# The adverse renal effects of prostaglandin-synthesis inhibition in the fetus and the newborn

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**OBJECTIVES:** To summarize experimental animal data and to provide a limited literature review on the adverse renal effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the developing fetus and the maturing newborn.
**DATA:** The experimental data were obtained from anesthetized, ventilated, six- to eight-day-old rabbits that received an intravenous bolus of either acetylsalicylic acid (ASA), ibuprofen (IBU) or indomethacin (INDO). In one set of experiments, ASA was also tested in 12-week-old (young adult) rabbits. Renal function was monitored with inulin and para-aminohippuric acid clearances measuring glomerular filtration rate (GFR) and renal blood flow. The renal vascular resistance was calculated. All three nonspecific cyclo-oxygenase-1 or -2 (COX-1/2) inhibitors caused remarkably similar reversible, oliguric, acute renal failure (ARF). In young adult animals, the side effects were attenuated. The underlying pathophysiology is related to the carefully maintained low GFR of the fetus and the newborn, dependent on a delicate interplay between vasoconstriction (angiotensin II) and vasodilation (prostaglandins [PGs]). When PG-synthesis is inhibited, the vasoconstriction is relatively unopposed, causing ARF.
**LITERATURE REVIEW:** The renal effects of fetal exposure to NSAIDs are discussed, as are new insights into the role of COX-1/2 for a normal nephrogenesis. COX-nil or COX-inhibited animals have long lasting renal structural injury. Fetuses exposed in utero to significant amounts of NSAIDs have at birth various degrees of renal insufficiency and structural renal defects with a very high mortality.
**CONCLUSIONS:** All NSAIDs, both specific and nonspecific COX inhibitors, have renal side effects in the immediate postnatal period and should, therefore, be given with the utmost caution. NSAIDs given during pregnancy for the prevention of toxemia, polyhydramnios and premature labour may affect fetal renal function and structure. In animal experiments, IBU was not less nephrotoxic than INDO, as suggested recently by human premature neonates.

**Key words:** *COX-inhibition; Fetus; Newborn; NSAIDs; Renal development; Renal function*

*Résumé à la page suivante*

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## Les effets néfastes de l'inhibition de la synthèse de la prostaglandine sur les reins des fœtus et des nouveau-nés : Un aperçu

**OBJECTIFS :** Résumer des données expérimentales sur des animaux et fournir une analyse bibliographique limitée des effets néfastes des anti-inflammatoires non stéroïdiens (AINS) sur les reins du fœtus en développement et du nouveau-né en voie de maturation.

**DONNÉES :** Les données expérimentales ont été obtenues sur des lapins de six à huit jours, anesthésiés et ventilés, qui avaient reçu un bolus intraveineux d'acide acétylsalicylique (AAS), d'ibuprofène (IBU) ou d'indométhacine (INDO). Dans une série d'expériences, l'AAS a également été évalué chez des lapins de 12 semaines (de jeunes adultes). La fonction rénale a été surveillée par clairance de l'inuline et de l'acide para-aminohippurique afin de mesurer le taux de filtration glomérulaire (TFG) et le débit sanguin rénal. La résistance vasculaire rénale a été calculée. Les trois inhibiteurs de la cyclo-oxygénase 1 ou 2 non spécifique (COX-1/2) ont causé une insuffisance rénale aiguë (IRA) oligurique et réversible remarquablement semblable. Chez les jeunes animaux adultes, les effets secondaires étaient atténués. La physiopathologie sous-jacente est reliée à un TFG du fœtus et du nouveau-né soigneusement maintenu bas, selon une interaction délicate entre la vasoconstriction (angiotensine II) et la vasodilatation (prostaglandines [PG]). Lorsque la synthèse des PG est inhibée, la vasoconstriction est relativement non compensée, ce qui provoque une IRA.

