Al-Mustaqbal University College
Department of Pharmacy
General Toxicology
4th stage
Lecture: 7

Cardiac Toxicology

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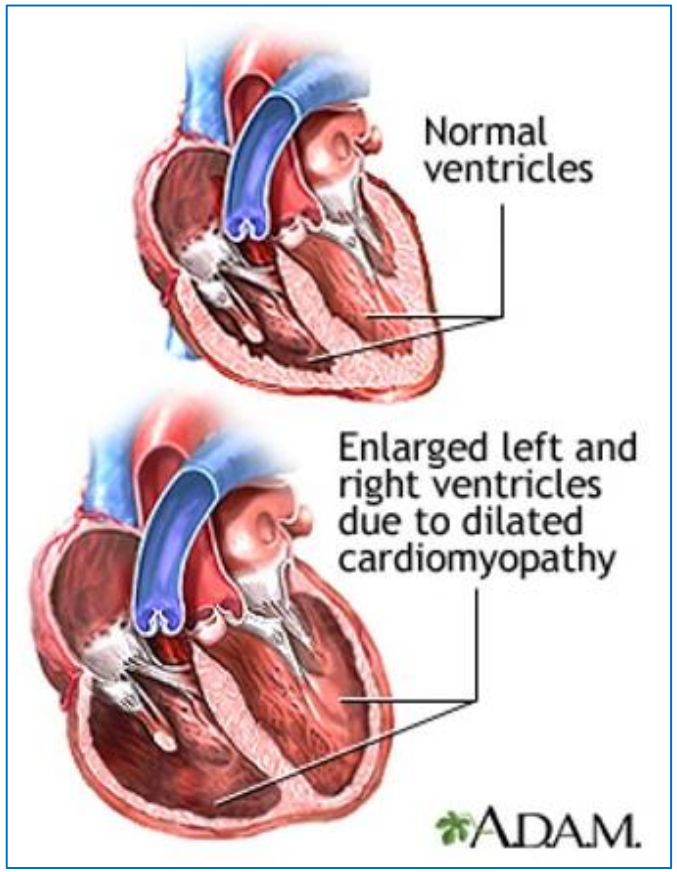
Toxicological Cardiomyopathy

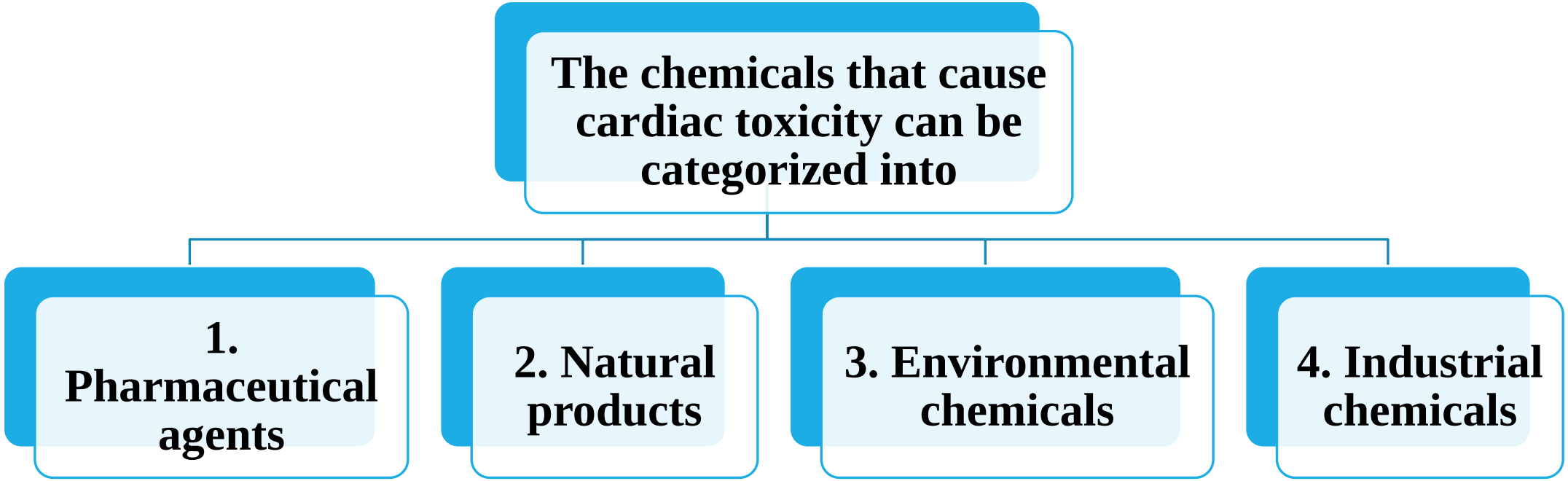
- ✓Many substances can cause cardiac toxic responses **directly** or **indirectly**.
- ✓However, **only** chemicals that **primarily** act on the heart be categorized as **cardiac toxic chemicals**.
- ✓**Clinically**, the most recognized toxicological cardiomyopathy is found in alcoholic heart muscle disease, which is often referred to as **alcoholic cardiomyopathy** (ACM).



