Warning to Skin Surgeons: Avoid a Potentially Lethal Propranolol Hydrochloride–Epinephrine Interaction in Cosmetic Surgery

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Propranolol hydrochloride, like other β-adrenergic blocking agents, is frequently used to treat hypertension, ischemic heart disease, some arrhythmias, and migraine headaches, as well as some common neurologic diseases. Epinephrine is used in combination with lidocaine as local anesthesia in dermatologic and cosmetic surgery. When patients receiving propranolol hydrochloride during surgery are exposed to epinephrine, they are at risk for a potentially lethal drug interaction.

The adrenergic nervous system is modulated by catecholamines that influence effector-organ cells through interaction with specific receptors, located on the cell surface. Designated as α- and β-adrenergic receptors, catecholamines may have an inhibitory or stimulatory effect, depending on their type and location.[1]

α-Adrenergic receptors mediate a variety of physiologic responses, including vasoconstriction, intestinal relaxation, and pupillary dilatation. β-Adrenergic receptors, on the other hand, mediate heart rate and contractility, vasodilatation, bronchodilatation, and lipolysis (Table 1).[2]

β-Adrenergic receptors in different tissues can be differentiated pharmacologically as β_1 receptors (present in heart and adipose tissue) and β_2 receptors (present in blood vessels and bronchial musculature).[2]

Cardiac blood vessels have only β-adrenergic receptors; peripheral blood vessels have both α- and β-adrenergic receptors.

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Because β-adrenergic blocking agents act on these receptors, we may note the response produced in several tissues along the activity of the sympathetic nerves. In this article, we will separately review the effects of propranolol hydrochloride, a β-adrenergic blocking agent, and epinephrine on α- and β-adrenergic receptors, as well as the consequences of combining both drugs and the treatment necessary if this interaction occurs.

PROPRANOLOL HYDROCHLORIDE

β-Adrenergic blocking agents have received tremendous clinical attention since their inception for treating hypertension, ischemic heart disease, certain arrhythmias, and migraine headaches, as well as some common neurologic diseases. Propranolol hydrochloride is a competitive β-adrenergic blocking agent with no agonist activity, serving as the prototype for other β-adrenergic blocking agents. It has equal affinity for β_1 and β_2 receptors, acting as a nonselective antagonist. Other β-adrenergic blocking agents, such as metoprolol tartrate and atenolol, have greater affinity for β_1 receptors than for β_2 receptors (β_1-selective agonists), which determines whether the drug is selective or nonselective against β_1 or β_2 receptors .

With cardioselective β_1 blocking agents (metoprolol tartrate and atenolol), it is possible to inhibit a cardiac

TABLE 1

Response of Effector Organs to Adrenergic Impulses

Effector Organ	Receptor	Response
Heart	β_1	Increase in heart rate, automatism, contractility, conduction velocity
Blood vessels		
General	α/β_2	Constriction/dilatation
Skin	α	Constriction
Brain	α	Constriction
Bronchial muscles	β_2	Bronchodilatation
Adipose cells	β_1	Lipolysis

TABLE 2

US Food and Drug Administration–Approved β-Adrenergic Blocking Agents

Agent	Cardioselectivity (β_1 Blocking Agents)	Mean Life, h
Propranolol hydrochloride	No	4–6
Pindolol	No	3–5
Timolol maleate	No	4–6
Nadolol	No	20–24
Atenolol	Yes	6–9
Metoprolol tartrate	Yes	3–6

response. Table 2 summarizes the nonselective and selective β-adrenergic blocking agents.

Propranolol hydrochloride is a pure antagonist; it does not stimulate β-adrenergic receptors, nor does it block α-adrenergic receptors. This is desired when treating diseases with propranolol hydrochloride; β-adrenergic blocking agents with partial activity may, for example, prevent profound bradycardia. Generally, and for the purpose of this article, the most important therapeutic effects of β-adrenergic blocking agents are cardiovascular. Because catecholamines have positive chronotropic and inotropic actions, β-adrenergic blocking agents decrease heart rate and myocardial contractility, especially during exercise. Short-term administration of β-adrenergic blocking agents decreases cardiac output, and peripheral resistance is increased from the blockade of vascular β_2 receptors; compensatory sympathetic reflexes activate vascular α-adrenergic receptors. Blood flow to all organs but the brain is reduced. β-Adrenergic blocking agents also significantly affect cardiac rhythm and automaticity by reducing the sinus rate and slowing atrioventricular node conduction. Furthermore, these agents reduce myocardial oxygen consumption. As antihypertensive agents, β-adrenergic blocking agents decrease high (but not normal) blood pressure. Despite the widespread use of β-adrenergic blocking agents as antihypertensive agents, the mechanisms of action behind this important clinical effect are not fully understood.[3]