**ANALYSE BIBLIOGRAPHIQUE :** Les effets de l'exposition des reins du fœtus aux AINS sont examinés, de même que de nouveaux aperçus sur le rôle du COX 1 et du COX 2 pour une néphrogenèse normale. L'absence de COX ou les animaux inhibés au COX présentent des lésions structurelles rénales permanentes. À la naissance, les fœtus exposés *in utero* à d'importantes quantités d'AINS présentent divers degrés d'insuffisance rénale et d'anomalies rénales structurelles, ainsi qu'un taux très élevé de mortalité.

**CONCLUSIONS :** Tous les AINS, de même que les inhibiteurs COX spécifiques et non spécifiques, ont des effets secondaires sur les reins dans la période postnatale immédiate, et ils devraient donc être administrés avec la plus grande prudence. Les AINS, administrés pendant la grossesse pour prévenir la toxémie, le polyhydramnios et le travail prématuré, peuvent nuire à la fonction et à la structure rénales du fœtus. Dans des expériences chez les animaux, l'IBU n'était pas moins néphrotoxique que l'INDO, tel qu'on pouvait récemment le supposer à l'observation de prématurés humains.

In recent years the use of nonsteroidal anti-inflammatory drugs (NSAIDs), all prostaglandin (PG)-synthesis inhibitors, has increased tremendously. This is particularly true for the adult population, but it is also seen in the paediatric population, especially in early infancy. Since 1976, recurrent boluses of NSAIDs are infused postnatally to promote the pharmacological closure of a hemodynamically significant patent ductus arteriosus, primarily in premature babies (1). NSAIDs are, however, also administered during pregnancy for the prevention and treatment of toxemia, polyhydramnios and premature birth. Because these agents easily cross the placenta, the fetus is readily exposed.

One of the side effects of NSAIDs is their renal vasoactive action that results in a diminution of the glomerular filtration rate (GFR) even to the point of (generally reversible) acute renal failure (ARF). The latter has already been described in infancy but a thorough evaluation of the renal effects of NSAIDs in the early neonatal period has been lacking.

Recently the renal effects of a variety of NSAIDs were evaluated in newborn rabbits, a well established animal model for the study of renal function in the term and particularly the premature human infant (2,3). To complete the picture, the emerging data on nonselective and selective inhibition of cyclo-oxygenase (COX)-1 and/or -2 in renal organogenesis, and on fetal renal functional adaptation are summarized. Extrarenal aspects of COX inhibition are not discussed.

The present overview does not pretend to give an exhaustive literature review or meta-analysis of the available data on the adverse (renal) effects of NSAIDs in general nor of all the available data on fetal and neonatal NSAID exposure in the experimental animal setting or the human newborn.

### BACKGROUND

The most well known NSAID is acetylsalicylic acid (ASA), and in 1899 it was registered as a trademark under the name of Aspirin, by Bayer (Germany). The identity of the researcher of this pioneering discovery has recently been questioned (4) but one can probably not argue with Bayer's claim that after more than 100 years, Aspirin still is the world's favourite painkiller. Nevertheless, it took some 70 years after Aspirin came on the market, before Piper and Vane (5) in 1969 could show that ASA inhibits the release of PGs. In 1971, Sir John Vane demonstrated that ASA and other NSAIDs block an enzyme in PG synthesis (6), whereas De Witt and Smith (7) in 1988 cloned the enzyme, that was eventually called COX-1. Shortly thereafter, Masferrer et al (8) defined the existence of a second enzyme involved in PG synthesis, called COX-2 (9). All previously known NSAIDs, such as ASA, ibuprofen and indomethacin are nonspecific COX inhibitors that are now joined by a newer and a more potent class of similar agents such as rofecoxib (Vioxx, Merck Frosst, Canada), that are mostly specific COX inhibitors and generally inhibit COX-2.

The two homodimeric isoforms COX-1 and COX-2 are the products of two different genes, with approximately 60% homology in the amino acid sequence. COX-1 is the product of a housekeeping gene, present in almost all mammalian tissues, mainly in stomach, platelets, vasculature and the kidney; it encodes a 2.8 kB transcript on chromosome 9. In contrast, COX-2 is not normally detected in most tissues, but can be produced by a variety of inflammatory cytokines and growth factors. The gene encodes a 4.5 kB transcript on chromosome 1.

