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Calcium channel blockers, beta-blockers and digitalis poisoning: management in the emergency room

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Abstract. – Calcium channel blockers and beta-blockers intoxications account for up to 65% of deaths for cardiovascular drugs, causing severe clinical symptoms refractory to standard medications. The most serious poisonings are those resulting from verapamil and propanolol ingestion. Both support and antidotic therapy are necessary for these potentially unstable patients. Supportive measures and the use of digoxin-specific antibody fragments are first line treatment for digitalis glycoside poisoning.

Key Words:

Calcium channel blockers, Beta-blockers, Digitalis, Glucagon, Digoxin-specific antibody fragments, Support therapy, Antidotes.

Introduction

Calcium channel blockers (CCB) and beta-blockers (BB) intoxications represent 40% of the pharmacological poisoning cases in the USA and account for 65% of deaths determined by cardiovascular drugs[1]. Treatment is often difficult because of the unresponsiveness to standard supportive medications. The therapeutic approach for digitalis glycoside poisoning has been radically modified since the introduction of digoxin-specific antibody fragments (Fab)[2]. The knowledge of the pharmacokinetic and pharmacodynamic properties of these compounds is pivotal for a rational choice of supportive and antidotal therapy in the treatment of these potential unstable and critical ill patients.

Calcium Channel Blocker and Beta Blocker Intoxication

Although CCB and BB have different mechanisms of action, their cardiovascular effect are similar. In fact, CCB interfere with calcium cell influx blocking "L" type voltage dependent channels[3], whereas BB lower intracellular cyclic AMP and thereby reduce intracellular calcium contents[4] (Figure 1). Since intracellular calcium plays a key role in cardiac automaticity, conductivity and contractility, intoxication from these drugs leads to an inhibition of sinus and atrio-ventricular (AV) node depolarization and to a depression of myocardial cell contractility[5].

Clinically patients with CCB or BB poisoning present profound bradycardia, possible AV block, severe ventricular dysfunction leading to acute impairment of cardiac output and cardiac arrest[1].

Effects of CCB and BB differ as regards the peripheral vessels. CCB determine vasodilation by lowering smooth muscle intracellular calcium content[6], whereas most BB cause vasoconstriction diverting catecholamines on constricting alfa adrenoceptors.

However differences exist also among the various classes of CCB. Benzothiazepines (diltiazem) and especially phenilalchilamines (verapamil) intoxications cause a more severe clinical picture, characterized by profound bradycardia, conduction disturbance (sinus arrest, asystole, AV block), vasodilation and hypotension[7]. Poisoning by derivates of dihydropyridine (nifedipine, amlodipine, felopidine) is characterized particularly by vasodilatation, while contractility, conductivity and chronotropicity remain relatively undisturbed because these drugs show a high vessel selectivity[8]. Some patients show even sinus tachycardia because of sympathetic overdrive secondary to vasodilation[1].

CCB toxicity presents often with hyperglycaemia because of insulin secretion impairment and peripheral enhanced insulin-resistance, worsening thereby metabolic acidosis secondary to cardiovascular shock[9].

As regards BB, sotalol overdose, in addition to bradycardia and hypotension, can cause torsade de pointes[10], while lipophilic BB (metoprolol, carvedilol, timolol and in particular propanolol), easily pass through the blood-brain barrier causing delirium, seizures and coma[11]. Exposure to a BB with membrane stabilizing activity (propanolol, acebutolol, metoprolol and labetalol) is associated with an QRS interval prolongation and an increased risk of cardiovascular morbidity[12].

Clinical symptoms of BB intoxication arise generally within 6 hours after ingestion, unless the patients ingested slow-release preparations[12].

Supportive Therapy

Patients with suspected CCB or BB intoxication should be immediately referred to an emergency department regardless of the ingested dose[13]. Ambulance transportation is recommended because of potential life threatening complications[13].

Supportive treatment of CCB and BB poisoning is nearly identical. Initial treatment includes vital parameters monitoring, airways management, ventilatory and circulatory support, if needed[14]. Even apparently stable patients can rapidly develop fatal arrhythmias and cardiac arrest during treatment.

