Seminars in Fetal & Neonatal Medicine (2005) **10**, 177–184

ELSEVIER

Seminars in FETAL & NEONATAL MEDICINE

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The pharmacologic closure of the patent ductus arteriosus

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KEYWORDS
Cyclooxygenase inhibitors;
Ibuprofen;
Indomethacin;
Patent ductus arteriosus;
Preterm infant;
Prostaglandin receptors;
Prostanoids;
Surgical ligation

Summary The ductus arteriosus is a fetal vessel that allows most of the blood leaving the right ventricle of the heart to bypass the lungs. Fetal patency of the ductus, and its spontaneous closure after birth, is the result of a balanced interaction of locally produced and circulating mediators (of which prostaglandins seem to be the most important), and the unique structure of the vessel wall. Persistent patency of the ductus occurs in almost 60% of very low birthweight infants. A significant left-to-right shunt through the ductus increases morbidity and mortality in premature infants. As prostaglandins play a major role in patency of the ductus, cyclooxygenase inhibitors are conventionally used to induce its closure. This chapter focuses on some of the basic mechanisms underlying ductal patency and the clinical attempts to diminish side effects associated with indomethacin, including the alternative use of ibuprofen.

Introduction

Patent ductus arteriosus (PDA) is the most common cardiovascular abnormality of the preterm infant. Its incidence is inversely related to gestational age, such that it affects up to 60% of infants less than 28 weeks gestation. A patent ductus is essential for fetal well-being because it allows 90% of the right ventricular output to bypass the high-resistance pulmonary vascular bed in utero. Prostaglandins play a major role in maintaining ductal patency during fetal life[1]; of the prostaglandins, PGE_2 is the most important ductus arteriosus relaxant. Postnatally, the ductus starts to close within the first few hours after birth and in the term infant is usually complete by 72 hours of age; in the preterm infant the closure usually takes longer. The increased postnatal oxygen tension, along with a decreased sensitivity of the ductus to PGE_2 as the fetus approaches term, facilitates its closure. The preterm infant is more sensitive to

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1744-165X/$ - see front matter
doi:10.1016/j.siny.2004.10.003

PGE_2, which makes cyclooxygenase (COX) inhibitors a feasible therapeutic modality. This chapter will address two interrelated aspects: (i) the basic mechanisms through which prostaglandins and, accordingly, COX inhibitors such as indomethacin function to elicit their effects on the ductus arteriosus; and (ii) the aspect related to efficacy of COX inhibitors in PDA closure by focusing on the more recent trials of indomethacin and ibuprofen.

Synthesis of prostanoids

PGE_2 is the most potent ductal relaxant among the five major prostanoids, PGE_2, $PGF_{2\alpha}$, PGD_2, PGI_2 and TXA_2.[2] COX enzymes are rate-limiting in converting arachidonic acid to prostanoids. The two separate genes encoding COX proteins are COX-1 and COX-2. Recently, a splice variant of COX-1, informally called COX-3, was also identified[3]; acetaminophen (paracetamol) has been proposed to target COX-3. COX-1 is mostly constitutive and COX-2 highly and readily expressed during inflammation. However, COX-1 also contributes significantly to prostaglandin generation in inflamed tissue. Along the same lines, COX-2 is normally expressed in a number of tissues independent of inflammatory stimuli, especially during development. For instance, COX-2 is highly expressed in kidneys and disruption of its gene (in mice) leads to fatal renal failure[4,5]; adverse renal effects have also been observed with COX-2 inhibitors.

COX-2 has been found to be expressed in the fetal ductus arteriosus (DA) of animals, and its expression appears to increase with advancing gestation to the point of being the main contributor to the local PGE_2 generation in this tissue at term.[4] The PGE synthases downstream of COX responsible for PGE_2 formation are composed of at least one cytosolic and two microsomal isoforms.[6] Microsomal PGE_2 synthase-1, which is believed to be tightly coupled to COX-2 in some conditions, seems to be the major catalyst of PGE_2 formation in the ductus and in turn governs ductal tone[7]; microsomal PGE_2 synthase-1 is also co-expressed and developmentally co-regulated with COX-2 in the ductus by a mechanism that involves platelet-activating factor.[7]

Relative role of COX-1 and COX-2 in regulating DA tone

Three selective COX-2 inhibitors so far have been approved in the US by the Food and Drug Authority (FDA) for use in humans suffering from a variety of inflammatory conditions but only two selective COX-2 inhibitors are currently on the market. So far, few human studies using COX-2 inhibitors have examined their effects on ductal patency and these studies have not involved direct administration of COX-2 inhibitors to newborns. In animals, selective inhibition of COX-2 increases ductal tone in porcine, ovine and murine tissues,[4,8,9] but in the higher species COX-2 inhibition was marginally effective compared to non-selective COX inhibitors. Correspondingly, a randomized trial, in women at risk for preterm delivery revealed that maternal administration of the selective COX-2 inhibitor celecoxib did not cause fetal ductal closure.[10] In addition to the relative lack of efficacy of COX-2 inhibitors on fetal and possibly preterm neonatal ductus, adverse renal effects are a serious concern in the premature infant.[11]

Interestingly, studies on the expression and role of COX-1 and COX-2 in the ductus have contributed in the understanding of the role of circulating prostaglandins in governing DA tone. Although COX-2 is by far the major source of PGE_2 in term porcine DA, inhibition of COX-2 in vivo does not affect DA diameter whereas COX-1 inhibitors are equivalently effective to the non-selective COX inhibitor indomethacin.[4] Along the same lines, COX-1 and COX-2 expression have — contentiously — not been detected in mice,[12] but disruption of the COX-2 gene affects DA tone.[8] Together, these studies suggest that: (i) DA patency depends to a significant extent on circulating prostaglandins; and (ii) selective COX-2 inhibition might not be a suitable option to close the DA.

Prostanoid receptors

Prostanoids exert their effects through receptors classified as DP, EP, FP, IP and TP, respectively, for PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and TXA_2; EP receptors are further divided into EP_1, EP_2, EP_3 and EP_4.[4] The eight known types of prostanoid receptors are each encoded by an individual gene. Prostanoid receptors belong to the superfamily of G protein-coupled receptors. EP_2, EP_4, DP and IP induce smooth muscle relaxation and are more closely related to each other than to the other prostanoid receptors; EP_1, FP, and TP receptors cause smooth muscle contraction and form another group based on sequence homology. EP_3 subtypes of the prostanoid receptor family employ as their primary effector pathway inhibition of adenylate cyclase through the $G\alpha_i$ family, resulting in most tissues in vasoconstriction. EP_3 can also couple to other G proteins, including $G\alpha_s$.