

## DRUG INFORMATION

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## CLINICAL PHARMACOLOGY

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### TOXICITY OF SSRI EXPOSURE VIA BREAST MILK

#### Question:

A 14 month old was breastfed until one month ago. The baby is very hyperactive and overstrung, although he has no actual resting tremor and his muscle tone appears normal. His mother has been on paroxetine 40 mg during this time. Could exposure to paroxetine via breast milk be responsible?

#### Answer:

##### *Paroxetine:*

Of the selective-serotonin reuptake inhibitors (SSRIs) available in New Zealand (citalopram, fluoxetine, paroxetine), we would generally consider paroxetine to be the preferred agent to use during breastfeeding because it has the lowest infant exposure via breast milk. The infant dose has been reported to be < 3% of the maternal dose, which is well less than the notional cut-off of 10% that guides drug safety. No adverse effects were observed in the fifteen infants who were studied<sup>[1,2]</sup>. However, it is may be difficult to identify adverse effects in neonates or infants. In one of these studies<sup>[1]</sup>, blood samples were taken from the breastfeeding infants for determination of paroxetine concentrations. No paroxetine was detected in the blood of seven infants while paroxetine was just able to be detected (but was not quantifiable) in the eighth infant.

In another series, paroxetine was not detected in the blood of 16 infants exposed via breast milk (limit of sensitivity 1 mcg/L; maternal paroxetine concentrations: < 1 - 136 mcg/L). Fourteen of these babies were reported to be > 95% breastfed and their age at time of sampling ranged from 2 to 26 weeks. Active questioning of the mothers did not reveal any adverse effects<sup>[3]</sup>.

Data associating paroxetine with adverse effects in suckling infants is limited. We are aware of a report associating agitation and difficulty feeding with paroxetine. Further details are lacking<sup>[4]</sup>.

There is substantial inter-individual variation (25-fold) in steady-state plasma concentrations of paroxetine. This is partially due to paroxetine being metabolised by cytochrome P450 2D6 (CYP2D6) which is subject to genetic polymorphism. Around 5-10% of Caucasians lack this enzyme and have reduced ability to eliminate paroxetine. This may lead to elevated paroxetine concentrations and increased pharmacological effect<sup>[5,6]</sup>.

Paroxetine has a mean half-life of 24 hours and no active metabolite<sup>[5]</sup>. This means that it carries less potential for accumulation in a breastfeeding infant compared with fluoxetine (half-life of the active metabolite, norfluoxetine is 1-2 weeks) and citalopram (half-life = 33 hours)<sup>[5]</sup>. However, as expected based on the considerable interindividual differences in plasma paroxetine concentrations, there is substantial variation in half-life of paroxetine (4 to 65 hours)<sup>[7]</sup>.

##### *Other SSRIs:*

##### *Fluoxetine:*

The infant dose for fluoxetine (includes the active metabolite, norfluoxetine) may be as high as 14% of the maternal dose, weight-adjusted<sup>[8]</sup>. Some authors have been unable to detect fluoxetine or norfluoxetine in the plasma or urine of suckling infants<sup>[9]</sup> while others report infant concentrations that are consistent with adult therapeutic concentrations<sup>[10,11]</sup>.

In a total of 15 infants exposed to fluoxetine via breast milk, no adverse effects were observed<sup>[8,9,12]</sup>. However other reports have described irritability<sup>[13]</sup>, colic<sup>[10]</sup>, reduced weight gain<sup>[13]</sup> and a tenuous association with seizure-like activity<sup>[11]</sup>. Recently, a case of hyperglycemia and glycosuria has been

reported in a 5-month-old infant exposed to fluoxetine during breast-feeding<sup>[4]</sup>. Symptoms resolved on cessation of the drug.

#### Citalopram:

The infant dose for citalopram is approximately 5% of the maternal dose, weight-adjusted<sup>[15,16]</sup>. Studies have failed to observe adverse effects in infants exposure to citalopram via breast milk<sup>[17]</sup>.

#### Sertraline and fluvoxamine:

Agitation has been reported with sertraline, but resolved despite continuation of breastfeeding<sup>[4]</sup>.

#### Conclusions:

There are isolated reports of adverse effects in breastfeeding babies exposed to SSRIs via breast milk. Although effects such as agitation and colic are plausible based on the pharmacology of these agents, it is extremely difficult to causally relate these effects to maternal drug therapy. The infant dose of paroxetine is low (<3%) indicating that adverse effects would not be expected in healthy term babies. However, given the substantial variability in steady-state paroxetine plasma concentrations, it is plausible that some infants may have higher concentrations than expected.

In this case, it seems unlikely that paroxetine is the cause of this child's hyperactivity since the effect has persisted for more than one month after discontinuation of breastfeeding. Even if the child were a poor metaboliser, they would still be expected to have eliminated the drug by this point in time. In the absence of the poor metaboliser status, the advanced age of this infant would be expected to be associated with enhanced clearance of paroxetine. Infant exposure would also be reduced by the presence of non-breast milk feeds eg. solids.

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