Paracetamol (N-acetyl-para-aminophenol) also known as acetaminophen is a chemical compound used in medical practice for analgesic and antipyretic effects since 1877. The mechanism of action is related to the cyclooxygenase (COX) activity, which is not fully inhibited as for nonsteroidal anti-inflammatory drugs (NSAIDs). Paracetamol selectively inhibits COX activities in the brain, indirectly by reducing COX, which must be oxidized in order to function. The role of paracetamol in the inhibition of COX-1 and COX-2 by its role in the function of peroxidases of these isoenzymes, the inhibition of phenoxyl radicals in COX-1 and COX-2 activity and the synthesis of prostaglandins is accepted. This role of inhibiting the synthesis of prostaglandins occurs when levels of arachidonic acid and peroxides are low, but not for their elevated levels [1,2]. In addition to analgesic and antipyretic effects, modulating the prostaglandin synthesis by selective inhibition of COX, a vascular modulator effect was described recently on the closure of the patent ductus arteriosus (PDA). This effect has been described in premature newborns, perhaps by decreasing the prostaglandin production. We present the case of a neonate, 39 weeks gestational age, normal birth weight who presented in the 10 th day of life with a cardiac murmur. Echocardiography evidenced a hemodynamically significant PDA, left ventricular enlargement, severe mitral regurgitation, patent foramen ovale and pulmonary hypertension. Although she was a 10-day-old full-term neonate paracetamol administration was attempted. Paracetamol was administered orally in the therapeutic dose of 15 mg/kg/dose, three times a day for three days. The effect was significant by reducing the diameter of the arterial duct (~50% of initial diameter), reducing the size of the left cardiac chambers, reducing the degree of mitral regurgitation from severe to mild, and disappearance of pulmonary hypertension. In conclusion, paracetamol use can change prognosis through the vaso-modulator on the PDA, at the age of 10 days, on a full-term neonate with a normal birth weight. This effect may also be present in full-term newborns and not only in preterm. Even if the PDA was not closed after three days, the hemodynamic impact disappeared and the child could avoid surgical ligation.

Keywords: paracetamol, patent ductus arteriosus, heart failure, pulmonary hypertension, severe mitral regurgitation

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prostaglandins. Constriction is also promoted by reduced levels of prostaglandins, of which prostaglandin E2 is the most important. Prostaglandin E2 is obtained from the action of prostaglandin H synthase-1/-2 and microsomal PGE synthase enzymes on arachidonic acid. Prostaglandins relax muscles and blood vessels due to specific G-protein- coupled receptors (EP2, EP3and EP4) on the muscle and endothelial cells. EP receptors activate adenylate cyclase, leading to increased concentrations of cyclic adenosine monophosphate (cAMP) which inhibits the sensitivity of the contractile proteins to calcium. An increase in the intracellular concentration of cyclic adenosine monophosphate and cyclic guanosine monophosphate is also caused by nitric oxide donors, such as sodium nitroprusside and glycyl trinitrate.

To achieve the closure of ductus arteriosus, the amount of enzymes involved in the formation of prostaglandins from arachidonic acid must be reduced. Prostaglandin-endoperoxide synthase inhibitors or cyclooxygenase inhibitors, such as NSAIDs (ibuprofen or indomethacin) and paracetamol, which despite being considered a weaker inhibitor showed promising results, can help treat patent ductus arteriosus. However, these drugs are more effective in the first few days after birth, because later vasodilators other than prostaglandin and inflammatory mediators have a more important role: vascular endothelial growth factor (VEGF), interleukin-6, interleukin-8, tumor necrosis factor-alpha (TNF-α), transforming growth factor beta, vascular cell adhesion molecule (VCAM-1), E-selectin, macrophage colony stimulating factor-1 (M-CSF 1), CD134 protein and interferon gamma [8-10].

Cyanoide inhibits the ductal closure mediated by the increase in oxygen, which suggests a possible role of hemoproteins like cytochrome a3 and cytochrome P450 in the contraction of ductus arteriosus. Given the role of the cytochrome P450 enzyme system (CYP) in the constriction of ductus arteriosus, the use of antacids (e.g. cimetidine, famotidine) in the neonates should be avoided due to their CYP inhibitory properties that might impair ductal closure [10,11].

