بسم الله الرحمن الرحیم

β/Calcium Channel Blockers Poisoning

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18 July 2021

Outlines

- Introduction (case presentation)
- Clinical manifestations
- Diagnosis
- Treatment

Bata blockers poisoning

- **Hypertension and other cardiovascular disorders**
- **migraine headaches,**
- **hyperthyroidism, tremor,**
- **anxiety,**
- **panic attacks**
- **…..**

Case 1

- A 26 yo woman
- 60 x 40mg tablets of Propranolol an hour earlier
- confused state
- GCS was 13, Blood glucose was 100.
- HR 60 bpm, BP 105/40 mmHg
  Sats 98% on 6L, RR 20,
- The ambulance have established IV access, but given nothing.
- On arrival the patient's GCS is 9-10 and within 5 minutes of arrival the patient has a generalized tonic colonic seizure lasting less than 30 seconds. ECG, Normal

Case 1

- The patient’s hemodynamic status changes.
- Vitals are:
  HR 45bpm
  BP 80/50 mmHg.

- ???????

Pharmacokinetics

	Adrenergic Blocking Activity	Partial Agonist Activity (ISA)	Membrane-Stabilizing Activity	Vasodilating Property	Log D[b]	Protein Binding (%)	Oral Bioavailability (%)	Half-Life (h)	Metabolism	Volume of Distribution (L/kg)
Acebutolol	β_1	Yes	Yes	No	0.52	25	40	2–4	Hepatic or renal	1.2
Atenolol	β_1	No	No	No	-2.03	<5	40–50	5–9	Renal	1
Betaxolol (tablets and ophthalmic)	β_1	No	Yes	Yes (calcium channel blockade)	0.56	50	80–90	14–22	Hepatic or renal	4.9–8.8
Bisoprolol	β_1	No	No	No	0.11	30	80	9–12	Hepatic or renal	3.2
Bucindolol[a]	β_1, β_2	β_2	NA	Yes (β_2 agonism and α_1 blockade)	NA	NA	30	8 +/− 4.5	Hepatic	NA
Carteolol (ophthalmic)	β_1, β_2	Yes	No	Yes (β_2 agonism and nitric oxide mediated)	-0.42	30	85	5–6	Renal	NA
Carvedilol (long acting form available)	α_1, β_1, β_2	No	Yes	Yes (α_1 blockade, calcium channel blockade)	3.16	~98	25–35	6–10	Hepatic	2
Celiprolol	α_2, β_1	β_2	NA	Yes (β_2 agonism, nitric oxide mediated)	NA	22–24	30–70	5	Hepatic	NA

Pharmacokinetics

Esmolol	β_1	No	No	No	-0.22	50	NA	~8 min	RBC esterases	2
Labetalol	$\alpha_1, \beta_1, \beta_2$	β_2	Low	Yes (α_1 blockade, β_2 agonism)	0.99	50	20–33	4–8	Hepatic	9
Levobunolol (ophthalmic)	β_1, β_2	No	No	No	0.56	NA	NA	6	NA	NA
Metipranolol (ophthalmic)	β_1, β_2	No	No	No	0.53	NA	NA	3–4	NA	NA
Metoprolol (long-acting form available)	β_1	No	Low	No	-0.34	10	40–50	3–4	Hepatic	4
Nadolol	β_1, β_2	No	No	No	-0.84	20–30	30–35	10–24	Renal	2
Nebivolol	β_1	No	NA	Yes (nitric oxide mediated)	NA	98	12–96	8–32	Hepatic	10–40
Oxprenolol	β_1, β_2	Yes	Yes	No	NA	80	20%–70%	1–3	Hepatic	1.3
Penbutolol	β_1, β_2	Yes	No	No	2.05	90	~100	5	Hepatic or renal	NA
Pindolol	β_1, β_2	Yes	Low	No	-0.19	50	75–90	3–4	Hepatic or renal	2
Propranolol (long-acting form available)	β_1, β_2	No	Yes	No	0.99	90	30–70	3–5	hepatic	4
Sotalol	β_1, β_2	No	No	No	-1.82	0	90	9–12	Renal	2
Timolol (tablets and ophthalmic)	β_1, β_2	No	No	No	-1.99	60	75	3–5	Hepatic or renal	2

[a]Xenobiotics in italics are not approved by the Food and Drug Administration. [b]Log D is the octanol/water partition coefficient at a pH of 7.
ISA = intrinsic sympathomimetic activity; NA = information not available; RBC = red blood cell; NA = not available.
Information from references 75, 77, 96, 169, 172, 175, 191, 251, and 268.

