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Review Article

A REVIEW ON THERAPEUTIC EFFECTS, DOSING, TOXICITY AND MANAGEMENT OF CALCIUM CHANNEL BLOCKERS AND BETA BLOCKERS

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Abstract

The use of calcium channel blocker and beta blocker depends on the particular condition of the patient. They are prescribed for conditions such as hypertension, atrial fibrillation, arrythmias etc. However both of these classes of drugs possess their own individual side effects such as stroke, hypoglycaemia, decreased vascular resistance etc if not properly prescribed or administered. The study aims to reveiw the detailed analysis of the therapeutic effects, doses that need to be adjusted for special groups, effects of toxic dose. In this way,we are able to get a better picture about calcium channel blockers and beta blockers.

Key words: Calcium channel blockers, beta blockers, Glucagon.

Introduction

Calcium channel blockers and beta blockers are classes of drugs which are mainly used for cardiovascular diseases .They are two of the most prescribed drugs in cardio vascular pharmacology .Beta-blockers were first developed by Sir James lack at the imperial chemical industries in the United Kingdom in 1962. They are considered one of the most important contributions to clinical medicine and pharmacology in the 20thcentury, and Sir James lack was awarded the Nobel Prize in 1988 for advances in medicine.

Beta-blockers are drugs that bind to beta-adrenoceptors and thereby block the binding of norepinephrine and epinephrine to these receptors. This inhibits normal sympathetic effects that act through these receptors. Therefore, beta-blockers are sympatholytic drugs.Some beta-blockers, when they bind to the beta-adrenoceptor, partially activate the receptor while preventing norepinephrine from binding to the receptor. These partial agonists therefore provide some "background" of sympathetic activity while preventing normal and enhanced sympathetic activity.

These particular beta-blockers (partial agonists) are said to possess intrinsic sympathomimetic activity (ISA). Some beta-blockers are also referred to as membrane stabilizing activity (MSA). This effect is similar to the membrane stabilizing activity of sodium-channels blockers that represent Class I anti arrhythmias.

Calcium channel blockers (CCB), calcium channel antagonists or calcium antagonists are several medications that disrupt the movement of calcium (Ca^{2+}) through calcium channels. Calcium channel blockers are used as antihypertensive drugs, i.e., as medications to decrease blood pressure in patients with hypertension. CCBs are particularly effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients. Calcium channel blockers are also frequently used to alter heart rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris. N-type, L-type, and T- type voltage dependent calcium channels are present in the zonaglomerulosa of the human adrenal, and CCBs can directly influence the biosynthesis of aldosterone in adrenocortical cells, with consequent impact on the clinical treatment of hypertension with these agents.

Mechanism of action

Beta blockers

In hypertension

Beta-blockers bind to beta-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both β1 and β2 adrenoceptors, although the predominant receptor type in number and function is β1. These receptors primarily bind norepinephrine that is released from sympathetic adrenergic nerves. Additionally, they bind norepinephrine and epinephrine that circulate in the blood. Beta-blockers prevent the normal ligand (norepinephrine or epinephrine) from binding to the beta-adrenoceptor by competing for the binding site.[1]

Beta-adrenoceptors are coupled to a Gs-proteins, which activate adenylyl cyclase to form cAMP from ATP. Increased cAMP activates a cAMP-dependent protein kinase (PK-A) that phosphorylates L-type calcium channels, which causes increased calcium entry into the cell. Increased calcium entry during action potentials leads to enhanced release of calcium by the sarcoplasmic reticulum in the heart; these actions increase inotropy (contractility). Gs-protein activation also increases heart rate (chronotropy). PK-A also phosphorylates sites on the

sarcoplasmic reticulum, which lead to enhanced release of calcium through the ryanodine receptors (ryanodine-sensitive, calcium-release channels) associated with the sarcoplasmic reticulum[2]. This provides more calcium for binding the troponin-C, which enhances inotropy. Finally, PK-A can phosphorylate myosin light chains, which may contribute to the positive inotropic effect of beta-adrenoceptor stimulation.Because there is generally some level of sympathetic tone on the heart, beta-blockers are able to reduce sympathetic influences that normally stimulate chronotropy (heart rate), inotropy (contractility), dromotropy (electrical conduction) and lusitropy (relaxation). Therefore, beta-blockers cause decreases in heart rate, contractility, conduction velocity, and relaxation rate.

Blood vessels

Vascular smooth muscle has β2-adrenoceptors that are normally activated by norepinephrine released by sympathetic adrenergic nerves or by circulating epinephrine. These receptors, like those in the heart, are coupled to a Gs-protein, which stimulates the formation of cAMP. Although increased cAMP enhances cardiac myocyte contraction (see above), in vascular smooth muscle an increase in cAMP leads to smooth muscle relaxation. The reason for this is that cAMP inhibits myosin light chain kinase that is responsible for phosphorylating smooth muscle myosin. Therefore, increases in intracellular cAMP caused by β2-agonists inhibits myosin light chain kinase thereby producing less contractile force (i.e., promoting relaxation).

Compared to their effects in the heart, beta-blockers have relatively little vascular effect because β2-adrenoceptors have only a small modulatory role on basal vascular tone. Nevertheless, blockade of β2-adrenoceptors is associated with a small degree of vasoconstriction in many vascular beds. This occurs because beta-blockers remove a small β2-adrenoceptor vasodilator influence that is normally opposing the more dominant alpha-adrenoceptor mediated vasoconstrictor influence.

In angina

They limit symptoms and prevent infarction and sudden death better than other drugs. Beta Blockers block sympathetic stimulation of the heart and reduce systolic BP, heart rate, contractility, and cardiac output, thus decreasing myocardial O2 demand and increasing exercise tolerance[3].

