Effects of Phenobarbital on Cerebral Blood Flow Velocity After Endotracheal Suctioning in Premature Neonates

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Objective: To examine the effect of phenobarbital administration on anterior cerebral artery blood flow velocity before and after endotracheal suctioning in premature neonates.

Design: Transcutaneous PO2 (TcPO2), heart rate, mean arterial blood pressure (MABP), and Doppler velocimeter blood flow of the left anterior cerebral artery were measured before and immediately after 3 consecutive endotracheal suctioning procedures in premature neonates. Intravenous phenobarbital (20 mg/kg) was administered immediately after the first procedure.

Setting: Neonatal intensive care unit.

Patients: Nine neonates with a mean birth weight of 807 g (range, 620-1060 g) and a mean gestational age of 27 weeks (range, 25-30 weeks) were studied at age 8 to 12 hours.

Results: Transcutaneous PO2 decreased in response to endotracheal suctioning before and after phenobarbital was given (P<.001). Changes in heart rate were not observed. There were increases in MABP and area under the velocity curve (AUVC) per minute in response to endotracheal suctioning before but not after phenobarbital administration (P=.046). Use of phenobarbital lowered the overall peak systolic blood flow velocity in response to endotracheal suctioning (P = .02, analysis of variance, interactions for the effect of phenobarbital therapy on the response to suctioning). Changes in end-diastolic blood flow velocity were not observed. There were decreases in the differences before and after endotracheal suctioning for MABP at 2 and 4 hours and for AUVC and peak systolic blood flow velocity 4 hours after phenobarbital was given (P = .04).

Conclusions: In very low-birth-weight neonates, endotracheal suctioning is associated with decreases in TcPO2 and increases in MABP and AUVC. Treatment with phenobarbital attenuates the increases in MABP and AUVC but not the decreases in TcPO2 after endotracheal suctioning.


PHENOBARBITAL is used for treatment of seizures and sedation in low-birth-weight neonates. Concern has been raised regarding treatment with phenobarbital because it has been shown to decrease cerebral blood flow during hypertension and hypotension in newborn piglets. In normotensive newborn piglets, phenobarbital exposure has been shown to result in transient dose-dependent decreases in mean arterial blood pressure (MABP) and cerebral blood flow; MABP and cerebral blood flow returned to baseline values within 60 minutes of administration. In human neonates, no effects on MABP or cerebral blood flow velocity were observed after administration of an intravenous dose of phenobarbital, 20 mg/kg.

Endotracheal suctioning increases MABP and cerebral blood flow velocity in human neonates. The objective of this study was to examine the effect of phenobarbital treatment on the responses of MABP and cerebral blood flow velocity to endotracheal suctioning in very low-birth-weight neonates.

RESULTS

The 9 neonates had a mean hematocrit of 0.44±0.02. Changes in hematocrit values were not observed during the study. The serum phenobarbital level achieved 4 hours after administration was within the therapeutic range (21.4±1.6 mg/dL).

As shown in Figure 1, TcPO2 decreased in response to endotracheal tube suctioning before and after treatment with phenobarbital (P<.001, ANOVA, main effects for endotracheal suctioning). There were no changes in heart rate during the...
PATIENTS, MATERIALS, AND METHODS

This study was approved by the institutional review board of Women and Infants Hospital of Rhode Island, Providence, and informed consent was obtained from the legal guardians of the newborns. Consecutive neonates were recruited after informed consent had been obtained and according to investigator availability. Only 1 neonate could be studied at a time. Neonates were enrolled from March 23, 1984, through December 30, 1984. The study had not been published previously because at the time of the original study, measures were made by tracing the velocimeter curves using a handheld device. To improve on the accuracy of our findings, we had to wait until computerized techniques became available, and, as outlined later, the tracings were then reanalyzed by digitalizing the original velocimeter tracings.

Nine neonates with a mean ± SEM birth weight of 807 ± 34 g and a gestational age range of 25 to 30 weeks were studied. All neonates were intubated, receiving conventional ventilatory support, and had 3.3 F umbilical arterial catheters (Argyle; Sherwood Medical Industries, St Louis, Mo) placed in the descending aorta at the level of the 8th to 10th thoracic vertebra for clinical monitoring of arterial blood gases and blood pressure. None of the neonates were paralyzed or treated with surfactant replacement therapy. Neonates were studied at age 8 to 12 hours.

