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Possible effects of repeated exposure to ibuprofen and acetaminophen on the intestinal immune response in young infants

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ABSTRACT

There has been an exponential increase in the frequency of immune deviations in young children. Consequently, research investigating environmental causes for this increase has become a Public Health priority. We have summarized the experimental observations and epidemiological data that could link repeated acetaminophen and ibuprofen exposure in early infancy to this increase. Recent observations on the maturational immunity of the intestinal sub-mucosal lamina propria underscore indeed the importance of prostaglandins (PGE2s). PGE2 appearing at this sub-mucosal level is a product of arachidonic acid metabolism mediated by type-2 cyclooxygenase (COX-2) situated on the membrane of many immune cells. Moreover, it seems that acetaminophen – like ibuprofen – also carries a non-selective inhibitory action on peripheral COXs, besides its central action. This inhibitory action of acetaminophen on COX2 only relates to physiological, low arachidonic acid concentrations. This explains the difference in anti-inflammatory effects. The impact of repeated inhibition of mucosal PGE2 synthesis due to COX-inhibitor exposure on maturational immunity has been demonstrated in animal experiments. Repeatedly exposed young animals do not develop tolerance to food antigens and exhibit autoimmune deviations. Several recent epidemiological studies have also reported on the magnitude of acetaminophen and ibuprofen exposure in children and the increase in immune deviations, it is important to better understand the potential negative impact of repeated inhibitions of prostaglandin synthesis by COX2s during infancy. Since acetaminophen and ibuprofen are commonly administered analgesics and antipyretics, a well-designed prospective strategy for pharmacovigilance and -epidemiology of COX-inhibitor exposure in infancy is urgently needed.

Introduction

The pre- and postnatal development of human immunity is remarkably continuous. The feto-placental unit builds up to promote a climate of immune tolerance to especially the pregnancy and is progressively driven in this way by the maternal immunity [1–6]. An elevation in the immune suppressive $CD4^+CD25^+$ regulatory T-cell subset is indeed common in a normal pregnant woman as well as a physiological immune imbalance in the sense of humoral immunity [7,8]. This immune climate also allows the fetus to get tolerance to him/her-self through upgraded native T-regulator cells (nTreg's) [3,4,6]. Just before and immediately following birth, a progressive immune equilibrium has to be reached at the intestine submucosal area between both classes of lymphocytes originating from the locally available naïve $CD4^+$ T lymphocyte cells: on the one hand the future helper lymphocyte cells (Th1, Th2, Th17 subsets) and, on the other hand, the ongoing **p**eripheral or **i**nduced regulatory T-cells (p/i-Treg $CD4^+CD25^+$, Th3, Tr1 subsets). This adequate but still immature Th differentiation at that time is largely controlled by cytokines produced by epithelial cells and the innate immunity in response to invasive microbial products. This progressive optimal equilibrium derived from these innate and adaptive immunities working together can really be viewed as being the result of a win–win cross-talk interface

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between the host and his invasive microbiota [9–12]. It not only allows for an optimal response against pathogens, adjusting in the same way the antenatal physiological immune imbalance, but also results in tolerance of the progressively selected commensal microbes. The latter mechanism of induced microbial tolerance will in turn help to get control of a tolerance against other environmental antigens, including dietary antigens [13,14]. This locally acquired immune equilibrium will thereafter be transposed in other epithelia after a maturation of the iTregs into the mesenteric lymphoid nodules. As demonstrated in animal models, an improvement of intestinal tolerance against environmental antigens will indeed help preventing immune deviations in other epithelia [15]. This progressively selected intestinal microbiota remains throughout life a key player for maintaining an optimal general immune development balancing between both types of Th differentiation [10,11]. The importance of physiologically secreted prostaglandins (PGE2s) in the intestine submucosal lamina propria has been underscored as key factors in the development of this overall tolerance [16–18]. Definitely, various repeated inadequate environmental stimuli in the early stage and during infancy (mode of delivery, antibiotics in excess in the early stage, etc.) may negatively affect this local intestinal immunity building during the first years of life through epigenetic changes which could influence the local intestine immunity, and as a consequence the overall immunity later on [19–23].

The search for environmental agents potentially responsible for those multiple immune deviations that are exponentially observed in young infants is therefore important and should be regarded as a Public Health priority [24–26]. Among those factors, xenobiotics other than antibiotics are also of high relevance. Recent data point-out the possible link between the prenatal and early postnatal use of analgesics (especially acetaminophen) and the increased risk of emergence of pathologies later on (autism, immune deviations) [27–30].