Biomarkers for CVS Injury

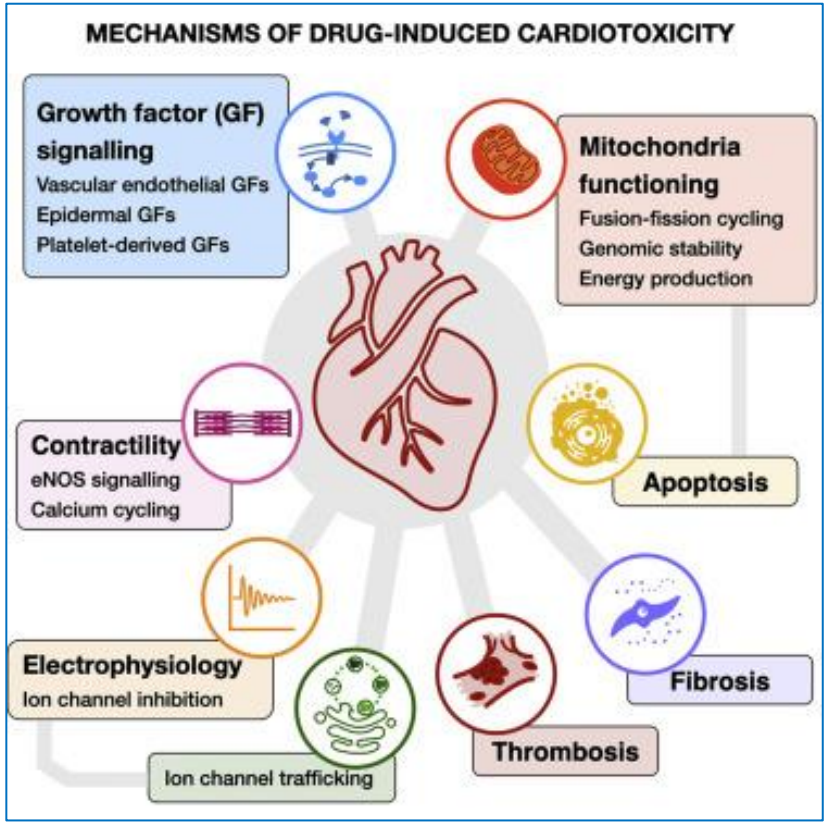
CARDIAC MARKERS	BACKGROUND	USE
Creatine kinase	Elevation of specific isoform CK-MB in the serum is a specific marker of acute myocardial infarction	Routinely used clinical and preclinical myocardial injury marker
Myoglobin	Elevation of serum myoglobin is likely reflective of the extent of myocardial damage, although not specific to cardiac muscle	Readily available clinical and preclinical marker, although lack of specificity has led to reduced utilization
B-type natriuretic peptide	Cardiac neurohormone secreted by the ventricular myocardium in response to volume and pressure over-load, and the release of BNP is a valuable indicator of heart failure	BNP is an important diagnostic marker as well as a drug used to alleviate congestive heart failure symptoms in cardiac decompensation. BNP has value for preclinical models of heart failure across species
Cardiac troponins	Cardiac troponin T (cTnT) and I (cTnI) are constituents of the myofilaments and expressed exclusively in cardiomyocytes. It is thus of absolute myocardial tissue specificity	"Gold Standard" for diagnosis of myocardial infarction. Value extends to preclinical safety and experimental models

Cardiac Toxic Chemicals



Pharmaceutical Agents

- ✓Cardiac toxicity of pharmaceutical chemicals is a major problem in drug development and their clinical application.
- ✓These chemicals can be simply classified as drugs used to treat cardiac disease and others used to treat noncardiac disease.