They also increase the threshold for ventricular fibrillation. Most patients tolerate these drugs well. Many β-blockers are available and effective. Dose is titrated upward as needed until limited by bradycardia or adverse

effects. Patients who cannot tolerate β-blockers are given a Ca channel blocker with negative chronotropic effects (eg, diltiazem, verapamil). Those at risk of β-blocker intolerance (eg, those with asthma) may be tried on a cardioselective β-blocker (eg, bisoprolol) perhaps with pulmonary function testing before and after drug administration to detect drug-induced bronchospasm[4].

Calcium Channel Blockers

In hypertension

CCBs promote vasodilator activity (and reduce blood pressure) by reducing calcium influx into vascular smooth muscle cells by interfering with voltage-operated calcium channels (and to a lesser extent receptor-operated channels) in the cell membrane. Interference with intracellular calcium influx is also important in cardiac muscle, cardiac conduction tissue and gastrointestinal smooth muscle[5] In cardiac tissues, CCBs have potential for negative inotropic, chronotropic and dromotropic activity while the gastrointestinal effects predispose to constipation. These effects vary with different agents according to ability to penetrate cardiac and other tissues, relative affinity for calcium channels in different tissues and the influence of reflux cardiac stimulation secondary to peripheral vasodilation. Dihydropyridine derivatives have pronounced peripheral vasodilator properties and intense reflex cardiac stimulation overcomes any direct cardiac effects. Verapamil and diltiazem are also vasodilators but the balance of actions is such that these drugs have noticeable cardiac effects including reduced heart rate (rate-limiting).

In angina

They may be used if symptoms persist despite use of nitrates or if nitrates are not tolerated. Ca channel blockers are particularly useful if hypertension or coronary spasm is also present. Different types of Ca channel blockers have different effects. Dihydropyridines (eg, nifedipine, amlodipine, felodipine) have no chronotropic effects and vary substantially in their negative inotropic effects. Shorter-acting dihydropyridines may cause reflex tachycardia and are associated with increased mortality in CAD patients; they should not be used alone to treat stable angina[6]

Longer-acting formulations of dihydropyridines have fewer tachycardic effects; they are most commonly used with a β-blocker. In this group, amlodipine has the weakest negative inotropic effects; it may be used in patients with LV systolic dysfunction.

Diltiazem and verapamil, other types of Ca channel blockers, have negative chronotropic and inotropic effects. They can be used alone in patients with β-blocker intolerance or asthma and normal LV systolic function but may increase cardiovascular mortality in patients with LV systolic dysfunction.

Therapeutic effects and dosing

In atrial fibrillation

Ventricular rate control

- ∑ Ventricular rate control to achieve a rate of less than 100 beats per minute is generally the first step in managing atrial fibrillation.
- ∑ Beta blockers[7] ,calcium channel blockers[8] ,and digoxin (Lanoxin) are the drugs most commonly used for rate control.

Drugs Commonly Used to Control Ventricular Rate in Patients with Atrial

Fibrillation

Drugs	Intial dosing	Maintenance dosing	Comments
Calcium channel blockers			
Diltiazem (Cardizem)	15 to 20 mg IV over 2 minutes; may repeat in 15 minutes	5 to 15 mg per hour by continuous IV infusion	Convenient; easy to titrate to heart rate goal
Verapamil (Calan, Isoptin)	5 to 10 mg IV over 2 minutes; may repeat in 30 minutes	Not standardized	More myocardial depression and hypotension than with diltiazem
Beta blockers			
Esmolol (Brevibloc)	Bolus of 500 mcg per kg IV over 1 minute; may repeat in 5 minutes	50 to 300 mcg per kg per minute by continuous IV infusion	Very short-acting; easy to titrate to heart rate goal
Propranolol	1 mg IV over 2	1 to 3 mg IV	Short duration of

	(Inderal)	minutes; may repeat every 5 minutes to maximum of 5 mg	every 4 hours	action; hence, need for repeat dosing

- ∑ Beta blockers and calcium channel blockers are the drugs of choice because they provide rapid rate control
- ∑ These drugs are effective in reducing the heart rate at rest and during exercise in patients with atrial fibrillation.
- ∑ Factors that should guide drug selection include the patient's medical condition, the presence of concomitant heart failure, the characteristics of the medication, and the physician's experience with specific drugs.
- ∑ Compared with beta blockers and calcium channel blockers, digoxin is less effective for ventricular rate control, particularly during exercise. Digoxin is most often used as adjunctive therapy because of its slower onset of action (usually 60 minutes or more) and its weak potency as an atrioventricular node–blocking agent. It can be used when rate control during exercise is of less concern. Digoxin is a positive inotropic agent, which makes it especially useful in patients with systolic heart failure.
- ∑ The calcium channel blockers diltiazem and verapamil are effective for initial ventricular rate control[9] in patients with atrial fibrillation. These agents are given intravenously in bolus doses until the ventricular rate becomes slower.

  Dihydropyridine calcium channel blockers (e.g., nifedipine, amlodipine, felodipine, isradipine, nisoldipine, are not effective for ventricular rate control.
- ∑ Physicians can use the “rule of 15” in administering diltiazem[10] to patients weighing 70 kg (154 lb): first, give 15 mg intravenously over two minutes, repeat the dose in 15 minutes if necessary, and then start an intravenous infusion of 15 mg per hour; titrate the dose to control the ventricular rate (5 to 15 mg per hour). Verapamil[11], in a dose of 5 to 10 mg administered intravenously over two minutes and repeated in 30 minutes if needed, can also be used for initial rate control.