- Toxicokinetic
- Toxic Dose
- One Pill can kill

Clinical Manifestations

System	*Manifestations*
Cardiovascular	Bradycardia, Hypotension, Conduction delays, Na blocking effect (propranolol) Prolonged QRS(propranolol) – QT (sotalol) Acebutolol → torsade de pointe,
Central Nervous System	Altered mental status, Coma, seizures
Pulmonary	Bronchospasm(unusual)
Metabolic	Acidosis, hypoglycemia(rare), Hyperkalemia

Diagnosis

- History, Clinical evalaution
- Laboratory testing:
- monitoring serum glucose and potassium levels.
- VBG/ABG
- Urine toxicology (Co-ingestion)
- CBC, BUN/Cr, ALT, AST, PT, PTT, INR, Na, Ca, P, Alb, Mg, …..
- ECG
- Echocardiogram

Management

- **ABCD (laryngoscopy)(BS)**
- **Bradycardia:**
- Atropine
- Glucagon

Atropine

- 1 mg IV (5-min intervals) until desired response
- Maximal dose: 3 mg IV is fully vagolytic

Glucagon

- 3-5 mg (1-2 min) …..> 10 mg IV bolus
- Glucagon infusion at the "response dose" per hour.

- **Precautions:**
- vomiting with risk of aspiration,
- Hyperglycemia
- mild hypocalcemia

Management
Hypotension

- **Isotonic IV fluid (20 cc/kg) (Range: 10-40 cc/kg), CVC (CVP)**
- **Glucagon (Antidote)**

Glucagon

- 3-5 mg (1-2 min) …..> 10 mg IV bolus
- Glucagon infusion at the "response dose" per hour.

- **Precautions:**
- vomiting with risk of aspiration,
- Hyperglycemia
- mild hypocalcemia

Calcium

- Calcium gluconate; 3 g;
- Calcium chloride: 1g slow IV push of 10% solution
- Persistent hypotension: same dose every 10 to 20 minutes up to a total of 9 g.

- **Precautions**

Administer slowly (not to exceed 0.5-1 mL/min) to avoid extravasation

Calcium

- It is important to monitor [Ca2+] every 30 to 60 minutes
- The main limitation of using CaCl2, however, is that it has significant potential for causing tissue injury if extravasated we recommend administration through a central venous line, intraosseous line or peripheral line if no other route is accessible.
- Adverse effects: nausea, vomiting, flushing, constipation, confusion, hypercalcemia, and hypophosphatemia.

Insulin

- 1 unit/kg of regular insulin + with 0.5 gm/kg of dextrose
- If BS > 300 mg/dL: No bolus (dextrose)
  - Infusion of regular insulin:1 unit/kg/h
  - Infusion dextrose: 0.5 gm/kg/h
- Blood Glucose: 100-250 mg/dL
- Complications of HDI: hypoglycemia and hypokalemia
- Glucose should be monitored every 15 to 30 minutes until stable and then every 1 to 2 hours
- BP: reassessed every 10 to 15 minutes, and if it remains depressed, the insulin infusion should be increased up to 10 units/kg/h as required (rarely higher).
- Concentrating the insulin infusion to 10 units/mL prevents fluid overload from large doses of insulin

Insulin

- Response: 15 to 60 minutes,
- Monitoring glucose and electrolytes for several hours after insulin is discontinued
- Start catecholamine infusion before the full effects of insulin are apparent.

Epinephrine (adrenaline)

- 1 mcg/min IV; titrate to effect
- **Precautions**
- Heart failure;
- Organic disease of the AV node and its branches
- Coronary artery disease, coronary insufficiency, diabetes, or hyperthyroidism and sensitivity to sympathomimetic amines;
- Heart rate >110 BPM: decrease infusion rate or temporarily discontinue infusion

Epinephrine (adrenaline)

- Echocardiographic monitoring
- Direct invasive measures of determining cardiac performance
- The infusion should be stopped immediately if the patient becomes more hypotensive or develops congestive heart failure.

Phosphodiesterase inhibitors

Amrinone, Milrinone

- Limited Experience
- limited by hypotension secondary to peripheral vasodilation.
- Difficult to titrate: long half-lives
- (30–60 minutes for milrinone,
- 2–4 hours for amrinone,
- ~2 hours for enoximone).
- …..> not routinely recommended, especially in patients without arterial and pulmonary artery pressure monitoring.

