Indomethacin Tocolysis Increases Postnatal Patent Ductus Arteriosus Severity

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ABSTRACT. Postnatally, therapeutic indomethacin administration is usually effective in mediating patent ductus arteriosus (PDA) constriction in premature infants. There are infants, however, who remain resistant to indomethacin and require more aggressive surgical intervention to facilitate ductal closure.

Indomethacin tocolysis has been reported to increase the incidence of persistent PDA in premature infants. It was our impression that infants exposed to antenatal indomethacin not only suffered from an increased incidence of PDA, but that they were more symptomatic from PDA and that for them, PDA was more resistant to medical closure. It is this observation that we sought to examine in this study.

Methods. **Medical records of all mothers and premature neonates with birth weight ≤1500 g, admitted to the neonatal intensive care unit of the Shaare Zedek Medical Center during 1996 and 1997, who survived for at least 1 week, were reviewed retrospectively. Data on maternal indomethacin and steroid exposure, birth weight and gestational age, and ductus status and treatment were analyzed. In our obstetrics department, indomethacin is the medication of choice to inhibit premature labor. Mothers who arrive in premature labor are started on indomethacin therapy, if delivery is not imminent.**

All infants ≤1500 g were studied by a pediatric cardiologist between 24 and 72 hours of life using two-dimensional echocardiography with color flow mapping to assess ductal patency. Decisions to treat were based on echocardiographic evidence of PDA, along with any of the following clinical signs: bounding pulses, diastolic pressure of ≤25 mm Hg, pulmonary plethora and/or cardiomegaly on chest x-ray, or increasing oxygen requirement with no other explanation. Initial treatment is with indomethacin, if there are no contraindications. Our general approach is to begin therapy with a continuous indomethacin infusion, followed by a course of bolus indomethacin if the infant does not respond. However, each attending neonatologist may treat according to his/her preference (ie, bolus vs continuous). All infants with PDA are followed with serial echocardiographic examinations until the ductus is closed.

Results. **A total of 105 premature infants met the above criteria. Thirty-six of these 105 infants had echocardiographic signs of a PDA (34.3%). Those with PDA were less mature (gestational age, 28.9 ± 2.6 vs 30.3 ± 2.6 weeks, respectively) and tended to be smaller (1060 ± 270 vs 1166 ± 261 g). Of the 36 infants with PDA, 15 (42%) resolved spontaneously and 21 (58%) were symptomatic and required treatment with indomethacin. There were no differences in gestational age or birth weight between infants whose PDA resolved spontaneously and those requiring indomethacin therapy. Four of the 21 (19%) treated infants remained unresponsive to indomethacin and required ductal ligation.**

Of 17 infants with PDA who responded to indomethacin therapy, 1 (6%) was treated with a single course of bolus indomethacin, to which he responded, and 16 (94%) were treated with continuous indomethacin and responded promptly. The differences in therapeutic responsiveness to initial treatment with continuous vs bolus indomethacin were not significant.

Of the 105 infants, 29 were exposed to indomethacin tocolysis. Those who were exposed to antenatal indomethacin and those who were not were well-matched with respect to birth weight and gestational age. Fifteen (52%) of the 29 exposed infants versus 18 (24%) of the 76 infants not exposed to antenatal indomethacin developed a PDA postnatally (relative risk = 2.1; 95% confidence interval: 1.22–3.74), and 45% of the antenatally exposed infants versus 12% of the nonexposed infants were symptomatic and required indomethacin (relative risk = 1.9; 95% confidence interval: 1.17–3.20). Four of the exposed infants versus none of the unexposed infants required surgical ligation.

Among the indomethacin-exposed infants, the nonresponsive and responsive infants were well-matched with regard to birth weight, gestational age, antenatal steroid exposure, and day of life on which indomethacin therapy was initiated. Multiple regression analyses found prenatal indomethacin exposure to be the most significant antecedent variable associated with both the incidence and the severity of PDA, as indicated by the need for indomethacin treatment.