- ∑ Although all calcium channel blockers can cause hypotension, verapamil should be used with particular caution because of the possibility of prolonged hypotension as a result of the drug's relatively long duration of action.
- ∑ Beta blockers such as propranolol and esmolol may be preferable to calcium channel blockers in patients with myocardial infarction or angina, but they should not be used in patients with asthma. As initial treatment, 1 mg of propranolol is given intravenously over two minutes; this dose can be repeated every five minutes up to a maximum of 5 mg. Maintenance dosing of propranolol is 1 to 3 mg given intravenously every four hours. Esmolol has an extremely short half-life and may be given as a continuous intravenous infusion to maintain rate control.
- ∑ Despite depressive effects on contractility (unless the ejection fraction is below 0.20), calcium channel blockers and beta blockers can be used for initial ventricular rate control in patients with heart failure[12] .Oxygen delivery to the heart is usually much improved once the ventricular rate is controlled (less than 100 beats per minute). A slower ventricular response rate also allows more filling time for the heart and, thus, improved cardiac output. However, the benefits of long-term treatment with calcium channel blockers[13] or beta blockers should be carefully weighed against the negative inotropic effects. Drugs for rate control can generally be stopped once sinus rhythm is restored.
- ∑ Limited data suggest that combination regimens provide better rate control than any agent alone.
- ∑ Both of them are effective in ventricular control, preference of the drug will be depending on the duration of action, patients condition, idiosyncrasy etc.

In Pregnancy

Calcium Channel Blockers

Generally, calcium channel blockers are administered in the second and third trimesters of pregnancy. Drug exposure usually has only minor effects on the fetus, if any, at this time.

It is in the first trimester when the major organ systems are formed that the fetus is most susceptible to a teratogen[14]. This critical period of development occurs from the fifth week from the last menstrual period through the tenth week of gestation. Since many of the developmental processes in the first trimester are calcium-

dependent, there is concern that the use of a calcium channel blocker during this time may cause fetal malformations or other adverse effects.

Risk during Breast Feeding

The WHO Working Group on Drugs and Human Lactation has classified verapamil as compatible with breast-feeding[15]. However, later it was found out that it is not recommended to use the agent while breastfeeding because the hearts of infants may be more susceptible to the pharmacologic effects of verapamil. Nifedipine is also transferred to breast-milk. The dose ingested by the infant is so small, however, that it is unlikely to have adverse effects. Diltiazem is also ingested in small amounts from breast milk, but the WHO Working Group has not concluded that it is safe to use while breast-feeding.

Nifedipine against Premature Labour

A number of drugs are used against threatening PTB, although only oxytocin antagonists have been designed specifically as tocolytic medication. Thus, DHP CCBs are utilized for this purpose, but they have not been licensed for tocolysis.

Many data demonstrate the efficacy of nifedipine, whereas little information is available on the action of nicardipine in PTB[16]. Nifedipine is used orally for both tocolysis and cardiovascular treatment. The appropriate dose of nifedipine for tocolysis is still under investigation. In a comparison of two dose regimens of oral nifedipine in a study on threatening PTB between gestational weeks 24 and 34, it was found that a high dose of the drug (20 mg loading dose, daily 120–160 mg for 48 hours, followed by 80–120 mg daily up to 36 weeks) did not have any advantage over a low dose (10 mg loading dose, daily 60–80 mg for 48 hours, followed by 60 mg daily up to 36 weeks) as regards uterine quiescence. In a small Bulgarian study, nifedipine (40 mg four times daily) delayed a large majority of the pregnancies (32 out of 41) with early contractions until normal term, without significant side-effects.

There have been reports of the lack of action of nifedipine in premature contractions. A placebo- controlled, randomized trial demonstrated that 20 mg of nifedipine administered every 4–6 hours did not maintain pregnancy or delay delivery as compared with the placebo group.In a recent trial, nifedipine-maintained tocolysis (80 mg/day orally for 12 days) did not result in a statistically significant reduction in adverse perinatal outcome or in a

significantly lengthened gestational duration in patients with threatening PTB, although the rate of adverse perinatal outcome was lower as compared with the control group. This result suggests that the use of nifedipine does not significantly delay labour. In twin pregnancies where nifedipine tocolysis was administered a switchover to subcutaneous terbutaline following hospitalization for recurrent symptoms of the threatening PTB had a positive impact on pregnancy prolongation and on the neonatal outcome. In another investigation, nifedipine was found to be more effective than indomethacin in inhibiting uterine contractions during the first 2 hours; however, there was no difference between indomethacin and nifedipine in delaying delivery for up to 7 days. Atosiban and nifedipine have been shown not to significantly differ in delaying delivery[17]. This limited evidence suggests no essential differences in the tocolytic efficacy of these two drugs. The oral administration, the lower costs and the possibly lower level of neonatal morbidity favour the use of nifedipine. Nicardipine has the advantageous feature over nifedipine that its intravenous administration is possible, and it is the first choice for some obstetricians in the management of PTB. However, intravenous nicardipine does not increase the duration of pregnancy in comparison with oral nifedipine. The median duration between treatment for PTB and delivery was significantly longer when nifedipine was used . Oral nicardipine is additionally an effective and well-tolerated tocolytic agent. It is able to arrest PTB more rapidly than parenteral magnesium sulphate. Nicardipine was earlier found to be as effective as salbutamol in the treatment of PTB, and it was suggested to have advantages especially in cases of pregnancy accompanied by hypertension, diabetes or maternal cardiopathy

A comparison of nicardipine with salbutamol in a small Tunisian study revealed no significant difference in the efficacies of the two compounds as concerns the average time for the disappearance of uterine contractions. However, fewer secondary adverse effects were detected with nicardipine, which was therefore proposed as the tocolytic of first choice.