Amrinone

- 0.75 mg/kg IV
- 5-10 mcg/kg/min maintenance infusion;
- 0.75 mg/kg may be given 30 min after therapy begins
- not to exceed 10 mg/kg/d

Mechanical Life Support

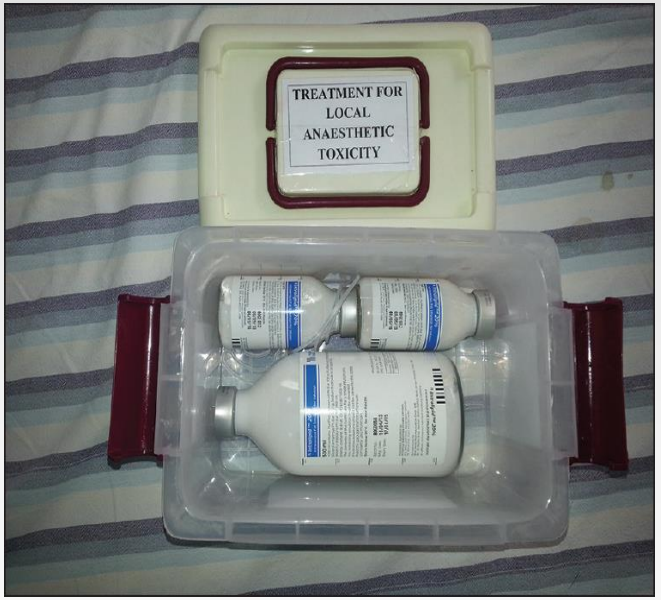
- Venoarterial extracorporeal membrane oxygenation (VA-ECMO), IABP
- In one report, a neonate was supported with VA-ECMO for 5 days and survived neurologically intact.
- In another series, a total of 13 of the 17 patients had long-term survival.
- for patients with cardiac arrest or refractory shock unresponsive to standard therapy.
- Given the high risk of complications, including severe bleeding, stroke, and intracranial hemorrhage, should be reserved for severely poisoned patients who are failing medical therapy.

Lipid Emulsion

- Cardiac arrest or circulatory failure that does not respond to usual therapy, especially if mechanical life support is not promptly available

The optimal dose: unknown.

- 1.5 mL/kg of 20% lipid emulsion
- Infusion: 0.25 mL/kg/min
- The bolus can be repeated in 3 to 5 minutes if necessary.
- Total dose: < 8 mL/kg



Lipid Emulsion

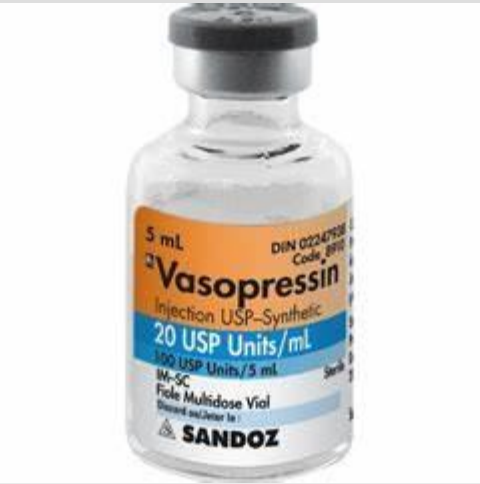
Lipid Emulsion

- However, there is a report of two cases of asystole developing immediately after IV lipid emulsion in two cases of β-adrenergic antagonist overdose.
- The authors postulate that asystole in these cases may have been caused by interaction of lipid emulsion with other resuscitation medications or “brief lack of oxygen in lipid-laden blood.”
- Because there is evidence that lipid emulsion can cause mechanical problems with VA-ECMO circuits, that lipid emulsion be withheld and the patient supported with cardiopulmonary resuscitation if ECLS can be initiated promptly

Lipid Emulsion

- This has been reported in vitro and clinically when lipid emulsion was used as parenteral nutrition for patients on ECMO but has not been reported in the overdose setting.
- Given these concerns and limited evidence supporting its efficacy in β-adrenergic antagonist overdose, lipid emulsion should not be used routinely in patients poisoned with β-adrenergic antagonists.
- It is reasonable to administer lipid emulsion in patients poisoned with a lipid-soluble β-adrenergic antagonist who have cardiac arrest or circulatory failure that does not respond to usual therapy especially if mechanical life support is not promptly available

Vasopressin



- Vasopressors
- Shock states
- Cardiopulmonary arrest
- Vasopressin was used without effect in a patient in cardiac arrest after metoprolol poisoning who subsequently survived after initiation of mechanical life support.
- The American Heart Association has removed vasopressin from its most recent Adult Cardiac Arrest Algorithm.