Exclusion criteria included (1) maternal antenatal barbiturate therapy; (2) neurologic abnormalities, including seizures, microcephaly, and chromosomal or genetic syndromes with brain abnormalities; and (3) development of any severe complications before or during the study period, such as pneumothorax or prolonged bradycardia.

MEASUREMENT PROCEDURES

All neonates had normal cranial ultrasound findings before enrollment in the study. Transcutaneous PO₂ (TcPO₂) (model 632; Kontron, Zurich, Switzerland) was monitored in all neonates. Continuous descending aortic blood pressure and heart rate were monitored through the umbilical arterial catheter, which was connected to a pressure transducer (model P 23ID; Gould Statlam, Oxnard, Calif) and a polygraph recorder (model 7D; Grass Instruments Co, Quincy, Mass). Arterial blood samples were obtained for measurement of serum phenobarbital concentrations and hematocrit values. Intermittent arterial blood gas determinations correlated with simultaneously obtained TcPO₂ values.

Although Doppler blood flow velocity measurements do not equal absolute blood flow, Hansen et al previously demonstrated a linear correlation between cerebral blood flow measured by radionuclide-labeled microspheres and area under the velocity curve (AUVC). Therefore, Doppler blood flow velocity can be used to provide a noninvasive estimate of cerebral blood flow in very low-birth-weight human infants.

In the present study, our intent was not to measure absolute changes in cerebral blood flow before and after endotracheal suctioning; rather, we used cerebral blood flow velocity as an estimate of cerebral blood flow and expressed the data as changes with reference to a procedure (endotracheal suctioning) and an intervention (treatment with phenobarbital). Doppler blood flow velocity measurements were performed on the left anterior cerebral artery with a continuous-wave form bidirectional Doppler velocimeter (model BV 318; Sonicaird, Fredericsburg, Va). Doppler blood flow velocity tracings were taken over the anterior fontanel by applying ultrasound transmission gel (Aquasonic; Parker Laboratories Inc, Orange, NJ) to the scalp and using a handheld 8-MHz pencil probe. The probe was directed on the parasagittal plane and adjusted to allow maximal audiometric output determined with earphones. Recordings were made just before and immediately after 3 consecutive endotracheal suctioning procedures spaced 2 hours apart. Ten cardiac cycles taken within 30 seconds of any given period with the highest peak systolic velocity tracings were analyzed to determine AUVC, peak systolic blood

study (P = .72, ANOVA, main effects for endotracheal suctioning). Mean arterial blood pressure increased after endotracheal suctioning before but not after phenobarbital treatment was administered (P = .01, ANOVA, interactions for the effect of phenobarbital treatment on the response to suctioning). Mean arterial blood pressure was higher after endotracheal suctioning before treatment with phenobarbital than after treatment. As shown in Figure 2, there was a statistically significant increase in AUVC per minute in response to suctioning before but not after treatment with phenobarbital (P = .03, ANOVA, interactions for the effect of phenobarbital treatment on the response to suctioning). Phenobarbital treatment lowered the overall PSBFV response to endotracheal suctioning (P = .02, ANOVA, interactions for the effect of phenobarbital treatment on the response to suctioning). There were no significant changes in the EDBFV values during the study (P = .13, ANOVA, main effects for endotracheal suctioning).

To demonstrate the modulating effect of phenobarbital therapy on the values before and after endotracheal suctioning, the values after suctioning were subtracted from those before suctioning for each procedure. As shown in Figure 3, there was a decrease in the differences for MABP 2 and 4 hours after treatment with phenobarbital (F = 6.20; P = .01, ANOVA). There were decreases in the differences for AUVC (P = .04, ANOVA) and PSBFV (P = .03, ANOVA) 4 hours after treatment with phenobarbital compared with the differences before phenobarbital had been given. The EDBFV differences did not change after phenobarbital administration (P = .39, ANOVA) (data not shown).

The purpose of our study was to examine the effects of phenobarbital administration on changes in anterior cerebral artery blood flow velocity resulting from endotracheal tube suctioning in ventilated very low-birth-weight neonates. We found that (1) endotracheal suctioning was associated with decreases in TcPO₂ and increases in MABP and AUVC per minute and (2) treatment with phenobarbital attenuated the increases in
flow velocity (PSBFV), and end-diastolic blood flow velocity (EDBFV).