A 12 leads ECG, blood drawings for renal and liver function, determination of glycaemia, electrolytes and blood gases should be performed.

An intravenous access for fluid resuscitation and drug administration should be immediately placed.

Sinus bradycardia, AV block and cardiac arrest should be treated according to the advanced life support algorithms[14]. In particular boluses of atropine 0.5 mg, repeated if needed up to 3 mg, associated with adrenalin ev 2-10 microg/min are commonly used for bradyarrhythmias.

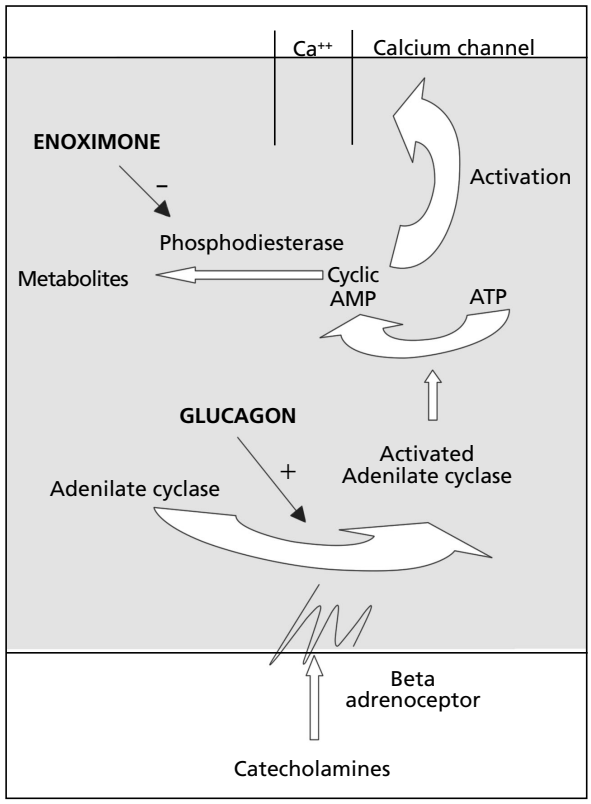

Figure 1. Mechanisms of action of glucagon and enoximone.

Unfortunately, these measures are often insufficient to restore hemodynamic stability and in most serious cases transthoracic or transvenous temporary cardiac pacing is necessary[15].

Cristalloids and vasopressors (isoproterenol, dopamine, dobutamine, epinephrine and norepinephrine) are first line treatment for hypotension and shock[16,17].

Decontamination

Gut decontamination procedures with gastric lavage should be performed within 1-2 hours after drug ingestion[18,19]. Repeated activated charcoal administrations (0.5-1 g/kg every 2-4 h for 48-72 h) are useful because CCB and BB have a prevalent liver metabolism with recycling in the bowel[19]. Hemodialysis and hemoperfusion techniques cannot be used for CCB because of their high volume distribution and their lipophilic properties[7]. These techniques are beneficial for some BB (atenolol, sotalol, nadolol, acebutolol)[19,20].

Antidotal treatment

Glucagon

Glucagon is usually accepted as first line treatment in the management of BB and verapamil overdose[21]. Glucagon is secreted by the alfa pancreatic cells and is able to enhance adenylate cyclase activity, increasing intracellular cyclic AMP levels (Figure 1) and calcium influx, inducing a chronotropic and inotropic response[22]. Initial dosage is 5-10 mg ev (150 microg/kg) in rapid bolus. The effect is evident after 1-3 min reaching a peak in 5-7 min and ending after 10-15 min. Repeated boluses every 10 min or a continuous infusion at a rate of 2-10 mg/h (50-100 microg/kg/h) may be necessary[23]. Side effects of glucagon administration are nausea, vomiting, hyperglycaemia, hypocalcemia[24].

Phosphodiesterase Inhibitors

Phosphodiesterase III inhibitors (enoximone) represent possible alternatives to glucagon in CCB and BB poisoning, as their inotropic effect is not mediated by beta adrenoceptors (Figure 1)[25].