The COXs are PG synthetases that catalyze the first step in the conversion of membrane-bound arachidonic acid

**TABLE 1**
**The major humoral factors playing a hemodynamic role in the maintenance of neonatal glomerular filtration rate**

| Hemodynamic role | Humoral factor |
|---|---|
| Vasoconstriction | Angiotensin II |
| | Endothelin |
| | Sympathetic nervous system |
| Vasodilation | Prostaglandins |
| | Atrial natriuretic peptide |
| | Bradykinin |
| | Endothelin-derived nitric oxide |
| | Adrenomedullin |

into PGs, eventually producing PGE2, prostacycline ($PGI_2$), $PGF_2$ and thromboxane ($TXA_2$), that are often specific for certain cell types.

The specific renal functional aspects of the COXs can be summarized as: directly regulating renal hemodynamics (and glomerular function) by their presence in the renal vasculature; indirectly regulating renal hemodynamics (and glomerular function) via activation or depression of the renin-angiotensin-aldosterone system through the presence of COX-2 in the macula densa; influencing epithelial water and solute transport via the presence of COXs in the thick ascending loop of Henle; and the collecting ducts as well as their influences on the renin-angiotensin-aldosterone system (10-12). In addition, the COXs have been shown to be involved in normal nephrogenesis (vide infra).

## COX-1/2 INHIBITION AND NEONATAL RENAL FUNCTION

The very low neonatal GFR (absolute inulin clearance: approximately 2 to 3 mL/min; corrected for mean adult body surface area: less than 20 mL/min/1.73m$^2$) is maintained by a delicate interplay between strong vasoconstrictory (mainly angiotensin II) and prominent vasodilatory renal forces (almost exclusively PGs), even when stressed (Table 1). The interested reader is referred to a recent review by Toth-Heyn, Drukker and Guignard (13) that discusses the various hemodynamic forces that regulate GFR in the newborn. When in the neonatal situation PG-synthesis is inhibited by the administration of NSAIDs, the already basically very high vasoconstrictor state of the newborn kidney is not sufficiently opposed anymore. This will lead to a reduction in renal blood flow (RBF), GFR and urine volume, or, in other words, to oliguric ARF. Fortunately the impairment of neonatal renal function due to NSAIDs is generally reversible but it, nevertheless, is a significant complication of the administration of NSAIDs in newborns (14). This is particularly true when there are additional factors that independently can cause ARF in the neonate, such as hypoxemia and septicemia.

### Experimental animal evidence

The studies reported here were done in the laboratory of the Pediatric Renal Division of the University Hospital (CHUV) in Lausanne, Switzerland by Professor J-P Guignard and coworkers. The neonatal rabbit has been used in this laboratory for many years to study neonatal renal physiology, and the results have consistently been shown to be applicable to the human, neonatal, renal situation, particularly in as far as the premature infant is concerned. The renal effects of ASA, indomethacin and ibuprofen were studied after acute intravenous administration in six- to eight-day-old, white, New Zealand rabbits. In one set of experiments, ASA was also tested in 12-week-old (young adult) rabbits with the same intravenous stat dose (per kilogram body weight) of ASA, as that given to the seven- day-old animals. The results have recently been published, including a complete description of the experimental setup (1,2). The animals were anesthetized (intraperitoneal and/or intravenous thiopental sodium [Pentothal, Abbott, Canada]) and artificially ventilated via a tracheostomy with an oxygen-enriched (approximately 40%) gas mixture whereas the respiratory rate was kept constant at 40 breaths/min and tidal volume was adjusted for age and weight. Body temperature was kept constant at approximately 39°C. The femoral vessels were used for solute infusion, arterial blood sampling and monitoring of mean arterial blood pressure. In the newborn animals urine was sampled by bladder catheter, whereas in older animals both ureters were catheterized. After surgery (newborns: approximately 60 min; 12-week-old: approximately 30 min) all animals received a constant infusion (newborns: 1 mL/min/100 g body weight; 12-week-old: 1 mL/min) of a special rabbit Ringer solution and inulin and para-aminohippuric acid(PAH)-clearances were performed for the determination of GFR and renal plasma flow (RPF), respectively. A 90 min equilibration period, followed by a 60 min (newborns) or 40 min (12-week-old animals) control period ensured that each animal could serve as its own control. Twenty-minute urine collections were started during the control periods and blood (newborns: 0.4 mL; 12-week-old: 1.2 mL) was withdrawn at the midpoint of the urine collections. The red blood cells were reconstituted in diluted human albumen and were reinfused. Eighty microlitres of plasma was used for immediate measurements of blood gases and hematocrit. The remainder of the plasma was frozen for later determination of electrolytes and renal function tests. At the conclusion of the entire experiment the animals were killed with a lethal intravenous dose of Pentothal. Just before the animals were sacrificed, blood was drawn from the femoral artery, and the renal vein for the measurement of PAH and the calculation of the PAH extraction factor.

