Non-steroidal Anti-inflammatory Drugs in Newborns and Infants

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KEYWORDS

• NSAIDs • Ibuprofen • Indomethacin • Paracetamol • Acetaminophen • Ketorolac • Cyclooxygenases • Newborns

KEY POINTS

- Non-steroidal anti-inflammatory drugs (NSAIDs) (indomethacin, ibuprofen) and acetaminophen are used in neonates and infants for pain and fever control, for patent ductus arteriosus closure, for prevention of intraventricular hemorrhage, and potentially for retinopathy of prematurity.
- NSAIDs inhibit cyclooxygenases (COX-1, COX-2) and peroxidases, thus, blocking prostaglandin synthesis from arachidonic acid.
- Pharmacokinetic/pharmacodynamic profiles of indomethacin, ibuprofen, and acetaminophen allow effective and safe dosing guidelines.
- Various modifications around these guidelines continue, including the route of administration (oral, rectal, intravenous), duration of therapy, rate of dosing (bolus vs continuous), and the dose itself.
- Emerging evidence that NSAIDs also inhibit caspases and cell death presents a novel target for pharmacologic interventions in neonatal diseases.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in newborns and children as antipyretic agents to control fever; as analgesic, anti-inflammatory, and vasoactive agents to manage pain and modulate inflammation; to close a symptomatic patent ductus arteriosus (PDA)[1]; and to prevent intraventricular hemorrhage

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(IVH) and, potentially, retinopathy of prematurity (ROP). This review focuses on the mechanisms shared by the various NSAIDs and their clinical pharmacology profiles in newborns and young infants. Understanding the molecular and clinical pharmacology of these commonly used drugs may aid in their rational, safe, and effective uses as well as discovery of potential clinical applications besides antipyretics, analgesia, and ductal closure.

The NSAIDs are composed of several molecular entities with diverse chemical structures but with a shared and common mechanism of action directed to arachidonic acid (AA) metabolism and the biosynthesis of prostaglandins (PGs) (**Figs. 1** and **2**). These actions result in the blockade of PG biosynthesis resulting in the known effects of NSAIDs on inflammation, analgesia, antipyretics, vasodilatation, or vasoconstriction. These common and shared pharmacologic actions are also reflected on their observed and well-known adverse effects on gastrointestinal, hematologic, renal, and other organ systems. These pharmacodynamic (PD) and adverse effects have been extensively reviewed elsewhere[2] and are not repeated here.

Inflamed tissues substantially increase PG biosynthesis. PGE_2 and PG prostacyclin (PGI_2) are the major prostanoids that mediate inflammation[3] via activation of their respective receptors, EP2 and IP receptors. Both PGE_2 and PGI_2 also decrease the threshold of nociceptor stimulation producing peripheral sensitization as well as central sensitization and increased excitability of the spinal horn neurons leading to increased pain perception.[3] PGE_2 can cross the blood-brain barrier and acts on its receptors on thermosensitive neurons in the hypothalamus causing fever or elevation of body temperature with increased heat generation and decreased heat loss.[3] PGE_2 also promotes and helps maintain vascular dilatation of the PDA.[1,4] All of these processes are modulated or inhibited by NSAIDs via blocking of the biosynthesis of PGE_2 and other prostanoids (see **Figs. 1** and **2**).

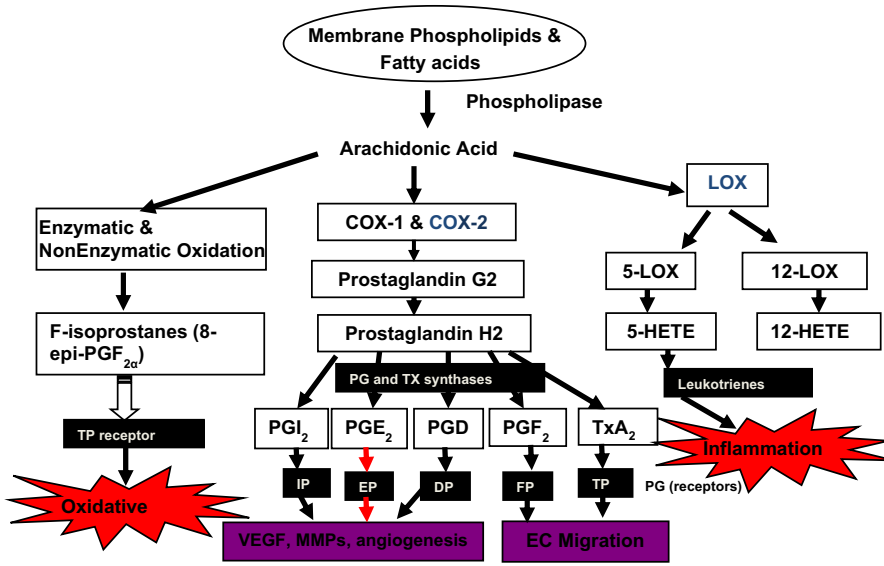

Fig. 1. AA metabolism and the biosynthesis of PGs and other eicosanoids. COX, cyclooxygenase; DP, Prostaglandin D Receptor; EC, endothelial cell; HETE, Hydroxyeicosatetraenoic acid; LOX, lipoxygenase; MMPs, matrix metalloproteinases; TxA_2, thromboxane A_2; VEGF, vascular endothelial growth factor.