Beta blockers

Use of beta-blockers during pregnancy may affect the growing fetus by slowing its heart rate, and lowering its blood sugar level and blood pressure. Beta-blockers can also pass to the infant through breast milk, causing low blood pressure, difficulty breathing and a slowed heart rate[18]. Women should inform their doctor if they are trying to get pregnant or become pregnant while on beta-blockers or are breastfeeding.

Beta-blockers are often administered specifically in order to reduce cardiac output, and thereby reduce the strain of pregnancy on the mother's cardiovascular system. In this regard, it could be argued that some impairment in fetal growth must be accepted to safeguard the mother's health; however, whether a threshold exists for acceptable growth restriction in relation to deteriorating maternal health is difficult to assess in a study like this[19].The final clinical decision towards choice and duration of beta-blockade in pregnancy should be made on an individual basis, with careful attention paid towards fetal growth.

In women with congenital or acquired heart disease treatment with oral beta-blockers was associated with an increased risk of fetal growth restriction.Oral beta-blocker treatment in women with heart disease should be used with caution in pregnancy, and fetal growth is monitored closely.

In Geriatrics

Calcium channel blockers

- ∑ These agents have performed particularly well in preventing stroke in elderly hypertensives. dihydropyridine CCBs reduce stroke by 10% compared with other active therapies.
- ∑ Much of this advantage may be related to their robust BP-lowering effects, which were evident in both the Antihypertensive Long-term Use Evaluation (VALUE) and ASCOT trials[20],where 4-5 mm Hg lower brachial artery systolic BP levels were noted in the first few months of CCB-based therapy compared with ARB- or beta-blocker-based treatment.
- ∑ The BP differences contributed to, but may not have fully accounted for, the superior outcome results of CCB treatment in these trials.
- ∑ CCBs are metabolically neutral and, except for peripheral edema, are relatively free of adverse effects.
- ∑ In principle, the lack of adverse metabolic effects may represent a major advantage of CCBs over diuretics for a population in which the metabolic syndrome/insulin resistance is becoming epidemic. However, this theoretical advantage has yet to be substantiated in clinical trials.
- ∑ On the basis of BP-lowering efficacy and outcomes data, CCBs are acceptable alternatives to diuretics for first-line treatment of hypertension in the elderly and may offer advantages in some patient groups[21],eg, those with the metabolic syndrome.

∑ While acquisition costs are substantially greater for CCBs than for diuretics and some other drug classes, drug costs represent only a fraction of the total cost of care of the hypertensive patient.

Beta blockers

Beta-blockers, usually in lower doses, are frequently prescribed to older people[22]. The safety of beta blockers is generally less when compared to calcium channel blockers. They can cause apnea, sleep deprivation etc in the elderly patients, tolerability of the patient will also be less. They can cause sedation, depression, sexual dysfunction etc

Toxicity

∑ Beta-blocker (BB) and calcium channel blocker (CCB) overdose patients are among the most complex patients with toxicologic[23] problems in the emergency department. They require massive resources both with respect to nursing and physician staff.

Effects

∑ BBs have effects on both the beta-1 and beta-2 receptors to varying degrees. Selectivity for one receptor subtype versus another is lost in overdose. The constellation of symptoms for beta-blockers includes hypotension, bradycardia, low blood sugar[24].

∑ The low blood sugar is a result of inhibition of the release of glucagonin[25] the pancreas.

∑ CCBs have different selectivity for the types of calcium channels which are affected. However, as with BB, CCBs lose their selectivity for peripheral versus central antagonism in overdoses.

∑ Calcium entry into the myocytes[26] in both the heart and peripheral smooth muscle is one of the last steps before muscle contraction.

∑ Calcium entry is also necessary for fusion of synaptic vesicles in the beta cells for insulin release.

∑ The lack of muscle contraction as well as a lack of insulin release leads to the calcium channel blocker constellation of symptoms: hypotension, bradycardia, high blood sugar.

	Heart rate	Stroke volume	Systemic vascular resistance
Beta blockers	Decreased	Depends	Elevated
Calcium channel blockers	Decreased	Decreased	Decreased

Clinical features of overdose

∑ For both BB and CCB overdoses, the heart rate will be low.

∑ For BBs, the stroke volume will vary depending on the beta-blocker and the severity of the overdose[27].

∑ There are some BBs which have intrinsic sympathomimetic effect which makes SV difficult to generalize.

∑ The stroke volume in CCB overdoses will almost always be decreased because of a lack of inotropy[28].

∑ The biggest difference between BBs and CCBs with respect to the hemodynamic properties, is the systemic vascular resistance. in BBs it will be elevated and in CCBs it will be decreased

Management of clinical features and complications

Effect of heart rate

∑ Beta-agonists increase chronotropy, inotropy, and dromotropy. While beta-agonists increase the speed of conduction through the cardiac myocytes, beta-blockers do not generally lead to a total lack of dromotropy or chronotropy[29].

∑ The heart will slow down, but it usually does not stop. This is not the case for CCBs. The patients who die early in their CCB overdose usually slide from bradycardia to asystole and they often have heart blocks[30].

∑ As such, if your patient is identified as being a CCB overdose, consider putting pacer pads on the patient immediately. If your patient has an episode of asystole, it is strongly recommended to insert a venous pacemaker. Having a paced heart does not necessarily mean that there is effective inotropy.

Effect of systemic vascular resistance

∑ In severe BB overdoses, the systemic vascular resistance is, as previously discussed, already very high.

∑ The addition of pressors may have a deleterious effect by decreasing end organ perfusion once the heart rate and stroke volume are starting to come up.

∑ The use of a phosphodiesterase inhibitor such as milrinone is intriguing for BBs as it should increase contractility and decrease SVR, but more needs to be researched in this area.

