Beneficial Effects of Acetaminophen on the Chemical Mediators Involved in the Closure of Patent Ductus Arteriosus

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Paracetamol (N-acetyl- para-aminophenol) also known as acetaminophen is a chemical compound used in medical practice for analgesic and antipyretic effects. The mechanism of action is related to the cyclooxygenase (COX) activity, which is not full inhibit as for nonsteroidal anti-inflammatory. Paracetamol selectively inhibits COX activities in the brain, indirectly by reducing COX, which must be oxidized in order to function. 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

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 full inhibit 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 persistent ductus arteriosus (PDA) [3]. This effect has been described in premature newborns, perhaps by decreasing the prostaglandin production, but not for full-term neonates. The decrease of prostaglandin E2 (PGE2) which has vasodilator effects results from increased metabolization into the lungs or by inhibition of the enzyme cyclo-oxygenase [4, 5].

Ductus arteriosus (DA) is a normal anatomical structure in the fetus, but soon after birth DA has to close. The closure is related to several factors, the most important being the seric level of prostaglandin (which has to decrease after birth the major part of it being produced by the placenta and locally) and the oxygen saturation (which has to increase after the lung respiration started). A DA wall constriction of the smooth muscular cells (reduced PG E2 level) followed by hypoxia of ductal vasa vasorum and consequent local angiogenesis with neointimal tissue, apoptosis, platelet aggregation and fibrosis are the mechanisms that favor ductal closure [6]. The persistence of ductus arteriosus (PDA) opened beyond 2-3 days postnatal is one of the most frequent congenital heart disease (CHD) and is described in 30- 60% of the premature newborns [7]. Depending on the diameter, length, anatomy PDA may have a hemodynamic impact on the left heart structure and function generating heart failure and/or pulmonary hypertension. If the PDA is hemodynamically significant there are several therapeutical options for closure of the PDA. In premature children, there are therapeutical drugs that have almost similar results on closure, indomethacin, ibuprofen and, recently, paracetamol. Choosing one of these drugs is related to the associated risks of cerebral or enteric hemorrhage, renal failure, which are more frequently associated with the indomethacin and ibuprofen. Usually, there is no closure effect on full-term, for which surgical techniques are also available.

The closure of ductus arteriosus in neonates is a vasodilatory response of the muscles to higher partial pressure of arterial oxygen (P a O 2) from 18–28 mm Hg in utero to 40–60 mm Hg after birth, to lower postnatal levels of prostaglandins E2 and I2, the latter being called also

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prostacyclin, to the nitric oxide released by the ductal endothelium and the stimulation of certain ion channels. The increased levels of O 2 inhibit voltage-dependent potassium channels in the smooth muscle cells of ductus arteriosus, which leads to high levels of intracellular calcium, vasoconstriction and depolarization of the ductal smooth muscle cells. 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 glyceryl 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), CD154 protein and interferon gamma [8-10].

Cyanide 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 prostanoids (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 prostanoids 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, 1 mg/kg/day, PO, Furosemide, 0.5 mg/kg/day X2, IV, Spironolactone, 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 therapeutical 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

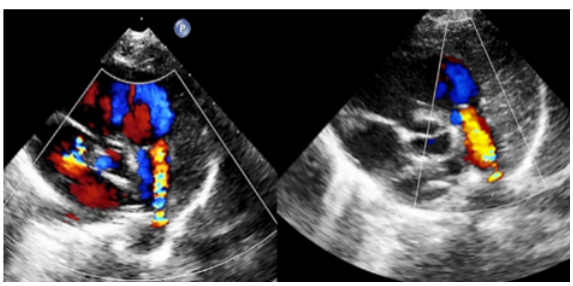

Fig. 1A. Patent ductus arteriosus before administration of paracetamol: 3.8 mm diameter. 1B. Patent ductus arteriosus after 3 days of paracetamol administration, 1.6 mm diameter

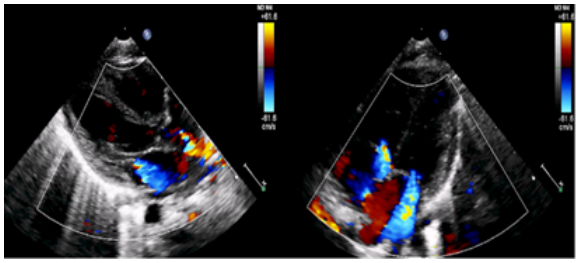

Fig. 2 A and B. Severe mitral regurgitation from parasternal long axis view of the left ventricle and apical four-chambers view.

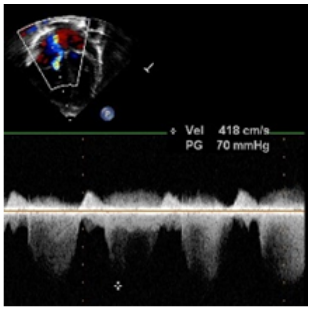

Fig. 3. Severe pulmonary hypertension measured on the basis of the tricuspid regurgitant jet. The systolic pulmonary pressure was estimated at 75 - 80 mmHg.

