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Continuing Education Activity

Ephedrine is a medication used to manage and treat clinically significant hypotension. It is in the sympathomimetic class of drugs. The FDA-approved primary indication for ephedrine is the treatment of clinically significant hypotension perioperatively. Induction of general anesthesia and ongoing anesthesia during operative cases results in vasodilatation and hypotension, requiring treatment with vasopressors. This activity illustrates ephedrine's indications, action, and contraindications in treating clinically significant hypotension. This activity highlights the mechanism of action, administration, contraindications, adverse event profile, and other key factors pertinent to interprofessional healthcare team members involved in caring for patients with clinically significant hypotension and related conditions.

Objectives:

- Identify the indications for treatment with ephedrine.
- Recognize common complications of managing clinically significant hypotension intraoperatively with ephedrine.
- Identify alternative options to treat significant intraoperative hypotension.
- Apply effective interprofessional team communication to improve outcomes for the patient requiring ephedrine.

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Indications

The FDA-approved primary indication for ephedrine is the treatment of clinically significant hypotension perioperatively. Induction of general and ongoing anesthesia during operative cases results in vasodilatation and hypotension, requiring treatment with vasopressors.

It is also frequently the agent of choice for hypotension induced by spinal or epidural anesthesia. In obstetrics, sympathectomy during spinal anesthetics results in hypotension in 80% of patients. Although phenylephrine selection is due to fewer effects on umbilical arterial acidity, ephedrine is a frequent choice due to less alpha-adrenergic action on the uterine vasculature, which preserves uterine blood flow.

It is sometimes given intramuscularly to achieve a longer-lasting effect. According to the American Society of Anesthesiologists Committee Task Force on obstetric anesthesia, ephedrine or phenylephrine can be utilized to treat hypotension during neuraxial anesthesia. However, in the absence of maternal bradycardia, phenylephrine is preferred.

Since ephedrine results in both alpha and beta-adrenoreceptor stimulation, it is most beneficial in the setting of hypotension along with bradycardia or a low-normal heart rate, and caution is necessary for patients with hypotension and coexisting tachycardia. Most vasopressors used during anesthesia should be viewed as a temporizing measure while determining and addressing the source of hypotension.

Another notable indication of ephedrine is for allergy relief. Due to the constriction of smooth muscle via alpha receptor binding and bronchi dilation due to beta-2 receptor agonism, most sympathomimetics, including ephedrine, work effectively to decrease allergic symptoms.

Oral formulations of ephedrine have been used historically to treat asthma via pulmonary vasoconstriction and reduction in airway edema along with beta-induced bronchodilation, but it is rarely used for this purpose in modern medicine due to unwanted cardiac effects and availability of more selective beta-agonists such as albuterol. Ephedrine is also available in a fixed-dose combination with guaifenesin to temporarily relieve mild asthma symptoms with an expectorant.

Other off-label indications include bronchoconstriction, myasthenia gravis, and weight loss(in the past). In the early 2000s, the drug became very popular among over-the-counter supplements because it was found to work synergistically with caffeine to promote weight loss by stimulating metabolism. However, ephedrine lost favor as a supplement after research established links to ventricular arrhythmias, nausea, and psychiatric issues with use.

Patients with myasthenia gravis may also benefit from treatment with ephedrine; however, evidence for its specific mechanism of action and benefit in this disease has not come from randomized controlled trials, and only observational and non-randomized trials are currently available. Lastly, case reports demonstrate using ephedrine to alleviate bronchoconstriction during induction for patients on beta-blocker maintenance therapy.

Mechanism of Action

Ephedrine, a stereoisomer to better-known pseudoephedrine, is a sympathomimetic amine with unique effects due to its indirect mechanism than other sympathomimetic agents like pseudoephedrine and phenylephrine. Ephedrine acts as both a direct and indirect sympathomimetic. It binds directly to both alpha and beta receptors; however, its primary mode of action is indirectly achieved by inhibiting neuronal norepinephrine reuptake and displacing more norepinephrine from storage vesicles. This action allows norepinephrine to remain in the synapse longer to bind postsynaptic alpha and beta receptors.

Ephedrine's indirect mechanism results in a sustained or even increased heart rate due to norepinephrine's ability to bind alpha and beta receptors, whereas more direct sympathomimetics like phenylephrine results in reflex bradycardia. While the indirect effect is most profound on arterial blood pressure, the direct vasoconstricting action functions more on the venous system. It is, therefore, effective in elevating central venous pressure when the patient is challenged with fluids.