∑ The systemic vascular resistance in CCB overdoses is easy to understand but will often be frustrating to the physician. Without the ability of calcium to enter the cell and lead to muscle contraction, the addition of pressor agents, even at very high dosages, may not lead to any improvement in the blood pressure.

Additionally, if there were to be some improvement in systemic vascular resistance, without a corresponding increase in inotropy, tissue perfusion again is compromised.

Effect of stroke volume

- ∑ Inotropic support is key in both BB and CCB overdoses.
- ∑ The emerging mainstay of treatment for this lack of inotropy is hyper-insulin euglycemic therapy (HIET), also known as High Dose Insulin therapy (HDI).
- ∑ In this treatment, the patient gets extremely large doses of insulin and enough sugar to maintain euglycemia.
- ∑ Experiments have shown that this improves inotropy.
- ∑ Normally the heart uses glycogen for energy, but during times of stress, it switches to glucose. The addition of supra-physiologic doses of insulin may allow more glucose to enter the heart through the GLUT-4 channel and thus help with inotropy, but it is unclear if this is the mechanism responsible.
- ∑ The important thing with respect to HIET is to rapidly titrate up the insulin level.
- ∑ A reasonable starting point would be 1 U/kg bolus and 1 U/kg/h of insulin. Titration up by 0.5 U/kg/h should be at most every 30 minutes and may be done faster. Because of the time needed to reach steady state (about 30 minutes), additional boluses timed with the increased rates may be considered. Insulin drip rates as high as 8-10 U/kg/h have been maintained for up to 72 hours without complication.
- ∑ If a patient becomes anuric then the amount of fluid the patient is receiving may become an issue and nephrologists may be hesitant to dialyze these patients due to their blood pressure. This has recently become the standard concentration at our hospitals for HDI. Successful implementation of HIET requires intensive nursing care and nurse understanding of appropriate treatment methods and potential pitfalls.
- ∑ One pitfall is what to do with a falling blood sugar. Checking of the blood sugar at least every 30 minutes during the titration phase. Should the patient become hypoglycemic while receiving these very high levels of insulin, the natural instinct is to decrease the insulin. However, this is less than ideal. Instead, more dextrose should be given.
- ∑ As BB overdoses already have low blood sugars, they may require very large amounts of dextrose (D10, D25 or even D50 drips). As CCB overdoses have decreased endogenous insulin secretion, they may require

very little supplemental dextrose. As the kidneys eliminate insulin and their function may be compromised, dextrose support may have to continue long after the insulin has been discontinued.

- ∑ The second important aspect is that the potassium will shift into the cells.
- ∑ Glucagon has traditionally been the drug of choice for the treatment of BB overdoses[31]. It increases cAMP through its own receptor. The usual dose is a bolus of 0.1 to 0.2 mg/kg, then a drip of 0.1-0.2 mg/kg/h. The problem is that this will usually deplete a hospital system, not just a hospital, of its supply of glucagon within 6-12 hours. Glucagon can be started for BB overdoses but additional therapy with HIET, calcium, atropine, and others may be required.
- ∑ Calcium is beneficial and necessary for chronotropy, inotropy and dromotropy. For CCB overdoses as we usually aim for an ionized calcium of between 2 and 3 times normal. For an adult, we may start with an initial bolus of 2-3 g of calcium chloride, and then a drip of 1g of calcium chloride per hour[32]. Calcium levels should be monitored as well as urine output. There has been at least one death attributed to hypercalcemia in a child as a result of anuria and subsequent hypercalcemia, but the ionized calcium was much higher than 2-3 times normal.

Toxicity Treatments of Calcium Channel Blockers

Initial management includes[33] rapid establishment of vascular access, supplemental oxygen, cardiac monitoring, and frequent blood pressure measurement. Because of the rapid onset of toxicity with normal-release preparations, induction of emesis is dangerous and contraindicated.

Focus on 4 Elements

- STABILIZATION
- DECONTAMINATION
- ANTIDOTE(S)
- SUPPORTIVE THERAPY Stabilization

Correct immediate life threatening complications. For CCB overdose most commonly hypotension and bradycardia. Intubation (Atropine).Atropine can be administered in the usual(0.5 to 1 mg, up to 3 mg for adults, and 0.02 mg/kg for children, minimum 0.1 mg)[34]. Atropine's effect has often been disappointing and short-lived, and multiple

doses risk anticholinergic poisoning. If symptomatic bradycardia or heart block persists, the next step is a pacemaker or chronotrope such as isoproterenol. A bolus of crystalloid fluid, 20 mL/kg or more, should also be infused early. Intravenous calcium salts have traditionally been given to most patients. Their effect on contractility is considerable, but their effect on bradycardia, AV block, and peripheral vasodilation is often poor.

GI Decontamination

Gastrointestinal (GI) decontamination may be considered because calcium channel blockers (CCBs) slow gastric motility and delay gastric emptying. Options include activated charcoal, gastric lavage, and whole-bowel lavage.

Activated charcoal

Activated charcoal has been demonstrated to significantly absorb immediate-release medications within 1 hour of ingestion and extended-release medications as long as 4 hours after ingestion. If the ingested dose is known, a 10:1 charcoal-to-drug weight ratio can be used to calculate the optimal dose of activated charcoal to completely bind the ingested drug. Otherwise, a 1-g/kg initial dose is recommended.

The potential benefit of decreased drug absorption must be weighed against the risk of gastric distention with subsequent aspiration. Any conditions predisposing to aspiration (eg, altered mental status, nausea, seizures) are contraindications to administration of activated charcoal. In patients with severe toxicity, interventions such as antiemetics and intubation with satisfactory sedation should be performed before administration of activated charcoal via a nasogastric tube.

