Necrotizing enterocolitis in preterm infants with patent ductus arteriosus: Does indomethacin increase the risk?

By: Christopher McPherson, Peter Gala, McCrae Smith, William Wilder, Scott Richter, J. Laurence Ransom, Rita Q. Carlos, Mary Ann V.T. Dimaguila, John E. Wimmer Jr.

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Abstract:

Objectives: To examine any association of necrotizing enterocolitis (NEC) and intestinal perforation (IP) in very low birth weight neonates with indomethacin treatment, cumulative dose or maximum plasma concentrations. *Methods:* This is a retrospective 9-year cohort study of very low birth weight infants (< 1500 grams) admitted to our neonatal intensive care unit. The incidence of NEC and IP in infants who received indomethacin for a PDA *(N* = 228) were compared to control infants who did not have PDA and received no indomethacin (S = 628). Factors which were statisticaily significant in a univariate analysis were then included in a logistic regression model to determine their significance. *Results:* NEC occurred in 14 (6.1 %) indomethacin-treated infants compared to 47 (7.5%) control infants. When the incidence of NEC or IP was restricted to events occurring within 14 days of indomethacin, infants (1.7%) had NEC. JP occurred in 14 (6.1 %) indomethacin-treated infants, but 10 had concurrent steroid therapy. IP also occurred in 4 (0.6%) controls. Multivariate logistical regression revealed a lower risk of NEC with indomethacin. The risk for NEC and IP is not increased with higher INDO doses or INDO concentrations. *Conclusions:* Indomethacin treatment for PDA does not increase NEC risk, and may decrease the risk. Indomethacin treatment is associated with an increased risk of IP, especially when combined with systemic glucocorticoids.

Keywords: Indomethacin | necrotizing enterocolitis | intestinal perforation | neonates | patent ductus arteriosus

Article:

1. Introduction

When indomethacin (INDO) became a widely accepted agent for patent ductus arteriosus (PDA) closure in premature infants, concerns of gastrointestinal toxicity were prominent in monitoring outcomes [1-3] Particularly concerning was the risk of causing necrotizing enterocolitis (NEC), since this illness is associated considerable morbidity and mortality [4,5]. Several studies suggested that a causal association between indomethacin therapy for PDA with NEC or intestinal perforation (IP) does exist [2,3,5,6]. This conclusion is confounded by data indicating that PDA is itself a cause of NEC [7]. More recent smdies did not demonstrate a causal relationship between indomethacin and NEC or IP [8-11). When combined with postnatal steroids, INDO was associated with NEC or IP [10-13]. This study is a retrospective cohort analysis, designed to further clarify whether INDO therapy is associated with an increased risk for NEC or IP. It provides a unique examination of the relationship of INDO dose and INDO concentration to gastrointestinal toxicity. We also consider the alternative argument that INDO may be protective of NEC.

2. Materials and methods

2.1. Study design and population

This study was approved by the IRB and exempted from individual informed consent. The data collection and analysis were all done retrospectively and no interventions were made for the purpose of the study. All very low birth weight infants ($\leq$ 1500 grams) admitted to the level III NICU at Women's Hospital between January 1997 and December 2005 were included in this retrospective analysis. Data was obtained from an ongoing access database maintained on a continuous basis and reported annually to the Vermont Oxford Network.

Infants who received indomethacin for a PDA (N =228) were compared to control infants who received no indomethacin and did not have a clinically or hemodynamically detectable PDA (N= 628). Patients were evaluated for PDA using echocardiography when clinical signs (e.g. murmur, wide pulse pressures, hypotension, etc.) of PDA were detected, or oxygen or ventilator demands raised suspicion of a silent PDA.

INDO was only used to treat echocardiography confirmed PDA. Patients who received indomethacin were dosed according to combined pharmacokinetic-pharmacodynamic modeling with ultimate dosing individualized to patient response [14,15]. Initial INDO doses were 0.25 to 0.3 mg/kg, and INDO plasma concentrations were measured 2 and 8 hours after each INDO dose. INDO doses were then individually adjusted based on clinical response or echocardiography proven PDA closure if symptoms of PDA resolved. Individual maintenance INDO doses ranged from 0.1 to 0.5 mg/kg every 8 -12 hours based on whether the effective INDO concentration is to be maintained or higher INDO concentrations were needed because of inadequate response.

