Bromocriptine and lactation suppression: are the risks acceptable?

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If a drug treatment is not really needed, at what point are the risks of adverse effects considered too high? This is the central question behind Herings and Stricker's study of cardiovascular adverse effects and the use of bromocriptine for lactation suppression [1].

Bromocriptine mesylate, a dopamine receptor agonist, is a semisynthetic ergot derivate. High doses (30-75 mg daily) are used for parkinsonism; low doses (2.5-5.0 mg daily) are used for prostatic tumours and for suppression of physiological lactation. Bromocriptine is used also in the treatment of prolactin-secreting adenomas, hyperprolactinaemia-related conditions such as galactorrhoea, menstrual disorders and infertility, and for growth hormone suppression.

Lactation is a self-limiting condition – the ability to lactate disappears rapidly if a woman is not breast-feeding. Discomfort occurs between 2-7 days after delivery but engorgement usually disappears in 1 to 2 days. A review of a number of studies concluded that the majority of women can be adequately treated with conservative, non-pharmacological aids such as a tight brassiere, avoidance of nipple stimulation and the use of cold packs, with or without minor analgesics.

The indication "prevention of postpartum breast engorgement" was introduced for bromocriptine in about 1980 in the United States as well as in many other countries worldwide. Bromocriptine has been widely used for the prevention of physiological lactation. Sandoz estimated in October 1994 that 23 million women worldwide had used Parlodel® and Pravidel®, its brands of bromocriptine, for lactation suppression [Lexchin J, personal communication]. Bromocriptine is effective in preventing lactation and postpartum breast engorgement only if prescribed before lactation begins. It is generally prescribed for 2 weeks, but many women need to take the drug for a third week because they experience rebound lactation after discontinuation of the drug. Adverse effects such as headache, nausea, dizziness, vomiting and rash were experienced by 5 to 20 per cent of women prescribed bromocriptine to suppress lactation in clinical trials. The most important adverse experience was hypotension, which was dose- and time-related. At the time of approval, there were no reports of hypertensive crises, seizures or cerebrovascular accidents.

Regulatory decisions

On 17 January 1995, the United States Food and Drug Administration (FDA) withdrew approval for the indication on the basis that the drug was "not shown to be safe for use for prevention of physiological lactation" [2]. Italy, South Korea, the United Arab Emirates, Saudi Arabia, Oman, Qatar, Bahrein and Kuwait have also recently withdrawn approval for this indication because of concerns about safety. In Canada, the manufacturer, Sandoz, voluntarily withdrew the indication in August 1994 and the

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health authorities notified prescribers that "the overall risk/benefit profile of bromocriptine does not favour its continued use in lactation suppression" [3].

However, bromocriptine is still used for lactation suppression in almost every other country worldwide, including all European countries except Italy and Estonia.

Background to the United States' regulatory action

By 1983, a number of serious adverse effects were reported in association with the use of bromocriptine to suppress lactation, including severe hypertension, seizures and strokes. Because of the seriousness of these adverse drug events, in 1983 the FDA requested labelling changes warning of cardiovascular risks. After three requests Sandoz finally complied with these labelling changes in 1987. Additional severe adverse drug events were reported to the FDA, including isolated hypertension, seizures, status epilepticus seizures and strokes. After lobbying for regulatory action by the National Women's Health Network and the Public Citizen Health Research Group, a consumer advocacy group, the FDA recommended in 1989 that none of the drugs then labelled for use in lactation suppression, including bromocriptine, should be used for this indication. They asked all manufacturers of these drugs to voluntarily remove the indication from their products' labelling. All but Sandoz complied with the request [4].

Between 1980 and 1994, 531 adverse drug events were reported in the United States following bromocriptine use in women of child-bearing age, including 32 reports of deaths, of which 14 were from strokes, 5 from heart attacks and 8 from hypertension. There were additional reports of 36 non-fatal strokes, 14 heart attacks, 73 cases of hypertension and 98 seizures [4 5]. Sandoz carried out a case-control study of risks of puerperal seizures and strokes in relation to bromocriptine use [6]. This study failed to allay the concerns of the FDA regarding the drug's association with seizures and the study was too small in size to characterize adequately the risk of stroke [4]. Seizures reported following bromocriptine occurred on average 5 to 6 days after women started taking the drug. In the general population, most postpartum seizures are eclamptic and occur within 48 h of childbirth. The FDA treated the late onset of the seizures as additional evidence of causation and criticized underreporting of late-onset seizures in the study by Rothman [6] because hospital readmission data were examined at only one of the three sites investigated.

A retrospective study on hypertension and bromocriptine use found a higher risk among women with pregnancy-induced hypertension who had used bromocriptine postpartum, but did not find significantly increased risks from bromocriptine alone. In some of the reports mentioning hypertension as an adverse drug event, confounding factors can be found, but some women had no history of hypertension, predisposing factors or concurrent drug use at all [7].

On the basis of these data, the FDA concluded that "in light of the limited benefit of using bromocriptine for the prevention of lactation and the effectiveness and lack of serious adverse effects of conservative treatments, the risk that bromocriptine may cause a serious adverse effect in postpartum woman is unacceptable" [4].