Gastric lavage

Gastric lavage is especially important for patients who may have taken a large dose of medication[35] or for those who have ingested sustained-release preparations.

However, the usefulness of gastric lavage is still debated. Weigh the risk of aspiration against the probability of removing undigested medications remaining in the stomach. Placement of an endotracheal tube protects the airway during the lavage and reduces the risk of aspiration.

If a gastric lavage is performed, use a large-bore orogastric hose. Sustained-release tablets, which are large and resistant to breakdown, may not fit through a simple Salem sump nasogastric tube.

Whole-bowel irrigation

If a patient has ingested a large number of CCB tablets, especially sustained-release tablets, the pills may aggregate to form bezoars and can be continuously absorbed for long periods. In this situation, the clinician may consider whole-bowel irrigation with polyethylene glycol (PEG). In adults, administer PEG at a rate of 1-2 L/h for 4-6 hours or until rectal effluent becomes clear. Whole-bowel irrigation is absolutely contraindicated if bowel sounds are absent. This suggests that an ileus, secondary to shock or drug toxicity, has occurred[36]. In these circumstances, large volumes of intestinal fluid lead to massive bowel distention, risking bowel perforation.

Coadminister activated charcoal in a 1 g/kg initial dose; activated charcoal administration can be repeated every 4 hours at half the initial dose. Because gastric emptying may be delayed, activated charcoal may be considered even if the patient presents several hours after the ingestion.

In children, care must be used never to administer sorbitol-containing products, because of the potential to induce electrolyte disturbances. In the rare instance of a large ingestion in a preschool age child, whole-bowel irrigation with PEG solution (Go-Lightly) may be used. The potential risks of GI decontamination should be kept in mind e.g. gastric lavage should probably be withheld in patients who are already bradycardia or have conduction disturbances. There is potential for delayed toxicity by sustained release preparations of calcium channel blockers due to delayed absorption

Calcium Salts

Intracellular hypocalcemia is prevalent in CCB overdose[37]. Therefore, calcium salts (gluconate or chloride) are logical first-line agents. It is well documented that the administration of calcium prior to the infusion of verapamil[38] or diltiazem can blunt the hypotensive response that often accompanies the intravenous use of these medications. In overdose, the results are often much less dramatic. Calcium may modestly improve conduction, inotropy, and blood pressure but significant ingestions rarely respond to calcium as the sole agent.The initial recommended dose is 13 to 25 mEq for the average-sized adult and may be followed by repeat boluses or by an infusion. If concomitant cardiac glycoside toxicity is suspected, parenteral administration of calcium should be approached cautiously. There is a theoretical risk of potentiating toxic intracellular calcium concentrations associated with digitalis toxicity.

Administration of calcium salts:

- Used to overcome CV effects of CCBs
- Calcium chloride: 3x bioavailable calcium than Ca-gluconate; nonacidotic patients
- Calcium gluconate: preferred in acidotic patients; less bioavailable calcium

Supportive Therapy [39]

Vasopressors

If volume expansion does not raise the blood pressure to the desired level, vasopressors (eg, dopamine, epinephrine) can stimulate myocardial contractility and cause vasoconstriction, thus supporting blood pressure and cardiac output. In the hypotensive and bradycardic patient, administer dopamine initially at medium-to-high doses early to support the heart rate. Failure to respond to the maximal dose of dopamine should prompt the addition of norepinephrine.

Various combinations of dopamine, norepinephrine, epinephrine, phenylephrine, vasopressin, and metaraminol have all been used in cases of hypotension and shock

Glucagon

Glucagon promotes calcium entry into cells via stimulation of a receptor that is considered to be separate from adrenergic receptors. Note that the actions of glucagon oppose those of insulin, yet both have beneficial effects in treating CCB toxicity.

Glucagon[40] is supplied as a lyophilized powder and must be reconstituted. The manufacturer includes an ampule of propylene glycol that can be used for single injections. However, administration of large amounts of propylene glycol (the same diluent that is used for phenytoin) causes hypotension and dysrhythmias.

For this reason, glucagon infusions and repeat doses should be reconstituted in D5W to avoid giving large amounts propylene glycol. If a positive clinical effect is noted after an initial IV bolus dose of 5-10 mg, an infusion can be continued at 5-10 mg/h. Note that such high-dose usage of glucagon exhausts a typical hospital pharmacy's supply within a few hours.

Administer glucagon (5-10 mg IV bolus up to 15 mg, followed by an infusion) after fluid resuscitation is performed for persistent hypotension. Since glucagon dilates the lower esophageal sphincter, vomiting and aspiration may occur; therefore, this treatment should only occur in an awake patient who can protect his or her own airway if

vomiting occurs. Pretreatment with an antiemetic and large-bore bedside suction should be used. If an initial bolus of 5 mg of glucagon has no effect on blood pressure, it is reasonable to double the dose. The recommended infusion rate for adults is 5-10 mg/h. The recommended pediatric dose is 50 mcg/kg IV over 5 minutes, followed by an infusion at 0.07 mg/kg/h.

Transvenous Pacing

Assists with electrical conduction.Does not correct negative inotropic effects of CCB or hypotension

Toxicity Treatments for Beta Blocker Toxicity

A. Airway support, adequate ventilation and oxygenation, IV access, foley catheter[41]

B. Hypotension

The following interventions are listed in order of importance for the treatment of Beta-adrenergic blocker poisoning.

1. Intravenous Fluid Boluses

They(10 ml/kg) may help restore blood pressure but the patient needs to be monitored closely for pulmonary edema.