In addition to indomethacin dose, data were also collected on other potential covariates including: gestational age, birth weight, 5-minute Apgar score, plurality, maternal hypertension

during pregnancy, presence of chorioamnionitis in mother at the time of birth, administration of surfactant as an indicator of early RDS, administration of postnatal steroids, presence of early infection at ≤ 3 days of life, presence of late infection at ≥ 7 days of life, pressor support as an indication of blood pressure instability, umbilical catheter placement, days with umbilical catheter, need for mechanical ventilation, and days on mechanical ventilation.

NEC and IP can be difficult to separate clinically [10, 16], which could confound results. Diagnosis of NEC or IP involved a shared evaluation by the attending neonatologist and consulting pediatric surgeon. In IP cases, the diagnosis was confirmed by exploratory laparoscopy or therapeutic surgery. This was also the case in approximately half the NEC cases, with the remainder diagnosed clinically and radiographically. Clinically, patients presented with recognized signs and symptoms such as feeding intolerance, abdominal distention, lethargy, ileus, and abdominal x-ray showing pneumatosis intestinalis or free air [4, 16, 17]. All neonates with NEC developed concurrent signs of suspected or confirmed sepsis, requiring antibiotic therapy.

Feeding strategies varied among patients with breast milk being preferred, and int1mt formula being used when breast milk was not available or contained contraindicated medications. Formula selection was made on an individual basis. Oral feeds were not initiated while the ductus was open or INDO doses were being administered, and were withheld for 48 hours after the last INDO dose. Feeding was started with 3 to 5 days at 10 to 20 mL/kg/day ("trophic feeds"), and then volume was increased by 10 to 20% of total feeds per day based clinical perceptions of how well each feeding increase was tolerated.

2.2. Statistical analysis

Based on an assumed NEC rate of7% in the control group, the sample size was sufficiently large for a power of 0.9, with an alpha of 0.05, to detect an increase to 8% in the 1\EC rate for indomethacin-treated PDA patients.

Variables (Table 1) were evaluated with multiple logistic regression. The base model included gestational age, 5 minute APGAR, and birth weight. The additional variables were screened for testing in the starting multivariate model based on their univariate prognostic value. Variables with univariate Wald chi-square p-values less than 0.25 were included in the final model. Ultimately, backwards elimination was used to derive a final model. Variables with p-values less than 0.05 were considered statistically significant. The final model was evaluated with the chi-square deviance test and Hosmer and Lemeshow goodness of fit test. All analyses were performed with SAS software (Cary, NC). Predictors of NEC were evaluated with multiple logistic regression. The base model included gestational age, 5 minute APGAR, and birth weight: these three variables have known clinical importance for predicting NEC. Twenty additional variables were screened for testing in the starting multivariate mode 1 based on their univariate prognostic value. Of these, ten were considered promising predictors (univariate Wald

chi-square; $p < 0.25$). Finally, backwards elimination was used to derive a final model from these 13 variables. Variables with p-values of less than 0.05 were considered statistically significant. The final model fit was evaluated with the chi-square deviance test and Hosmer and Lemeshow goodness of fit test. Additional variables retained in the final models were total INDO, late infection, ventilation duration, ventilation insult, and OAC/UVC insult. All analyses were performed with SAS (Cary, NC) software.

Table 1. Demographic comparison of neonates with PDA + INDO treatment and controls

	Indo (228)	No Indo (628)
Gestational Age (wks)	26.7*	28.7
Birthweight (g)	860*	1060
5-minute APGAR (median)	7	7
Plurality (median)	1	1
Chorioamnionitis (%)	4.8	4
Maternal HTN (%)	23.7	29
Early infection (%)	0.9*	0.5
Late infection (%)	31.1*	11.6
Pressor support (%)	45.6*	16.4
Pressor support (days)	l.6*	0.5
Surfactant (~lo)	74.6*	42.5
UVC/UAC placed(%)	96.5*	69.6
UAC/UVC (days)	7.9*	4
Ventilator(%)	91.2*	55.1
Ventilator (days)	16.2*	6.1

*$p < 0.01$.

