Feasibility of mouse continuous intravenous infusion for fertility and embryo-foetal development studies

Richard S. Bartlett*, Hans van Wijk
Covance Laboratories Ltd., Harrogate, UK

The rat and rabbit are routinely used in pre-clinical reproductive and developmental toxicity (DART) studies. However, there are instances where they are not suitable models and the mouse is used as an alternative species. For studies requiring intravenous administration in mice, the test article can be administered as a slow bolus injection via the tail vein. However, this approach is only recommended for short term studies (up to 7 days) and for administration durations of less than 5 min due to adverse effects on tail quality with longer dosing. We have previously developed a mouse catheterised continuous intravenous infusion technique using a surgically implanted femoral vein catheter with tail cuff exteriorisation, and have shown its utility on general toxicology studies. However, the reliability of this method decreased over time, with a success rate of only 74% after 28 days on study because of tail cuff constraints due to animal growth. Additionally, infusion methods have not been developed for mouse DART studies. Therefore, the aims of the present study were (1) to determine whether a larger diameter tail cuff (6 mm) could extend the continuous infusion duration, and (2) to determine the feasibility of evaluating DART parameters in mice continuously infused using this method in a combined fertility and embryo-foetal development study. 33 CD-1 female mice (approximately 7–9 weeks old) were surgically implanted with a femoral vein catheter exteriorised with a 6 mm tail cuff, allowed to recover for at least 6 days, and then intravenously administered 0.9% sodium chloride, by continuous infusion (4 mL/(kg h)) for at least 2 weeks prior to pairing, during pairing (with uncatheterised males) and through Gestation Day (GD) 18 (42 total days). On GD18, females were killed and uterine contents examined. During the first two weeks of the study, technical failure occurred in 8 females; this was attributed to the larger diameter of the tail cuff, which slipped down and allowed the catheter to be chewed by the mouse. One female was removed from study due to technical failure during the mating period (prior to mating). Of the 24 female mice remaining on study at the end of pairing, 23 (96%) were successfully mated and 22 of those (96%) were confirmed pregnant. Catheter failures or poor tail conditions resulted in early removal of 5 additional mice. However, those surviving to necropsy, uterine and foetal data were within background ranges, indicating no effects of continuous infusion on any reproductive or developmental parameters. It is therefore concluded that continuous intravenous infusion via cannulation of the femoral vein and exiting at the tail using a tail cuff is a viable method of intravenous dosing for mice in DART studies. The larger tail cuff did not increase reliability of the infusion technique for a period greater than 28 days, therefore separate fertility and embryo-foetal development studies are recommended for mice.

http://dx.doi.org/10.1016/j.reprotox.2012.05.045

Pregnancy outcomes after in utero exposure to Baclofen

Nathalie Bernard*, Annie-Pierre Jonville-Bera, Patrick Carlier, Marie Boyer, Christine Damase-Michel, Thierry Vial, Jacques Descottes

*Pharmacovigilance Centers of Lyon, France
†Pharmacovigilance Centers of Tours, France
‡Pharmacovigilance Centers of Paris Fernand Widal, France
§Pharmacovigilance Centers of Marseille, France
¶Pharmacovigilance Centers of Toulouse, France

The French Network of Pharmacovigilance Centers

Introduction: Baclofen is an antispasmodic drug 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 high doses reported ophalmolecule, microcephaly, vertebral arch widening and incomplete ossification in several species. Human data consist of isolated cases of normal pregnancies, and one case of neonatal seizures attributed to baclofen withdrawal. The aim of this study was to describe pregnancy outcomes after in utero exposure to baclofen.

Methods: Prospective pregnancies with a known outcome recorded by the French network of Pharmacovigilance Centers were analyzed. Maternal history and drug exposures were collected during the first contact, and pregnancy outcomes were documented at follow-up. Retrospective cases were analyzed separately.

Results: A total of 42 cases were included, of which 3 were retrospective cases. Among the 39 prospective cases, the mean maternal age was 30.9 ± 5.3 years and the mean gestational age at the time of request was 12.1 ± 7.6 weeks after the last menstrual period. Baclofen was administered orally in all cases, but one. Patients were exposed during the 1st trimester, except one treated only during the 3rd trimester. The mean daily dose was 31.1 ± 23.1 mg (5–90 mg), mainly for multiple sclerosis (n = 12) and spinal cord trauma (n = 12). There were 31 live births (2 premature babies), 1 stillbirth attributed to chorioamnionitis and 7 elective abortions including 1 after diagnosis of anencephaly. An additional case of major malformation (bilateral kidney duplication) was observed among 32 examinable newborns. The rate of major congenital malformations was 6.25% [95%CI = 0.008–0.21%]. Four babies exposed up to delivery presented with neonatal symptoms: myoclonus (50 mg baclofen, codeine), tremulations (90 mg baclofen, clonazep, myoclonic), hyaline membrane disease (1 in a premature baby, 1 in a full-term baby with c-section). Three retrospective cases were collected: 1 baby with corpus callosum lipoma, nasal epidermoid cysts, and tremulations at birth (60 mg baclofen, clonazepam) and 2 cases of respiratory diseases (1 neonatal death in a premature baby, 1 full-term baby, both with c-sections).

Conclusion: Although our sample size is small, 2 cases involving the CNS as observed in animal studies, could suggest a potential target organ in humans. Moreover, we describe neonatal symptoms possibly due to baclofen exposure until delivery, including withdrawal symptoms after high-dose baclofen and concomitant exposure to benzodiazepine or opiates. Although possibly due to c-section or prematurity, pulmonary adverse events are reminiscent of rares cases of respiratory depression in treated patients.

http://dx.doi.org/10.1016/j.reprotox.2012.05.046