PG-synthesis inhibition was tested after the control (urine collection) periods with an intravenous pulse dose of either ASA, ibuprofen or indomethacin, followed by several experimental clearance urine collections and blood was

**TABLE 2**
**Renal functional data in four groups of neonatal white New Zealand rabbits, exposed to an acute intravenous stat dose of NSAIDs. Groups A and B received 40 mg/kg body weight of acetylsalicylic acid (ASA), group C received 0.2 mg/kg body weight of ibuprofen and group D received 2 mg/kg body weight of indomethacin. The data are presented as mean percentage changes (Δ%) of the experimental data after the administration of one of the NSAIDs versus the control data in the same animal group**

| Treatment group | Age | UV (Δ%) | GFR (Δ%) | RBF (Δ%) | RVR |
|---|---|---|---|---|---|
| Group A – ASA | 7 days | –41 | –34 | –52 | +153 |
| Group B – ASA | 12 weeks | –5* | –22† | –16† | +20* |
| Group C – ibuprofen | 7 days | –38 | –36 | –36 | +61 |
| Group D – indomethacin | 7 days | –42 | –45 | –45 | +55 |

**P<0.001 versus ASA 7days; †P<0.01 versus ASA 7days. GFR Glomerular filtration rate (measured as inulin clearance); RBF renal blood flow (measured as para-aminohippuric acid [PAH] clearance equals renal plasma flow [RPF] with correction of the hematocrit [Htc] as follows: Renal blood flow [RBF]=RPF[1-Htc]); RVR Renal vascular resistance (calculated as mean arterial pressure divided by RBF); UV Urine volume*

again drawn at the midpoint of these collections and the red cells were reinfused as before.

The animal experiments were performed in more than 10 groups of animals (generally n>10) with different doses of the NSAIDs. The most important information was obtained in four animal groups.

- Group A (n=10; age 6.6±0.3 days; weight 120.1±5.1 g): 40 mg/kg body weight of ASA.
- Group B (n=12; age 12±0.1 weeks; weight 2.477±106 g): 40 mg/kg body weight of ASA.
- Group C (n=13; age 6.2±0.2 days; weight 111.4±3.5 g): 0.2 mg/kg body weight of ibuprofen.
- Group D (n=8; age 7.5±0.5.days; weight 110.7±3.7 g): 2mg/kg body weight of indomethacin.

**Analytic procedures:** Urine volumes were determinated gravimetrically and blood gas determinations were performed with a pH blood analyzer. Wright's automatic authrone and the Bratton and Marshall methods were used to determine inulin and PAH concentrations, respectively. Sodium and potassium were measured by flame photometry. The plasma protein concentration was estimated by refractometry.

**Calculation of the data:** The clearances of inulin and PAH were calculated from standard equations representing GFR and RPF, respectively. The PAH extraction factor used for the calculation of RPF was 0.55±0.04% for newborn animals and 92.2±1.9% for the 12-week-old animals. The other renal functional parameters were calculated with the following equations:

- RBF = RPF/(1-hematocrit);
- renal vascular resistance (RVR) = mean arterial blood pressure/RBF; and
- filtration fraction = GFR/RPF.