3. Results

Demographic data and presence of risk factors for neonates to develop KEC or IP are listed in Table 1. Indomethacin-treated neonates had significar1tly lower gestational age and birth weight, lower Apgar scores, and higher incidence of other risk factors associated with NEC or IP. As was observed in a similar examination of risk factors for ~EC and its association with indomethacin [11], we identified gestational age, birthweight, mechanical ventilation, exposure to surfactant, exposure to postnatal glucocorticoids, and umbilical artery catheters important statistical factors to include in our multivariate analysis. We also found statistically important differences in the incidence of early and late-onset culture-confirmed infections, the need for vasopressor support, the need for intubation and the length of time on mechanical ventilation, and duration of umbilical artery or umbilical vein catheter placement (Table 1) These all favored the control group as being at less risk of NEC.

When infants treated with indomethacin were followed over the entire course of their NICU stay, there was a similar incidence of NEC between infants treated with indomethacin for PDA and infants with no PDA and no indomethacin therapy (6.1% vs. 7.5%, $p > 0.10$). There was a

significantly increased risk of IP associated with indomethacin therapy for PDA (6.14% vs. 0.64%, $p < 0.01$). The postnatal age of neonates developing NEC was a median of29 days (range 6 to 68 days), and for neonates developing IP was a median Of 9 days (range 2 to 75 days). The postnatal ages did not differ for the INDO and control groups developing NEC or IP.

As with the study by Attridge et al. [I 0], we required that NEC or IP occur within 2 weeks of exposure to INDO to reasonably link INDO as a cause. Analyzing data with this restriction, there is a significant decrease in the incidence of NEC between infants treated with INDO for PDA and infants with no PDA and no indomethacin therapy (1.7% vs. 7.5%, $p < 0.01$). The significantly increased risk of IP remains in the PDA/indomethacin group compared to controls (5.2% vs. 0.6%, $p < 0.001$) The IP rate however is largely impacted by the cases where postnatal glucocorticoids were administered (Fig. 1). Only 4 (1.7%) cases occurred in the INDO group, and one case (0.2%) in the control group, where glucocorticoids were not potentially involved. On a separate note, because of their significance in the Attridge study [10] we also recorded the early use of hypotension treatment. Of the 14 IP cases, *9* neonates were treated with early blood pressure medications, i.e. dopamine, dobutamine, or both, at various doses.

Multivariate logistical regression revealed similar favorable results concerning the aggressive treatment of PDA with indomethacin and causal relationship with NEC. Indomethacin treatment for PDA was associated with a decreased risk of KEC, controlling for gestational age, 5 minute APGAR, birth weight, late infection, ventilation duration, ventilation insult, and UAC/UVC insult (p-value = 0.0265). A Hosmer and Lemeshow goodness of fit test finds no evidence to reject the hypothesis that indomethacin treatment for PDA is not a statistically significant risk factor for NEC (p-value = **0.37).**