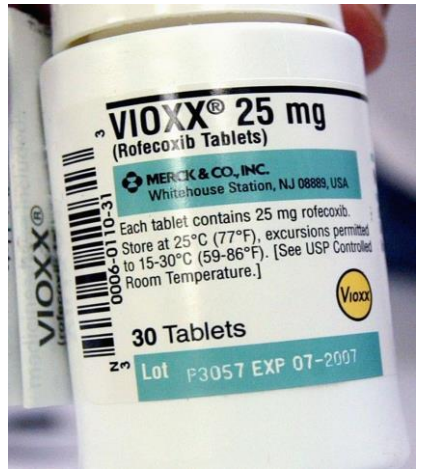


Pharmaceutical Chemicals

- ✓Cardiac drugs can cause cardiotoxicity that is either related or not related to their therapeutic action.
- ✓Drugs such as digitalis, quinidine, and procainamide often cause acute arrhythmia, which is reversible upon cessation of their use.
- ✓While catecholamines may cause cardiac toxicity through oxidative stress, rather than by their action on the sympathetic nervous system.

Pharmaceutical Chemicals

- ✓The cardiotoxicity of **noncardiac** drugs limits their uses.
- ✓For instance, the anticancer **Adriamycin**, can produce severe cardiac toxicity that limits its use.
- ✓**Rofecoxib** is a selective COX-2 inhibitor used as an anti-inflammatory drug, but it causes **QT prolongation** and increases the risk for **sudden cardiac death**.



Antiarrhythmic Agents

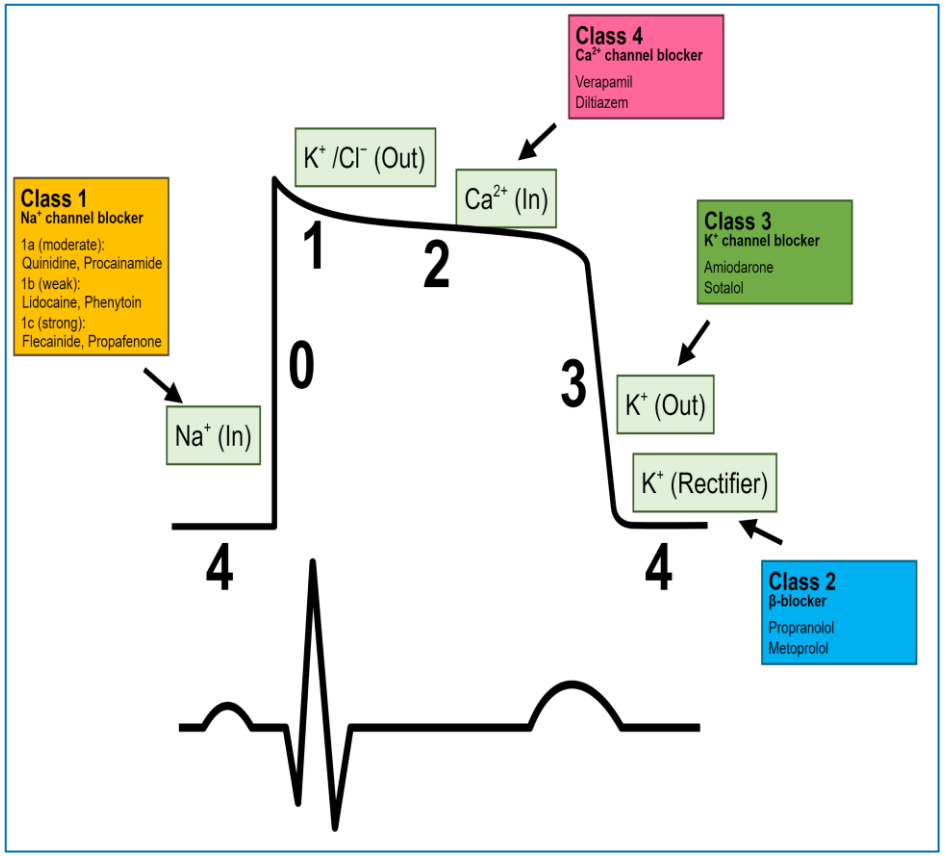
✓**Antiarrhythmic drugs have historically been classified based upon a primary mechanism of action:**