Incidence of adverse effects

How many women are really at risk? The objective of the study by Herings and Stricker, published in this journal, is to estimate the incidence of cardiovascular and cerebrovascular adverse effects due to bromocriptine [1]. They used a historical cohort of 2,130 women who had used bromocriptine. Because they could not find cardiovascular adverse effects that were related to bromocriptine use, they estimated the incidence of bromocriptine-induced cardiovascular events to be less than 1 in 6,000. How does this compare with other data?

Since 1977, the Canadian Adverse Drug Reaction Monitoring Program has received 58 reports concerning women of child-bearing age, 3 of which were serious (1 woman died) [2]. In Australia, the Adverse Drug Reactions Advisory Committee reported 164 adverse reactions following the use of bromocriptine in postpartum lactation suppression over a 22-year period [8]. However, these were voluntary reports and were not related to utilization figures, so the incidence cannot be derived from them.

In France there were over one million prescriptions for bromocriptine for lactation suppression during the period 1985-1993. A French pharmacovigilance study reported 115 adverse drug reactions. They included reports of 20 cardiovascular and 41 neurological adverse effects. There were 12 cases of hypertension, of which 5 involved complications: eclampsia (2 ×), ischaemic stroke (2 ×) and severe headache (1 ×). In one case hypertension returned when bromocriptine was reintroduced, adding weight to the likelihood that the drug was responsible for the reaction. There were 2 cases of vasospasm, 3 cases of arterial thrombosis, including 1 death, and 3 myocardial infarctions. The neurological adverse effects consisted of 16 cases of hallucinations (2 suicide attempts, including 1 death), 16 cases of severe headache, 4 cases of convulsions and 5 cases of ischaemic stroke or cerebral haemorrhage. In some of these cases, contraindications to bromocriptine use were present and/or another ergot derivative was prescribed, leading to potential interactions. The authors stressed the need for more cautious prescribing [9].

The data from the United States, France, Canada and Australia originate from a spontaneous reporting system. Spontaneous reporting systems are mainly intended to produce signals about potential new adverse drug reactions. The reporting rate is seldom stable over time and the reported frequency of the adverse effects is at a minimum level because prescribers are often unaware of the relation between drug use and the adverse event [10]. Therefore, these figures cannot be used to estimate reliably the frequency of adverse events and should be criticized on the basis of incomplete reporting of the cardiovascular and neurological adverse effects in the puerperium.

The French data showed that 24 serious side-effects were spontaneously reported among approximately 1,000,000 bromocriptine users. It is impossible to know what proportion of actual adverse events this represents [10]. However, if it is assumed that about 10% of the adverse events were reported, an incidence of 1 per 4,200 users can been estimated. This means that for a reliable estimation of the incidence of cardiovascular and cerebrovascular adverse effects, a cohort of many tens of thousands of bromocriptine users is needed. Therefore it is not surprising that Herings and Stricker found no relation between the use of bromocriptine and cardiovascular and cerebrovascular events in their cohort of 2,130 women. Their study is valuable in suggesting an upper limit of the incidence, but more reliable figures require a much larger cohort, which probably cannot be found in the Netherlands.

Doubtful benefits

Although the study by Herings and Stricker failed to determine the incidence of adverse effects, it also failed to provide assurances of safety. The authors acknowledge this in their conclusion by strongly advising against bromocriptine use for suppression of lactation. They recommend prescribing bromocriptine for lactation suppression only when it is medically indicated. This is similar to labelling restrictions in some countries for use "where medically indicated", which is empty advice if a medical indication for lactation suppression is not defined clearly. Since bromocriptine is used before the onset of lactation, women who might experience more discomfort from breast engorgement cannot be predetermined. Some doctors interpret a medical indication liberally and recommend the drug to all women who do not wish to breast-feed; others restrict it to women who have experienced a stillbirth or late miscarriage. However, for women who have suffered a stillbirth non-drug alternatives also are less risky and avoid the possibility of rebound lactation 2 weeks after the stillbirth.

The study by Herings and Stricker was too small to provide a useful basis to make regulatory decisions. They estimate that fewer than 3 of the approximately 15,000 Dutch women exposed to bromocriptine for lactation suppression are likely to develop serious cardiovascular and cerebrovascular adverse effects each year. Although in the light of public health this number seems small, for the individual woman the risk of a serious adverse effect is identical whether she lives in the Netherlands, where 15,000 women per year are prescribed the drug, or in the United States, where 300,000 to 600,000 women received it before the indication was banned. Regulatory decisions about drug safety need to be based on the potential risks faced by each individual who uses the drug.

The number and severity of adverse drug events and the circumstantial evidence of possible causality (rechallenge, timing of events) were strong enough to cause several regulatory authorities to withdraw this indication. They made this decision in the light of the limited benefit of using bromocriptine and other lactation suppressant drugs, because these drugs often delayed rather than prevented lactation and because effective non-drug alternatives exist such as cold packs, breast binding with or without mild analgesics. Recently, three independent assessments advised against the use of lactation suppressants [11-13].

The weight of evidence from adverse reaction reports in several countries is already strong enough. If even a very small number of women die or become disabled as a result of using bromocriptine for lactation suppression, the number is much too high. These drugs are not worth using for an indication for which they are not really needed.

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