At the time of the original study, measures were made by tracing the velocimeter curves using a handheld device. After computerized techniques had become available, the tracings were reanalyzed by digitalizing the original velocimeter tracings to improve on the accuracy of our original findings. Each cardiac cycle tracing was digitalized into 300-dpi images in “.pcx” format using a scanner (MF5-6000CS Flatbed Image Scanner; Mustek Inc, Irvine, Calif) and imaging software (Picture Publisher, version 4.0ak; Micrografx, Richardson, Tex). The images were then calibrated and further digitalized (UN-SCAN-IT software; Silk Scientific Inc, Orem, Utah) into data by manually tracing the velocimeter tracings with points placed in the middle of each curved line. Between 199 and 314 points were manually placed for each tracing. The AUVC was measured using the trapezoidal rule of area measurement and then corrected to square centimeters per minute using the heart rate determined for each cardiac cycle imaged. The PSBFV was measured in centimeters per second as the lowest Y-value on the velocimeter curve, and the EDBFV was measured in centimeters per second as the lowest Y-value at the end of each cardiac cycle. The measurements obtained from the 10 cardiac cycle tracings for each period were then averaged. These means were then used for the statistical analysis.

To test the reproducibility of the digitalization and measuring procedures of the Doppler blood flow velocity curve tracings, one cardiac cycle was scanned 24 separate times, evenly distributed among the other cycles that were scanned. The mean AUVC for the test tracings was 78.5 cm²/min (range, 77.6-79.1 cm²/min). The coefficient of variation for the intraintralibility of the Doppler velocity digitalization and measuring procedures was 0.12%.

INTERVENTION PROCEDURES

Consistency of the endotracheal suctioning was maintained by one of us (G.H.B. or B.S.B.) performing the procedure. One milliliter of sterile isotonic sodium chloride solution was placed into the endotracheal tube. The neonate’s head was turned to the right; 3 insufflations were given with 100% oxygen through a ventilation bag, and a suction catheter was used to suction the endotracheal tube for approximately 3 seconds. This procedure was then repeated with the head turned to the left.

Immediately before and after the suctioning procedure, TcPO₂, heart rate, MABP, and left anterior cerebral artery blood flow velocity were measured. Immediately after the first suctioning procedure and measurements, arterial samples were obtained for determination of hematocrit values. Thereafter, phenobarbital, 20 mg/kg body weight, was given intravenously. The endotracheal suctioning procedure and the measurements before and after suctioning described above were repeated 2 and 4 hours after phenobarbital administration. Immediately after the last suctioning procedure and measurements, arterial blood samples were obtained for measurement of serum phenobarbital concentrations and hematocrit values.

STATISTICAL ANALYSIS

Repeated-measures analysis of variance (ANOVA) with 2 repeated factors was used to analyze the effects of endotracheal suctioning and treatment with phenobarbital on changes in TcPO₂, heart rate, MABP, AUVC, PSBFV, and EDBFV during the studies. When a significant difference was found by ANOVA, the Newman-Keuls post hoc test was used to identify specific differences. To determine the modulating effect of phenobarbital on the MABP, AUVC, PSBFV, and EDBFV on changes before and after endotracheal suctioning, the values after suctioning were subtracted from those before suctioning for each procedure; the differences at the 3 periods were then compared by ANOVA for repeated measures. When a significant difference was found by ANOVA, the Newman-Keuls post hoc test was used to detect differences among the 3 suctioning procedures. All values are expressed as mean ± SEM. Differences were considered statistically significant at $P<.05$. For all tests, 2-tailed values were used.

MABP, AUVC per minute, and PSBFV but not the decreases in TcPO₂ after endotracheal suctioning. Therefore, phenobarbital therapy modulates the response of anterior cerebral artery blood flow velocity to endotracheal suctioning in very low-birth-weight neonates.

Our findings are consistent with those of previous studies that demonstrated that suctioning of the endotracheal tube in ventilated premature infants and dogs results in significant increases in MABP and decreases in arterial oxygen tension. However, the reductions in TcPO₂ after endotracheal suctioning were not in the hypoxic range, most likely because our suctioning procedures were standardized. Endotracheal suctioning was performed in a controlled fashion by the investigators, and 100% oxygen was administered via bag ventilation, thus potentially limiting the reductions in systemic oxygenation in response to suctioning. Others also found that administration of supplemental oxygen attenuates hypoxia during tracheobronchial hygiene.

