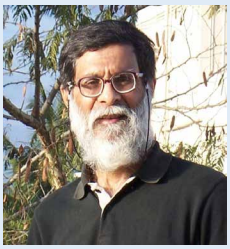
Clinical and Practical **Psychopharmacology**

Gestational Exposure to Benzodiazepines, 3:
Clobazam and Major Congenital Malformations

Chittaranjan Andrade, MD



Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

Clobazam is a 1,5-benzodiazepine that has been approved for use, in various parts of the world, as an add-on treatment for seizure disorders and as a treatment for anxiety. Pharmacoepidemiological data from different countries show that a small percentage of women with epilepsy (WWE) receive clobazam during pregnancy. Surprisingly, there has been little to no discussion in literature on the teratogenicity of clobazam. A network meta-analysis published in 2017 found a markedly elevated rate of overall and specific major congenital malformations (MCMs) with clobazam; whereas statistical significance was not established in any analysis, the 95% compatibility intervals did suggest increased risk. In the same meta-analysis, however, the risk with clobazam was not elevated in polytherapy. Indications of increased MCM risk also emerged in data from India and Sri Lanka. In all studies, the exposure numbers were small and information on trimester of exposure was unavailable. Given the nature of the data, adjustment for confounding would not have been possible. It is concluded that there appears to be a signal for an increased risk of MCMs in the infants of WWE who use clobazam during pregnancy. This signal merits examination in data that exist in national registers and pregnancy registries.

J Clin Psychiatry 2019;80(6):19f13151

To cite: Andrade C. Gestational exposure to benzodiazepines, 3: clobazam and major congenital malformations. *J Clin Psychiatry.* 2019;80(6):19f13151.

To share: https://doi.org/10.4088/JCP.19f13151

Most benzodiazepines are 1,4 benzodiazepines; clobazam is a 1,5 benzodiazepine; the numbers refer to the position of the nitrogen atoms in the diazepine ring of the benzodiazepine nucleus.[1] As with most other benzodiazepines, clobazam has anxiolytic[2] and anticonvulsant[3] actions and has been approved for both anxiety and epilepsy in different parts of the world.[4] A special advantage with clobazam, relative to 1,4 benzodiazepines, is that it is less sedating; it produces less cognitive and psychomotor impairment; and its use is less likely to result in dependence. These advantages may arise from its unique structure.[2] Clobazam, including generic clobazam, is available in the United States, with the approval being for the adjunctive treatment of seizures associated with the Lennox-Gastaut syndrome.[4]

Uncontrolled epilepsy is associated with unacceptable risks of morbidity and mortality.[5] Gestational exposure to epilepsy is associated with adverse gestational outcomes and adverse perinatal/neonatal outcomes that are not adequately explained by antiepileptic drug (AED) use.[6] It is usual, therefore, for AEDs to be continued during pregnancy in women with seizure disorders.

Earlier articles in this column examined AED use during pregnancy[7–9] and the use of benzodiazepines in pregnancy.[10,11] In this context, there is little discussion on the teratogenicity of clobazam. The present article therefore qualitatively reviewed the subject, drawing upon the results of an unrestricted PubMed search, conducted on November 3, 2019, using the search term *clobazam* with *pregnancy, teratogenicity,* and *malformation*s, separately. Articles included in the meta-analysis of Veroniki et al[12] were not examined because the findings of this meta-analysis are presented.

Use of Clobazam in Pregnancy

Clobazam is an infrequently used AED; when prescribed, it is usually an add-on medication. Its use in pregnant women with epilepsy (WWE) is therefore uncommon. This may explain why there is so little discussion on the teratogenic effects of the drug. A few recent studies on the pharmacoepidemiology of clobazam in pregnancy are summarized below.

Data from an antenatal clinic in Chandigarh, India, showed that, during 2011–2016, 2 (2.0%) of 99 pregnant WWE receiving AED monotherapy were receiving clobazam.[13] At this center, the use of clobazam in pregnant WWE significantly increased during 2011–2015 as compared with 1987–1994[14]; this finding is hardly surprising, though, giving that the usefulness of clobazam in epilepsy was better established during the later time window than during the earlier one.