Conclusions. **We have demonstrated that prenatal indomethacin exposure increases both the incidence and the clinical severity of postnatal PDA, as manifested by increased need for therapeutic indomethacin and surgical ligation. Furthermore, we have shown it to be a more significant risk factor than gestational age, birth weight, or antenatal steroid exposure in both the development and the severity of postnatal PDA. These data should be considered in considerations as to choice of tocolytic therapy.** ***Pediatrics*** **1998;102(5). URL: http://www.pediatrics.org/cgi/content/full/102/5/e56;** ***indomethacin, patent ductus arteriosus (PDA), tocolysis surgical ligation, premature neonate.***

ABBREVIATION. PDA, patent ductus arteriosus.

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During the transition from intrauterine to extrauterine existence, the ductus arteriosus is transformed from a vital component of the fetal circulation into an unnecessary and even deleterious appendage to the neonatal circulation. As such, it is normally programmed physiologically to constrict automatically shortly after birth. In premature infants, however, spontaneous closure often is delayed, resulting in persistent patency of the ductus arteriosus (PDA), which may require medical intervention to promote closure. To date, the most widely used pharmacologic agent for this purpose is indomethacin. Postnatally, therapeutic indomethacin administration is usually effective in mediating PDA constriction in premature infants. There are infants, however, who remain resistant to indomethacin and require more aggressive surgical intervention to facilitate ductal closure.

Indomethacin tocolysis has been reported to increase the incidence of persistent PDA in premature infants.[1] It was our impression that infants exposed to antenatal indomethacin not only suffered from an increased incidence of PDA, as reported, but that they were more symptomatic from PDA and that for them, PDA was more resistant to medical closure. It is this observation that we sought to examine in this study.

METHODS

Medical records of all mothers and premature neonates with birth weight ≤1500 g, admitted to the neonatal intensive care unit of the Shaare Zedek Medical Center during 1996 and 1997, who survived for at least 1 week, were reviewed retrospectively. Data on maternal indomethacin and steroid exposure, birth weight and gestational age, and ductus status and treatment were analyzed. In our obstetrics department, indomethacin is the medication of choice to inhibit premature labor. Our obstetrics protocol for antenatal indomethacin is one dose of 100 mg per rectum followed by 25 mg, po, four times per day. Mothers who arrive in premature labor are started on indomethacin therapy, if delivery is not imminent.

All of our infants weighing ≤1500 g studied by a pediatric cardiologist between 24 and 72 hours of life using two-dimensional echocardiography with color flow mapping to assess ductal patency. Decisions to treat are based on echocardiographic evidence of PDA, along with any of the following clinical signs: bounding pulses, diastolic pressure of ≤25 mm Hg, pulmonary plethora and/or cardiomegaly on chest x-ray, or increasing oxygen requirement with no other explanation. Initial treatment is with indomethacin, if there are no contraindications. Our general approach is to begin therapy with a continuous indomethacin infusion,[9] followed by a course of bolus indomethacin if the infant does not respond with closure of the ductus. However, each attending neonatologist may treat according to his/her preference (ie, bolus vs continuous). All infants with PDA are followed with serial echocardiography until the ductus is closed.

Analysis of Data

χ^2 analyses were used to examine independence between categorical variables (eg, incidence of PDA, percent treated with indomethacin). Then multivariate analysis was performed using multiple logistic regression models constructed alternatively using presence or absence of PDA and the need for indomethacin treatment as dependent variables and other measured variables, including gestational age, birth weight, antenatal indomethacin administration, and antenatal steroid treatment, as independent variables. Correlation coefficients and P values were calculated and used to estimate the relative contribution of the variables.