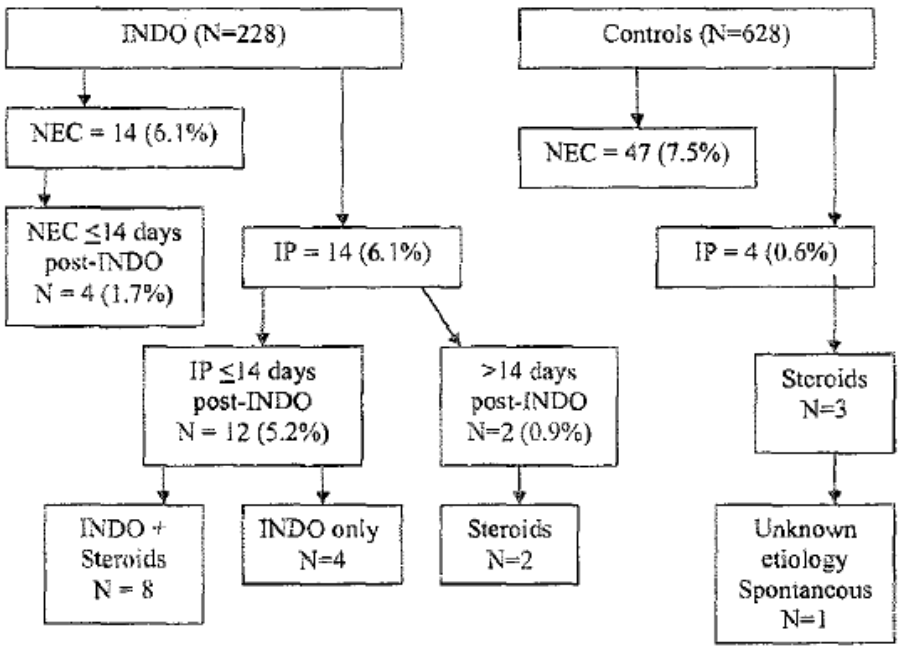

Fig. 1. Summary of rates ofNEC ancl!P in neonates treated with indomethacin (INDO) and controls.

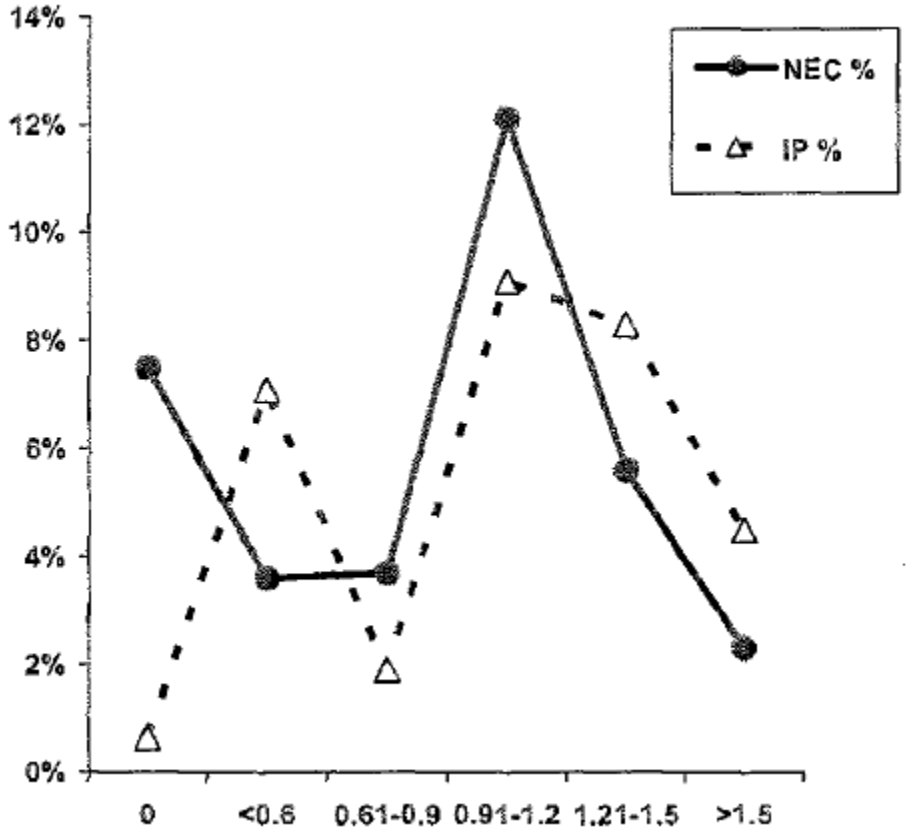

Fig. 2. Relationship of cumulative INDO dose in mg/Kg to percent of patients with NEC or IP for all events occurring any time after INDO doses. INDO close categories were selected to allow sufficient patient numbers in each group: 0, 62R patients; 0.1-0.6 mg/Kg, 28 patients; 0.61--0.9 mg/Kg, 54 patients: 0.91-1.2 mg/Kg, 66 patients; 1.21-l.S mg/Kg, 36 patients; and ≥ 1.51 mg/Kg, 44 patients. x-axis = cumulative INDO dose (mg/Kg); y-axis =%of patients with event any time post-INDO.

