

Baclofen and pregnancy

Proposal for an ENTIS collaborative study

1. Study title

Pregnancy outcome after in utero exposure to baclofen: an ENTIS collaborative study.

2. Background

Baclofen is a gamma-aminobutyric acid (GABA) agonist approved for the alleviation of spasticity in patients with multiple sclerosis or spinal cord disease. It can be administered orally or by the intrathecal route to lower systemic exposure.

Reprotoxicity studies at very high doses in rats identified omphalocele, microcephaly, and vertebral arch widening, which is considered an indicator of spina bifida induction. In other studies, incomplete ossification was observed at high doses in rat and rabbit fetuses. In contrast, other studies in rats, mice, and rabbits reported negative teratogenicity findings.^{1,2,3}

Human data on first trimester exposure to baclofen consist of 14 cases including only 4 cases after oral intake.⁴⁻¹³ No case of malformation has been reported. One additional case of congenital inguinal hernia was reported in a newborn whose mother ingested 200 mg baclofen and other drugs in a suicide attempt at 14 weeks after the last menstrual period (LMP).¹⁴ Owing to the period of exposure, the role of baclofen can be ruled out in this malformation.

Furthermore, neonatal seizures were observed in a 7-day-old baby whose mother had been taking oral baclofen 80 mg/day throughout pregnancy. As seizures promptly resolved after baclofen administration, the authors concluded they were caused by baclofen withdrawal.⁶

In a preliminary analysis, we investigated the outcome of 39 pregnancies prospectively collected by the French pharmacovigilance centers including 38 cases exposed during the first trimester.¹⁵ Two newborns had major birth defects (anencephaly, bilateral kidney duplication) and 4 babies exposed up to delivery experienced neonatal symptoms: myoclonus in one exposed to 50 mg baclofen plus codeine, tremor in one exposed to 90 mg baclofen plus clonazepam, and hyaline membrane disease in 2 (1 premature baby, 1 full-term baby after C-section).

Considering the possible increasing off-label use of baclofen for alcohol dependence therapy, at least in France¹⁶, it is anticipated that more women may be exposed during pregnancy. Thus, a prospective controlled study is required to evaluate if baclofen exposure during pregnancy is associated with an increased risk of adverse outcomes.

3. Study target

To evaluate the risk of early in utero exposure to baclofen and to describe neonatal symptoms after 3rd trimester baclofen exposure.

4. Prospective study

Design.

Inclusion of all prospectively-collected cases from 1st January 1990 up to 28th February 2012. Accordingly, the last possible 1st contact will be in February 2012, because of the duration of pregnancy and the time needed to complete the follow-up.

- Study group: pregnant women exposed to baclofen between week 4 and week 12 after the last menstrual period (LMP), whatever the indication, and with prospectively ascertained outcome. Patients exposed to major teratogens (acitretin, isotretinoin, methotrexate,

mycophenolate, thalidomide, valproic acid) or patients with malignancies or malignancy-related conditions are excluded.

- General control group: pregnant women exposed to a non-teratogenic agent (see appendix I) with prospectively ascertained outcome. Patients with malignancies or malignancy-related conditions are excluded.

Matching: maternal age \pm 2 years, gestational age at inclusion \pm 2 weeks, year of counseling \pm 2 years, TIS or country.

No disease control group will be used in this study as alternate drugs are infrequently used. As a matter of fact, in our French database, only 3 pregnant women have been exposed to dantrolene - the only other drug used in France to treat spasticity - without any co-exposure to baclofen. Moreover, only baclofen may also be used for alcohol dependence treatment.

Sample size.

- Study group: any patient meeting the inclusion criteria will be included in the study. Owing to the number of women in our own database (approximately 40), at least 100 patients are expected to be enrolled in the exposed group.

- Control group General: 3 control patient for each exposed woman.

Primary objectives.

Rate of major birth defects, rate of spontaneous abortion.

Secondary objectives.

Intrauterine growth retardation (IUGR) in malformed and non-malformed newborns, prematurity rate (< 37 gestational weeks), rate of elective terminations of pregnancy (ETOPs).

Description of postnatal symptoms.

Confounders.

- Matching: maternal age, gestational age at inclusion, year of counseling, TIS or country.

- Adjustments: parity, previous spontaneous abortions, previous children/fetuses with major birth defects, tobacco, alcohol intake.

Statistical analysis.

- Continuous endpoints comparison: Student's t test.

- Categorical endpoints comparison: χ^2 test or Fisher's exact test when assumptions for χ^2 are not met.

- If a difference is pointed out: logistic regression analysis taking into account all identified possible confounding factors.

- Statistical significance set at *P* value of less than 0.05 (two-sided).

With 100 exposed cases the study has a 80% power of detecting a 3.5-fold increase in malformation rate, assuming a 3% baseline risk.

5. Retrospective study

As baclofen may be associated with adverse pregnancy outcome, in particular neonatal symptoms, an analysis of retrospective collected cases can be useful. This analysis will include

- Retrospectively ascertained major malformation after baclofen exposure between weeks 4 and 12 after LMP.

- Retrospective cases of neonatal symptoms after baclofen exposure up to delivery.

6. Proposed timeline.

1. October 2012-November 2012: draft protocol to ENTIS scientific committee for review and modifications.

2. December 2012-February 2013: data collection of exposed pregnancies for whom outcome is available and can be abstracted for the study. The last possible 1st contact for prospective cases will be February 2012 because of the duration of pregnancy and the time needed to complete follow-up.

3. February 2013-April 2013: data analysis, manuscript preparation and submission.

7. Data collection and evaluation.

Participation of TISes requires at least 5 prospective cases with their respective controls.

Data should be sent by e-mail using the excel file "Baclofen study data" (Appendix II). There is one excel sheet for each patient group (study group, general control group, retrospective cases).

In case of adverse outcome (for example malformed baby, pathological examination of a malformed fetus, postnatal symptoms requiring hospitalisation ...), please send the complete medical file scanned by email or fax (33 4 72 11 69 85).

Malformation cases: each case of malformation will be reviewed and classified by a birth defect specialist.

Proposed lead investigator: Nathalie Bernard, Lyon TIS

Funding Source: internal resources

Appendix I: Proposed list of substances that may be considered as non-teratogenic agent (non restrictive):

- Topical dermatological drugs, except retinoids
- Paracetamol, codeine except in case of fever > 39°C
- Penicillins and erythromycin, except new generations or in case of chronic disease or fever
- Ibuprofen (except if used beyond week 24 after LMP)
- Antiemetic drugs: doxylamine, metoclopramide
- Eye drops, except new drugs
- Calcium-, magnesium- or aluminium-containing antacids
- X-ray and MRI examinations, except examinations of the lower abdomen and pelvis or when a contrast media is used
- Oral contraceptive stopped before 8 weeks after LMP
- Single use of dental or cutaneous local anaesthetics
- Low-dose vitamin D
- Low-dose vitamin A (< 6000 UI/day)
- Topical or systemic acyclovir/valaciclovir
- Antihistamines H1, including new generation antihistamine drugs, except drugs marketed for less than 10 years
- Homeopathy except mother-tincture
- Vaccine, except live vaccine or vaccination complicated by fever > 39°C in the first trimester
- Cosmetics, household products...

In general, patients treated for chronic diseases (i.e. asthma, chronic inflammatory diseases, pre-pregnancy diabetes, epilepsy, hypertension....) cannot be considered as controls.

Appendix II: Excel file "Baclofen study data"

References.

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