RESULTS

A total of 105 premature infants met the above criteria. Of these, 36 (34.3%) had echocardiographic signs of a PDA. Those with PDAs were less mature (gestational age, 28.9 ± 2.6 vs 30.3 ± 2.6 weeks, respectively; $P = .01$) and tended to be smaller (1060 ± 270 vs 1166 ± 261 g; $P = .053$). Of the 36 infants with PDA, 15 (42%) resolved spontaneously and 21 (58%) were symptomatic and required treatment with indomethacin. There were no differences in either gestational age or birth weight between those infants whose PDA resolved spontaneously and those requiring indomethacin therapy. Four (19%) of the 21 treated infants remained unresponsive to indomethacin and required ductal ligation.

Of 17 infants with PDA who responded to indomethacin therapy, 1 (6%) was treated with a single course of bolus indomethacin to which he responded, and 16 (94%) were treated with continuous indomethacin and responded promptly. Of the treatment failures who proceeded to ligation, 1 was treated initially with bolus indomethacin followed by a second course of continuous indomethacin, and 3 were treated initially with continuous indomethacin, followed by a second course with bolus indomethacin. The differences in therapeutic responsiveness to initial treatment with continuous versus bolus indomethacin were not significant ($P = -.45$).

Influence of Prenatal Indomethacin

Of the 105 infants, 29 were exposed to indomethacin tocolysis. Those who were exposed to antenatal indomethacin and those who were not were well-matched with respect to birth weight and gestational age (Table 1). Fifteen (52%) of the 29 exposed infants versus 18 (24%) of the 76 ($P = .012$) infants not exposed to antenatal indomethacin developed a PDA postnatally (relative risk = 2.1; 95% confidence interval [CI]: 1.22–3.74) (Fig 1). Forty-five percent of the antenatally exposed infants versus 12% ($P = .0006$) of the nonexposed were symptomatic and required indomethacin therapy (relative risk, 1.9; 95% CI: 1.17–3.20). Four of the exposed infants versus none of the unexposed infants ($P = .006$) required surgical ligation.

Among the indomethacin-exposed, the nonresponsive and responsive infants were well-matched with regard to birth weight (889 ± 255 vs 1078 ± 351; $P = .36$), gestational age (25.7 ± 1.7 vs 28.7 ± 3.6; $P = .15$), antenatal steroid exposure (78% vs 100%; $P =$

TABLE 1. Antenatal Indomethacin and PDA

	Not Exposed to Antenatal Indomethacin	Exposed to Antenatal Indomethacin	Significance
Total	76	29	
Birth weight	1128 ± 248	1131 ± 319	$P = .95$
Gestational age	30.0 ± 2.6	29.2 ± 2.8	$P = .17$
No. with PDA	18 (24%)	15 (52%)	*$P = .012$
No. symptomatic	9 (12%)	13 (45%)	*$P = .0006$
No. nonresponsive to Indo	0 (0%)	4 (14%)	*$P = .006$

* $P < .05$.

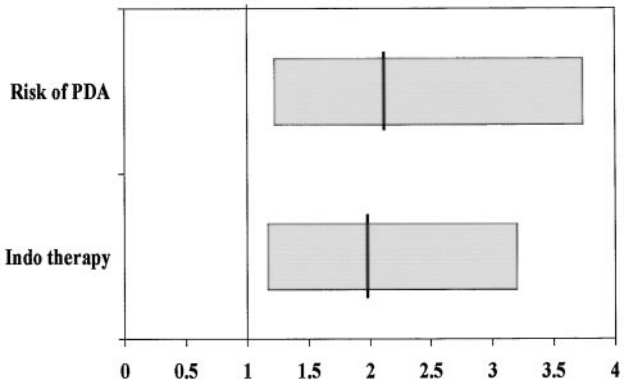

Fig 1. The top indicates the relative risk (vertical line) of developing a postnatal PDA in indomethacin-exposed infants versus nonexposed infants. Relative risk and 95% CIs (horizontal bar) were calculated by multivariate linear regression. Results show that incidence is increased significantly. The bottom indicates the relative risk (vertical line) of a postnatal PDA being symptomatic and requiring medical therapy for closure in indomethacin-exposed infants versus nonexposed infants. Relative risk and 95% CIs (horizontal bar) were calculated by multivariate linear regression. Results show that risk is increased significantly.