1. **Na+ channel blockers (class I)**
2. **β-adrenergic blockers (class II)**
3. **K+ channel blockers (class III)**
4. **Ca2+ channel blockers (class IV).**

✓**However, this classification is artificial because most drugs have multiple mechanisms of action.**

Class I Antiarrhythmic Agents

- ✓**These are primarily Na+ channel blockers, such as disopyramide, flecainide, lidocaine, mexiletine, procainamide, and quinidine.**
- ✓**Blockade of cardiac Na+ channels results in a reduction of conduction velocity, prolonged QRS duration, and decreased automaticity.**



Class I Antiarrhythmic Agents

✓**The primary concern of Na+ channel blocker toxicity is that proarrhythmic effects are seen at a much higher incidence in those patients with:**

1. **Previous history of myocardial infarction**
2. **Acute myocardial ischemia**
3. **Other cardiac complications**

Class II Antiarrhythmic Drugs

- ✓These are β-adrenergic receptor-blocking drugs, including acebutolol, esmolol, propranolol, and sotalol.
- ✓These drugs lead to opposite effects to that of catecholamines and are useful for the treatment of supraventricular tachycardia.
- ✓The main adverse cardiovascular effect of β-adrenergic receptor antagonists is hypotension.
- ✓These drugs may also exacerbate AV conduction deficits (e.g., heart block) and promote arrhythmias.

Class III Antiarrhythmic Drugs

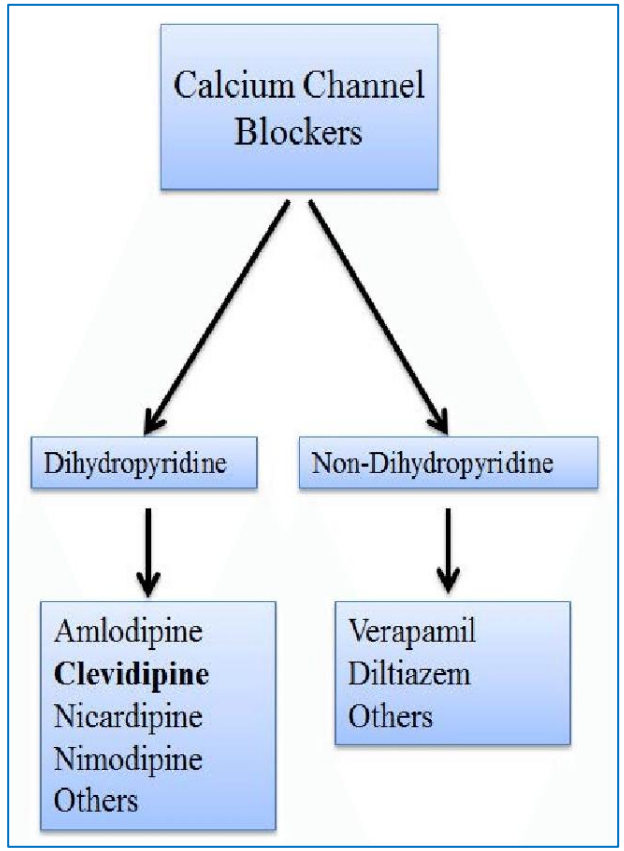
- ✓**These are primarily K+ channel blockers including amiodarone, bretylium, dofetilide, ibutilide, quinidine, and sotalol.**
- ✓**Blockade of K+ channels increases action potential duration and increases refractoriness.**
- ✓**The most noticeable adverse effect of these drugs is QT prolongation and torsadogenesis.**
- ✓**Amiodarone and quinidine also block Na+ channels, whereas sotalol inhibits β-adrenergic receptors in the heart.**