Methylene blue

- Vasoconstrictor
- Refractory vasodilatory shock
- Atenolol and amlodipine.
- Dose: 1 mg/kg/ over 10 minutes (improvement in blood pressure 20 minutes after)
- The routine use of either vasopressin or methylene blue is not recommended in patients with β-adrenergic antagonist poisoning

Ventricular Pacing

- Pacing increases the heart rate with no increase in cardiac output or blood pressure.
- Decreases blood pressure perhaps secondary to loss of organized atrial contraction or because of impaired ventricular relaxation
- Unresponsive to pharmacologic therapy
- Torsade de pointes unresponsive to magnesium
- Ventricular pacing is not recommended except for heart rate control in patients with an IABP.

Magnesium sulfate

- 2 g IV over 1-2 min; a second 2 g bolus;
- infusion of 3-20 mg/min
- Patients not responding to the initial bolus
- Recurrence of arrhythmias
- **Precautions:**
- heart block in digitalized patients;
- Monitor respiratory rate, deep tendon reflex,
- Renal function when electrolyte is administered parentally;
- In overdose, calcium gluconate, 10-20 mL IV of 10% solution, can be given as antidote for clinically significant hypermagnesemia

Special Circumstances

- **Sotalol:**
- correction of hypokalemia and hypomagnesemia,
- Overdrive pacing and magnesium infusions for prevention of recurrent episodes of Torsade
- Lidocaine, nicorandil?
- **Peripheral vasodilation** (Carvedilol, Labetalol, ..):
- **N**orepinephrine or phenylephrine,
- glucagon

Special Circumstances

- **Membrane-Stabilizing Effects (Acebutolol, Betaxolol, Carvedilol, Oxprenolol, and Propranolol):**: **sodium bicarbonate**
- Wide QRS, ventricular dysrhythmias, or severe hypotension
- Sodium bicarbonate would not be expected to be beneficial in sotalol-induced ventricular dysrhythmias and, by causing hypokalemia, may actually increase the risk of torsade de pointes
- 1 to 2 mEq/kg given as an IV bolus. This should either be followed by an infusion or by repeated boluses as needed.

Hypotension

- **Isotonic IV fluid (20 cc/kg)**
- **Glucagon**
- **Calcium (chloride or gluconate)**
- **Insulin/Glucose**
- **Epinephrine, Norepinephrine, Dopamine, Isopretrenol, ….**
- **Amrinone, Milrinone**
- **IABP, ECMO**
- **Lipid emulsion**

Hypotension

- In critically ill patients, there may not be enough time for this stepwise approach, and multiple treatments may be started simultaneously.
- Advanced hemodynamic monitoring, when available, is advisable to guide therapy for all patients receiving catecholamine pressors or phosphodiesterase inhibitors.

Management

- Seizure: Benzodiazepines
- Hemodialysis (Atenolol, Nadolol, sotalol, and Acebutolol)
- Technically difficult because of hypotension and bradycardia
- Reasonable in certain circumstances such as patients with severe toxicity from a water-soluble β-adrenergic antagonist whose blood pressure is maintained with mechanical life support.

- **Consider hemodialysis *only when treatment with glucagon and other pharmacotherapy fails*.**

Management

- **Gastric lavage :** within 1-2 hours of ingestion (toxic dose).
- **WBI:** sustained release; (1–2 L in adults)
- **Activated charcoal**: within 4 h of ingestion (1 g/kg PO)
- MDAC: (0.5 g/kg every 4–6 hours), sustained-released agents
- Do not mix with milk, or ice cream (decreases absorptive properties)
- MDAC should not be administered to a patient with inadequate GI function (eg, hypotension, diminished peristalsis sounds)

- **Precautions:** charcoal ileus

- The patient’s hemodynamic status changes.
- Vitals are:
  HR 45bpm
  BP 80/50 mmHg.

- ???????

SUMMARY

- Supportive and symptomatic care,
- Atropine
- Glucagon, calcium salts
- HDI/Glucose
- Catecholamine infusions (Adrenaline,…..)
- Phosphodiesterase inhibitors (Amrinone,..)
- IV lipid emulsion
- Mechanical support of circulation (ECMO, IABP, …)
- Pacing

Disposition

Regular: 6 hours

Sotalol: 12h (ventricular dysrhythmias 9 hours after ingestion).

