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# Comparison of developmental toxicity of selective and non-selective cyclooxygenase-2 inhibitors in CRL:(WI)WUBR Wistar rats – DFU and piroxicam study

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**Abstract**

*Background:* Cyclooxygenase (COX) inhibitors are one of the most often ingested drugs during pregnancy. Unlike general toxicity data, their prenatal toxic effects were not extensively studied before. The aim of the experiment was to evaluate the developmental toxicity of the non-selective (piroxicam) and selective (DFU; 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl) phenyl-2(5H)-furanon) COX-2 inhibitors.
*Methods:* Drugs were separately, orally once daily dosed to pregnant rats from day 8 to 21 (GD1 = plug day). Doses were set at 0.3, 3.0 and 30.0 mg/kg for piroxicam and 0.2, 2.0 and 20.0 mg/kg for DFU. Fetuses were delivered on GD 21 and routinely examined. Comprehensive clinical and developmental measurements were done. The pooled statistical analysis for ventricular septal (VSD) and midline (MD) defects was performed for rat fetuses exposed to piroxicam, selective and non-selective COX-2 inhibitor based on present and historic data.
*Results:* Maternal toxicity, intrauterine growth retardation, and increase of external and skeletal variations were found in rats treated with the highest dose of piroxicam. Decrease of fetal length was the only signs of the DFU developmental toxicity observed in pups exposed to the highest compound dose. Lack of teratogenicity was found in piroxicam and DFU-exposed groups. Prenatal exposure to non-selective COX inhibitors increases the risk of VSD and MD when compared to historic control but not with selective COX-2 inhibitors.
*Conclusion:* Both selective and non-selective COX-2 inhibitors were toxic for rats fetuses when administered in the highest dose. Unlike DFU, piroxicam was also highly toxic to the dams. Prenatal exposure to selective COX-2 inhibitors does not increase the risk of ventricular septal and midline defects in rat when compared to non-selective drugs and historic control.
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*Keywords:* COX-1; COX-2; Cyclooxygenase; Gastroschisis; Non steroidal anti inflammatory drugs; NSAID; Omphalocele; Prenatal toxicity; Umbilical hernia; Ventricular septal defect

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## 1. Introduction

Most of the rheumatic diseases are not alleviated during pregnancy but remain active or even exacerbated. Most of the spondyloarthropaty and systemic lupus erytematosus patients and 10–20% of rheumatoid and psoriatic arthritis pregnant patients still need pharmacological control of pain, stiffness and other inflammatory complications. Notwithstanding, that immunosuppressive and biological active agents, like anti-TNFα and anti-ILs antibodies were introduced, the cyclooxygenase (COX) inhibitors are still the most often prescribed drugs for such clinical situations (Ostensen and Skomsvoll, 2004). The human studies showed that these drugs inhibit ovulation and caused miscarriage. They are contraindicated after gestational week 32 since the drugs may constrict ductus arteriosus, reduce renal blood flow and prolong gestation. On the other hand these drugs have been used as tocolytic agents to prevent preterm labour (Hayes and Rock, 2002; Kozer et al., 2003; Li et al., 2003; Ostensen and Skomsvoll, 2004). In contrast to animal data, lack of teratogenicity was reported for COX inhibitors in human. Other anti-rheumatic pharmaceutics, like corticosteroids and methorexate are less prescribed during pregnancy since they have higher prenatal toxicity or are prohibited due to teratogenic activity, respectively (Briggs et al., 1998; Ostensen and Skomsvoll, 2004).

Until 1998 when the first selective COX-2 inhibitor (celecoxib) was marketed, only non-selective COX inhibitors were available. The drugs, also called aspirin-like or non-steroidal anti-inflammatory drugs (NSAID), are more toxic since they block both constitutive (COX-1) and inducible (COX-2) cyclooxygenase izoenzymes (Peskar et al., 2002; Burdan and Korobowicz, 2003). Unlike previous observation the two forms are expressed physiologically. However, the COX-2 was detected only in some organs like the brain, different parts of the gastro-intestinal tract, urinary and reproductive system (Schwab et al., 2003). Their expression was also noted in various fetal tissue (Stanfield et al., 2003; Streck et al., 2003). The third, paracetamol-sensitive isoenzyme (COX-3) was detected only in the mature central nervous system (Schwab et al., 2003).

The most often reported complications of nonselective COX inhibitors include gastrointestinal, renal and hepatic toxicity, and various allergic reactions. The selective COX-2 inhibitors, also known as coxibs, have been better tolerated by gastric mucosa, but other side effects are the same as for non-selective drugs (Burdan and Korobowicz, 2003). The recent studies showed that coxibs could increase number of acute ischemic cardiac incidence (Garcia-Rodriguez et al., 2004; Mamdani et al., 2004). Unlike adult toxicity, their prenatal data is spare and limited to the animal studies. They showed that COX-2 inhibitors caused intrauterine growth retardation and increased the number of skeletal developmental variations (Gross et al., 1998; Reese et al., 2000; Burdan et al., 2003). Elevation of preimplantation and postimplantation loss, vascular complications and prolonging gestational time were also reported (Reese et al., 2000; Shafiq et al., 2004). Such observations were partially confirmed in manufacturer studies with celecoxib and rofecoxib (PDR, 2003). However, those results were never fully published in available journals.

The current article presents results from an ongoing scientific project taken to evaluate prenatal toxicity of COX inhibitors, in particular, their chondrotoxic effect which was never evaluated in fetuses on the molecular level. The aim of this paper is to show the developmental toxicity of piroxicam – a non-selective COX inhibitor and DFU [5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl) phenyl-2(5H)-furanon] which is selective COX-2 blocker without any available prenatal toxicological data. The drugs were chosen since both provide highly anti-inflammatory activity with different COX-1 and COX-2 specificity (Brideau et al., 1996; Riendeau et al., 1997). The calculated ratio, derived with the whole blood assay rich 0.11 and 346 for piroxicam and DFU, respectively (Brideau et al., 1996).

The piroxicam manufacturer studies showed lack embryotoxicity and teratogenicity in rats and rabbits treated with dose 2.0, 5.0 and 10.0 mg/kg on gestational day (GD) 6–15 and 7–18, respectively (Perraud et al., 1984). However, maternal dead, pre- and postimplantation loss, prolonged gestation and labour were found in groups where the drug was administered in different periods of the pregnancy. The developmental results were partially confirmed by Sakaim et al. (1980). Powell and Cochrane (1982) observed prolonged parturition in 70–100% of dams subcutaneously, twice daily exposed to piroxicam in dose 0.1–0.5 mg (GD 18–22). No adequate human data was located. The only information comes from the Michigan Medicated Study (Briggs et al., 1998). From 229101 completed pregnancies, 161 piroxicam exposed newborns were found.

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