OBSTETRICS

Antenatal exposure to sulindac and risk of necrotizing enterocolitis

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OBJECTIVE: Most studies of tocolytics are underpowered to assess drug effects on rare adverse neonatal outcomes. Our aim was to optimize statistical power to assess the influence of sulindac on the rare but severe outcome of necrotizing enterocolitis (NEC) by performing a case-control study.

STUDY DESIGN: A priori sample size of 78 in each group was estimated to detect a 2.5-fold increase in nonsteroidal antiinflammatory drug exposure in NEC cases. Maternal-neonatal charts were reviewed from 2007 through 2012 to yield 110 NEC cases: 68 patients with confirmed NEC by Bell's stage II criteria, and 42 with suspected NEC. Cases and controls (N = 131, matched according to gestational age at delivery, plurality, and delivery date) were compared in rates of antenatal exposures to nonsteroidal antiinflammatory drugs, other tocolytics, and maternal-neonatal characteristics and complications.

RESULTS: Cases and controls were delivered at a mean of 28 weeks. Approximately 52% of the total cohort received tocolytics (26% indomethacin, 15% sulindac, 32% calcium channel blockers, 32% beta-sympathomimetics), with no differences in frequency of use between cases and controls. While there was no difference in indomethacin exposure between cases and controls, antenatal exposure to sulindac was independently associated with increased risk of NEC (adjusted odds ratio, 5.33; 95% confidence interval, 1.38—20.57; $P = .02$), even after adjustment for other factors significantly associated with NEC.

CONCLUSION: Our data demonstrate an adverse association of sulindac with NEC. These findings deserve further investigation and using sulindac as a tocolytic agent requires caution.

Key words: indomethacin, necrotizing enterocolitis, nonsteroidal antiinflammatory drugs, sulindac, tocolytics

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Preterm labor is a common antecedent event leading to preterm birth, the leading cause of neonatal mortality in the United States.[1,2] Tocolytic agents, which inhibit myometrial contractions, are commonly prescribed in an effort to stop preterm labor. Most tocolytics have been inadequately evaluated with studies poorly designed without a control group, small numbers, or heterogeneous definitions of preterm labor. As such, the American Congress of Obstetricians and Gynecologists (ACOG) states in its most recent practice bulletin on management of preterm labor that evidence supports the use of a single first-line tocolytic agent, such as a beta-adrenergic agonist, calcium channel blocker, or nonsteroidal antiinflammatory drug (NSAID), in an attempt to achieve short-term prolongation of pregnancy to allow administration of antenatal corticosteroids.[2] However, there is significant variation in the maternal and fetal side-effect and risk profile of the current medications used for tocolysis of preterm labor. As such, the assessment of risk to mother, fetus, and newborn becomes even more important when obstetricians must decide which tocolytic is most appropriate for the pregnant patient with preterm labor.

NSAIDs are commonly used as tocolytics for management of preterm labor by inhibition of prostaglandins. Prostaglandins play a central role in the processes of cervical ripening and labor onset, as controlled by cyclooxygenase (COX)-1 and -2. The 2 most common NSAIDs used for tocolysis, indomethacin and sulindac, have similar pharmacologic properties, although act differently to inhibit prostaglandin receptors. Indomethacin is a nonselective COX inhibitor, while sulindac is a selective COX-2 inhibitor. With concern that indomethacin can cause adverse effects in the fetus and newborn, including oliguria, oligohydramnios, early closure of the ductus arteriosus, periventricular leukomalacia, and in particular, necrotizing enterocolitis (NEC),[3-7] some obstetricians may prefer

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sulindac considering it to be a more potent, but selective COX-2 inhibitor.

Sulindac is a pro-drug rather than an active drug, and is metabolized into its active form in the liver. While it has been shown to cross the placenta, it has been suggested to have less adverse effects as the fetal liver cannot make the active metabolite as efficiently.[8] In comparative trials with indomethacin, while sulindac has been shown to be as effective as indomethacin in treating preterm labor and delaying subsequent delivery,[9] it appears to have less deleterious effects on the newborn such as renal insufficiency or premature ductal closure.[10] However, there are few randomized trials studying efficacy of sulindac in treating preterm labor, and very little information on adverse neonatal effects of the drug.

Given the paucity of data regarding the use of sulindac during pregnancy and subsequent neonatal outcomes, our objective was to determine if there is an association with antenatal exposure to sulindac with the severe adverse neonatal outcome of NEC. Similar to what has been seen with indomethacin, we hypothesized that antenatal exposure to sulindac would increase risk for NEC, through the mechanism of increased vasoconstriction, which would decrease fetal intestinal blood flow.