The total treatment dose for each indomethacin-treated neonate was analyzed to examine any relationship between this variable and development of NEC or IP. Indomethacin total doses ranged from 0.25 to 3.55 mg/kg, and indomethacin maximum concentrations ranged from 0.67 to 5. 77 mg/L (1.87 to 16.10 μmol/L). The mean (SD) for indomethacin doses for the three groups were: 1.06 (0.56) mg/Kg for INDO-controls; 1.28 (0.85) mg/Kg for NEC; and 1.06 (0.35) mg/Kg for IP. None of these are statistically different from the others. No trend was found toward increased NEC or IP risk with higher doses of indomethacin, whether all NEC and IP events were included (Fig. 2), or only those with an event within 14 days of completing indomethacin therapy (Fig. 3). Maximum indomethacin plasma concentration, also appear to lack any

statistical relationship to NEC or IP. Indomethacin concentrations (mean, SD) were: 2.44 (1.05) mg/L (6.81, SD 2.93 for INDO controls; 2.32 (0.46) mg/L (6.48, SD 1.29 ,μmol/L) for NEC; and 2.47 (1.00) mg~l. (6.89, SD 2.79 μmol/L) for IP. None of these groups were statistically different from each other. Furthermore, the rates of NEC or IP were not different at different indomethacin plasma concentration categories (Figs 4 and 5). The lack of a clear dose-response and concentration-response relationship, makes it more likely that indomethacin does not cause NEC. For IP, systemic glucocorticoids appear to be a major risk, accounting for 13 of 18 IP cases (Fig. 6), and indomethacin may exaggerate this risk as an additive or synergistic toxicity. The risk of IP was 7.1 times greater for combined indomethacin+ systemic steroids (25%) than for indomethacin alone (3.5%), and 11.4 times the risk for systemic steroids alone (2.2%). IP was rare (0.2%) in the absence of systemic steroids or indomethacin.

4. Discussion

The etiology of NEC is unknown, but multiple risk factors have been implicated in its pathogenesis. The risk of NEC is greatly increased by early birth and very low birth weight, occurring in about 7% of neonates below 1500g birth weight [4]. Near term fetal lambs were shown to have increased risk of adverse gastrointestinal effects from either the presence of a PDA or from indomethacin exposure in lambs with closed ductus arteriosus [18]. This was due to reduced blood flow to the terminal ileum, placing this area at higher risk for intestinal ischemia. PDA has also been shown to be a risk factor for XEC in premature infants [7]. Cassady et al. established that surgical closure of the PDA on day l of life reduces the risk of KEC in neonate with birth weight below 1000 g from 30% in untreated neonates, to 8% with PDA ligation [7] Infants in our study with a PDA treated with indomethacin therapy and the control patients, showed a similar rate of NEC to the prophylactic ligation group in the study by Cassady and colleagues [7].