EPINEPHRINE

Epinephrine is a potent stimulator of both α- and β-adrenergic receptors; therefore, it has complex effects

on many organs. Particularly prominent are its effects on the smooth muscles of the heart and the circulatory system in general. Epinephrine is among the most potent vasopressor drugs and, if administered rapidly intravenously, stimulates an important dose-proportional increase in blood pressure. It especially affects systolic blood pressure, increasing pulse pressure. The blood pressure increase is mediated by (1) direct myocardial stimulation that increases the strength of ventricular contraction, (2) increased heart rate, and (3) constriction in many vascular beds. Pulse rate is at first accelerated but may be slowed at the peak of the blood pressure rise as a compensatory vagal discharge. Normally, peripheral resistance will later decrease from the dominant action on vascular β_2 receptors in skeletal muscle.[3]

PROPRANOLOL HYDROCHLORIDE–EPINEPHRINE INTERACTION

When propranolol hydrochloride and epinephrine are used concomitantly, a potentially lethal scenario exists. It is important to consider that propranolol hydrochloride inhibits or antagonizes β receptors and that epinephrine stimulates α receptors. When these effects predominate, they lead to increased blood pressure that is unopposed, since the β-receptor vasodilator effect is blocked. The more complete the β-receptor blockade, the more severe the hypertensive effect. Following this effect is reflex bradycardia that is mediated by the aortic arch and the carotid baroreceptors; the β-receptor blockade worsens the reflex bradycardia by limiting the cardiovascular system's response to this stress. Increased peripheral vascular resistance increases cardiac work because of epinephrine's inability to stimulate a β-receptor–mediated chronotropic or inotropic response, which could potentiate this reflex bradycardia. The physician may therefore face a patient in an extreme hypertensive state that could end in cardiac arrest (Figure).[1,4]

In short, a propranolol hydrochloride–epinephrine interaction may lead to a hypertensive crisis with reflex bradycardia, stroke, and cardiac arrest.[4]

Dzubow[5] has suggested that these reactions may be dose related, idiosyncratic, or unrelated to this combination of drugs. His study indicated that epinephrine diluted in water in ratios up to 1:200,000 is safe. However, why take the chance? Experience has taught us a different point of view and has made us much more cautious.

Several years ago, before this interaction was known and while performing surgery on a patient with facial basal cell carcinoma, we were surprised when the patient developed hypertension and bradycardia following concomitant use of the drugs. Fortunately, the patient recovered completely.[6] We later noted the same reaction in 2 other patients—one undergoing blepharoplasty and the other, liposuction—following concomitant use of the drugs. In the patient undergoing blepharoplasty, the resident in charge forgot that these drugs should not be combined and the surgery was stopped. In the patient undergoing liposuction, the cardiologist who performed the preoperative evaluation believed that there were no dangers in combining propranolol hydrochloride and epinephrine and prescribed propranolol hydrochloride to the patient. The solution was to never send any preoperative patients to that cardiologist. Lamentably, no data exist, even today, on the incidence of propranolol hydrochloride–epinephrine interaction. It seems safest to avoid the risk altogether.