Insulin

The inotropic effect of insulin has been long established[26]. In the CCB and BB intoxication insulin has been proposed at high dosages (0.5-1 IU/kg/h) with a continuous glucose infusion to maintain euglycaemia[27]. Insulin administration in fact switches cell metabolism from fatty acid to carbohydrates and restores calcium fluxes, improving thereby cardiac contractility.

Calcium

Treatment of choice in CCB poisoning is calcium administration[1]. Repeated boluses of 10 mEq every 10-15 minutes may be given, but total acute calcium administration should not exceed 45 mEq to avoid superimposed hypercalcemia induced arrhythmias[7]. The administration route should be a central vein to avoid the risk of skin necrosis.

However, in severe verapamil acute poisoning, calcium administration may be less effective because calcium channels are totally blocked, and increasing the extracellular calcium concentration does not contribute significantly to increase the calcium intracellular content. Some studies show that adrenaline proves to be a more effective drug than calcium compounds in this setting, probably acting as calcium channel "opener"[28]. The effectiveness of verapamil poisoning treatment could be further improved administering the calcium preparation prior to adrenaline[29].

Sodium Bicarbonate

Administration of sodium bicarbonate in membrane stabilizing drug intoxications (propanolol, metoprolol, acebutolol and labetalol) may be helpful in increasing intracellular sodium content, antagonizing thereby cardiac toxicity[30].

New Antidotes

New antidotes for verapamil poisoning, like 4 aminopyridine, a potassium channel inhibitor, and Bay K 8644, a calcium channel activator, have been extensively studied in animal models[7]. Their introduction in clinical practice may improve the effectiveness of CCB intoxication treatment.

Patients must be always admitted in an intensive care unit.

Asymptomatic patients should be monitored for at least 6 h after drug ingestion if they took a sustained-release preparation and 12 h if they took sotalol.

Digoxin Intoxication

Digoxin and digitoxin are the most important digitalis glycosides, steroid compounds present in many plants (*digitalis purpurea and lanata, oleander*). The pharmacokinetic properties of digoxin after oral administration are a gastrointestinal absorption of 55-75%, a large distribution volume, low plasma protein link, onset of action in 15-30 minutes, peak effect reached in 90-300 minutes, an average half life of 36 to 48 hours and a predominantly renal excretory pathway[31]. Digitoxin exhibits a higher gastrointestinal absorption (90%), a lower distribution volume, onset of action in 25-120 minutes, a peak effect reached in 4 to 12 hours, an average half life of 4 days and a predominantly hepatic excretion pathway with enterohepatic cycle and renal excretion of metabolites[31].

Digitalis glycosides inhibit the active transport protein Na^+, K^+ ATPase, the enzymatic equivalent of the sodium pump. Inhibition of active Na+ transport results in increased intracellular Na+ content, which promotes transmembrane Na^+-Ca^{++} exchange, resulting in augmentation of myocyte Ca^{++} content[32]). Digitalis induces also an increased Ca^{++} influx through sarcolemmal Ca^{++} channels[33]. This intracellular Ca^{++} increase produces a positive inotropic response in atrial and ventricular myocytes. On the other hand, inhibition of the sodium transmembrane transport induces a series of electrophysiological effects ranging from decreased sinus automaticity, decreased AV node conduction velocity and a decrease of atrial and ventricular effective refractory period[31].

Digitalis glycosides exert also indirect cardiac effects through vagal activation, probably enhancing baroceptor sensitivity and through central stimulation. The action of digoxin on AV conduction and on the AV node refractory period, which it prolongs, is primarily dependent on increased vagal tone and only to a minor extent on the direct effect of glycosides[31]).

Digoxin intoxication can be acute (suicide, accidental ingestion, contact with plants) or chronic (patients who take accidentally higher dose of digoxin or develop renal failure).

Acute digitalis intoxication is characterized by high electric instability and it is associated with high mortality. Acute poisoning becomes clinically evident when digoxin plasma concentration exceeds 2 ng/ml or digitoxin exceeds 3.5 ng/ml. In chronic intoxications, cardiotoxicity may be evident even when digoxinemia ranges within therapeutical limits[2]. Symptoms emerge within 12 h after drugs ingestion, but may be very precocious in severe poisoning.