Extended-release: 24-hour observation.

SUMMARY

- In addition to supportive and symptomatic care,
- The most important initial therapies: glucagon and calcium salts
- HDI together with glucose is recommended early in the course of treatment if the response to the initial therapy is not rapid and complete.
- Catecholamine infusions should be closely monitored and large doses are typically required.
- Patients who fail treatment with glucagon, insulin, and catecholamines are critically ill and may respond to IV lipid emulsion therapy, phosphodiesterase inhibitors, or mechanical support of circulation.
- Fortunately, this aggressive therapy is rarely required.

CALCIUM CHANNEL BLOCKERS

TABLE 60–2 Classification of Calcium Channel Blockers Available in the United States

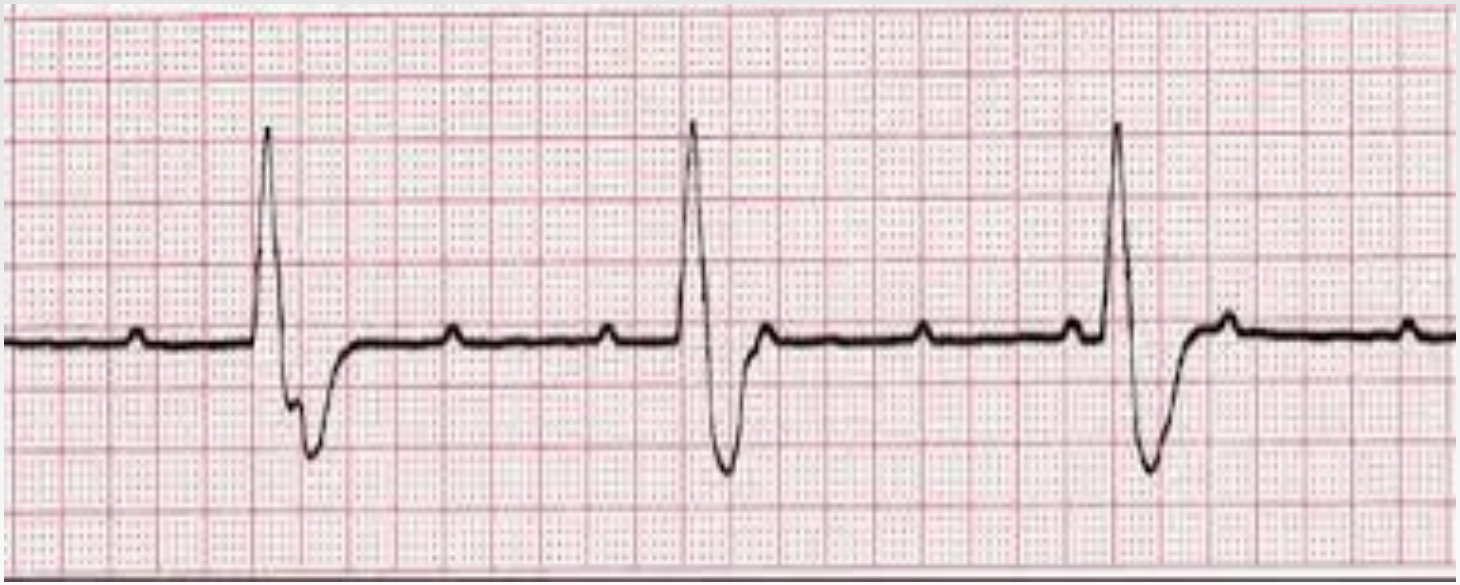
Class	*Specific Compounds*	*Volume of Distribution (L/kg)*	*Time to Peak* Concentrations (h)*
Phenylalkylamine	Verapamil	3–5	1–2
Benzothiazepine	Diltiazem	5.3	2–4
Dihydropyridines	Amlodipine	21	6–12
	Clevidipine	0.17	<1
	Felodipine	10	2.5–5
	Isradipine	3	1–2
	Nicardipine	8.3	1–4
	Nifedipine	0.75	2.5–5
	Nimodipine	2	1–2
	Nisoldipine	1.6	>6

*All are oral ingestion of an immediate release formulation: at therapeutic doses.