.86), and day of life on which indomethacin therapy was initiated (2.5 ± 1.3 vs 1.5 ± 0.5; $P = .17$).

Combined Analysis

Multiple regression analyses found prenatal indomethacin exposure to be the most significant antecedent variable associated with both the incidence of PDA and PDA severity, as indicated by the need for indomethacin treatment (Table 2).

DISCUSSION

Indomethacin has been used for >20 years as a successful tocolytic agent. However, indomethacin does cross the placenta and, in most infants, causes in utero ductal constriction, increasingly significant at >31 weeks' gestation.[2,3] This constriction generally is reversible, resolving after discontinuation of the indomethacin. Our data confirm the observations of Norton and associates[1] that indomethacin tocolysis increased postnatal PDA incidence. These observations are, however, somewhat different from the findings of Eronen and co-workers,[4] who noted no increased incidence of PDAs requiring indomethacin therapy among infants exposed to antenatal indomethacin. Although Eronen et al[4] described a trend that did not reach statistical significance toward increased need for surgical ligation in these infants, our data now demonstrate definitively that indomethacin tocolysis also increases the clinical severity of the resulting PDAs, as manifested by increased need for therapeutic indomethacin. Furthermore, it is a more significant risk factor than gestational age, birth weight, or antenatal steroid exposure in both the development and the severity of postnatal PDA.

TABLE 2. Multiple Regression Data

	Correlation Coefficient (r)	*P* Values
PDA		
Prenatal indomethacin	0.23	.07
Steroid exposure	0.04	.72
Birth weight	0.0001	.63
Gestational age	0.03	.24
Overall regression		.03
Power of the performed test with $\alpha = 0.05$		.92
Therapeutic indomethacin		
Prenatal indomethacin	0.26	.01
Steroid exposure	0.04	.66
Birth weight	0.0002	.44
Gestational age	0.004	.83
Overall regression		.01
Power of the performed test with $\alpha = 0.05$		.96

After in utero constriction, the subsequent ability of the ductus to recontract in response to oxygen or indomethacin appears to be limited, possibly reflecting early ischemic damage to the inner muscle wall.[5] Gittenberger-de Groot described cytolytic necrosis in the media of the ductus after functional constriction, preceding full anatomic closure.[6] Ductal necrosis also has been described in response to chronic hypoxia,[7] with similar histologic changes observed in intrauterine growth-retarded fetuses.[8] All of these infants have a diminished capacity for subsequent ductal constriction, manifesting clinically as a loss of ductal responsiveness and decreased sensitivity to indomethacin.

In 1995,[9] our group introduced 36-hour continuous indomethacin infusion to treat PDA, and although each attending neonatologist may determine whether to treat with either bolus or continuous indomethacin, most do begin with the continuous infusion. As such, it is important to note that our overall 19% indomethacin failure rate is quite consistent with failure rates quoted in the medical literature,[10,11] and that within our population, there was no difference in the responsiveness to continuous versus bolus indomethacin, implying that our approach is not associated with reduced therapeutic efficacy. Much larger numbers, however, would be needed to prove efficacy definitively.

In the current study, 1 responder and 1 nonresponder were treated initially with bolus indomethacin. To avoid possible bias and/or confusion associated with use of different therapeutic administration protocols, each of the statistical calculations cited above was repeated with these two infants removed from the study group. None of the results were affected adversely. Thus, we feel it is acceptable to analyze all of the infants in a single group. Clinical factors influencing therapeutic responsiveness and the pathophysiology thereof are likely to be qualitatively similar regardless of mode of administration. We believe, therefore, that these observations are relevant to all premature infants with PDA treated with indomethacin.

In summary, we have demonstrated that not only does prenatal indomethacin constitute a risk factor for PDA development, but also for PDA severity and resistance to therapy. Furthermore, it is the most significant risk factor among those studied in the development of these outcomes. These data should be considered in considerations of choice of tocolytic therapy.

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