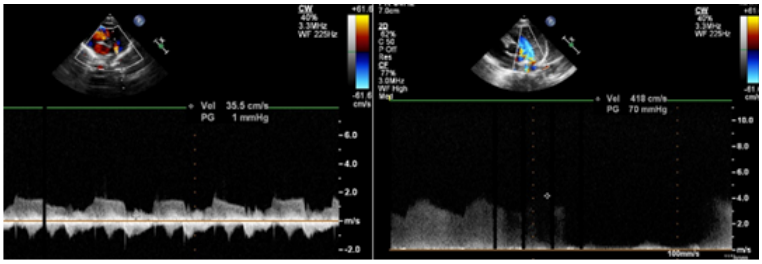

Fig. 4 Echocardiographic hemodynamic evaluation of the shunt through the PDA. A. Bidirectional flow through the PDA with a right-to-left shunt in systole and left-to- right shunt in diastole. B. Exclusive left-to- right shunt both in systole and diastole through the PDA after the paracetamol administration

was 70 mmHg, with an exclusive left-to- right shunt (fig. 4B).

Results and discussions

Congenital Heart Disease (CHD) is an important cause of cardiovascular mortality and morbidity especially in newborn and infant by bronchopulmonary dysplasia, pulmonary hemorrhage (PH), with prolonged need for assisted ventilation, necrotizing enterocolitis (NEC), and acute renal failure due to increased pulmonary blood flow or *ductal steal* effect with reduced peripheric flow [6,7,13]. In an attempt to save children with cardiac malformations, cardiovascular surgery is called. More and more CHDs are resolved by interventional methods, useful both in precise diagnosis and as therapeutic methods [14-17].

PDA is one of the CHDs in which interventional closure is achieved with a very high chance of success and a very low rate of complications, even in newborns, sometimes excluding contrast media administering due to its nephrotoxic effect [18]. Most of the time this method is reserved for children over the age of 6 months or over the weight of 6 kg. Other solutions are either using drugs (in premature infants with no contraindications to NSAIDs or surgical (for the most difficult cases where there are contraindications for medication as renal impairment, gastrointestinal haemorrhage, cerebral haemorrhage, increased hemorrhagic risk by thrombocytopenia, sepsis, NEC, intestinal perforation, PH, hepatic damage with severe hyperbilirubinemia) [6,13]. The risk of developing renal insufficiency is increased by the presence of prematurity and immaturity of the kidney function, by the concomitant use of other potentially toxic drugs (furosemide, gentamicin, contrast media) [18,19].

Paracetamol has been used as a therapeutic alternative for PDA closure, in 2011 for the first time [6]. It has been shown that paracetamol has similar effectiveness in comparative studies as indomethacin, ibuprofen, but without being associated with the side effects of NSAIDs.

The effects appear to be similar for both intravenous and oral administration [20-24]. Oncel et al. were the first to report the effect of the paracetamol on PDA closure in a study on extremely low birth weight infants comparing oral paracetamol with ibuprofen in preterm infants [25]. Yang et al. in a study on 87 patients demonstrated also lower plasma and urinary PGE2 levels in premature newborns, in paracetamol group when comparing to ibuprofen, but with similar closure rate (paracetamol 70.5% vs ibuprofen 76.7%) [20]. A comparable result was noticed by Bagheri et al. in a study on 129 premature newborns, with a closure rate of 82.1% for the oral paracetamol group vs 75.8% for the oral ibuprofen group [26]. When paracetamol is administrated after the age of 14 days, it seems that the closure rate of PDA diminished extremely, up to 18%. This is related to the presence of lower levels of PGE2, and also for the patients already treated twice by ibuprofen [7]. Watanabe et al. obtained closure of the PDA using intravenous indomethacin in 4 of 7 newborns (57%) with birth weight over 2500 g [27]. The alternative to drug closure of the PDA especially for premature with low or very low birth weight is surgical ligation with all its possible complications.

In the case presented, the age was of 10 days, and she born at 39 weeks gestational. For such situations, it is not recommended to use NSAIDs to close the PDA, the anatomical structure of the DA being different between the preterm and the full-term at the time. However,considering the hemodynamic impact of a large PDA, the severity of mitral regurgitation and pulmonary hypertension, we accepted the use of oral paracetamol for a safer profile in the context of low expectations in terms of PDA closure.

The therapeutic regimens generally used in the literature for the drug closure of PDA using paracetamol in premature newborns are 7.5-15 mg/ kg/dose 4 times a day for a period of 3-6 days [13]. In our patient, after the administration of 15 mg/kg/dose 3 times a day, three days consecutively, the DA diameter decreased by ~50% (from 3.8 mm to 1.6 mm). The impact of this reduction was significant, due to the disappearance of the signs of the severity of both mitral regurgitation and pulmonary hypertension. This may be due to the effect of paracetamol on reducing the plasma concentration of circulating prostaglandins. The effect of paracetamol over the circulating prostaglandins was studied and it is well known. As the adverse effects of paracetamol use, the transient increase in liver enzymes has been noted in the literature, particularly associated with the use of higher doses over a longer period. This adverse effect was not seen in our patient.

Conclusions

In preterm newborns, paracetamol was demonstrated efficient for PDA closure in several studies in the medical literature. Paracetamol can also be administrated 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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