Stimulation of alpha-1-adrenergic smooth muscle receptors within vasculature results in a rise in systemic vascular resistance and, consequently, systolic and diastolic blood pressure. Direct stimulation of beta-1 receptors by ephedrine and norepinephrine increases cardiac chronotropy and inotropy. Finally, beta-2-adrenergic receptor stimulation in the lungs results in bronchodilation with ephedrine administration, though it is not as pronounced as its cardiovascular effects.

Pharmacokinetics

Absorption: Oral ephedrine attains peak plasma concentration at 1.8 hours and has a bioavailability of 88%.

Distribution: Oral ephedrine has a volume of distribution of 215.6 Liters. Ephedrine can cross the placental barrier.

Metabolism: Ephedrine is metabolized into norephedrine. The parent drug and its metabolite are both excreted in the urine.

Elimination: Limited clinical data after intravenous administration of ephedrine endorses similar observations of urinary excretion. The plasma elimination half-life of ephedrine after oral administration is approximately 6 hours. The urinary excretion of ephedrine is increased in acidic urine. nephrolithiasis induced by an excessive dose of ephedrine has been treated with urinary alkalinization.

Administration

Dosage Formulations

- Ephedrine sulfate oral tablet: 25 mg
- Ephedrine hydrochloride intravenous solution: 23.5 mg/5 mL
- Ephedrine sulfate intravenous solution: 5 mg/mL; 50 mg/mL
- Fixed dose combination of oral ephedrine hydrochloride 12.5 mg/guaifenesin 200 mg

For the treatment of asthma, 25 mg tablets are used every four hours as needed, and the maximum dose should not exceed 150 mg in 24 hours. For adults, bolus dose recommendations are 5 to 10 mg, and intramuscular doses for a prolonged desired effect are 25 to 50

mg. Ephedrine requires dilution before intravenous use.

When treating hypotension, cardiovascular effects via the indirect mechanism depend on adequate native norepinephrine stores. Tachyphylaxis will develop with prolonged and repeated use as this depletes endogenous norepinephrine stores. For this reason, it is administered in intravenous boluses when used intravenously and rarely as a continuous infusion.

Specific Patient Populations

Patients with Hepatic Impairment: No dosage adjustments have been provided in the package insert. Use with caution.

Patients with Renal Impairment: According to the manufacturer's prescribing information, ephedrine and its metabolite are excreted in the urine. In patients with kidney disease, excretion of ephedrine is affected with a corresponding increase in elimination half-life, which will lead to the slow elimination of ephedrine and consequently prolonged pharmacological effect and potential adverse reactions. Therefore, carefully monitor patients with renal impairment after the initial bolus dose for adverse events.

Pregnancy Considerations: Though ephedrine is frequently used in obstetric patients just before and during delivery, there is insufficient data to support using the drug in earlier stages of pregnancy, and no animal reproductive studies have been performed, making it a category C drug in pregnancy**.** Ephedrine should be given to a pregnant woman only if indicated.

Breastfeeding Considerations: A single published case report indicates that ephedrine is present in human breast milk. Nonetheless, no information is available on the effects of ephedrine on the breastfed infant or the effects on milk production. Clinicians should consider the risk-benefit analysis for the mother's clinical requirement for ephedrine and adverse reactions in the breastfed child from ephedrine. Administration to the nursing women is not recommended as there is a higher-than-usual risk for infants, according to the package insert.

Pediatric Patients: The FDA has not formally established safety and effectiveness in pediatric populations. However, it is used off-label to treat hypotension induced by anesthesia.

Elderly Patients: The dose of ephedrine should be initiated at the low end of the dosing range, considering the higher frequency of decreased hepatic, renal, or cardiac function.

Adverse Effects

Ephedrine may produce palpitations, headache, dizziness, nausea, vomiting, restlessness, and anxiety in the conscious patient. Ephedrine is also arrhythmogenic, and clinicians should be cautious when administering patients predisposed to arrhythmias or taking other arrhythmogenic

medications, particularly digitalis. When used long-term, the catecholamine excess can result in contraction band necrosis of the myocardium, which predisposes the heart to ventricular arrhythmias.

Another common effect of ephedrine is an alteration in the time until the onset and duration of action of other drugs. This effect is most notable during induction when giving ephedrine to a hypotensive patient before rocuronium.

Additionally, ephedrine may be hepatotoxic, but there seems to be unclear evidence. This idea stems from case reports where ephedra species containing several compounds resulted in liver damage instead of a direct correlation.

A less common effect experienced mostly by illicit users of ephedrine and its derivatives is the development of radiolucent urological ephedrine-containing stones and paranoid schizophrenia.

