Effect of Mydriatics on Blood Pressure in Premature Infants

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Premature infants treated with oxygen concentrations exceeding room air are at risk of developing retrolental fibroplasia (RLF). Since binocular indirect ophthalmoscopy is required to detect the early retinopathy in these premature infants, safe and effective pupillary dilatation becomes an integral factor in diagnosing the acute retinopathy of prematurity. We performed two independent studies to assess the vasopressor activity of topical mydriatics in premature newborns. The first investigation (Study 1) was performed using standard mydriatic agents in triple instillations. The second study utilized a single combination mydriatic which had not previously been available on the premature nurseries at North Carolina Memorial Hospital, Chapel Hill, North Carolina. Data from both protocols comprise the present report.

Materials and Methods

Study 1: Mydriasis was achieved by multiple drop instillation (3) in 52 premature infants considered at risk of developing retrolental fibroplasia. Twenty similar premature infants from the same nursery comprised the control group (Table 1). The treatment group received one drop of aqueous phenylephrine 2.5% onto each eye followed within one minute by a single instillation of tropicamide 1.0%. Each infant received an additional drop of each agent at approximately five and ten minutes. Because of its effectiveness in inducing mydriasis, this triple instillation had become the standard dilatation regimen for premature infants at North Carolina Memorial Hospital. The control infants received three instillations from an identical appearing bottle containing normal saline. Nurses who were unaware of the treatment regimen measured systolic blood pressures over the brachial artery using a 4.5 centimeter cuff and doppler ultrasonic device. The blood pressures were measured prior to drop instillation for both the controls and treatment groups and again at approximately 5, 15, 30, 45, and 60 minutes after the third instillation.

Study 2: The mydriatic combination contained final concentrations of aqueous phenylephrine 2.5%, tropic-
mide 0.5% and cyclopentolate 0.5% as described by Caputo. The mydriatic was coded “A” while an identical bottle coded “B” contained sterilized isotonic saline. Thirty premature infants comprised the study group (Table 2). Control systolic blood pressures were determined prior to drop instillation. Infants were randomly assigned to receive a single instillation into each eye from either bottle “A” or “B”. Systolic blood pressures were recorded at 5, 15, 30, 45 and 60 minutes. Each infant then received onto each eye one drop of the alternate solution, and systolic blood pressures were recorded again at 5, 15, 30, 45 and 60 minutes. The data presented herein represents the mean ± standard errors of systolic blood pressures.

Results

Study 1: There was no significant difference in the level of prematurity between the treated and the controlled groups (Table 1). The systolic blood pressure was increased 3.9 ± 2.0 (mean ± S.E.) mm Hg at 15 minutes in the treated group (Figure 1). To minimize the possibility that significant increases in blood pressure in the treated group were obscured by lower control blood pressures, 20 treated infants were matched to 20 control infants for initial systolic blood pressure, race and sex. When the data were reevaluated by these matching criteria, no significant increase in systolic blood pressure occurred (Figure 2). Though no signifi-
cant increases in systolic blood pressure occurred, an acute elevation in blood pressure occurred after topical phenylephrine 2.5% which will be described in the following brief case report.

CASE REPORT

A 28-week, 964 gm Caucasian male received mydriatics on day 37 of life, aqueous phenylephrine 2.5% and mydriacyl 1% one drop of each approximately every five minutes for three instillations. Routine indirect ophthalmoscopy was safely performed which revealed retinopathy of prematurity stage 1A (right eye). The infant was therefore re-examined seven days later (44 days of life) using the same dilatation regime. Within 15 minutes of the third instillation, systolic blood pressure rose from a baseline 63 mm Hg to 98 mm Hg. The infant became pale, hypotonic and had a tachycardia exceeding 200 beats per minute. Respirations were irregular with occasional periods of apnea requiring manual ventilation with bag and mask. Systolic blood pressure remained elevated for 150 minutes with the maximum level being 108 mm Hg at 120 minutes. By 180 minutes the blood pressure, pulse, respiration and clinical appearance had all returned to baseline levels (Figure 3).

Study 2: In the thirty infants who received the combination mydriatic in randomized, double-masked fashion, there was no significant increase in systolic blood pressure at 5, 15, 30, 45 and 60 minutes after receiving the mydriatic, when compared to normal saline (Figure 4). Maximum pupillary dilatation appeared between 75-90 minutes after instillation such that adequate indirect ophthalmoscopy could be performed at 120 minutes.