As the glycosides influence every excitable tissue, including gastrointestinal and central nervous systems, poisoning with these compounds may cause cardiac and systemic symptoms[34]. Cardiac toxicity is mainly related to the decrease of potential action and the arising of oscillatory afterpotentials, associated with high intracellular calcium levels[31]. ECG signs of glycoside intoxication are extrasystolic bigeminism, junctional arrhythmias, bradycardia, various degrees of AV block, ventricular tachycardia (VT) and ventricular fibrillation (VF)[35]. Hypokalemia increases the cardiac tissue automaticity during digoxin poisoning while hyperkalemia seems to interfere particularly with the cardiac conductivity abnormalities[31]. Hypercalcemia may worsen the risk of fatal arrhythmias.

Systemic glycoside poisoning symptoms and signs include nausea, vomiting, diarrhoea, visual disturbances, disorientation, mental confusion and hallucinations[34].

Supportive Therapy

As for CCB and BB intoxications, digoxin poisoning may lead to fatal ventricular arrhythmias and cardiac arrest.

Liver and renal function test, determination of electrolytes, blood gases and plasma level of glycosides and a 12 leads ECG must be performed at the arrival in the Emergency Department.

Monitoring of vital parameters, ventilatory and hemodynamic support and fluid resuscitation should immediately be undertaken, if necessary.

The flow-charts of the advanced life support must be applied in cases of cardiac arrest or life threatening arrhythmias[14]. In particular, bradycardia and AV block should be managed with atropine and transthoracic pacing if necessary, as described before[36]. Ventricular arrhythmias with signs of cardiac failure should be treated with DC shock. First line pharmacological approach in these cases is lidocaine (50 mg iv in 2 min, every 5 min for VT, 100 mg or 1-1.5 mg/kg in VF or pulselessness VT)[37]. Alternative to lidocaine is phenytoin 100 mg by slow intravenous infusion every 5 min [37].

Electrolyte disturbances should be promptly treated as necessary.

Decontamination

Decontamination therapy with cautious gastric lavage should be performed within 1 hour after drug ingestion; these procedures may worsen the bradycardia because of additional vagal stimulation. Activated charcoal

should be administered (0.5-1 g/kg every 2-4 h for 48-72h), particularly in cases of digitoxin intoxication.

Hemodialysis and hemofiltration are not useful because of the high plasma protein link of the glycosides.

Antidotal Treatment

The development of digoxin specific antibodies fragments (Fab) has changed the management of both digoxin and digitoxin poisoning[2]. Equimolar doses of anti digoxin Fab fragments completely bind digoxin *in vivo*. Even if the plasmatic free levels of glycosides are very low, Fab administration is associated with rapid improvement of cardiac symptoms, in particular of AV blocks[38]. In patients with rapid onset of toxicity symptoms there are higher levels of free digoxin and digitoxin, as the tissue distribution will not have yet occurred, and Fab administration is particularly useful.

Indications for Fab administration include severe arrhythmias, symptomatic bradycardia, AV blocks with hyperkalemia and digoxin levels over 10 ng/ml or digitoxin levels over 25 ng/ml[39].

The approximate dose of Fab in mg is 60 times the digoxin body burden in mg[40].

Practically, the amount of Fab to administrate may be calculated from glycoside plasma concentration according to the following formula: plasmatic concentration (ng/ml) × 0.0056 for digoxin, 0.00056 for digitoxin (conversion factor for distribution volume in mg) × weight in kg = total digoxin or digitoxin amount in the body × 60; (for instance: digoxin plasmatic levels of 20, in a patient weighting 70 kg: 20 × 0.0056 × 70 = 7.84 mg × 60 = 480 mg).

If plasmatic glycosides levels are not available, the following formula may be used:

ingested dose in mg × 0.80 (absorption conversion factor) × 0.60.

If the ingested amount of glycosides is unknown, 380 mg of Fab should be administered. If the clinical picture does not improve, administration should be repeated[40].

Fab are given intravenously over 15-30 min after dilution to at least 250 ml with plasma protein solution or 0.9 sodium chloride solution.

Effects of Fab administration are observed 30-60 minutes after drug administration, with a peak effect reached in 4 hours.

Side effects include hypokalemia and skin rash.

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