2. Glucagon: Glucagon has become an accepted antidote to beta-blocker poisoning because it stimulates cAMP synthesis independent of the beta-adrenergic receptor.

Glucagon has shown positive inotropic and chronotropic effects despite beta-receptor blockade in numerous animal models and in humans.

Several animal studies and case reports have also demonstrated a benefit in CCB toxicity, though many treatment failures have been noted as well. Side effects include dose-dependent nausea and vomiting, hyperglycemia, hypokalemia, and allergic reactions.2-5 mg IV push (may give up to 10 mg IV push), then 2-5 mg/hour (may titrate up to 10 mg/hr as necessary) in normal saline and titrate as necessary. Do not use the phenol-containing diluent supplied by the manufacturer as it is intended for IM administration.

3. Catecholamines

Most severely poisoned patients will require addition of catecholamines to accelerate the heart rate (chronotropy), enhance AV conduction (dromotropy), and restore tone to peripheral vessels (vasotropy). Most experience and

success have been reported with isoproterenol and dopamine, often in combination. Isoproterenol infusion can begin at 2 to 10 µg/min (0.1 µg/kg/min in children), but much higher rates may be needed. Unlike β-blocker overdose, however, the β-adrenergic receptor remains intact, and lower catecholamine infusion rates have generally been effective (e.g., dopamine 5 to 30 µg/kg/min). Epinephrine, norepinephrine, and dobutamine have also led to successful outcomes. Isoproterenol or dobutamine alone may not reverse or may even exacerbate peripheral vasodilation; therefore, it is logical to add a vasopressor such as norepinephrine, metaraminol, phenylephrine, or high-dose dopamine.

Continuous intra arterial and pulmonary artery pressure monitoring are required during prolonged treatment with the following agents.

a. Isoproterenol (direct Beta-1 and Beta-2 agonist)

O.1 mcg/kg/min and titrate rapidly to effect. Fantastically high infusion rates as high as 800 mcg/min have been reported in cases of severe beta-blocker poisoning.Beta-2 mediated peripheral vasodilation may potentially exacerbate hypotension.

b. Dobutamine (direct Beta-1 agonist; theoretically useful but clinical experience is limited)

Dobutamine is likewise a logical agent for BB toxicity but it is not always effective. Pure alpha agonists should be utilized with caution in BB poisoned patients because the unopposed alpha stimulation may result in heart failure.2.5 mcg/kg/min and titrate rapidly to effect

c. Epinephrine (direct Beta-1 Agonist, Beta-2 Agonist, Alpha-1 agonist)

1 mcg/kg/min and titrate rapidly to effect. As much as 6 mg has been administered over one hour for the treatment of beta-blocker poisoning.

4. Amrinone or Milrinone:

Inotropes which increases intracellular cAMP activity by inhibiting the enzyme phosphodiesterase III. As seen for glucagon, increased cardiocyte cAMP activity increases intracellular calcium, which improves inotropy. However, increase intracellular cAMP activity in vascular smooth muscle produces relaxation, peripheral vasodilation, and reduced systemic vascular resistance, thus potentially exacerbating hypotension. They must not be considered a first-line agent, and should be used in combination with another vasopressor/inotrope such as epinephrine.

Amrinone: 1 mg/kg IV bolus over 2 minutes followed by 5 to 20 mcg/kg per minute.

Milrinone: 50 mcg/kg IV bolus over 2 minutes, then 0.25-1.0 mcg/kg/min.

5. Other Treatment Modalities to Consider for Refractory Hypotension

Calcium: Case reports have demonstrated that calcium chloride may be effective in treating hypotension from isolated beta-blocker poisoning as well as combined calcium channel blocker and beta-blocker poisoning.

Calcium Chloride 1-2 grams (10-20 ml 10% CaCl2) IV bolus over 5 minutes, repeat every 10-20 minutes.

Insulin Therapy

Insulin works to reverse the effects of beta blocker/ calcium-channel blocker overdose by 2 mechanisms. In the toxicity-induced shock state, cardiac cells pref-erentially use carbohydrate instead of free fatty acid for metabolism, which is compensated by hepatic glycogenolysis[42] Calcium-channel blockers also inhibit pancreatic insulin secretion via blockade of L-type calcium channels on islet cells. This causes insulin deficiency, hyperglycemia, and acidosis. High-dose insulin/euglycemic therapy enables cardiac cells to metabolize carbohydrates without increasing myo- cardial oxygen demand. It also allows cells to take in glucose from the bloodstream via activation of the glucose transporter family of receptors, improving both hyperglycemia and acidemia. It is theorized that insulin therapy is more effective than calcium, glucagon, or epinephrine because it does not induce free fatty acid use or increase myocardial work. Insulin has also been shown to improve myocardial contractility and vasomotor tone and to increase the uptake of lactate, all of which aid in the resolution of shock in the beta blocker and calcium-channel blocker overdose patient.

Hyperinsulinemic Euglycemia (Experimental but promising)

Insulin has demonstrated positive inotropic effects when administered in conjunction with dextrose in experimental canine models of beta-blocker poisoning. This inotropic effect is believed to be due to better carbohydrate delivery and utilization by cardiac cells, as well as increases in intracellular calcium. High dose insulin has not been evaluated in human cases of beta-blocker poisoning.

Hyperinsulinemic euglycemia[43] (HIE) refers to the use of high doses of insulin (1-10 units/kg) with concurrent glucose infusion to maintain euglycemia. The rationale for this approach is twofold. First, insulin by itself has inotropic properties. Second, it promotes the more efficient utilization of glucose by myocytes during stressed

states. HIE was recently shown to improve cardiac performance and increase survival in canine models of propranolol and verapamil toxicity. This approach is showing promise at the bedside as well. Patients who remained hypotensive despite calcium, glucagon, and vasopressors were treated with HIE. Patients shows improved hemodynamic parameters and all survived to hospital discharge.

