EFFECTS OF INDOMETHACIN ON PROSTAGLANDIN E2 AND THROMBOXANE B2 CONTENTS OF TRACHEAL LAVAGE FLUIDS IN PREMATURE INFANTS

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Abstract—A prospective longitudinal study was conducted in 14 premature infants intubated and receiving ventilatory support from birth, in order to evaluate the levels of prostaglandins E2 (PGE2) and thromboxane B2 (TxB2) in the tracheal lavage fluids (TLF) after treatment with indomethacin. Eight were treated with indomethacin, a cyclooxygenase inhibitor, for patent ductus arteriosus and the others served as controls. Infants who received indomethacin during the first postnatal week had significantly lower levels of eicosanoids in TLF during the first week. Our results suggest that levels of eicosanoids in TLF of premature infants are related to an inflammatory reaction and may serve as an index of the infant's overall clinical condition.

INTRODUCTION

Thromboxane A2 and prostaglandins are released by the lungs in significant amounts and are involved in the pathogenesis of various experimental lung diseases including pulmonary arterial hypertension and increased pulmonary vascular permeability (1–4) and in human diseases such as adult respiratory distress syndrome (5) and asthma. The potential role of eicosanoids and platelet-activating factor in the pathophysiology of bronchopulmonary dysplasia (BPD) has been also suggested (6). Increased numbers of neutrophils and macrophages in both the air spaces and interstitium suggested the development of an inflammatory response and confirmed the importance of inflammatory cells in the pathogenesis of these lung diseases (7, 8). The purposes of this study were to evaluate the levels of PGE2 and TxB2 in the TLF of intubated premature infants...
and to evaluate the influence of indomethacin on eicosanoid levels in tracheal secretion.

MATERIALS AND METHODS

Premature infants admitted in the neonatal intensive care unit during the first six months of 1986 and intubated and receiving ventilatory support were included in this prospective study. However, only infants intubated for more than two weeks after birth were kept for this study. A group of eight premature infants were treated with indomethacin (0.2 mg/kg/dose every 12 h for three doses) for closure of patent ductus arteriosus. This group was compared to another group of six infants who did not receive indomethacin.

Tracheal lavage fluid was collected 24-48 h after treatment with indomethacin. Tracheal suction is part of the usual management of intubated infants. For this purpose, 0.5 ml of isotonic NaCl solution is injected in the endotracheal tube and reaspirated from both bronchi following several breaths in sterile containers. Three samples of TLF were collected at 2-h intervals twice a week. The samples were pooled each day and total volume was measured. The tracheal lavages then were centrifuged 5 min at 12,000 g and 1 ml of supernatant was used to measure the eicosanoid concentration by enzyme immuno assay. The assay was performed according to the method of Pradelles et al. (9). Then 50 μl of different dilutions of the samples were included with 50 μl of conjugated eicosanoid–acetylcholinesterase and 50 μl of specific antiserum in an anti-rabbit IgG precoated 96-well plate. After an overnight incubation at 4°C, the plate was washed and the enzyme substrate plus Ellman’s reagent were added for 60-120 min at 25°C. The plate then was read at 414 nm. The concentration of each eicosanoid was determined according to a standard curve using a microcomputer program developed in our laboratories. Results are expressed as nanograms of eicosanoid released per milliliter of TLF. The results in the table and figures are expressed as mean ±SEM.

RESULTS

Eight babies were treated with indomethacin compared to six controls, and Figure 1 shows the postnatal profile of the levels of PGE₂ and TxB₂ in the TLF of the two groups. Infants who received indomethacin had significantly lower levels of both eicosanoids during the first postnatal week (P < 0.05). The levels of PGE₂ and TxB₂ were 1.28 ± 0.4 and 2.24 ± 0.85 ng/ml, respectively, in control TLF and 0.28 ± 0.7 and 0.12 ± 0.04 ng/ml in indomethacin-treated infants. Control levels of PGE₂ and TxB₂ in TLF remained fairly stable over the period of six weeks. The level of PGE₂ in treated patients rose slowly and reached control levels after approximately three weeks whereas the TxB₂ level of treated patients returned to control levels only after five weeks.