The hypothesis: potential long term immune adverse effects arising from an excessive inhibition of intestinal peripheral prostaglandins (PGE2s) synthesis in infancy

Acetaminophen and Ibuprofen use in neonates and children

Acetaminophen

The more prolonged and repetitive use of acetaminophen has increased in premature infants, newborns and children because this drug corresponds to the criteria sought by clinicians, i.e. analgesia with a relatively wide therapeutic index and with very limited short term side effects [31]. The sites of action of this old drug are probably multiple and, for some, still hypothetical. The reader is referred to the most recent reviews on acetaminophen [32,33]. In the context of this article, its finally recognized action as an inhibitor of peripheral cyclooxygenase type-2 (COX2) will only be considered here [34,35]. Indeed, in addition to its action on cerebral cyclooxygenase type-1 (COX1), which seems to remain its major site of action (pain, fever), acetaminophen is also an inhibitor of prostaglandin synthesis in peripheral tissues, with apparent selectivity of action centered on COX2 [32–35]. The peroxidase function of COX is actually the site of the inhibitory action of acetaminophen [32–35]. This inhibition is more pronounced for low concentrations of arachidonic acid, its substrate, i.e. at rather physiological concentrations. This action on endothelial peripheral COX2 may also explain the positive action recently observed on the closure of the ductus arteriosus in preterm neonates [36–38]. In these physiological conditions, PGE2 are especially synthesized by COX2 in intact cells. In contrast, the inhibitory action of acetaminophen is lower in the presence of high arachidonic acid concentration and peroxides, which makes it a very poor anti-inflammatory molecule, much less potent than non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen or indomethacin. This lack of inhibitory effect on peroxidase in the presence of high concentrations of arachidonic acid and peroxides seems also explain the absence of anti-platelet effect and the better gastrointestinal tolerability of acetaminophen.

Ibuprofen

Ibuprofen, derived from aryl-propionic acid, is a NSAID with non-selective and reversible inhibitory action on COX-1 and COX-2 [39]. It differs from the acetyl salicylic acid whose action on both COXs is irreversible. It has a central and peripheral action and is particularly active in the presence of high concentrations of arachidonic acid, which gives it a much more effective anti-inflammatory power than acetaminophen. In neonatology, ibuprofen is used nowadays to close the ductus arteriosus where it was compared to indomethacin [40]. Only three doses are required in most cases. In children, ibuprofen is used for its analgesic, antipyretic and anti-inflammatory action [39].

Adverse potential immune consequences due to excessive PGE2 synthesis inhibition in infancy and in childhood

In pediatrics, acetaminophen and ibuprofen are over the counter analgesic and antipyretic drugs most commonly used in young children by parents, sometimes largely in excess. Both medications are often used in an alternating fashion while the latter practice is also questionable as it is supported only by few scientific arguments with often conflicting results [41,42]. A better understanding of the immunity of the intestinal sub-mucosal lamina propria has also demonstrated the important role of physiologically secreted PGE2s on its development in the presence of low level of arachidonic acid [16–18]. These locally secreted PGE2's originate from the transformation of arachidonic acid by COX-2 found on the membranes of a large number of immune cells present at the submucosal level (see the related chapter on PGE2's). At low concentration, they allow an immune stability at full length of the life through the permanent induction and stabilization of the peripheral induced T-lymphocyte regulator (iT-reg's) cells derived from the locally naïve $CD4^+$ T-cells [17,18,43,44]. The potential risk of repeated local inhibition of the synthesis of these physiologically secreted PGE2s in the intestine submucosal area, caused by the systemic administration of non-selective COX-2 inhibitors, has been demonstrated in young animal experiments [16]. These animals who are repeatedly exposed to a non-selective anti-COX drug do not develop the anticipated tolerance to food antigens and display immune deviations, either of the allergic or autoimmune type [16,45]. There is currently too little scientific evidence to allow translation as such from the animal to the human being. However, it seems that the vast majority of the physiological mechanisms of immune induction found in the submucosal lamina propria are quite similar in humans in their scientific and biochemical concepts although with biochemical players sometimes differently involved [46].

The question of the potential risk of repeated inhibition of PGE2s synthesis in infancy arises therefore in connection with this suspected repetitive or excessive use of non-selective anti-COXs in young children. The suspicion of a possible interference of ibuprofen and acetaminophen with the general physiological role of prostaglandins is growing up in view of a recently observed increase in immune deviations [27–30,47] with the repetitive or excessive use of acetaminophen in children. It is therefore relevant to ask the question if there is a possible harmful potential influence of excessive or repeated administration of overall non-selective COX inhibitors on the postnatal immune development of young children.