Class III Antiarrhythmic Drugs

- **Amiodarone prolongs action potential duration and effective refractory period of Purkinje fibres and ventricular myocytes the most common adverse cardiovascular effect of amiodarone is bradycardia.**
- **Amiodarone may also have cardiotoxic effects by stimulating excessive Calcium uptake, especially in the presence of procaine.**

Class IV Antiarrhythmic Drugs

- ✓These are Ca^{2+} channel blockers and include **bepridil, diltiazem and verapamil**.
- ✓These drugs exert **negative** inotropic and chronotropic effects thus they may produce **bradycardia**.
- ✓In contrast, the **dihydropyridine** Ca^{2+} channel blockers such as amlodipine, felodipine and nicardipine typically induce a **reflex tachycardia**.



Inotropic Drugs

✓**Drugs involved in this category include:**

1. **The cardiac glycosides**
2. **Ca^{2+} sensitizing agents**
3. **Catecholamines**
4. **Other sympathomimetic drugs**

✓**Inotropic drugs may exert cardiotoxic effects through extensions of their pharmacological action.**

Cardiac Glycosides

- ✓These (digoxin and digitoxin) are inotropic drugs used for the treatment of **congestive heart failure**.
- ✓The mechanism of inotropic action of cardiac glycosides involves **inhibition of Na^+/K^+ ATPase**.
- ✓Consequently, cardiotoxicity may result from **calcium overload**, potentially including a reduction in resting membrane potential (less negative), and **premature** ventricular **contraction** or **ectopic** beats.

Cardiac Glycosides

✓**The principal adverse cardiac effects of cardiac glycosides include:**

1. **Slowed AV conduction with potential block**
2. **Ectopic beats**
3. **Bradycardia.**

✓**During an overdose, when the resting membrane potential is significantly altered, and ectopic beats are prevalent, ventricular tachycardia may develop and can progress to ventricular fibrillation.**

Ca^{2+}-Sensitizing Drugs

✓**Calcium sensitizing drugs, including adibendan, levosimendan, and pimobendane, are useful as inotropic drugs for the treatment of heart failure.**

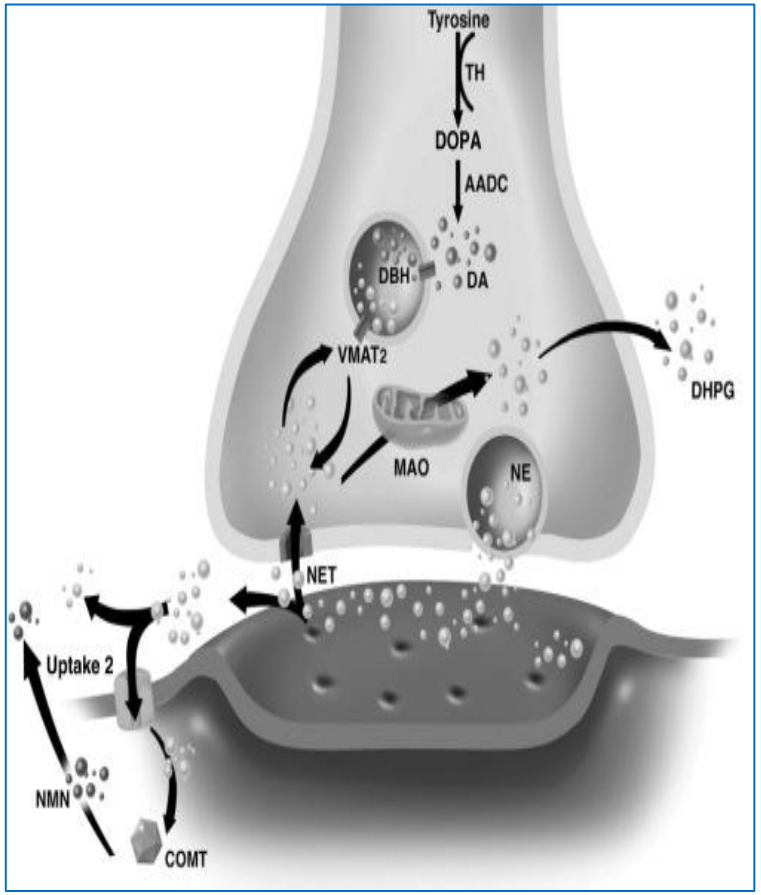
✓**In contrast to the main mechanism by which many other inotropic drugs act through elevating intracellular-free Ca^{2+}, these drugs increase the Ca^{2+} sensitivity of cardiac myocytes, thereby avoiding Ca^{2+} overload.**