Acetaminophen (paracetamol), a derivative of acetanilide and a peroxidase inhibitor, has shown various effects on prostaglandin production and on serotonergic, opioid, nitric oxide and cannabinoid pathways. Paracetamol was used for the first time for ductal closure by Hammerman in 2011. Acetaminophen inhibits the peroxidase moiety of the prostaglandin synthase enzyme, decreasing prostaglandin synthesis. At low concentrations paracetamol stimulates and at high concentrations it inhibits the synthesis of prostaglandins.

Cyclooxygenase, called also prostaglandin H2 synthetase is the enzyme responsible for the metabolism of arachidonic acid to the prostanooids (e.g. prostaglandins, thromboxanes). There are two active areas of this enzyme: the cyclooxygenase and the peroxidase region. Unlike NSAIDs, which act on prostaglandin synthase at the cyclooxygenase region, paracetamol act at the peroxidase region. The conversion from arachidonic acid to the prostanooids occurs in two stages, requiring activity at the cyclo-oxygenase region to produce the unstable intermediate hydroperoxide, prostaglandin G2 (PGG2), which is then converted to prostaglandin H2 (PGH2) by peroxidase [12].

We present the case of a full-term 10-day-old female newborn presented asymptomatic, with a hemodynamically significant PDA, associated with severe mitral regurgitation, patent foramen ovale, left ventricle dilatation, severe pulmonary hypertension for which we decided to attempt PDA closure using orally paracetamol, which proved to help the patient by reducing the inner diameter to ~50% of the initial measurement after 3 days of treatment.

Paracetamol administered did not close the duct but change the course of the disease avoiding surgical ligation.

**Experimental part**

**Clinical case**

A 10-day-old neonate, female came for echocardiographic evaluation of a significant heart murmur. The patient was born by cesarean section on request, on the term, 39 weeks gestational age. The patient was rank II and the birth parameters were birth weight 3040g, length 50cm, Apgar score 9. No peri and postpartum problems were noticed. Clinical examination on admission revealed a comfortable patient with insignificant findings at clinical examination except for the presence of a third-degree cardiac systolic murmur with rhythmic heart sounds. Laboratory tests on blood were drawn at admission and were within normal limits.

A patent ductus arteriosus (PDA) with significant hemodynamic impact (fig. 1A), significant left ventricular enlargement, severe mitral regurgitation (fig.2A), patent foramen ovale and severe pulmonary hypertension (fig.3) were diagnosed by echocardiography. The PDA diameter was 3.8 mm and the shunt was bidirectional, from right to left in systole and from left to right in diastole (fig. 4A) and had a significant impact on the cardiac structure and function. Pharmacological treatment for significant left heart dilatation, pulmonary hypertension was started using angiotensin-converting enzyme inhibitors (Captopril 1mg/kg/day, PO, Furosemide, 0.5 mg/kg/day ×2, IV, Spirinolactone, 1 mg/kg/day, PO). In this clinical picture of a significant PDA, associated with severe mitral regurgitation, and severe pulmonary hypertension we thought that closure of the PDA is mandatory for the child. After balancing the therapeutic possibilities, although the neonate was a full-term 10-day-old girl, PDA closure was attempted by paracetamol administration.

Parental consent was obtained before paracetamol administration. Paracetamol was administered orally in the therapeutic dose, 15 mg/kg/dose, 3 times per day for three days consecutively. The effect was significant by reducing the diameter of the arterial duct, to 1.6 mm (fig.1B) (more than 50% reduction), reducing the size of the left chambers, reducing the degree of mitral regurgitation from severe to mild, and disappearance of pulmonary hypertension. The gradient through the PDA after paracetamol administration was 3.8 mm diameter. 1B. Patent ductus arteriosus after 3 days of paracetamol administration, 1.6 mm diameter
In preterm newborns, paracetamol was demonstrated efficient for PDA closure in several studies in the medical literature. Paracetamol can also be administered in full-
term neonates with normal birth weight, even in the 10 th
day after birth, but with fewer chances for closure.

Even if the PDA was not closed using this therapeutic
regimen, safety paracetamol administration for PDA
closure changed the prognosis of a 10-day- old newborn
with severe mitral regurgitation due to hemodynamic
significant PDA, LV dilatation and severe pulmonary
hypertension and it was considered a therapeutical
success.

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