Anesthesiology
64:812–814, 1986

Phenylephrine Eyedrops and Anesthesia

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Ophthalmic phenylephrine is widely used in the perioperative period to induce pupillary dilatation. During the last decade a number of case reports and controlled studies have elucidated the potential effects of phenylephrine eyedrops and helped to define the limitations and the safe dosage of ophthalmic phenylephrine.[1–5] These studies have a bearing on the practice of anesthesiology and an understanding of the effects of different concentrations of ophthalmic phenylephrine may improve anesthetic care. Two cases are presented in which ophthalmic phenylephrine led to hemodynamic changes in anesthetized patients.

REPORT OF TWO CASES

Patient 1. A three-week-old, 3.5 kg, healthy neonate underwent a congenital cataract extraction. No premedication was given. Monitors (ECG, blood pressure (BP) cuff with Doppler transducer, precordial stethoscope, and temperature probe) were applied as general anesthesia was induced and maintained with halothane (up to 2%) in an oxygen (2 l) and N_20 (4 l) mixture by mask. An intravenous infusion of 5% dextrose with lactated Ringers was administered while the ophthalmologist instilled two drops of 10% phenylephrine hydrochloride in the left eye. Glycopyrrolate, 0.05 mg, and succinylcholine, 1.5 mg/kg, were given intravenously and the trachea was intubated under direct vision. Endotracheal tube placement was confirmed by the presence of bilaterally equal breath sounds and symmetrical chest movements. Three to five minutes after intubation, the patient slowly turned dusky, then cyanotic with acrocyanosis being particularly pronounced. Endotracheal tube placement and patency were again confirmed. Continuous oxygen monitoring established the delivery of an adequate fraction of inspired oxygen. Anesthetic gases were discontinued and hyperventilation with 100% oxygen was instituted. Blood pressure, using a Doppler sensor on the upper extremity, was unobtainable, although temporal artery pulsations were present. The ECG indicated a progressive slowing of the heart rate, decreasing from 160 to 60 beats/min. S-T segment depressions and T wave changes were obvious. Both pupils were dilated. Periorbital edema and erythema, with patches of blanching, were noted on her left eyelids. During the ensuing 10 min, the patient's color gradually improved; pulses and blood pressure became obtainable. Her heart rate (HR) increased and the ECG changes, S-T segment depressions, and T wave changes disappeared. The pupillary diameters did not change. According to the ophthalmologist, the neonate had received 2.5% phenylephrine, cyclopentolate, and tropicamide eyedrops on three occasions during the preceding 24 h, the last dose being administered 3 h earlier. The patient awoke, was evaluated, and then reanesthetized with halothane in an oxygen–nitrous oxide mixture. The remainder of the anesthesia and surgery was uneventful.

Patient 2. A 54-yr-old woman was admitted for a vitrectomy. Her medical diagnosis comprised stable chronic renal insufficiency, diabetes controlled with insulin for 17 yr, and long-standing hypertension that was controlled with prazosin 1 mg tid. During the previous 11 months she was hospitalized twice for congestive heart failure and was treated with digoxin and increasing doses of furosemide. On admission, physical examination appeared normal without evidence of pulmonary or cardiac disease. Her weight was 75 kg and her height was 1.65 meters. Blood pressures were 140–180/70–90 mmHg. A chest x-ray indicated clear lung fields and absence of cardiac enlargement. The ECG was consistent with an old inferior myocardial infarction. Pertinent serum values consisted of a fasting glucose of 280 mg/dl, creatinine 2.4 mg/dl, blood urea nitrogen 38 mg/dl, and electrolytes within a normal range. She received no premedication. In addition to the standard external monitors, a Swan Ganz catheter and a radial arterial line were placed prior to induction of general anesthesia. Hemodynamic parameters while awake included radial arterial BP of 170/90 mmHg, pulmonary artery pressures (PAP) of 30/10 mmHg, pulmonary capillary wedge pressures (PCWP) of 9 mmHg, and an HR of 80/min in sinus rhythm. Anesthesia was induced with diazepam, 12.5 mg, fentanyl, 0.5 mg, and isoflurane vaporized in oxygen delivered by mask. Relaxation was obtained with pancuronium, 5 mg. Radial arterial pressures stabilized at 140/80 mmHg, PAP at 20/9 mmHg, and HR at 65/min. Direct laryngoscopy was performed and 160 mg of lidocaine was applied to the larynx and trachea using a laryngotracheal injector. Hemodynamic stability continued during the subsequent intubation and positioning of the patient, which took 20 min. During the surgical preparation, however, two drops of 10% phenylephrine hydrochloride were applied to her left eye. Within minutes the BP increased from 125/70 to 200/90 mmHg, PAP increased to 45/32 mmHg, and the PCWP increased to 30 mmHg. The ECG demonstrated an increase in HR of 70 to 95/min in sinus rhythm, without obvious ischemic changes in limb or precordial (V_5) ECG leads. These acute changes were treated with nasal nitroglycerin and increasing concentrations of isoflurane. Over a 5- to 10-min period, the BP, PAP, PCWP, and HR returned to values within the normal range. The remainder of the operation and the postoperative course were uneventful.

