DRUG INFORMATION
Jonathan Banks
Bob Buckham
Sharon Gardiner

Canterbury DHB
District Health Board
Te Poari Hauora o Waitaha

CLINICAL PHARMACOLOGY
Murray Barclay
Evan Begg
Chris Hutchinson
Petra Lowe
Jane Vella-Brincat
Mei Zhang

SAFETY OF BUPROPION IN BREASTFEEDING

Question:
A breastfeeding woman is being treated with bupropion for depression. Is this safe?

Answer:
Infant exposure: A literature search[1-6] revealed two reports describing the use of bupropion in breastfeeding women[7,8].
In the first report, Briggs *et al.,* [7] measured the concentrations of bupropion and its three major active metabolites (hydroxybupropion, threohydrobupropion, erythrohydrobupropion) in maternal plasma and milk in one subject throughout a dosing interval. The woman (72 kg) had been taking bupropion 300mg per day for depression and was breastfeeding a 14 month old baby twice daily.
The concentrations of bupropion, threohydrobupropion and hydroxybupropion that these authors measured in milk can be used to estimate the 'dose' that an average baby might ingest via milk per day (erythrohydrobupropion concentrations in plasma and milk were too low to quantify; < 0.025 mg/L). The infant dose is calculated to be approximately 3% of the maternal dose, weight-adjusted based on the following assumptions: the metabolites have equal activity to the parent drug, the peak milk concentrations (2 h post-dose) represent a 'worst-case' scenario and an average baby ingests 0.15 litres of milk per kilogram of body weight per day. This is below the arbitrary cut-off of 10% that has been used to guide safety during lactation[4].
Neither bupropion nor its metabolites were detected in the infant's plasma (3.7 h post-feed; 8.5 h post-maternal dosing; limit of detection = 5 mcg/L for bupropion and 200 mcg/L for metabolites), although this may partially reflect the advanced age of this infant and the low number of feeds per day. No adverse effects were noted in the suckling infant by the mother or the paediatrician.
Note: The milk to plasma (M/P) ratio of bupropion in this report varied from 2.4 - 8.5 over the dosing interval (M/P(AUC) ratio = 4.4). Some authors may suggest that because bupropion is concentrated in milk, it should not be used in breastfeeding. However, as can be seen here, the M/P ratio does not necessarily give a good indication of the 'dose' the baby will receive in milk (because of distributional factors).

In the second report, Baab *et al.*[9] measured bupropion and hydroxybupropion serum concentrations in two mother-infant pairs. Both mothers received bupropion 150mg per day. Their babies were 17 and 40 weeks' old and breastfeeding provided 100 and 80% of their nutritional intake, respectively. The concentrations of bupropion and hydroxybupropion were below the limit of quantification (< 5-10 mcg/L for bupropion and < 100-200 mcg/L for hydroxybupropion) in both infants and no adverse effects were observed[9].

Prolactin: Bupropion has complex effects on dopamine including blocking its reuptake[1] which may impact on prolactin release. In humans, bupropion has been associated with decreased or unchanged prolactin concentrations[2]. Two studies reported no effect of single-doses of bupropion on plasma prolactin concentrations in healthy vounteers and individuals with hyperprolactinemia[10,11]. One animal study determined that bupropion increased hypophysial stalk dopamine concentrations and reduced suckling-associated prolactin release in rats[12]. Reduced prolactin concentrations may be associated with reduced milk volume.

The impact of regularly administered bupropion on milk supply is not known [Note: most antidepressants eg. selective-serotonin reuptake inhibitors carry the potential to increase prolactin concentrations[2]].

Toxicity of bupropion: The most frequently encountered side effects of bupropion are agitation, headache, insomnia, tremor, dry mouth and gastrointestinal upset. Seizures are a rare but well-documented toxicity of bupropion but usually occur with high doses, overdoses, or in individuals who are at increased risk of seizures such as those with head trauma. Bupropion has also been associated with various neuropsychiatric effects including psychosis[1].

The American Academy of Paediatrics advises caution with the use of psychoactive drugs in lactation because of the possible effects of exposure on the developing infant[3]. However, post-partum psychiatric problems such as depression are relatively common and the benefits of breastfeeding well-established. In most circumstances, it would be regarded as acceptable to breastfeed babies while a mother is on an antidepressant. However, preference should be placed upon using agents with good clinical data, low infant exposure and lack of reports of toxicity. Among the agents of choice for treating depressed lactating women are paroxetine (infant dose 1 – 3% of the maternal dose, weight-adjusted) and citalopram (approximately 5%)[11].

Other factors: Other factors to consider include the age of the infant who is to be exposed via milk, (as for example, premature infants would have reduced ability to eliminate drugs via metabolism or the urine), the maternal dose and the number of feeds per day. In addition, bupropion's major metabolites are reported to have half-lives that are substantially longer than that of the parent (8 – 24 h), suggesting accumulation will occur with repeated dosing[1].

Conclusions:

Available data describing the safety of bupropion in breastfeeding is limited to three case reports. These data suggest that infant exposure is low and unlikely to pose important risk to a healthy term infant. The possibility of effects on prolactin is also a cause for concern. In general, it would seem preferable to use an antidepressant such as paroxetine for which there are more data supporting use. If this is not appropriate, then we would advise usual practices of trying to minimise infant exposure by avoiding feeding at likely peak concentrations in milk (about 2 h post-maternal dose-ingestion) and monitoring the infant for evidence of side effects eg. irritability, failure to thrive, altered sleep pattern and poor suckling. The possibility of effects on milk supply should also be considered.

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