PREVENTION

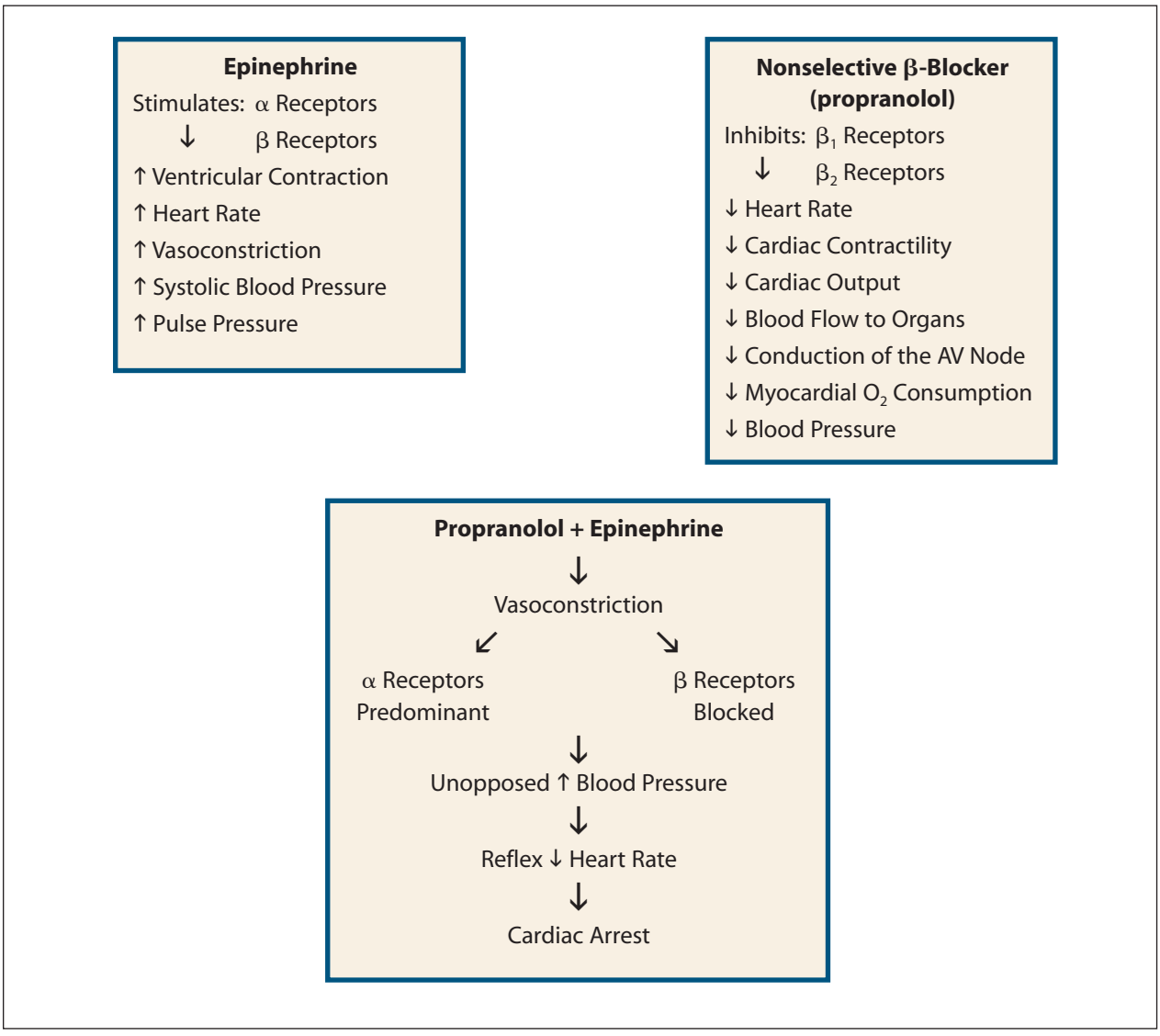
A complete clinical history is all that is necessary in preventing this drug interaction. If a β-adrenergic blocking agent (propranolol hydrochloride, timolol maleate, and pindolol) is to be used, and if epinephrine needs to be used as local anesthesia for procedures such as blepharoplasty, face-lift, and liposuction, after written agreement with the cardiologist, the β-adrenergic blocking agent must be stopped at least 24 hours presurgery and substituted with oral clonidine hydrochloride 0.1 mg the morning of surgery. To avoid a potential rebound from excessive adrenergic effects, it is necessary to remember that nonselective β-adrenergic blocking agents must not be stopped abruptly. Patients should check with their cardiologists on cessation of the β-adrenergic blocking agent.

Substitution with a selective β-adrenergic blocking agent or, even better, employment of clonidine hydrochloride (a selective α_2 agonist with central action), apart from increasing the effectiveness of intravenous sedation, potentiates local anesthesia and may prevent epinephrine-induced arrhythmias.[7] If epinephrine is not entirely necessary (eg, for a skin biopsy), it is preferable that surgery be performed without epinephrine.

TREATMENT

If a propranolol hydrochloride–epinephrine interaction occurs, the recommended course of action is to stop the surgery. Reflex bradycardia may be controlled by atropine. Hypertension may be managed with a strong α-adrenergic blocking agent (eg, intravenous chlorpromazine hydrochloride), an intracellular calcium channel blocker (eg, intravenous hydralazine hydrochloride), or a β-selective agonist (eg, aminophylline).[1] Blue code emergency drugs are necessary at all times in order to offer convenient management.

Propranolol Hydrochloride–Epinephrine Interaction



Cardiovascular effects of propranolol hydrochloride and epinephrine when administered separately and their dangerous interaction. AV indicates atrioventricular.

CONCLUSION

Dermatologic surgeons must be aware of the dangers of a propranolol hydrochloride–epinephrine interaction and must be prepared to prevent it or respond quickly with adequate treatment should an interaction occur. Caution must always guide our steps.

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