**Statistical analysis:** The data for the two (or three) control and experimental periods (n=4) were given as the mean±SEM for the animal groups. The statistics were calculated on the basis of the individual values. Differences of the mean of the control and experimental data within each group of animals were established by the Friedman and Wilcoxon signed-rank test for nonparametric statistics. Comparisons between groups were analyzed by the unpaired Student's *t*-test or by factorial analysis of variance, as required. Percentage changes were calculated for each parameter in each animal and only the means of these individual data are presented. A P<0.05 was considered statistically significant.

**Results:** The measured and calculated results are presented as percentage change (Δ%) of the mean experimental data in relation to the mean control data, obtained in the basic state of the same animals (Table 2). It is obvious that the percentage changes in urine volume, GFR, RBF and RVR in the approximately seven-day-old animals (groups A, C and D) were almost identical for the three NSAIDs, all nonselective COX inhibitors (Table 2). The similarity among the results in many animal experiments is remarkable. We interpreted these data to show that acute intravenous boluses of the three tested agents all caused severe vasoconstriction with a significant rise in RVR, accompanied by a fall in RBF, GFR and urine volume. The greatest rise in RVR was seen in the seven-day-old animals receiving ASA. In all instances, the oliguric ARF was reversible. The percentage changes seen in the 12-week-old, young adult rabbits of group B, that were given intravenous ASA in a dose of 40 mg/kg body weight, were significantly ameliorated compared with the changes seen in the seven-day-old animals receiving the same dose/kg body weight of ASA (P<0.01 to 0.001) (Table 2). This indicates that the severe renal vasoconstrictive response after the administration of ASA is apparently a specific neonatal phenomenon, disappearing over time with maturation of renal function.

Recent data from the laboratory in Lausanne show that nimesulide, a preferential COX-2 inhibitor, has neonatal renal effects similar to those described for the nonspecific COX inhibitors (unpublished data).

## INTRAUTERINE COX-1/2 INHIBITION

### Renal morphogenesis

Nephrogenesis in the human fetus starts at five weeks' gestation and develops via two temporary, partly functioning

stages (the pro- and mesonephros), ending with the formation of the primary final kidney, the metanephros. The latter has a dual origin: the ureteric bud that branches and ultimately forms the collecting system, and the metanephric blastema consisting of clusters of mesodermic or mesenchymal cells, the forerunners of renal parenchymal tissue. The very specific reciprocal signalling process between the ureteric bud and the metanephric mesenchyme is one of the keystones of understanding kidney development, presently thought to be controlled and regulated by many genes (and gene products), including a variety of cytokines and growth factors with their specific receptors (15,16). Whereas COX-1 probably does not influence renal morphogenesis and fetal renal function, COX-2 can be detected in embryos toward mid-gestation, its intensity increasing during the remainder of renal morphogenesis (17,18). Congenital COX-2-nil (-/-) mice are born with small kidneys that have few immature glomeruli, dysplastic tubules, medullary hypoplasia and cortical microcysts. Basically the same picture is seen when COX-2 is inhibited in mice and rats during pregnancy. The greatest effect of the COX-2 inhibition, however, was seen postnatally in mice and rats at a stage comparable to 24 to 32 weeks' human gestation. The immunoreactivity of COX-2 in these animals peaked in the first two weeks after birth and thereafter decreased (19). Inactivation of the COX-2 gene in mice from birth to six weeks of age resulted in normal prenatal and early postnatal renal development. Thereafter progressive organ-specific renal dysplasia was observed, first affecting the last generation of formed nephrons, later the entire kidney. Over time cystic degeneration of renal tissue was seen with loss of renal function without rise in blood pressure (20).

**Fetal renal function**

Indomethacin given to pregnant rhesus monkeys caused renal hypoplasia in the offspring and a rise in plasma renin activity with renal vasoconstriction (increased RVR) in fetal lambs, leading to a reduction in RBF (21,22). Prolonged in utero exposure of human fetuses to high dose NSAIDs was reported by Kaplan et al (23) and van der Heijden et al (24); the newborns all had various degrees of oliguria-anuria with severe renal insufficiency and a high mortality rate. The histological picture of the kidneys described by these two groups of investigators was rather similar with small glomeruli and tubular damage, including glomerular and cortical (micro)cysts and ischemic changes in the deep cortex. These histological findings seem to be more or less the same as observed in the above quoted animal experiments with absence or inhibition of COX. Recently, the preferential COX-2-inhibitor nimesulide, given from the 26th week of pregnancy, was shown to result in the birth of a baby with end-stage renal failure (25). The kidneys were of normal size for the length of gestation, with slightly increased echogenicity and reduced corticomedullary differentiation. No histology was reported.