DISCUSSION

In the first patient, severe peripheral vasoconstriction and reflex bradycardia occurred. Increased cardiac afterload may have induced left ventricular distention and subendocardial ischemia leading to cardiac failure and hypotension. Laboratory evidence suggests that even normal ventricles will fail when depressed by halothane and afterloaded with phenylephrine.[6,7] Alternatively, phenylephrine may have caused coronary artery spasm, myocardial ischemia, and cardiac failure. The absence of

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Received from the Department of Anesthesiology, University of Michigan Hospitals, Ann Arbor, Michigan 48109. Accepted for publication January 7, 1986.

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Key words: Anesthesia: ophthalmic. Complications: hypertension. Pharmacology, vasoconstrictor: phenylephrine eyedrops.

peripheral pulses is consistent with either hypotension or hypertension. A Doppler flow probe will, however, detect flow in both conditions.[8] Ten per cent phenylephrine is not recommended in neonates and infants.†

In the second case, sufficient phenylephrine was absorbed systemically to induce vasoconstriction leading to hypertension, thereby increasing left ventricular afterload with resultant left ventricular failure as evidenced by a PCWP of 30 mmHg. During halothane and isoflurane anesthesia, intravenous phenylephrine increases the incidence of myocardial segmental wall motion abnormalities, which is suggestive of myocardial ischemia. Increased myocardial wall tension and/or alpha-mediated coronary vasoconstriction are thought to be the cause.[9]

Phenylephrine hydrochloride is a powerful, predominantly direct-acting, $alpha_1$ receptor stimulant with little effect on $alpha_2$ or beta receptors. The distribution of $alpha_1$ receptors comprises the myocardium and the coronary arteries, although their physiologic role proves complex and is not fully elucidated.[10] Cardiovascular actions of phenylephrine feature vasoconstriction of the systemic, pulmonary, and coronary arteries with decreased cardiac output and reduced renal, splanchnic, cutaneous, and limb blood flow. Mydriasis and shrinkage of mucous membranes occur after both local and systemic applications.[11] The duration of action after intravenous administration of therapeutic doses lasts from 15 to 20 min. The predominant site of inactivation after parenteral administration is the monoamine-oxidase system in the liver. Phenylephrine's pressor response is potentiated by oxytocics, monoamine-oxidase inhibitors, tricyclic antidepressants, reserpine, and guanethidine.[12]

Systemic effects of phenylephrine eyedrops range from occipital headache and dysrhythmias to angina, myocardial infarction, cardiac arrest, and death.[1,13,14] Patients with cardiovascular disease, diabetes mellitus, and autonomic neuropathies as well as infants and geriatric patients are more prone to experience systemic effects.[1,3] Two double-blind studies of awake neonates weighing 907 to 4350 gm found a consistent hypertensive effect and blanching response after the administration of 10% phenylephrine eyedrops.[2,15] No hypertensive responses were observed in the control groups receiving either normal saline or 2.5% phenylephrine eyedrops. Since complete mydriasis was achieved with the 2.5% solution within 25 to 30 min, only one drop of 2.5% phenylephrine per eye is recommended by the authors.[15] Blanching of the skin after ocular and cutaneous administration of even 2.5% phenylephrine was noted in this study. In the second study a single eyedrop combination of 2.5% phenylephrine, 0.5% cyclopentolate, and 0.5% tropicamide provided maximal mydriasis in 60 min. This drug combination had a mydriatic effect superior to the effects of the agents administered individually. No systemic effects were observed. On the other hand, in a third study, 80% of awake, low-birthweight neonates had a hypertensive response when given even 2.5% phenylephrine eyedrops. Tropicamide and cyclopentolate, when given alone or in combination, provided adequate mydriasis.[3] These cycloplegics are effective mydriatic, atropine-like agents with a shorter onset and duration of action than atropine, lacking the cardiovascular properties of phenylephrine.[11]

