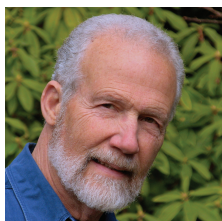


Different Outcomes Depending on Indication

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MANY DRUGS ARE USED FOR VARIOUS INDICATIONS, and a certain indication may need to be considered when drug interactions are evaluated. Sometimes different uses for a drug mean different doses or durations of therapy. For example, taking a few doses of a nonsteroidal anti-inflammatory drug (NSAID) for a minor sports injury is not likely to affect a patient's response to antihypertensive medications, whereas the use of long-term high-dose NSAIDs for osteoarthritis may result in a clinically important interaction.

Sometimes, the outcome of a drug interaction depends on the indication for one of the drugs, but the outcome is due to factors other than differences in dose or duration. For example, the interaction between epinephrine and beta-adrenergic blockers has both dose-related and non-dose-related differences in outcome depending on the indication for the epinephrine.

MECHANISM OF THE INTERACTION

Normally, epinephrine stimulates beta-1 receptors (increasing heart rate and contractility), beta-2 receptors (producing vasodilation), and alpha-1 receptors (producing vasoconstriction). The usual result is an increase in heart rate, with only a small increase in mean blood pressure because there is both beta-2 vasodilation and alpha-1 vasoconstriction. If a systemic dose of epinephrine is given after a noncardioselective beta-blocker, however, the beta-2 vasodilatory effects are blocked, leaving unopposed alpha-1 vasoconstriction, and an acute hypertensive response ensues.

This is an extraordinarily well-documented drug interaction that has been shown in dozens of studies involving healthy subjects and patients.¹⁻³ In some cases, the reflex bradycardia in response to the hypertensive reaction is severe and cardiac arrhythmias have also occurred. The hypertensive reactions to epinephrine do not occur, however, if the patient is taking a cardioselective beta-blocker. Patients on mixed alpha/beta-blockers, such as labetalol and carvedilol, also seem to be somewhat protected, probably because the alpha blockade reduces the degree of vasoconstriction.

NONANAPHYLACTIC PATIENTS

In a patient on a nonselective beta-blocker who is given epinephrine for reasons other than anaphylaxis, the indication is important because it tends to dictate the epinephrine dose. The use of epinephrine in local

anesthetics for routine dental procedures or local dermatologic procedures, such as Mohs' surgery, seems to pose little risk of a hypertensive reaction.⁴ Large amounts of local anesthetic plus epinephrine used in facial plastic surgery, however, have resulted in hypertensive reactions, as has subcutaneous epinephrine injections to treat patients with allergic reactions (but not actually in anaphylaxis).^{5,6}

ANAPHYLACTIC PATIENTS

In patients on nonselective beta-blockers who are experiencing anaphylaxis, the limited evidence available does not suggest that patients are at risk of a hypertensive reaction if given systemic doses of epinephrine. A number of case reports suggest that patients on beta-blockers who develop anaphylaxis may be less responsive, rather than hypersensitive, to epinephrine. Clinical studies of whether patients in anaphylaxis who, on beta-blockers, are resistant to treatment have been somewhat conflicting, but it remains a possibility. One confounding factor is that most studies did not differentiate between nonselective beta-blockers and cardioselective beta-blockers when assessing whether beta-blockers reduced response to epinephrine in anaphylaxis.

RECOMMENDATIONS

Consider avoiding the use of beta-blockers in patients who may be at increased risk of anaphylaxis (eg, people who carry epinephrine for self-injection). If a beta-blocker is indicated, cardioselective agents may be preferable because they do not cause a hypertensive reaction if a systemic dose of epinephrine is needed.

Experts on anaphylaxis do not recommend avoiding epinephrine in the treatment of anaphylaxis in patients on beta-blockers. They point out that beta-blockers are more likely to cause a lack of response to epinephrine than an acute hypertensive reaction.⁷

In patients on nonselective beta-blockers who have an allergic reaction, but not impending anaphylaxis, recognize that a systemic dose of epinephrine is likely to result in an immediate hypertensive response. Most patients can withstand an acute hypertensive episode without sequelae, however, so the benefit/risk of using epinephrine must be carefully weighed. Again, the concern over acute hypertension is moot if the patient is taking a cardioselective beta-blocker. ♦

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