Paradoxical reaction to epinephrine induced by beta-blockers in an anaphylactic shock induced by penicillin

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Increased risk of severe and resistant anaphylactic shock is a rare and not widely known adverse effect of β-blocker treatment. It is illustrated in a case of refractory anaphylactic shock occurring in a 47-year-old woman who received β-blockers. Actually, β-blockers increase the release of anaphylactic mediators, decrease the cardiovascular compensatory changes to the anaphylactic shock and promote paradoxical reflex vagotonic effects when using epinephrine. ***European Journal of Emergency Medicine*** **13:358–360 © 2006 Lippincott Williams & Wilkins.**

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Introduction

As indication of β-adrenergic antagonists, usually named β-blockers, has increased in recent years, impact of β-blockers on allergic reaction has become unexceptional. These drugs increase production of anaphylactic mediators and reduce compensatory mechanism usually seen during allergic reaction. Potentiated anaphylaxis reactions by β-blockers, however, are understudied in the literature, and thus, often unrecognized by clinicians. Specific treatments have to be administered. We present a report of a refractory anaphylaxis in a patient with drug-induced β-blockers with paradoxical reaction after epinephrine injections.

Case report

At 0815 h, the French emergency call centre of the Hauts-de-Seine (SAMU-Centre 15) received a call for a woman who fainted. No other information was available. A basic life support team was sent (fire fighters): the 47-year-old lady fainted a second time in front of the trained first-aiders. A prehospital medical intensive care unit (prehospital medical ICU) was sent.

At 0854 h, the emergency physician took care of the patient. The woman was conscious. She suffered from hypertension treated by a β-blocker (acebutalol, 400 mg daily). She had an anaphylactic shock owing to penicillin a long time ago. The day of the incident, she had accidentally taken amoxicillin, instead of pristinamycin for a small infection (she had taken her son's medication instead of her own). She realized her mistake and took orally 40 mg of prednisolone.

Severe hypotension was noted with an undetectable blood pressure and a heart rate at 70/min. No respiratory distress or laryngo-bronchospasm was found, with a correct transcutaneous oxygen saturation at 100% with oxygenotherapy (started by basic life support team). Systemic reaction signs were also present with profuse sedation, general erythema and facial oedema (without uvula oedema). Nothing else was identified upon clinical examination.

Immediate treatment for anaphylactic shock was administered with intravenous infusion of crystalloids, two intravenous injection of 0.1 mg of epinephrine within 5 min. Methylprednisolone (80 mg) and dexchlorpheniramine (5 mg) were also administrated intravenously. After the first injection of epinephrine, an inappropriate reaction with nausea, paleness, and bradycardia at 25/min appeared, treated initially by atropine (1 mg). After the second injection, the same adverse effect occurred. Blood pressure remained momentary at 84/42 mmHg, and was again undetectable. A third intravenous injection of epinephrine (0.1 mg) stabilized systolic blood pressure at 80 mmHg and heart rate at 70/min. The prehospital medical ICU transferred the patient immediately to the ICU, without other side effects. Same haemodynamic parameters were observed on admittance to ICU, with only persistence of erythema (considered as a vasoplegic reaction). After 24 h, evolution was favourable after

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infusion of low volumes of isotonic saline (500 ml). No other medication was administered. The patient was discharged alive from the hospital with advice to consult an allergologist. The risk of worsened anaphylaxis reaction due to β-blockers was not mentioned.

Discussion

Beta-blockers are frequently used in the treatment of cardiovascular disease and hypertension, angina pectoris or certain types of cardiac arrhythmias. These drugs may worsen anaphylaxis [1,2]. They are thus contraindicated in patients with history of anaphylactic shock.

Although some studies report rare individual cases [1,3,4], these specific adverse effects are underidentified by clinicians. Our case report emphasizes the difficulties of management of anaphylactic shock in patients receiving β-blockers [5].

Guidelines for the management of anaphylactic shock [6–8] involve initial intravenous injection of epinephrine by titration (i.e. 0.1 mg every minute) to obtain sufficient blood pressure [9–11]. Initial management was correct in our case report, but β-blockers interfered with the treatment.