Two prospective trials, which included mildly hypertensive and diabetic patients, revealed minor changes of hemodynamic parameters in awake patients treated with 10% phenylephrine. Headaches, however, did develop in the absence of blood pressure increases.[16,17] When ophthalmic phenylephrine is administered to awake adults with autonomic nervous system dysfunction or moderate to severe cardiovascular disease, it elicits different hemodynamic responses. In patients with idiopathic orthostatic hypotension, one drop of 2.5% phenylephrine in each eye caused an average pressor response of 44/27 mmHg with an average maximum pressure of 204/107 mmHg. Blood pressure rose within 10 min and lasted at least 60 min.[18] Ten per cent ophthalmic phenylephrine administered in the preoperative period consistently led to pressor responses in patients with insulin-dependent diabetes.[19] Hypersensitivity to exogenous catecholamines is common in patients with autonomic dysfunction such as the Shy-Draeger and Riley-Day syndromes, parkinsonism, amyloidosis, and high spinal cord injuries.[20,21] A high incidence of autonomic dysfunction is present in diabetic patients with a long history of exogenous insulin use.[22]

Systemic drug absorption after ocular administration is thought to occur mainly *via* the nasal mucosa after passage through the lacrimal system.[23] Therefore, maneuvers aimed at closing the puncta of the lacrimal ducts are advocated in order to reduce systemic absorption. Closure of the eyelids over administered drops entraps the drug under the lids and enhances absorption.[24] Although the corneal and conjunctival epithelium is relatively impermeable under physiologic condition, trauma, instrumentation, inflammation, and medications such as proparacaine, phenylephrine, and benzalkonium chloride can damage the epithelium, leading to increased permeability.[4,25] Once epithelial permeability has increased, systemic uptake of ocularly applied medications might be enhanced by the conjunctival hyperemia induced by general anesthesia. Furthermore, mydriatic eyedrops irritate the unanesthetized eye and induce lacrimation, blinking, and squeezing of eyelids.[4] These reflex responses change the systemic absorption of the eyedrops by dilution and dispersion, leading to reduced absorption if overflow onto

† American Hospital Formulary Service Drug Information. Bethesda, MD, American Society of Hospital Pharmacists, 1984.

the cheeks occurs or increased absorption if drainage through the nasolacrimal system predominates. General anesthesia abolishes such reflexes and reduces lacrimation.[26] Considering its potential for adverse responses, alternatives to 10% phenylephrine eyedrops are preferable. In adults, wide (7 mm) pupillary dilatation can be obtained with a single drop of combinations of 0.5% cyclopentolate and 2.5% phenylephrine or 0.5% tropicamide plus 2.5% phenylephrine within 60 min. Prior use of 0.5% proparacaine eyedrops significantly increases mydriasis.[4] Maximal mydriasis for phenylephrine solutions occurs between 60 to 90 min, with an average of 75 min. The half-time for recovery for the 1% solution is 2.66 h. Minimal additional mydriasis is obtained when solutions stronger than 5% phenylephrine are used.[5]

Conclusion

Following ocular instillation of phenylephrine, the amount absorbed systemically depends on the dosage, concentration, and the method of administration as well as on conjunctival permeability. Local and general anesthesia promote systemic uptake. In order to obtain optimal dilatation shortly after induction of general anesthesia, mydriatics and cycloplegics should be administered 30–60 min prior to induction. Adequacy of dilatation can then be assessed before induction, and supplemental doses could be given at a time when cardiovascular control is still relatively uncompromised. Administration of phenylephrine shortly after induction of general anesthesia should be discouraged, but if necessary the lowest concentrations of phenylephrine (up to 2.5%) should be used, thereby limiting the side effects and interactions with general anesthetics.

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