Beta-Adrenergic Blockers + Epinephrine (Draft 2)

Order of administration	Epinephrine given in the presence of beta-blockade																														Beta-blocker given after epinephrine
Epinephrine route of administration	Inhaled	Ophthalmic Epinephrine	Epinephrine combined with local anesthetic				Injection Resulting in Systemic Epinephrine Effects																								
Dental use			Y	N																											
Dermatologic use				Y	N																										
Plastic surgery use					Y	N																									
Epinephrine indication							Patient in Anaphylaxis	Anaphylaxis Prevention	Indication Other Than Anaphylaxis (including allergic reactions not expected to lead to anaphylaxis)																						
Beta-blocker									Carteolol Levobunolol Nadolol Penbutolol Pindolol Propranolol Sotalol	Timolol					Atenolol			Bisoprolol			Esmolol		Metoprolol			Nebivolol				Betaxolol	Labetolol	Carvedilol	
Route of administration										Oral	Eye gel	Eye Drops																			
Dose > 100 mg/d?															Y	N								Y	N						
Is CrCl <40 mL/min?																Y	N	Y	N												
Dose > 20 mg/d?																			Y	N											
Dose > 300 µg/kg/mL																					Y	N									
Is patient CYP2D6 PM?												Y	N											Y	N	Y	N				
Patient taking a CYP2D6 inhibitor?													Y	N											Y	N	Y	N			
Dose > 10 mg/d?																											Y	N			
Dose 20mg/d or more?																													Y	N	
Acute hypertensive reaction is unlikely	○[1]	○[1]	○[2]	○[2]			○[5]				○[8]						○			○		○				○			○[20]	○[21]	○[22]
Hypertensive reaction may occur, but benefit likely to outweigh risk								○[6]																							
Acute hypertensive reaction is likely									◆[7]	◆[7]		◆[23]	◆[24]																		
Acute hypertensive reaction is possible					■[3]	■[4]								■[8]	■[9]	■[10]		■[10]	■[11]		■[12]		■[13]	■[14]	■[15]		■[16]	■[17]	■[18]		■[19]			

○ = No special precautions. ■ = Assess risk and take action if necessary. ◆ = Use only if benefit outweighs risk

Footnotes:

1. Inhaled or ophthalmic epinephrine can sometimes produce systemic effects, but it does not seem likely that it would result in a significant hypertensive reaction.
2. Epinephrine is often combined with local anesthetics to prolong the effect of the anesthetic. The amount used in routine dental procedures or in dermatologic practice (e.g., Moh's surgery) is unlikely to produce a hypertensive reaction with beta-blockers. One study in healthy subjects given a dental injection of lidocaine plus 45 mcg of epinephrine, pretreatment with a nonselective beta-blocker (pindolol) produced only a slight (8%) and transient increase in systolic blood pressure. Large amounts of epinephrine with local anesthetic may cause hypertensive reactions (see footnote #3 below).
3. Hypertensive reactions have been reported in patients receiving local anesthetics plus epinephrine for facial plastic surgery (for such use, go to first line of decision table and follow "Injection for Systemic Effects")
4. In most other cases where epinephrine is used with local anesthetic, the amount of epinephrine absorbed systemically would not be sufficient to produce a hypertensive reaction. But if large amounts are used (such as with facial plastic surgery) acute hypertension may occur.
5. In patients on beta-blockers who are actually in anaphylaxis, administration of epinephrine tends to have very little (positive or negative) effects. So there is general consensus that epinephrine should be given to treat anaphylaxis, but one should also be ready to use alternative measures (fluids, etc.) if the response to the epinephrine is inadequate.
6. If epinephrine is used to prevent anaphylaxis in a beta-blocker treated patient who has been exposed to a potentially anaphylaxis-producing event (e.g., a wasp sting), it is recommended to give the epinephrine as usual. Since the patient is not yet in anaphylaxis, a hypertensive reaction may occur, but the potential benefit of the epinephrine almost certainly outweighs the risk of the acute hypertensive reaction.
7. When a systemic dose of epinephrine is given to a person on one of these nonselective beta-blockers, an acute hypertensive reaction is almost certain. Systolic BPs of 250 mm/Hg are not uncommon. Most people can probably withstand a short episode of such a hypertensive reaction without permanent sequelae, but strokes have occurred in susceptible patients. Thus, it is best to avoid this reaction if possible. If a patient is likely to receive systemic epinephrine, it would be prudent to use a cardioselective beta-blocker.
8. Timolol is a nonselective beta-blocker, but systemic absorption of epinephrine from the eye gel appears to be minimal compared to the drops (10 times higher with the drops). Thus a hypertensive reaction is unlikely. With aqueous timolol eye drops, however, many cases of systemic beta-blockade have been reported, so a hypertensive reaction is possible.
9. At doses over 100 mg/day, atenolol can result in nonselective beta-blockade.
10. Atenolol and bisoprolol undergo renal elimination, and may produce nonselective beta-blockade with significant renal impairment.
11. At doses of 20 mg/day or higher, bisoprolol can result in nonselective beta-blockade
12. At doses over 300 mcg/kg/min, esmolol can result in nonselective beta-blockade
13. At doses over 100 mg/day, metoprolol can result in nonselective beta-blockade.
14. Metoprolol is metabolized by CYP2D6, and patients who are deficient in CYP2D6 (PMs) may develop higher metoprolol plasma concentrations and nonselective beta-blockade.
15. Metoprolol is metabolized by CYP2D6, and patients who are receiving moderate to potent CYP2D6 inhibitors may develop higher metoprolol plasma concentrations and nonselective beta-blockade. Moderate to potent CYP2D6 inhibitors include: abiraterone, amiodarone, bupropion, cinacalcet, clobazam, diphenhydramine, duloxetine, fluoxetine, haloperidol, mirabegron, paroxetine, propafenone, quinidine, ritonavir, terbinafine, and thioridazine.
16. At doses over 10 mg/day, nebivolol can result in nonselective beta-blockade.
17. Nebivolol is metabolized by CYP2D6, and patients who are deficient in CYP2D6 (PMs) may develop higher nebivolol plasma concentrations and nonselective beta-blockade.
18. Nebivolol is metabolized by CYP2D6, and patients who are receiving moderate to potent CYP2D6 inhibitors may develop higher nebivolol plasma concentrations and nonselective beta-blockade. Moderate to potent CYP2D6 inhibitors include: abiraterone, amiodarone, bupropion, cinacalcet, clobazam, diphenhydramine, duloxetine, fluoxetine, haloperidol, mirabegron, paroxetine, propafenone, quinidine, ritonavir, terbinafine, and thioridazine.
19. Large doses of betaxolol may result in nonselective beta-blockade. [to do: define "large"]
20. Labetalol is a nonselective beta-blocker but it has some alpha1-blocking effects. Study in healthy subjects found that in the presence of labetalol, epinephrine did not produce a systolic hypertensive reaction, but did produce a diastolic pressor response.
21. Carvedilol, like labetalol is a nonselective beta-blocker with alpha1-blocking effects (see #20 above). There is some evidence, however, that with long-term administration of carvedilol, the alpha-blocking effects dissipate. It is not known if long-term carvedilol causes acute hypertension following systemic epinephrine, but study in healthy subjects given carvedilol for 2 weeks suggested that hypertension may not occur.
22. Systemic doses of epinephrine normally act for only a short time (minutes) so if a beta-blocker is given after the epinephrine, no interaction would be expected.
23. Timolol is a nonselective beta-blocker, and timolol eye drops have been shown to produce systemic beta-blockade. Timolol is metabolized by CYP2D6, and patients who are deficient in CYP2D6 (PMs) have been shown to develop higher timolol plasma concentrations following timolol ophthalmic aqueous drops.
24. Timolol is a nonselective beta-blocker, and timolol eye drops have been shown to produce systemic beta-blockade. Timolol is metabolized by CYP2D6, and patients who are taking moderate to potent CYP2D6 inhibitors may develop higher timolol plasma concentrations following timolol ophthalmic aqueous drops. Moderate to potent CYP2D6 inhibitors include: abiraterone, amiodarone, bupropion, cinacalcet, clobazam, diphenhydramine, duloxetine, fluoxetine, haloperidol, mirabegron, paroxetine, propafenone, quinidine, ritonavir, terbinafine, and thioridazine.

NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone , University of Arizona; John Horn, Philip Hansten, University of Washington