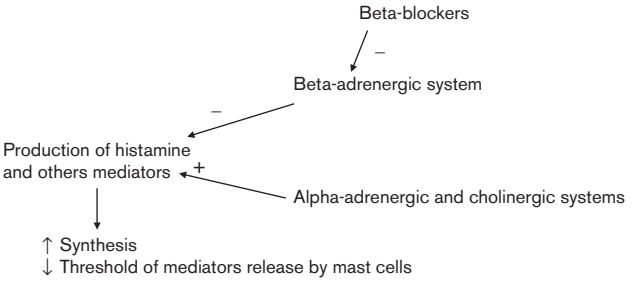
The ineffectiveness of epinephrine or the promotion of undesired α-adrenergic and vagotonic effects has been previously reported for patients exposed to β-blockers [12–14].

Beta-blockers worsen allergic reaction, acting on anaphylactic mediators and interfering with the treatment usually used in this case.

Beta-blockers can influence release of anaphylactic mediators via modulation of adenylcyclase [15,5]. Alpha-adrenergic and cholinergic systems are known to induce production of these mediators when β-adrenergic system inhibits their production (Fig. 1). It is supposed that β-adrenergic antagonists increase the release of histamine and other mediators of anaphylaxis from mast cells via elevation of the cellular level of cyclic adenosine 3′,5′ monophosphate, and lowering the threshold of mediator release by mast cells and basophils [12,13,16,17].

Beta-blockers radically alter the pharmacodynamy of epinephrine. They block the expected β antianaphylactic actions of epinephrine, thus facilitating unopposed α-adrenergic and reflex vagotonic effects that can lead to increased anaphylactic mediator release with extreme bradycardia, such as in our observation [1,12,14]. Conductions abnormalities were described [3,4,14]. Case reports with cardiac arrest in patients receiving β-blockers were also found, with one potentiated by β-blocking eye drops [1,13,17]. General erythema and undetectable blood pressure were described, and above all, a bradycardia at 40/min that was resistant to atropine, isoprenaline or epinephrine. One case was lethal, and one was treated with glucagon.

Fig. 1



Pathway illustration of α, β-adrenergic and cholinergic systems, and β-adrenergic antagonists, in anaphylaxis.

Beta-blockers also inactivate α-activators by nonspecific competition, in addition to competitive inhibition of β-adrenergic receptors [18]. Thus, cardiovascular compensatory changes to the stress of profound anaphylactic shock, mediated through adrenergic system, did not occur because of drug-induced β-adrenergic blockage [9, 12–14,17]. The relative advantage of cardioselective β-blockers was suspected [14]. However, this remains uncertain because adrenoreceptors that modulates mediator release can be either β-1 or β-2 antagonists, as in our clinical observation [12].

If anaphylaxis occurs in a patient receiving a β-blocker drug, it should be treated promptly with epinephrine, but with increased dose such as 2 or 5 times more at each injection than the usual dose of anaphylactic shock [10,19]. In fact, dosage of the β-adrenergic agonists needs to be much higher than usual in order to competitively overcome the pharmacologic β-adrenergic blockade [18]. Intravenous atropine may be useful, especially for heart block (0.5 to 1 mg) [4,20]. No clear indication, however, exists for the combination of atropine and epinephrine.

Intravenous glucagon has been effective for shock in some patients who were unresponsive to β-adrenergic agonists [21], with 1–5 mg doses, depending on authors [7,8,10,12,19,22]. This may reflect a direct action of glucagon on cardiac cyclic adenosine 3′,5′ monophosphate that is independent of the β-adrenergic receptor.

Intravenous antihistamine H1 and corticosteroids should also be administrated as usual, together with large volumes of intravenous fluids [10,12].

Conclusion

This case report emphasizes the increased risk of severe and resistant anaphylactic shock in patients treated by β-blockers, particularly the paradoxical reaction to epinephrine administration. Identifying these high-risk patients should be recommended before initiation of anaphylactic treatment and at best when emergency calls occurred. Beta-blockers must be used with extreme caution by clinicians when there is an anaphylactic shock history.

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