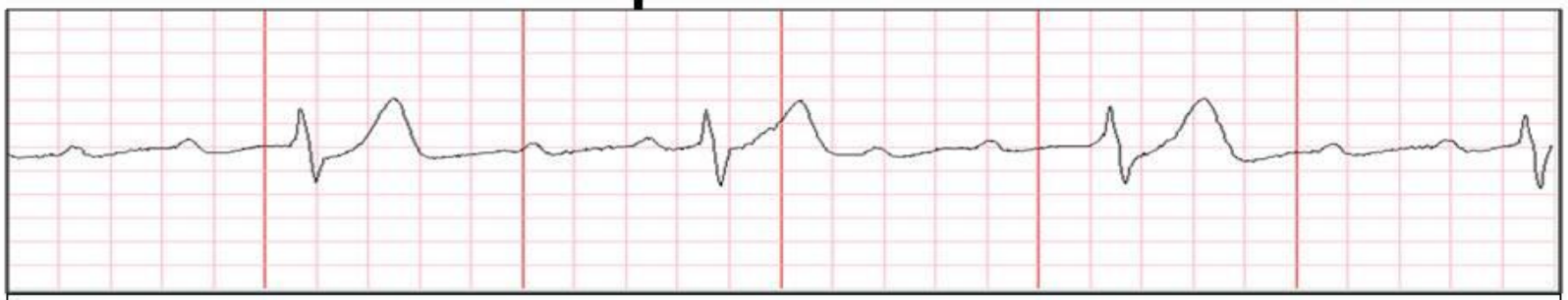
Clinical manifestations

- Nausea and vomiting: not a typical feature
- Fatigue, dizziness, and lightheadedness.
- Hypotension and bradycardia, Reflex tachycardia (Mild, Mod. dihydropyridine)
- Syncope, altered mental status, coma, and sudden death
- Idioventricular rhythms, and complete heart block, (nondihydropyridine)
- Junctional escape rhythms
- ARDS
- Hyperglycemia

Complete Heart Block or Third-Degree Atrioventricular (AV) Block



Third Degree AV Block
aka Complete Heart Block

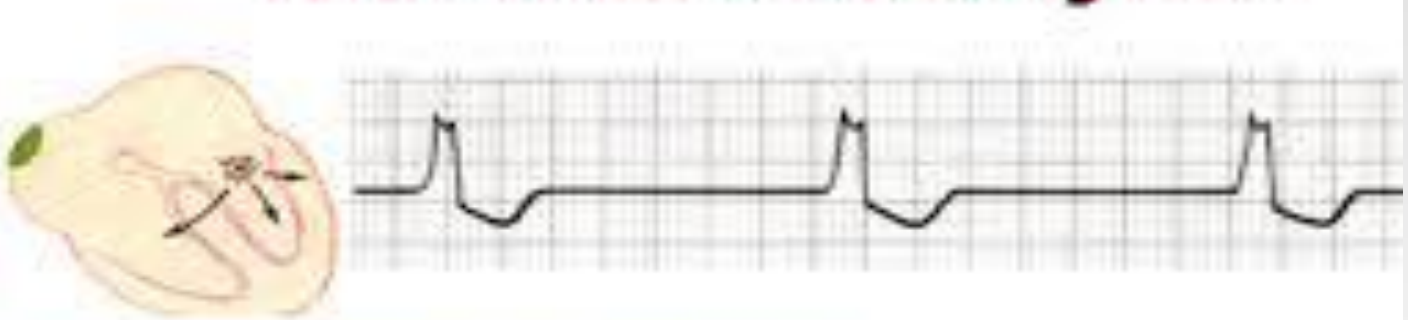


ECG Recognition:

- In sinus rhythm with complete AV block, the PP and RR intervals are regular but the P wave has no relationship with the R wave.
- The PR interval varies because there is really no P and QRS relationship.
- The ventricular rate is usually 40-60 bpm and narrow when it is driven by a junctional pacemaker (AV node).
- The QRS is wide and less the 40 bpm when an infra-Hisian pacemaker takes over.