Data from a pregnancy registry in Kerala, India, showed that, during 1998–2015, 11 (0.6%) of 1,809 pregnant WWE had received clobazam.[15] In Sri Lanka, between 2011 and 2015, 30%–33% of 96 WWE received clobazam across the 3 trimesters of pregnancy.[16] Data from the EUROmediSAFE consortium found that, among AEDs prescribed to pregnant women during 2007–2016, clobazam was prescribed to 5 (0.5%) of 1,057 women in Emilia Romagna, Italy; 0 (0.0%) of 1,722

women in Tuscany, Italy; 44 (10.4%) of 422 women in France; and 91 (3.1%) of 2,956 women in the United Kingdom.[17]

Clobazam and Major Congenital Malformations

A network meta-analysis of the major congenital malformation (MCM) risk with AEDs[12] did not provide rates for specific and overall MCMs with AEDs; however, the odds ratio (OR) was 3.48 for increased overall MCM risk with clobazam monotherapy, and the ORs were markedly increased, in the 5–23 range, for specific MCMs such as cardiac malformations, hypospadias, and cleft lip or cleft palate. In all cases, these ORs were not statistically significant, but this could be because the number of exposures to clobazam monotherapy was small (11, in all). The confidence intervals around the ORs, however, were strongly compatible with an increase in risk.

Curiously, in the same network meta-analysis,[12] in 9 women exposed to clobazam and oxcarbazepine, the risk of MCMs was nonsignificantly decreased (OR, 0.41). This contrasted with the findings for clobazam monotherapy. Perhaps higher doses had been used in monotherapy; unfortunately, dosing data were not provided.

Data from the Kerala Registry of Epilepsy and Pregnancy[18] showed that 160 WWE received clobazam in monotherapy (n = 9) or polytherapy (n = 151) during pregnancy. The MCM rate was 22.2% for clobazam monotherapy and 9.4% for overall exposure to the drug in either monotherapy or polytherapy. To put these numbers in perspective, the MCM rate with other AED monotherapies ranged from a low of 2.6% in 36 WWE exposed to lamotrigine to a high of 9.0% in 268 WWE exposed to valproate. There was no MCM in 6 women exposed to topiramate in monotherapy. The MCM rate for combined monotherapy and polytherapy exposure ranged from a low of 1.8% in 55 WWE exposed to lamotrigine to a high of 10.2% in 353 WWE exposed to valproate and an even greater high of 27.3% in 22 women exposed to topiramate. The MCM rate was 3.5% in AED-unexposed healthy control women and 5.6% in AED-unexposed WWE.

Galappatthy et al[16] reported that there were 5 infants with MCMs born to 96 WWE who were treated with AEDs during pregnancy. All 5 women had received carbamazepine; 2, in addition, had received clobazam.

There were no data on clobazam in a meta-analysis of congenital malformations associated with the monotherapy treatment of epilepsy in pregnancy.[19] Clobazam was not examined in a report of data on MCMs with AEDs, drawn from the EURAP registry.[20] A recent meta-analysis of studies on the teratogenicity of benzodiazepines presented no information on clobazam.[21]

Critical Comments

Wherever data on gestational exposure to clobazam have been available, they have suggested an increased risk of MCM in WWE. This risk has generally been larger than the risk with other AEDs. However, in all cases, the number of exposures to clobazam was small, information on dosing was often unavailable, no information on trimester of exposure was presented, and no adjustment for confounding was possible. Thus, the literature reviewed cannot support an argument that gestational exposure to clobazam is associated with teratogenic risk; it merely suggests that there is a signal that must be examined in observational studies that extract information from national registers and pregnancy registries.

In this context, one must be mindful of overenthusiastic precautions. For example, lamotrigine exposure during pregnancy was once believed to increase the risk of cleft lip and cleft palate; now, lamotrigine is recognized to be one of the safest AEDs for use during pregnancy. Protecting mothers and babies, therefore, becomes a delicate balancing act.[22] Until formal recommendations become available, clinical decision-making must be shared between physicians and patients.

Parting Notes

The use of clobazam during pregnancy has been associated with an increased risk of intrauterine growth retardation and preterm birth; however, as with the data on clobazam and MCM risk, these findings were based on a small number of exposures and confounding could not be ruled out. Clobazam was not associated with fetal loss; again, the number of exposures was small, and so one needs to interpret the findings with caution.[9]

Published online: November 26, 2019.

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