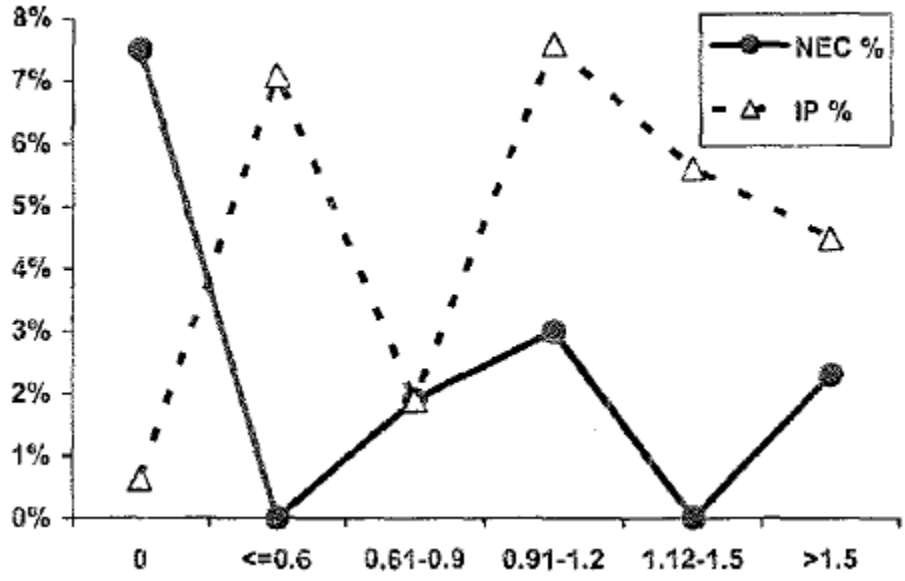

Fig. 3. Relationship of cumulative INDO dose in mg/Kg to percent of patients with NEC or IP for events that occurred between starting INDO and 14 days after completing INDO. rNDO dose categories were selected to allow sufficient patient numbers in each group: 0, 62R patients; 0.1-0.6 mg/Kg, 28 patients; 0.61-0.9 mg/Kg, 54 patients; 0.91-1.2 mg/Kg, 66 patients; 1.21-1.5 mg/Kg, 36 patients; and ≥ 1.51 mg/Kg, 44 patients. x-axis = cumulative INDO dose (mg/Kg); y-axis =%of patients with event :s:; 14 days post-INDO.

Some studies link the treatment of POA with indomethacin to an increased risk of 1\'EC. Nagaraj et al. [3] reported KEC and focal perforation problems in 21 (26%) of 82 infants treated with indomethacin for POA. The high rate of gastrointestinal complications (13 NEC, 8 local perforation) may partly be explained by the unusual indomethacin regimen of 0.2 mg/kg every 8 hours given orally or rectally. A comparison group of 30 patients managed conservatively or with surgical ligation, had only 3 NEC episodes for a gastrointestinal complication rate of 1 0%. Given the known local gastrointestinal toxicity of oral NSAIDs, few centers are using oral indomethacin as a treatment for PDA closure. Grosfeld and colleagues [5] examined 252 premature infants with symptomatic POA given intravenous indomethacin in an attempt to close the ductus arteriosus. Surgical ligation was performed in 11% of patients, and 35% of infants developed NEC after INDO therapy. Factors associated with the onset of NEC included gestational age less the 28 weeks, birth weight less than 1 kg, and prolonged ventilator support. The patients with PDA who received indomethacin therapy were compared with a control group of 764 infants with similar sex, birth weights, and gestational ages without POA or indomethacin therapy. NEC occurred in 13.7% of control patients vs. 35% in indomethacin-treated group *(JJ* < 0.02). Fujii et al. [6] compared treatment with INDO in the first 48 hours of life to avoid the necessity ofPDA ligation versus standard symptomatic treatment with indomethacin after48 hours of life in 65 extremely premature infants (< 27 weeks). The study concluded that early use reduced the need for PDA ligation (5% vs. 35%, $p = 0.033$) but increased the risk Of NEC (20% vs. 0%, $p = 0.011$). Of the 30 infants<27 weeks gestational age receiving early therapy, only 1 patient required surgical ligation but 6 developed NEC. Three of the KEC patients also received dexamethasone. Of the 32 infants < 27 weeks gestational age receiving standard therapy, 6 underwent surgical ligation, but none developed NEC. These data suggest a correlation between the early use of indomethacin and the development of NEC in extremely premature infants.

Other studies provide evidence against indomethacin causing NEC at higher rates than PDA surgical closure or a control group without PDA [8,9, 11, 19]. These are generally better designed and larger trials than those associating NEC with indomethacin therapy. Some trials found that exposure to indomethacin on days l-3 of life was associated with IP, but later exposure was not associated with increased IP risk [10]. Our use of indomethacin varied as treatment was started only after PDA became symptomatic, often beyond the third day of life. This study also noted the importance of concurrent systemic glucocorticoids and early use of vasopressors. We also had several patients treated with dopamine or dobutamine, but since their

use paralleled indomethacin use and presence of PDA, we could not distinguish their possible role in IP.

The use of both indomethacin and systemic glucocorticoids has been associated with increased risk for NEC [11] and IP [10,20], even when indomethacin alone did not cause a statistically significant increase. Paquette et al. [12] also failed to show an association between indomethacin therapy and IP, but when the combination of early indomethacin and dexamethasone was examined, patients were 9.6 times more likely to develop IP. Watterberg et al. [13] were forced to discontinue their trial of early hydrocortisone to prevent bronchopulmonary dysplasia, because of the high rate of IP. In the prophylactic indomethacin plus hydrocortisone group, IP occurred in 12% of patients, compared to 2% with hydrocortisone alone and 1% with indomethacin alone. Stark et al. [20] reported IP rates of 19% with combined dexamethasone and indomethacin and 5% of indomethacin alone. This was significantly higher than placebo, where no IP cases occurred. The combination of indomethacin and systemic steroids seems to be particularly toxic to the gastrointestinal mucosa. This seems to be the case in our study also, where 8 of 12 IP cases were exposed to both indomethacin and systemic steroids.