Discussion

Drugs administered with the intention of inducing only a local action are often absorbed in sufficient quantities to cause hazardous systemic effects. Phenylephrine, a direct-acting sympathomimetic amine, causes peripheral vasoconstriction as well as increased systolic and diastolic blood pressure. Fraunfelder, using data supplied to the National Registry of Drug-induced Ocular Side-effects, has reported adverse effects of 10% phenylephrine to be severe hypertension, subarachnoid hemorrhage, and ventricular arrhythmias in 32 adults whose ages ranged from 44-78 years. Myocardial infarctions, associated with arrhythmias and hypertension were reported in 15 subjects, 11 of whom died. Similarly, acute pulmonary edema and hypertension has been cited in an infant with a ventricular septal defect after a single instillation of 10% phenylephrine topically in each eye.

Two small, double-masked studies utilizing 12 infants each have emphasized the pressor effects of topical 10% phenylephrine. In each study systolic blood pressures were increased a mean 12-14 mm Hg within 15 minutes.
after a single drop of 10% phenylephrine to each eye. Neither report documented elevations of blood pressure after single instillations of 2.5% phenylephrine. Caputo, using triple instillations of 10% phenylephrine in each eye to six neonates, produced increases in blood pressures from 10-26 mm Hg at 30 minutes. Though Carpé reported no pressor effects in 25 neonates after single instillations of 10% phenylephrine, France later pointed out that these systemic effects had probably been missed by the investigators. Caputo, using 12 neonates (mean birth weight = 2163.3 ± 103.2 gm and gestational age of 36.7 ± 0.9 weeks) found no increase in systolic blood pressure after triple instillation of 2.5% phenylephrine.

Our study in 52 infants of significantly lower birth weight similarly showed no statistically significant increase in systolic blood pressure. The one instance of acute hypertension after triple instillations of 2.5% phenylephrine occurring in an infant whose birth weight was 964 gm reemphasizes the vasoconstrictor effects of this alpha adrenergic stimulant. If the body mass of this neonate on the 44th day of life was estimated to be approximately 1 kg, then six drops from commercial ophthalmic preparations would deliver volumes varying between 40-70 μL. It has been estimated that six drops of theoretical 50 μL each would deliver a total 7.5 mg to the 1 kg infant assuming 100% absorption. This dosage would be equivalent to a 15 times overdose if the same drug had been administered systemically. It is therefore clear from the present study as well as others that low-dose single instillation mydriatics are safe and effective for both mydriasis and cycloplegia in neonates. Combinations such as we used in Study 1, though usually safe, may be associated with occasional adverse reactions. We do not completely understand why hypertension developed in a patient who had not responded in that manner one week earlier. Though our data suggests that multiple instillations are usually safe, we cannot explain the hypertensive crisis that occurred in the second day’s examination. The mydriatic effect from the single instillation was equal to the multiple instillations in this study. These observations in low birth weight neonates reemphasizes the fact that 2.5% phenylephrine produces the same mydriatic effect as the 10% solutions. In a study involving 32 adults, it was demonstrated that less than 0.5 mm mydriasis was achieved when concentrations of phenylephrine were increased from 5% to 10%. Since there is no increase in mydriatic effect with increased concentration, their small body mass places the premature neonates at increased risk of phenylephrine overdose from multiple topical instillations. Therefore, it seems prudent to use the least concentration, yet the most effective combination of mydriatics for routine indirect ophthalmoscopy on premature infants suspected of having retinopathy of prematurity.
Summary

Systolic blood pressure (SBP) was measured by doppler methods at 5, 15, 30, 45, and 60 minutes in 52 premature infants after triple instillation of aqueous phenylephrine 2.5% and tropicamide 1.0%. Systolic blood pressures were insignificantly increased 3.9 ± 2.0 mm Hg (mean ± S.E.) at 15 minutes when compared with controls matched for initial blood pressure, birth weights and age at examination. Though a 964-gm, 28-week Caucasian male with retinopathy of prematurity had an uneventfully dilated, pupillary dilatation one week later with triple instillations of phenylephrine 2.5% and tropicamide 1.07% was accompanied by an acute increase in systolic blood pressure to 108 mm Hg at 15 minutes, which remained elevated for 150 minutes. A new lower dose, single instillation mydriatic became available whose final concentration was phenylephrine 2.5%, tropicamide 0.5% and cyclogyl 0.5%. A single drop was found to produce mydriasis equal to the triple instillation regime. The single administration produced no significant effect on systolic blood pressure in 30 low birth weight infants (birth weight less than 1750 gm) when compared with balanced salt solution (placebo) in a randomized, double-masked study. Mechanisms of acute hypertension after topical mydriasis are discussed.

References