Our findings are also consistent with those of previous studies that have shown that phenobarbital administration temporarily abolishes the hypertensive peaks in arterial blood pressure in stressed premature infants and attenuates the rise in mean aortic blood pressure in response to routine nursery procedures. However, phenobarbital treatment did not attenuate the reductions in TcPO₂ in response to suctioning.

Consistent with previous findings, endotracheal suctioning was associated with a 21% increase in anterior cerebral Doppler blood flow velocity (AUVC) before phenobarbital was administered.

The mechanism for the increase in cerebral blood flow velocity with suctioning cannot be ascertained with certainty from our study. Although the increase in blood flow velocity was associated with an increase in MABP and a decrease in TcPO₂ during endotracheal suctioning, it is unlikely that the changes in these variables account for the increase in cerebral blood flow velocity with suctioning in our very low-birth-weight neonates. Autoregulation of brain blood flow is an important homeostatic mechanism by which perfusion is maintained relatively constant over a wide range of systemic blood pressures in
adults. Consequently, cerebral blood flow increases in response to changes in systemic blood pressure only when the cerebral circulation becomes pressure passive. Although the range of autoregulation is relatively narrow in the premature fetal lamb and newborn, the precise range of autoregulation in very low-birth-weight infants is not known. Nevertheless, the increase in MABP that we observed after suctioning was most likely within the range of autoregulation for low-birth-weight neonates, and the mean increase in blood pressure from 32 to 38 mm Hg was most likely not sufficient to exceed the autoregulatory range of these neonates.

The reduction in TcPO₂ from a mean of 9.6 to 6.8 kPa in response to suctioning did not reach the hypoxic range. In the early neonatal period (age 8-12 hours), this level of oxygenation was most likely sufficient to provide the neonates with adequate systemic oxygenation. Nevertheless, the cerebral circulation is sensitive to changes in arterial oxygen content. Although the modest decreases in TcPO₂ might have been sufficient to reduce the arterial oxygen content such that cerebral blood flow, reflected by AUVC, increased to maintain cerebral oxygen delivery constant. Although the modest increases in MABP, per se, most likely did not exceed the autoregulatory range in these neonates, we cannot rule out the possibility that the decreases in TcPO₂ with potential secondary effects on cerebral blood flow velocity, along with the increases in MABP, might have impaired cerebral autoregulation in these very low-birth-weight neonates.

Several other mechanisms might have accounted for the suctioning-related increases in Doppler blood flow velocity in our very low-birth-weight neonates. Endotracheal suctioning might have shifted the behavioral state of our neonates to a more alert state. In the perinatal period, state-related increases in brain blood flow have been reported. In addition, endotracheal suctioning also simulates sympathtoexcitatory receptors in the large airways and results in increased sympathetic activity.

Treatment with phenobarbital attenuated the increases in MABP and Doppler blood flow velocity but did not affect the reductions in TcPO₂ associated with endotracheal suctioning. As outlined earlier, it is unlikely that the increase in MABP resulted in a pressure-passive increase in Doppler blood flow velocity in our neonates. Consequently, the decrease in MABP after phenobarbital treatment and endotracheal suctioning cannot account for the lack of increase in anterior cerebral Doppler blood flow velocity (AUVC) after phenobarbital therapy and endotracheal suctioning.

The mechanism(s) by which phenobarbital attenuated the increases in Doppler blood flow velocity in re-
response to endotracheal suctioning cannot be determined by our study. Nonetheless, several mechanisms might have accounted for the decreases in blood flow velocity after phenobarbital treatment. Phenobarbital has been shown to decrease cerebral oxygen consumption in newborn piglets, to decrease brain glucose utilization in adult humans, and to increase smooth muscle vascular tone in vitro. In addition, reductions in cerebral blood flow and metabolic rate of oxygen have been demonstrated in adult humans during deep sleep. Thus, the sedative effect of phenobarbital also might have affected blood flow velocity by altering the sleep-wake state in our very low-birth-weight neonates and/or by attenuating alert/awake state-related increases in brain blood flow that might have accounted for the decreases in blood flow velocity after phenobarbital treatment.

We conclude that endotracheal suctioning of very low-birth-weight neonates results in significant decreases in TcPO\textsubscript{2} and increases in MABP and anterior cerebral blood flow velocity. Phenobarbital treatment modulates these changes by abolishing the effects of endotracheal suctioning on MABP and anterior cerebral blood flow velocity.

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