Materials and Methods

To identify possible tocolytic risks on the rare outcome of NEC, we performed a case-control study to evaluate the association between antenatal exposure of prostaglandin inhibitors (indomethacin and sulindac) and NEC. The study was approved by the institutional review boards of a high-volume tertiary delivery hospital (Good Samaritan Hospital, Cincinnati, OH) and its referral children's hospital (Cincinnati Children's Hospital Medical Center). We identified patients born at the delivery hospital, from Jan. 1, 2007, through Aug. 31, 2012, using problem lists created by the attending neonatologists and screening for the key words "NEC" and "necrotizing enterocolitis." Study exclusions were major congenital anomalies, especially congenital heart defects or intestinal pathology that may predispose to NEC (eg, gastroschisis or omphalocele), monochorionic twins, and triplet and higher-order multifetal gestations.

The outcome of confirmed NEC was defined by abnormal abdominal X-ray that showed pneumatosis, free air, or portal venous gas (Bell's stage II), in conjunction with a week-long period of nothing by mouth and antibiotics. We also collected data on cases of suspected NEC, without clear radiographic findings, but included a history of bloody stools, abdominal distension, and NEC treatments, such as nothing by mouth and antibiotics for 1 week. If the infant progressed to surgical management requiring transfer to the referral children's hospital, that hospital chart plus any operative reports were reviewed to determine gross anatomical findings.

The charts of all women and their infants who met inclusion criteria were reviewed for the variables of interest, and data abstracted. A quality assurance review of 10% of the charts by a second investigator found discrepancies in $<5\%$ of all data variables collected. Maternal demographic characteristics analyzed as possible confounders were mother's age, gravidity, parity, race, ethnicity, history of premature delivery, history of cesarean delivery, and presence of labor prior to delivery. Pregnancy complications included hypertensive disease (chronic, gestational, or preeclampsia), diabetes (preexisting or gestational), prolonged rupture of membranes, oligohydramnios, preterm labor, or antenatal hospitalization. Information on exposure to antenatal corticosteroids, magnesium sulfate, other tocolytics, alcohol, and other drugs was also collected. Specific characteristics of NSAID use, including gestational age at initiation of treatment, total milligrams administered, length of treatment, and latency period between treatment and delivery were reviewed.

Data collected on neonatal characteristics included gestational age, sex, weight at birth, and birthweight percentile according to intrauterine growth curves by Olsen et al.[11] Fetal growth restriction was defined as a birthweight $<10\%$ for gestational week of birth. Data were collected on neonatal outcomes of interest including respiratory distress syndrome (per neonatologist assessment, surfactant administration, or as seen on chest x-ray by the radiologist), bronchopulmonary dysplasia (receiving supplemental oxygen at 36 weeks' postconceptual age), need for surfactant administration, need for inotropic medications, postnatal treatment with prophylactic indomethacin or hydrocortisone, patent ductus arteriosus (as documented by neonatologist's clinical examination or echocardiography), or postnatal treatment of ductus arteriosus with indomethacin or ibuprofen.

To obtain 80% power with alpha error of 5% and assuming a prevalence of NSAID use in the case group of 60% and 40% NSAID use in the control group, we calculated a sample size of 78 cases plus 78 controls to detect a 2.5-fold increase in NSAID exposure for cases compared to controls. The approximate rate of NSAID use at the study institution was known a priori and was used to estimate the exposure frequency in the control group. The effect size of 2.5-fold increase in exposure frequency was chosen as a clinically relevant exposure difference. To select controls, we requested medical records department provide a random list of newborn patients, matched by gestational age, plurality, and delivery date as close as possible to each of the cases, distributed across the same years of the study.

The data were analyzed using software (SAS 9.3; SAS Institute Inc, Cary, NC). Differences between categorical and continuous variables were tested using χ^2 or Fisher exact test where necessary, and t test or Kruskal-Wallis test, respectively, in an unpaired analysis. When both twins born to 1 mother qualified for the study, we randomly selected 1 twin to include in the analysis. Multivariate logistic regression was used to estimate the relative influence of a variety of risk factors on risk of NEC, first looking at all cases of NEC (suspected and confirmed) and then doing a sensitivity analysis, with only confirmed cases, after removing suspected NEC cases and infants with possible spontaneous bowel perforation. Backward selection yielded a final model of statistically influential and