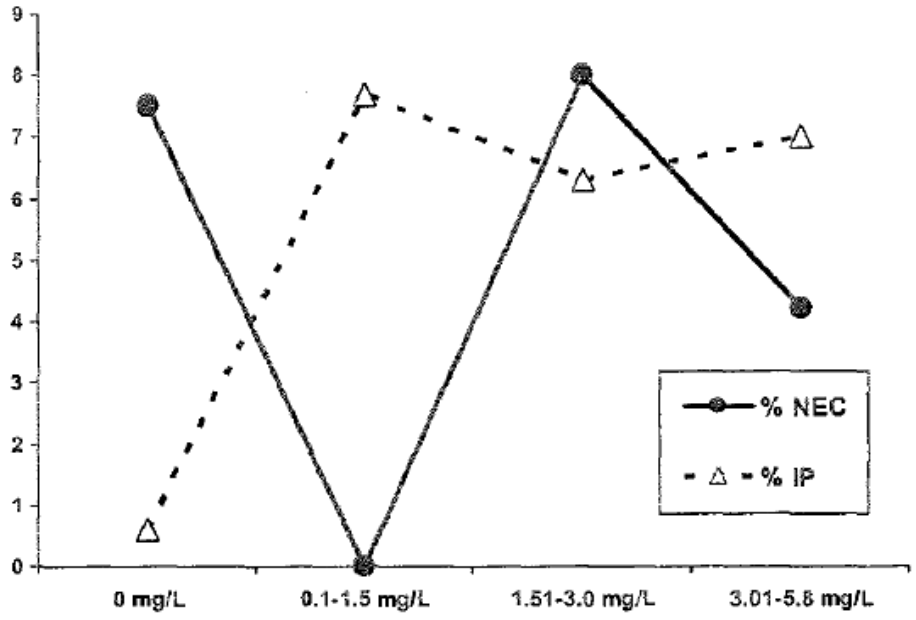

Fig. 4. Relationship of highest INDO plasma concentration (mg/L) to percent of patients with NEC *or* IP for all events. INDO concentration categories were selected to allow sufficient patient numbers in each group: 0 mg/L, 628 patients; 0.1-1.5 mg/L (0.28-4. 19 μmol/L), 26 patients; LSl-3.0 mg/L (4.22-8.38 μmol/L), 112 patients; and 3.01-5.8 mg/L (8.41-16.21 μmol/L), 71 patients. x-axis =highest INDO concentration (mg/L); y-axis =% of patients with event any time post-INDO.

