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LETTER TO THE EDITORS

Acetyl salicylic acid treatment in neonatal Bartter syndrome—a commentary letter

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Antenatal Bartter syndrome is an autosomal recessive disorder caused by loss-of-function mutations in genes encoding for the renal outer medullary potassium channel (RomK) or the sodium–potassium-2-chloride co-transporter (NKCC2) [1]. Given that NKCC2 is sensitive to inhibition by furosemide and requires RomK for proper functioning, defects in either transport protein severely impair salt reabsorption in the thick ascending loop of Henle, thereby mimicking chronic administration of furosemide. Apart from the occurrence of transient hyperkalemia in patients with mutant RomK, which reflects their requirement to secrete potassium into the urine by the distal tubules, the phenotypes of NKCC2- and RomK-deficient patients are undistinguishable: polyuria shortly after birth with isosthenuria, excessive renal prostaglandin E_2 production, and hyper-reninism with hypokalemic alkalosis.

Fluid losses in affected patients can be life-threatening and are managed with compensation of urinary losses of water and electrolytes. This approach may actually aggravate the polyuria, resulting in a total fluid intake of up to 50 ml/kg/h, which equals 1 liter of fluid per day in a 1-kg patient [1]. Because the oral administration of such large quantities of fluids is technically challenging in premature babies, non-steroidal anti-inflammatory drugs (NSAID), such as indomethacin, are routinely administered to reduce diuresis and saluresis [1]. NSAID inhibit prostaglandin production by blocking the enzymatic activity of cyclo-oxygenase (COX). COX exists as two unique isoforms, namely, COX-1, which is expressed constitutively in the renal vasculature and in principal cells of the collecting duct, and COX-2, which is an inducible enzyme whose renal expression is restricted to a few cells of the macula densa and the vasculature. In states of salt and or volume depletion, COX-2 expression is significantly up-regulated in cells of the macula densa through a mechanism by which low intracellular chloride levels induce COX-2 via p38 MAPK. Consistent with its renal induction, COX-2-selective NSAID have been demonstrated to be as effective as the unselective NSAID indomethacin in reducing polyuria in patients with antenatal Bartter syndrome [2]. These data prove that COX-2 plays a key role in the signaling cascade leading to polyuria in antenatal Bartter syndrome.

Inhibition of COX-2 also reduces hyper-reninism and hypokalemia in patients with antenatal Bartter syndrome. This effect should actually further aggravate salt loss secondary to decreased angiotensin II and aldosterone levels; therefore, other means of salt conservation must exist. First, COX-2-derived prostaglandin E_2 production has direct diuretic effects. Various prostaglandin E_2 receptors are expressed in the renal tubules, and these have been implicated in this phenomenon; however, their precise contributions remain unclear. Second, both COX-2-selective NSAID and -unselective NSAID reduce the glomerular filtration rate, thereby further reducing renal salt and water losses. Collectively, the salt-retaining tubular and vascular effects of NSAID obviously dominate over the salt loss resulting from the reduced angiotensin II and aldosterone levels.

Even though robust evidence from animal and human studies proves a key role of COX-2 in the pathophysiology of antenatal Bartter syndrome, only rofecoxib, a highly selective COX-2 inhibitor whose use had to be discontinued because of cardiovascular side effects, has been

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reported as a therapeutic modality in a single infant with an extreme variant of antenatal Bartter syndrome [3]. The argument that avoidance of COX-2-selective inhibitors might be due to the requirement of COX-2 activity for normal glomerular development up to the 34th week of gestation can readily be discarded by the fact that unselective NSAID, such as indomethacin, also exert their beneficial effects in antenatal Bartter syndrome by inhibiting COX-2. However, avoidance of COX-2-selective NSAID is probably prudent given our lack of experience with these drugs in neonates.

The best reason in favor of using traditional NSAID, such as indomethacin, as standard drugs in treating antenatal Bartter syndrome is the solid body of clinical experience accumulated in using this drug to treat numerous premature neonates drug to promote closure of an open ductus arteriosus. Although necrotizing enterocolitis has been reported in premature babies treated with indomethacin, it is difficult to conclude that this is causally related to indomethacin given the relatively high incidence of necrotizing enterocolitis in premature babies.

From a pharmacological point of view, the use of indomethacin instead of aspirin is much more plausible because the relative COX-2 selectivity of indomethacin in vivo is roughly 20-fold higher than that of aspirin [4]. In other words, equal inhibition of COX-2 by aspirin (as compared with indomethacin) will result in a much more profound—but unnecessary—inhibition of COX-1 in platelets and the intestinal mucosa, thereby potentially causing severe bleeding disorders and gastrointestinal side effects.

Finally, it appears counterintuitive to treat preterm neonates with aspirin while the Federal Drug Administration (as requested by the American Association of Pediatrics) requires manufacturers of aspirin to label their products with a warning that this drug may trigger Reye's syndrome in children. This warning also applies to the patient described in the case report, especially when considering that treatment with NSAID is continued well beyond infancy, thus placing the child at an avoidable risk for Reye's syndrome.

Taken together, it does not come as a surprise that aspirin reduces polyuria and loss of electrolytes in a patient likely to be affected by antenatal Bartter syndrome because aspirin also inhibits COX-2. It is, however, somewhat questionable to base a therapeutic decision solely on an assumption (i.e., the risk of necrotizing enterocolitis is greater with indomethacin than with aspirin) despite a clear warning of the American Association of Pediatrics concerning the use of aspirin in children while reasonably well-studied drugs are available for neonatal patients.

This case report underscores once more the need for controlled trials or at least registries when it comes to treating rare diseases.

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