Drug-Drug Interactions

- Augmentation of the blood pressure: Clonidine, oxytocin, and propofol can increase blood pressure when administered with ephedrine.[27][28]
- Interactions that antagonize the pressor effect: α-adrenergic antagonists, β-adrenergic antagonists, and reserpine can antagonize the vasopressor effect of ephedrine.
- Guanethidine: Ephedrine may inhibit the neuron blockage induced by guanethidine, resulting in loss of antihypertensive efficacy.
- Rocuronium: Ephedrine may decrease the onset time of neuromuscular blockade when used with rocuronium for intubation if administered simultaneously. No interventions are needed.[24]
- Theophylline: Concomitant use of ephedrine and theophylline may increase nervousness and insomnia.
- Cardiac glycosides: Administering ephedrine with a cardiac glycoside, such as digitalis, may increase the likelihood of arrhythmias. Monitor patients on digoxin who are administered ephedrine.[29]

Contraindications

Ephedrine is contraindicated in a patient with acute hypertension or tachycardia. Ephedrine increases both chronotropy and inotropy and therefore increases myocardial oxygen demand, and its use requires caution in patients with ischemic heart disease or heart failure. It should also be avoided when tachycardia is undesirable, such as aortic stenosis. Alpha-adrenergic stimulation caused by ephedrine results in the contraction of the smooth muscle at the base of the bladder, resulting in resistance to urine outflow, and caution is necessary for patients with urinary retention and prostatic hyperplasia.

Ephedrine should be avoided or used with caution within 14 days of MAOI therapy due to excessive norepinephrine availability at the synapse, which could cause a hypertensive crisis through the indirect sympathomimetic effect of ephedrine.

Norepinephrine and phenylephrine are other appropriate choices to maintain blood pressure post-spinal anesthesia. Norepinephrine was shown to have fewer episodes of hypotension than ephedrine, and phenylephrine showed less extensive effects on umbilical artery acidity.

Monitoring

Although there are no specific drug monitoring requirements, variations in gene codons for receptor type can yield various sensitivities to ephedrine. Specifically, variations at codons 16 and 27 for the beta-2 adrenoreceptor have significant differences in ephedrine requirement to combat hypotension post-spinal anesthesia. Due to the variation in responses and the fact that vasoactive medications can immediately affect blood pressure, heart rate, and pulse oximetry require close monitoring.

Toxicity

According to the manufacturer's prescribing information, an overdose of ephedrine can cause a rapid rise in blood pressure. In the case of an overdose, careful blood pressure monitoring is recommended. If blood pressure rises to an unacceptable level, parenteral antihypertensive agents can be administered at the clinician's discretion.

Signs and Symptoms: The principal manifestation of ephedrine poisoning is hypertension and convulsions. A case report of cardiomyopathy and spinal artery vasospasm leading to quadriplegia has been noted.

Treatment: If respirations are shallow or cyanosis is present, secure the airway and provide mechanical ventilation.

Antidote: For hypertension, 5 mg phentolamine mesylate diluted in saline may be administered slowly intravenously, or clinicians may give 100 mg orally. Convulsions may be controlled by benzodiazepines.

Enhancing Healthcare Team Outcomes

Though anesthetists and certifiedregistered nurse anesthetists (CRNA) are some of the only providers to administer ephedrine routinely, they do not do so within a vacuum. All interprofessional healthcare team members, including physicians, mid-level practitioners, nurses, and pharmacists providing care for the patient, should know its effects and different routes of administration. When given intravenously, drug effects are often of short duration (minutes), and tachyphylaxis is common. However, if given intramuscularly, the vasopressor effects typically remain for 60 to 90 minutes.

These effects are significant in the labor and delivery ward. Patients often receive intramuscular ephedrine injections following a spinal block to attenuate the sympathectomy and nausea that frequently accompany spinal blockade. The effects of an IM injection may last much longer than the procedure itself, and nurses and clinicians should not rely on hypotension as the primary indicator of postpartum hemorrhage, as IM ephedrine may mask this sign.

When planning to use ephedrine, the pharmacist should verify the dose and that there are no significant drug-drug interactions and report these findings to the clinical team. Nursing must be mindful of the adverse effects of the drug and be prepared to inform the clinician regarding their observations. Nurse anesthetists (CRNAs) are also commonly involved in administration, so they must collaborate on dosing and administration with the pharmacist. Monitoring the patient following administration is the responsibility of all team members, and they must all be empowered to speak up if there are any concerns so interventions can be initiated if necessary.

These examples show how all interprofessional team members, including MDs, DOs, NPs, PAs, nurses, specialists, and pharmacists, can optimize outcomes related to ephedrine therapy while mitigating its adverse effects. [Level 5]

Review Questions

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