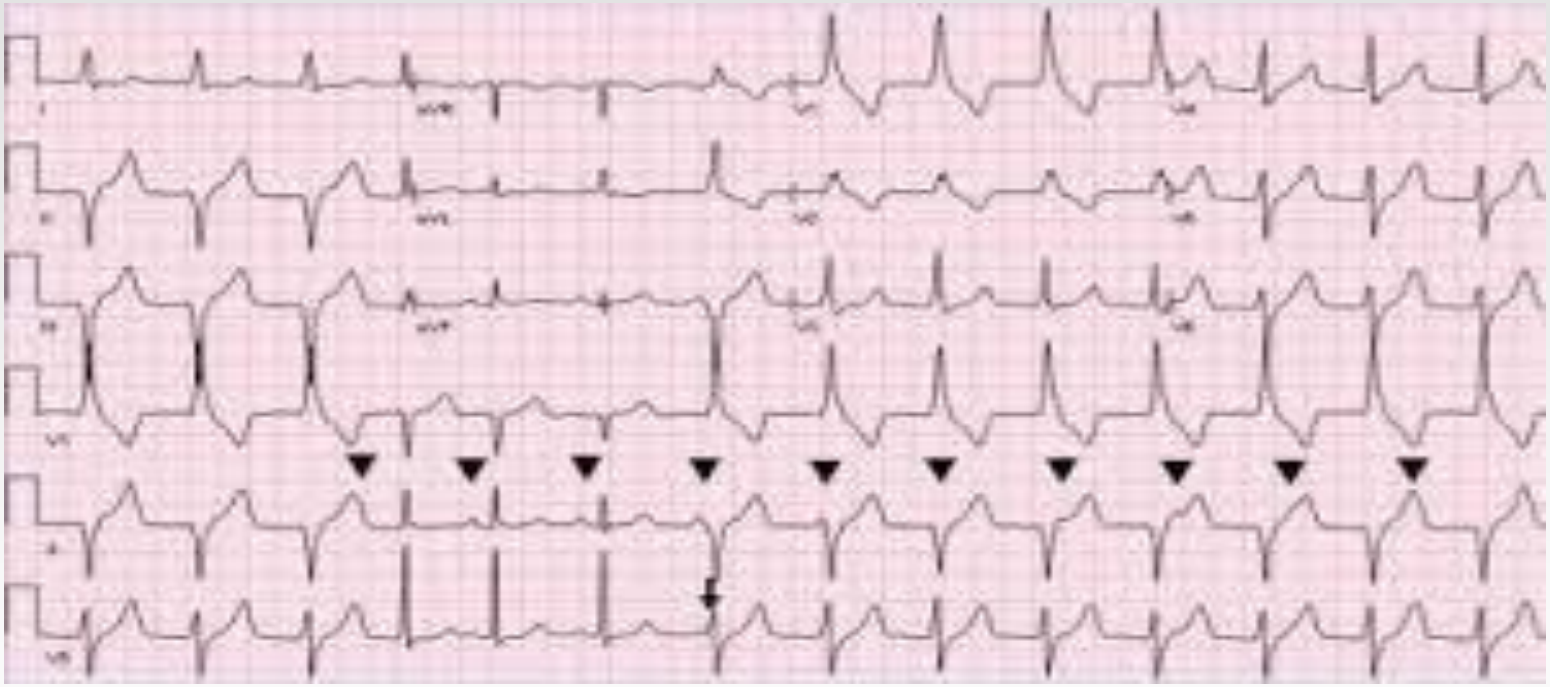
@ecgrhythms

Idioventricular Rhythm



- Originates in ventricles
- QRS is wide, bizarre; no p waves
- Rhythm is ~ regular
- Rate: 20-40 bpm
- Causes
  - end-stage cardiac disease