## DISCUSSION

The NSAIDs are no longer only 'painkillers' used primarily in rheumatic and orthopedic afflictions. Aspirin is taken by millions of the aged population because of its anticlotting mechanism that targets $TXA_2$ in platelets. At the time of this writing we are even informed that NSAIDs may possibly prevent or postpone Alzheimer's disease (26).

The favourable aspects of all NSAIDs, the nonspecific and the specific COX inhibitors, are offset by their hematological, gastrointestinal and renal side effects. In the present paper only the latter adverse action of these drugs is highlighted, and then again only during pregnancy and in early postnatal life.

In adults the major renal side effects of NSAIDs are seen in elderly people and, in particular, in those with a preexisting impairment of renal function (27,28). This may have its parallel in the sensitivity of the newborn to these drugs since at birth renal function is physiologically very low. The extremely low GFR of the newly born cannot be described as renal insufficiency because, in health, the newborn renal function is quite capable of maintaining normal fluid and electrolyte balance and does not interfere with rapid growth and maturation. The newborn kidney is, however, limited in its adaptive response to endogenous or exogenous adverse stimuli. This certainly hold true for the administration of drugs such as the NSAIDs that have a prominent vasoactive action.

The neonatal animal experiments described in this paper clearly show that PG-synthesis inhibition by three nonspecific COX inhibitors (ASA, ibuprofen and indomethacin) causes very rapid, reversible vasoconstriction with a reduction in GFR, leading to temporary oliguric ARF. These factors should be considered by all who administer NSAIDs to sick newborns and, particularly, infants with compounding risk factors for developing ARF, such as anoxemia and/or septicemia. In addition, the described animal studies clearly show that the renal hemodynamic response to PG-synthesis inhibition is far more pronounced in neonatal animals than in (young) adult rabbits and, thus, rather specific for the newly born.

The presented animal data also raise some doubt about the recent observations that ibuprofen is less 'nephrotoxic' than indomethacin for the closure of a patent ductus arteriosus (29,30). These clinical observations in premature babies were very careful in the evaluation of the neonatal and cardiology data, less so in as far as the renal data are concerned. Caution is needed with the present use of ibuprofen instead of indomethacin in this situation. Drukker and Guignard (31) emphasized this point in a letter to the editor. The reservations regarding the use of NSAIDs in the newborn period also relate to the new specific COX inhibitors. As outlined earlier, preliminary data obtained with the administration of nimesulide, a preferential COX-2 inhibitor, to newborn rabbits are similar to those described for ASA, ibuprofen and indomethacin. In other words: please be careful with all NSAIDs from Asprin to rofecoxib (Vioxx, Merck Frosst, Canada). The experi-

mental animal data that are summarized in the present paper are the only well-controlled renal neonatal observations available on the action of nonselective COX inhibitors at a very early age, albeit in animals. These time-honoured neonatal animal studies have repeatedly been shown to reflect the renal response of term and particular preterm human infants. In delicate premature humans such careful renal studies have not been done and because of their invasive nature will be almost impossible to obtain in the near future.

In closing, I feel compelled to emphasize again the danger of administering nonspecific and specific COX inhibitors during pregnancy. As the literature review presented in this paper shows, the fetal side effects of these drugs may have grave, long lasting renal consequences, both in as far as morphological renal injury is concerned as well as regarding renal structure and function of the fetus, the newborn and beyond. The toxic renal effects of the various agents obviously depend on their dose and length of administration. A recent paper reviews the use of NSAIDs as tocolytic agents and proposes ways to minimize (not abolish!) their fetal toxicity (32).

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