Ca^{2+}-Sensitizing Drugs

- ✓**The possibility that such Ca^{2+}sensitizing drugs interfere with diastolic function (relaxation) and may contribute to ventricular arrhythmias.**
- ✓**Other Ca^{2+}sensitizing drugs include the xanthine oxidase inhibitors allopurinol and oxypurinol, which have been shown to increase the contractile force but decrease Ca^{2+} transient amplitude.**

Catecholamines

- ✓These neurotransmitters exert a **wide range** of cardiovascular effects because of their ability to activate **α- and β-adrenergic receptors**.
- ✓A number of **synthetic** catecholamines have been developed for the treatment of **cardiovascular** disorders and other conditions such as **asthma** and **nasal** congestion.



Catecholamines

- ✓**Inotropic and chronotropic catecholamines used to treat bradycardia, or cardiac decompensation following surgery include epinephrine, isoproterenol, and dobutamine.**
- ✓**More selective β2-adrenergic receptor agonists used for bronchodilatory effects in asthma include albuterol, formoterol, salmeterol, and terbutaline.**

Catecholamines

- ✓**High circulating concentrations of catecholamine may cause cardiac myocyte death.**
- ✓**Many of the catecholamines and related drugs have been shown to induce cardiac myocyte hypertrophic growth in vitro.**
- ✓**Catecholamine-induced cardiotoxicity involves increased heart rate, enhanced myocardial oxygen demand, and an overall increase in systolic arterial blood pressure.**

CNS Acting Drugs

✓**Some of the central nervous system (CNS)–acting drugs have considerable effects on the cardiovascular system, including:**

1. **Tricyclic antidepressant (TCAs)**
2. **General anaesthetics**
3. **Opioids**
4. **Antipsychotic drugs**

Tricyclic Antidepressants

- ✓**TCAs including amitriptyline, doxepin, imipramine, and protriptyline have significant cardiotoxic effects, particularly in cases of overdose.**
- ✓**The effects of TCAs on the heart include ST-segment elevation, QT prolongation, SVT and VT, and sudden cardiac death.**
- ✓**In addition, as a result of the peripheral α-adrenergic blockade, TCAs cause postural hypotension.**

Tricyclic Antidepressants

- ✓ **Although many of these adverse effects are related to the quinidine-like actions, anticholinergic effects, and adrenergic actions of these drugs.**
- ✓ **The tricyclics also have direct actions on cardiac myocytes and Purkinje fibers, including depression of inward Na^+ and Ca^{2+} and outward K^+ currents.**

Antipsychotic Drugs

- ✓As with TCAs, the most prominent adverse cardiovascular effect of antipsychotic drugs is **orthostatic hypotension**.
- ✓However, the **phenothiazines** (e.g., chlorpromazine and thioridazine) may exert **direct** effects on the myocardium, including **negative inotropic** actions and **quinidine-like** effects.
- ✓Some ECG changes induced by these drugs include **prolongation of the QT and PR intervals** and **depression** of the ST segment.
- ✓Through **anticholinergic** actions, **clozapine** can produce substantial elevations in heart rate (**tachycardia**).

General Anesthetics

- ✓**General anaesthetics as exemplified by desflurane, halothane, isoflurane, and methoxyflurane.**
- ✓**They have adverse cardiac effects, including reduced cardiac output by 20% to 50%, depression of contractility, and production of arrhythmias.**
- ✓**These anaesthetics may sensitize the heart to the arrhythmogenic effects of endogenous epinephrine or to β-receptor agonists.**

General Anesthetics

✓**Halothane** has been found to

1. **Block** the **L-type** Ca^{2+} channel and **modify** the **responsiveness** of the contractile proteins to activation by Ca^{2+}.
2. **Decreases** cardiac output and blood pressure.
3. Causes a **negative inotropic** effect by its **direct** action on cardiac myocytes.
4. **Antagonize β-adrenergic receptors**.

