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NEONATAL BILIRUBIN PRODUCTION-CONJUGATION IMBALANCE: EFFECT OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY AND BORDERLINE PREMATUREITY

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Background: The serum total bilirubin (STB) at any point in time represents bilirubin production minus bilirubin conjugation and excretion. Equilibrium between these processes should result in STB concentrations falling within the physiologic range. Hyperbilirubinemia may occur when bilirubin production exceeds the body's ability to eliminate it. Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is associated with increased hemolysis and diminished bilirubin conjugation.

Objective: To evaluate the relationship between production and conjugation of bilirubin in the pathophysiology of jaundice, in a cohort of glucose-6-phosphate dehydrogenase (G-6-PD) - deficient neonates, with especial emphasis on borderline prematurity.

Methods: A cohort of term and near-term, healthy, male G-6-PD deficient neonates was sampled close to the beginning of the 3rd day post-delivery. A bilirubin production-conjugation index was comprised of COHbc/TCB (unitless), where COHbc (blood carboxyhemoglobin corrected for inspired CO, an index of bilirubin production) and TCB (serum total conjugated bilirubin, a reflection of bilirubin conjugation), were measured from identical blood samples. High index values reflect imbalance between these processes. COHbc, and unconjugated and conjugated bilirubin fractions, were measured by gas chromatographic and reverse-phase high performance liquid chromatographic techniques, respectively. Values for COHbc and TCB individually, and the production-conjugation index, respectively, were studied in relation to STB concentrations. In addition, values for the subgroup of near-term neonates (35-37 weeks gestational age) were compared with those of the term infants.

Results: Fifty-one neonates were sampled at 51 ± 8 hrs. COHbc values did not correlate with STB ($r=0.22$, $p=0.15$). TCB did correlate inversely with STB ($r= -0.42$, $p=0.004$), while there was a positive correlation between the production-conjugation index and STB ($r=0.45$, $p=0.002$). Values [median (interquartile range)] for the production-conjugation index were significantly higher in the near-term ($n=8$) than term neonates [2.31 (2.12-3.08) vs. 1.05 (0.53-1.81), $p=0.003$]. Further analysis pinpointed this difference to gestational age related changes in TCB, but not COHbc, values.

Conclusions: Increasing values for the production-conjugation index, in tandem with STB values, demonstrate that jaundice in G-6-PD deficient neonates is the result of imbalance between production and conjugation of bilirubin. Our results confirm predilection for inefficient bilirubin conjugation over increased hemolysis in the pathogenesis of G-6-PD deficiency associated neonatal jaundice. Diminished bilirubin conjugation may place near-term neonates at especial risk for bilirubin production-conjugation imbalance, with the potential of severe hyperbilirubinemia.

References

1. Kaplan M, Muraca M, Hammerman C, Rubaltelli FF, Vilei MT, Vreman HJ, Stevenson DK. Imbalance between production and conjugation of bilirubin: A fundamental concept in the mechanism of neonatal jaundice. *Pediatrics* 2002;110;(4). URL: <http://www.pediatrics.org/cgi/content/full/110/4/e47>.
2. Kaplan M, Vreman HJ, Hammerman C, Leiter C, Abramov A, Stevenson DK. Contribution of haemolysis to jaundice in Sephardic Jewish glucose-6-phosphate dehydrogenase deficient neonates. *Br J Haematol* 1996;93:822-827.
3. Kaplan M, Rubaltelli FF, Hammerman C. Conjugated bilirubin in neonates with glucose-6-phosphate dehydrogenase deficiency. *J Pediatr* 1996;128:695-697.
4. Kaplan M, Muraca M, Hammerman C, Vilei MT, Leiter C, Rudensky B, Rubaltelli FF. Bilirubin conjugation, reflected by conjugated bilirubin fractions, in glucose-6-phosphate dehydrogenase-deficient neonates: a determining factor in the pathogenesis of hyperbilirubinemia. *Pediatrics* 1998;102(3). URL: <http://www.pediatrics.org/cgi/content/full/102/3/e37>.
5. Kaplan M, Renbaum P, Levy-Lahad E, Hammerman C, Lahad A, Beutler E. Gilbert's Syndrome and glucose-6-phosphate dehydrogenase deficiency: A dose dependent genetic interaction crucial to neonatal hyperbilirubinemia. *Proc Natl Acad Sci USA* 1997;94:12128-12132.
6. Kaplan M, Hammerman C, Renbaum P, Levy-Lahad E, Vreman HJ, Stevenson DK. Differing pathogenesis of perinatal bilirubinemia in glucose-6-phosphate dehydrogenase-deficient *versus* – normal neonates. *Pediatr Res* 2001;50:532-537.
7. Muraca M, Blanckaert N. Liquid-chromatographic assay and identification of mono- and diester conjugates of bilirubin in normal serum. *Clin Chem* 1983;29:1767-1771.
8. Vreman HJ, Stevenson DK, Zwart A. Analysis for carboxyhemoglobin by gas chromatography and multicomponent spectrophotometry compared. *Clin Chem* 1987;33:694-697.