Accelerated Idioventricular Rhythm



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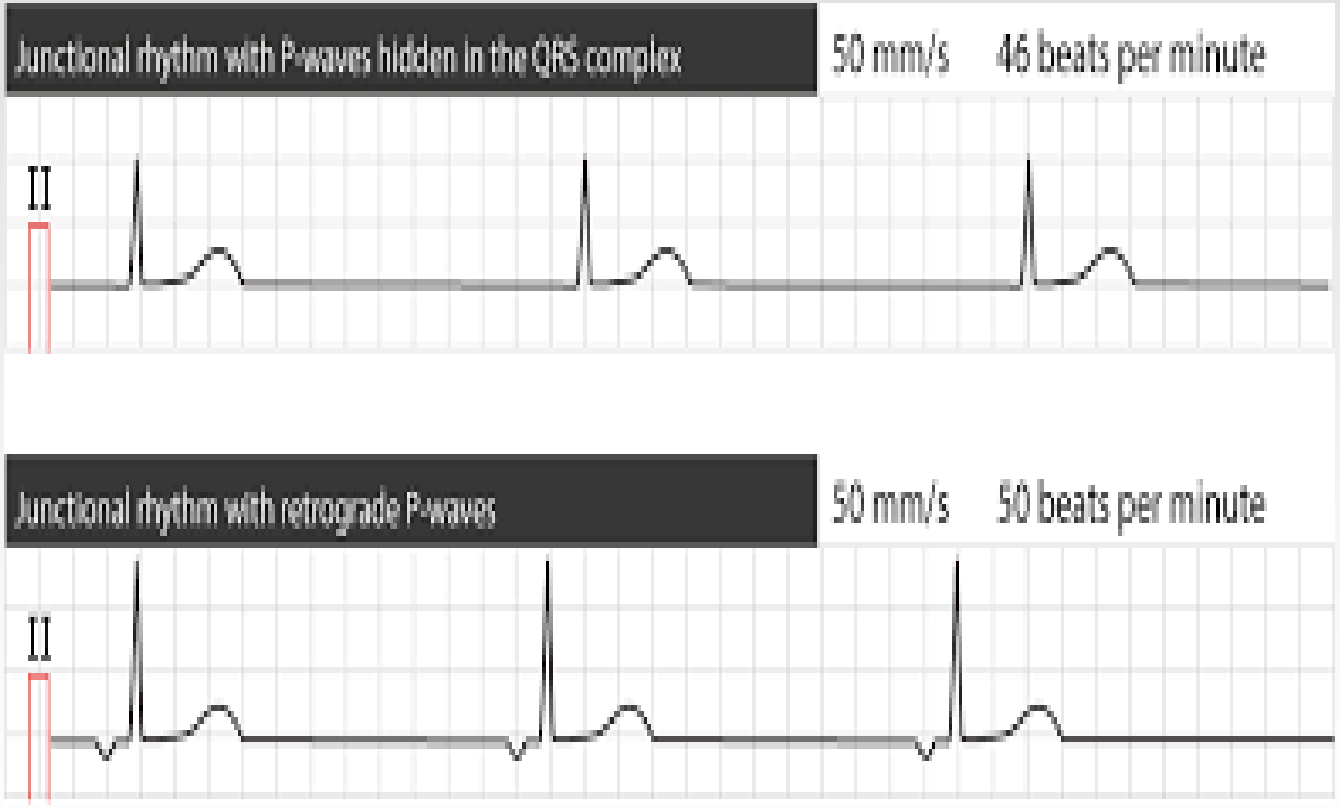
AIVR is a wide QRS ventricular rhythm with rate of 40-120 bpm.


Junctional rhythm with P-waves hidden in the QRS complex
50 mm/s
46 beats per minute
II
Junctional rhythm with retrograde P-waves
50 mm/s
50 beats per minute
II

Treatment (Hypotension)

- Fluid bolus of 10 to 20 mL/kg of crystalloid.
- Atropine,
- Calcium,
- Insulin,
- Glucagon,
- Isoproterenol, dopamine, epinephrine, norepinephrine,
- Phosphodiesterase (PDE) inhibitors (amrinone)
- Aggressive fluid resuscitation should not be given to patients with congestive heart failure, evidence of ARDS
- The long-term use of vasopressors such as norepinephrine or dopamine can result in tissue ischemia and should be avoided, when possible, in favor of HDI therapy.
- Critically ill patients: multiple therapies simultaneously.

Molecular adsorbents recirculating system (MARS)

- A specific extracorporeal albumin dialysis
- Molecular adsorbents recirculating system therapy has the unique ability to selectively remove from circulation **protein-bound xenobiotics** that are not cleared by conventional hemodialysis.
- The use of MARS therapy was successfully used in three patients with severe nondihydropyridine CCB poisoning.
- Despite potential application, we recommend the use of VA-ECMO

- Molecular adsorbents recirculating system (MARS) therapy is a blood detoxification system based on albumin dialysis that is able to remove albumin-bound and water-soluble substances selectively.

DISPOSITION

- Signs or symptoms of toxicity: ICU
- Criteria for safe discharge:
- “Immediate-release” : GI decontamination, serial ECGs over 6 to 8 hours, asymptomatic.
- “Sustained-release”: 24 hours monitoring even if they are asymptomatic.
- This precautionary approach is particularly important for toddlers and small children in whom even one or a few tablets may produce significant toxicity.

Summary

- Aggressive decontamination of patients with exposures to sustained-release products should begin as soon as possible and should not be delayed while awaiting signs of toxicity.
- HDI therapy early in the clinical course
- Fail to respond to all pharmaceutical interventions (Atropine, Calcium, Glucagon, HDI, Catecholamines): lipid emulsion, adjunctive hemodynamic support, such as VAECMO, IABP, Pacing

منابع

- –Goldfrank’s Toxicologic Emergencies 9th Edition , 2019

- www.emedicine / Emergency Medicine / Toxicology


با تشکر و سپاس

Questions?