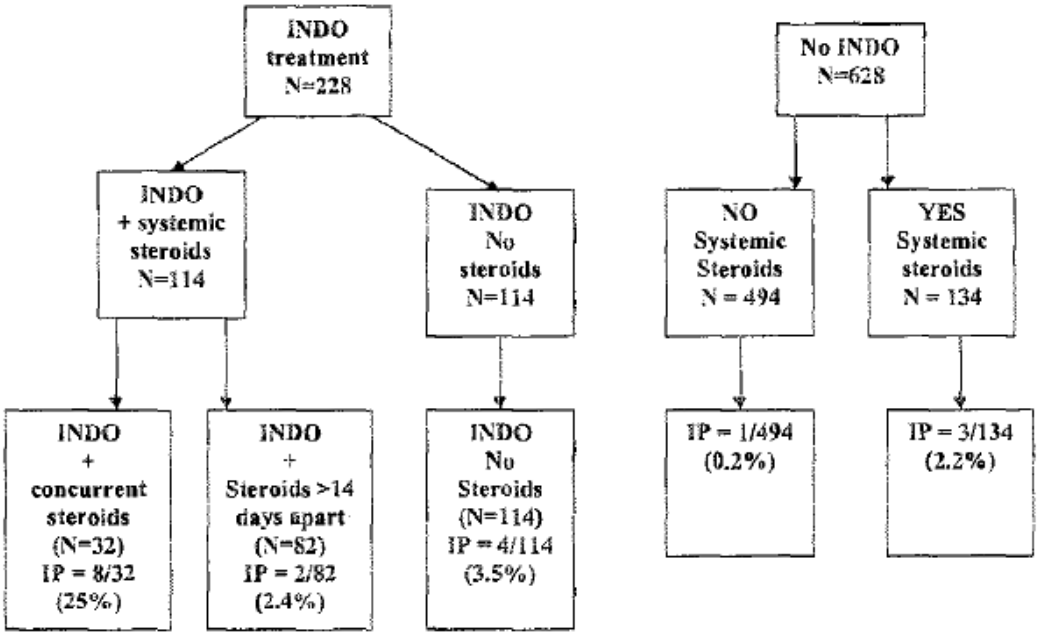

Fig. 5. Risk for IP among neonates exposed to indomethacin (INDO) and systemic steroids alone or in combination.

Our results strengthen the argument that indomethacin docs nm cause NEC, but rather is frequently used in neonates at high risk for ~EC. While the reason for an apparent reduction in NEC rate with INDO treatment is unclear, the process of inflammation is known to be important in the pathogenesis of NEC and perhaps it is the anti-inflammatory effects of INDO that account for any benefit [17]. Also, stabilizing or closing the PDA may help reduce the risk of NEC [8]. These reasons are speculative and needs confirmation in future studies. On the other hand, IP does appear to be more likely to occur when indomethacin is used, particularly in combination with systemic glucocorticoids. There are several theories about the reason for the high IP risk when indomethacin is combined with steroids, including: thinning of the muscularis and thickening of the adjacent mucosa; and inhibition of local prostacycline and nitric oxide production, resulting in diminished perfusion of the watershed areas of the ileum [16].

The need to close PDA in very-low-birth-weight infants is supported by most practitioners, based on clinical and research observations [21-23]. The options to date have been pharmacologic with indomethacin, or more recently ibuprofen, and surgical ligation. Recent studies have created profound concerns about the adverse impact of surgical closure of PDA on neurosensory function, chronic lung disease and mortality [24-26]. It is likely that pharmacologic closure of PDA will be increasingly important, and higher doses may be used to achieve PDA closure in over 90% of patients [16, 27].

The relationship of indomethacin doses and concentrations in neonates to the development of NEC and IP, two gastrointestinal complications associated with indomethacin treatment has not previously been examined. This is in part because standard indomethacin doses are traditionally

used precluding the opportunity to explore the impact of a wide range of doses. A previous paper by Sperandio et al. [27] explored a wide range of indomethacin doses to achieve a PDA closure rate of 98%. These authors report only 1 case of IP in 129 neonates treated with indomethacin, although this was one of the 61 infants who received> 1.5 mg/kg total indomethacin dose. The rate of NEC was 6% in neonates receiving ~ .5 mg/kg, and only 3% in those receiving > .5 mg/kg, suggesting an absence of a relationship with a total indomethacin dose. Our study failed to identify a relationship with NEC or IP and increasing indomethacin doses or concentrations (Figs 2-5).

There are several limitations to our study. These limitations are similar to other retrospective cohort studies related to indomethacin toxicity. The cohorts in this study are different in several demographic features. These include the indomethacin group being significantly less mature, smaller, requiring more blood pressure support and more respiratory support. The study actually reflects the impact of PDA and indomethacin versus a control group with neither of these problems. However, considering the other increased risk factors for NEC, it is impressive that the indomethacin-treated patients actually had less NEC. Another potential issue is the impact of other management changes that may have occurred during this 9-year study. However, we did not see a directional change in the rate of NEC or IP associated with different years.

5. Summary

Indomethacin treatment for PDA is not associated with NEC and may actually be protective of NEC caused by hemodynamically significant PDA. IP however, is associated with indomethacin treatment, and is a particularly high risk when indomethacin and systemic corticosteroids are combined. This is the first study to examine the relationship of indomethacin dose and concentrations to NEC or IP using such a wide range of doses and concentrations. Since neither NEC nor IP were associated with increasing doses of indomethacin, higher dosing strategies with indomethacin need not be avoided purely on the basis of concerns for gastrointestinal toxicity.

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