This therapy takes effect gradually, often requiring as long as an hour to improve the patient's hemodynamic status, when dosing is optimized. Because of this slow onset, the need for euglycemic insulin therapy must be anticipated and the infusion should be instituted when it first becomes apparent that the patient will suffer refractory hypotension due to lack of response to stan- dard therapy (including glucagon). High-dose insulin therapy will require frequent glucose monitoring (as often as every 15 minutes or more frequently) and glucose supplementation until the patient's serum glucose is stabilized on a given insulin dose. Serum potassium will shift to the intracellular compartment during therapy and back into serum when therapy is terminated, so potassium should be supplemented conservatively and with caution. As with any insulin infusion, the intra- venous tubing used must be flushed with insulin- containing solution to saturate binding sites on the tubing with insulin to ensure delivery of prescribed amounts of insulin.

Currently, an insulin bolus of 1 unit/kg body weight has become an accepted starting point, fol-lowed by insulin infusions started in the range of 1 unit/kg body weight/h and titrated upward to as high as 10 units/kg/h, depending on the degree of hypotension present. Toxicology consultation is advised to assist with dosing. This therapy should be started as early as possible, before the patient is in ex- tremis. Insulin dosing requirements for beta blocker-poisoned patients may be lower than those required to treat calcium-channel blocker-poisoned patients. Insulin therapy requires time to produce hemody- namic improvement, and care should be taken not to taper insulin therapy too rapidly upon hemodynamic improvement or the benefit may be lost.

6. Non-pharmacologic Interventions

Intra-aortic balloon counter pulsation

The Intra-Aortic Balloon Pump[44] (IABP) is a circulatory assist device that is used to support the left ventricle. The IABP uses counterpulsation where aortic blood is displaced with the inflation and deflation of the balloon catheter, which is timed to the cardiac cycle[19].Couterpulsation provides both an augmented diastolic arterial pressure and an

decreased end-diastolic pressure. The balloon is connected to a console that regulates the inflation or deflation of the balloon with the passage of helium. Helium is used as it is easily dissolved in blood and prevents the risk of air emboli if the catheter ruptures[19].

Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) is a technique that temporarily takes over the function of the heart and lungs during surgery, maintaining the circulation of blood and the oxygen content of the body. The CPB pump itself is often referred to as a heart–lung machine or "the pump". Cardiopulmonary bypass pumps are operated by perfusionists, medically directed by anesthesiologists, and surgically directed by cardiac surgeons who connect the pump to the patient's body.

CPB is a form of extracorporeal circulation. Cardiopulmonary bypass is commonly used in heart surgery because of the difficulty of operating on the beating heart.

CPB mechanically circulates and oxygenates blood for the body while bypassing the heart and lungs. It uses a heart–lung machine to maintain perfusion to other body organs and tissues while the surgeon works in a bloodless surgical field. The surgeon places acannula in right atrium, vena cava, or femoral vein to withdraw blood from the body. The cannula is connected to tubing filled with isotonic crystalloid solution. Venous blood that is removed from the body by the cannula is filtered, cooled or warmed, oxygenated, and then returned to the body. The cannula used to return oxygenated blood is usually inserted in the ascending aorta, but it may be inserted in the femoral artery.

The patient is administered heparin to prevent clotting, and protamine sulfate is given after to reverse effects of heparin. During the procedure, hypothermia is maintained; body temperature is usually kept at 28ºC to 32ºC (82.4–89.6ºF). The blood is cooled during CPB and returned to the body. The cooled blood slows the body’s basal metabolic rate, decreasing its demand for oxygen. Cooled blood usually has a higher viscosity, but the crystalloid solution used to prime the bypass tubing dilutes the blood.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is a simplified form of CPB sometimes used as life-support for newborns with serious birth defects, or to oxygenate and maintain recipients for organ transplantation until new

organs can be found. The term extracorporeal membrane oxygenation (ECMO) was initially used to describe long-term extracorporeal support that focused on the function of oxygenation. Subsequently, in some patients, the emphasis shifted to carbon dioxide removal, and the term extracorporeal carbon dioxide removal was coined. Extracorporeal support was later used for postoperative support in patients following cardiac surgery. Other variations of its capabilities have been tested and used over the last few years, making it an important tool in the armamentarium of life and organ support measures for clinicians. With all of these uses for extracorporeal circuitry, a new term, extracorporeal life support (ECLS), has come into vogue to describe this technology.

C. Arrhythmias

Arrhythmias are usually bradyarrhythmias, making atropine the first-line intervention. It is not uncommon for beta-blocker induced bradyarrhythmias to be refractory to atropine therapy. Cardiac pacing will generally follow atropine for the treatment of refractory bradyarrhythmia.

Atropine: 0.5 to 1.0 mg (0.02 mg/kg in kids) IV every 2 to 3 minutes to a maximum dose of 3 mg.

D. Bronchospasms

Brochospasms can occur as a part of beta blocking activity of the drug. Aerosolized or nebulized Beta-2 agonist such as albuterol

E. Seizures

Diazepam and, if necessary, phenobarbital.

Conclusion

Calcium channel blockers appear to be safe for mother and fetus when used for the treatment of hypertension, cardiac arrhythmias, angina and pre-term labor in pregnant women. Teratogenicity with these agents has been demonstrated in animals, but no cases of possible human malformation or deformity have been reported. However, it must be recognized that human studies have been very limited. It is recommended that a drug only be used during pregnancy if the potential benefit outweighs any potential risk to the fetus.

Conflict of Interest

The authors do not have any conflict of interest.

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