitteriness, irritability, poor gaze control, and myoclonus. The results of a computed tomography scan and electroencephalogram were unremarkable. On day 4 the infant passed a bloody stool and became lethargic. An abdominal roentgenogram showed pneumatosis intestinalis, and necrotising enterocolitis (NEC) was diagnosed. On day 5, paroxetine and desipramine concentrations were measured (table 1). Because an interaction between paroxetine and desipramine<sup>4</sup> was suspected to be the reason for the high desipramine concentration of the mother, the dose of desipramine was reduced from 150 to 50 mg/day. The child continued to have difficulty feeding and alternated between periods of pronounced irritability and somnolence until discharge at day 22.

**Patient 3**

This girl was born at 38 weeks gestation (birth weight 3.5 kg) to a 22 year old woman who used paroxetine (20 mg/day) and buspirone hydrochloride (30 mg/day) throughout pregnancy, which was complicated by gestational diabetes. The infant was hypotonic, and Apgar scores of 6 and 7 were assigned. She developed hypoglycaemia shortly after delivery which required intravenous dextrose. On day 2–3, she developed NEC with pneumatosis intestinalis, thrombocytopenia, and leukopenia. This was treated for 10 days with antibiotics and bowel rest. She had difficulty tolerating oral feeds because of emesis. She was often irritable or lethargic, needing to be woken up for feeds. She was discharged on day 24.

Table 1 Serum drug concentrations of patient 2

	Day 5	Day 15
Paroxetine (µg/l)*		
Mother	Not done	792
Infant	48	<10
Desipramine (µg/l)†		
Mother	1064	522
Infant	70	<10

\*Although there is no close correlation between serum concentrations and effects of paroxetine, 20 mg/day of the drug typically results in serum concentrations of about 12–90 µg/l in adults.

†The usual therapeutic concentration of desipramine is 125–300 µg/l.

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#### Patient 4

This infant was born at 38 weeks gestation (birth weight 3.2 kg) to a 35 year old woman with gestational diabetes and depression treated with paroxetine (20 mg/day) and trazodone (50 mg/day). In addition, she took diphenhydramine (25 mg each night). The baby received naloxone in the delivery room to counteract narcotics received in labour. Apgar scores of 6 and 9 were assigned. She became hypoglycaemic at 40 hours of age, which was controlled with intravenous dextrose. On admission, she was lethargic and poorly responsive to noxious stimuli. She was jittery and her tone and primitive reflexes were decreased. The serum concentration of paroxetine was 66 ng/ml and trazodone was undetectable on admission. Her appetite and activity improved and she was discharged at 5 days of age.

#### Discussion

Although the safety profiles of the four relatively common SSRIs, fluoxetine, fluvoxamine, paroxetine, and sertraline, are similar, the after marketing study showed that withdrawal symptoms are most often reported with paroxetine in adult patients.<sup>3</sup> In a double blind, placebo controlled randomised trial of paroxetine for panic disorder, 19 (35%) of 55 patients had symptoms associated with discontinuation of the drug compared with seven (14%) of 52 patients in the placebo group.<sup>5</sup> The relatively short elimination half life of paroxetine (17 hours) may be one of the contributing factors. However, it is not clear why the other SSRIs with short half lives such as fluvoxamine (15 hours) and sertraline (23 hours) have a lower incidence.

In one study, maternal use of a prototype SSRI, fluoxetine, during the third trimester was associated with poor neonatal adaptation—that is, jitteriness, tachypnoea, hypothermia, etc—in as many as one third of the exposed infants.<sup>1</sup> Whether this is common to other SSRIs is unclear. The incidence of the adverse events observed in the present paroxetine series is not known, because the size of the population base—that is, the number of pregnant women receiving paroxetine—could not be accurately estimated.

In adults, SSRI withdrawal symptoms include non-specific symptoms such as dizziness, paraesthesia, tremor, anxiety, nausea, and emesis, which typically occur two days after the last dose and continue for an average of 10 days.<sup>3</sup> A hyposerotonergic state has been hypothesised to explain these symptoms.<sup>6</sup> Our four cases suggest that maternal paroxetine use may be associated with a risk of perinatal complications. In particular, the two cases of NEC, which is unusual in term infants, are of concern.

Four concomitant drugs that may have contributed to the clinical pictures of these infants are desipramine (patient 2), buspirone (patient 3), trazodone (patient 4), and diphenhydramine (patient 4). Desipramine, buspirone, and trazodone are antidepressant drugs. They enhance the actions of serotonin in the central nervous system by inhibiting its reuptake

#### Key messages

- Paroxetine withdrawal syndrome was suspected in four neonates exposed to the drug in utero at maternal doses ranging from 20 to 120 mg/day
- The symptoms and abnormalities included, but were not limited to, jitteriness, vomiting, irritability, hypoglycaemia, and necrotising enterocolitis
- Close observation is warranted for neonates exposed to paroxetine in utero

(desipramine and trazodone) or by directly acting as an agonist (buspirone). Desipramine and trazodone also inhibit cerebral noradrenaline (norepinephrine) reuptake and  $\alpha_1$ -adrenergic receptors. Diphenhydramine, an antihistamine, inhibits histamine receptors ( $H_1$  blocker). All drugs in this report, including paroxetine, inhibit muscarinic-type cholinergic receptors. On their withdrawal, cholinergic rebound may occur.<sup>6</sup> However, there is no known link between a hypercholinergic state and NEC.

Platelet activating factor in the intestine may have a pivotal role in the development of NEC,<sup>7</sup> probably by enhancing platelet aggregation. SSRIs reduce platelet serotonin by inhibiting its uptake, and exhibit potent protection against repetitive platelet aggregation.<sup>8</sup> They occasionally cause platelet dysfunction and bleeding.<sup>9,10</sup> Although this is highly speculative, rebound activation of platelets may occur after SSRIs are withdrawn, predisposing the neonate to a hypercoagulable state, which further leads to NEC.

Although exposure to other antidepressant drugs is likely to have additional effects, given the relatively common use of SSRIs for women of child bearing age, SSRI withdrawal syndrome in neonates needs to be clearly characterised.

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