Anti-inflammatory Agents

- ✓**NSAIDs include aspirin, Ibuprofen, and Diclofenac, they are classified as nonselective NSAIDs because they are inhibitors for both COX-1 and COX-2.**
- ✓**Inhibition of COX-1 is associated with GI toxicity because COX-1 exerts a protective effect on the lining of the stomach.**
- ✓**NSAIDs have been developed including rofecoxib, celecoxib, and valdecoxib, which are selective inhibitors of COX-2.**

Anti-inflammatory Agents

- ✓The **cardiovascular** events induced by COX-2 inhibitors are presumably related to **thrombotic events** and other sequelae related to the **downregulation of prostacyclin production**.
- ✓Studies have also indicated the link of rofecoxib to **long QT syndrome** and the increased **risk for Torsades** and **sudden cardiac death**.

Aminoglycosides

- ✓ **These include amikacin, gentamicin, kanamycin, netilmicin, streptomycin, and tobramycin.**
- ✓ **Aminoglycosides inhibit the uptake or binding of Ca^{2+} at sarcolemmal sites, thus reducing the concentration of membrane-bound Ca^{2+} available for movement into the myoplasm during depolarization of the sarcolemma.**
- ✓ **Gentamicin is a representative aminoglycoside and has an inhibitory action on slow inward Ca^{2+} channels in heart muscle.**

Macrolides

- ✓These include azithromycin, clarithromycin, dirithromycin, and erythromycin.
- ✓Erythromycin is associated with QT prolongation and cardiac dysrhythmias that is characterized by polymorphic ventricular tachycardia (Torsades).
- ✓These effects occur primarily in patients with underlying cardiac disease.

Fluoroquinolones

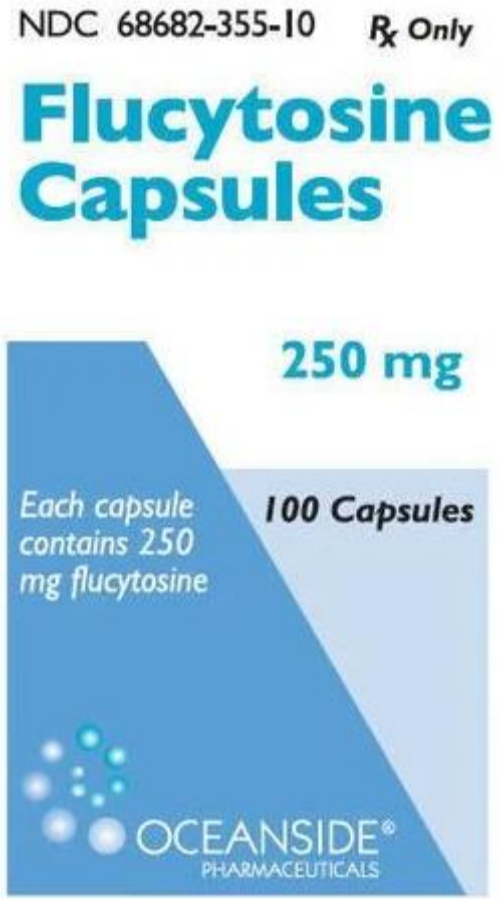
- ✓ **Grepafloxacin, moxifloxacin, and sparfloxacin are associated with QT prolongation in perhaps a higher incidence than macrolides.**
- ✓ **Grepafloxacin was removed from the U.S. market because of the relatively high incidence of QT prolongation and the risk of Torsades de Pointes.**

Antifungal Agents

- ✓**Antifungal agents, such as amphotericin B, may depress myocardial contractility by blocking the activation of slow Ca^{2+} channels and inhibiting the influx of Na^{+}.**
- ✓**Ventricular tachycardia and cardiac arrest have been reported in patients treated with amphotericin B.**

Antifungal Agents

- ✓**Flucytosine** is another antifungal drug that has been associated with **cardiotoxicity**.
- ✓However, flucytosine may be converted to **5-fluorouracil** by gastrointestinal microflora in humans, which then may be **absorbed** systemically and induce **cardiotoxicity.**
- ✓**Cardiac arrest** has been reported in individuals receiving flucytosine.



THANK YOU
FOR YOUR ATTENTION