Drug-Related Problems in Elderly

The ECG Changes

Presented by, Wei-Ren Lan
Cardiovascular Medicine
Internal Medicine
Mackay Memorial Hospital
Taipei
Drug-related problems are common in the elderly

1. drug ineffectiveness
2. adverse drug effects
3. Over-dosage
4. Under-dosage
5. drug interactions

Among ambulatory people ≥ 65, adverse drug effects occur at a rate of about 50 events per 1000 person-years.

Hospitalization rates due to adverse drug effects are 4 times higher in elderly patients (about 17%) than in younger patients (4%)

However, adverse effects are thought to be preventable in almost 90% of cases in the elderly (compared with only 24% in younger patients).
Reasons for Drug-Related Problems

Drug-drug interactions
- the elderly often take many drugs (polypharmacy)
- particularly vulnerable to drug-drug interactions
- use medicinal herbs and other dietary supplements

Age-related changes in pharmacodynamics and pharmacokinetics:
- gastric pH altering medications, bioavailability and clearance dramatically change with aging
- changes become the most pronounced after age 75, when kidney and liver function become limited.

Inadequate monitoring:
- are especially important for elderly patients.
- Lack of close monitoring, especially after new drugs are prescribed, increases risk of adverse effects and ineffectiveness.

Inappropriate drug selection

Over-dosage
Issues We Will Address Today

Role Of The ECG in Drug intoxication

How To Approach The ECG In The Overdose Patient

Various Drugs Related ECG Manifestations

Summary: Toxicologic Algorithm
Issues We Will Address Today

Role Of The ECG in Drug intoxication

How To Approach The ECG In The Overdose Patient

Various Drugs Related ECG Manifestations

Summary: Toxicologic Algorithm
Cardiotoxicity from poisoning is one of the leading causes of death among these patients.

It is thus crucial for clinicians to rapidly recognize cardiotoxicity.

are rapidly available in a matter of minutes.

The waveforms and intervals produced by the electrical forces of depolarization and repolarization enable physicians to identify normal and abnormal patterns that may represent cardiac or extra-cardiac disturbances.

Cardiotoxic agents have effects on specific ion-channels (particularly sodium, calcium, and potassium) that produce important changes in the action potential as well as resting potential.

Issues We Will Address Today

Role Of The ECG in Drug intoxication

How To Approach The ECG In The Overdose Patient

Various Drugs Related ECG Manifestations

Summary: Toxicologic Algorithm
How To Approach The ECG In The Overdose Patient

**Rhythm – Rate**

- The origin of the rhythm (supraventricular, ventricular)
- The existence of **bradycardia** with or without AV-block and **tachycardia** (with narrow or wide ventricular complexes)
- The presence of **ectopy** should be noted and may represent enhanced automaticity (e.g. cardioactive steroid toxicity, sympathomimetics) or severe electrolyte disturbances
- Life threatening dysrhythmias such as ventricular tachycardia, ventricular fibrillation and complete AV-block should be addressed immediately according to Advanced Cardiac Life Support (ACLS) guidelines

How To Approach The ECG In The Overdose Patient

PR Interval

- A prolonged PR interval can be an early sign of Beta adrenergic antagonism, calcium channel antagonism, or cardioactive steroid (e.g. digoxin) effect.

- An increasing PR interval preceding blocks defines type 1 second degree AV-block.
- A constant PR interval preceding missed atrial beats in Type 2 Second degree AV-block.
- Independent atrial and ventricular activity is characteristic of third-degree AV-block.
How To Approach The ECG In The Overdose Patient

QRS Interval

- Manifestations of sodium channel blockade can be found in the duration or the axis of the QRS complex.

- When accompanied by anticholinergic or sympathomimetic effects, the resulting rhythm may resemble ventricular tachycardia.

How To Approach The ECG In The Overdose Patient

**QT Interval**

- The QT interval is often prolonged in overdoses involving cardiotoxicity.
- A prolonged QRS due to sodium or calcium channel antagonism may also prolong the QT interval.
- Many drugs are known to produce acquired long QT in both therapeutic dose and overdose.

Issues We Will Address Today

Role Of The ECG in Drug intoxication

How To Approach The ECG In The Overdose Patient

Various Drugs Related ECG Manifestations

Summary: Toxicologic Algorithm
Sodium Channel Blockade

The sodium channel blockers bind to the transmembrane sodium channels and decrease the number available for depolarization.

This creates a delay of sodium entry into the cardiac myocyte during phase 0 of depolarization.

As a result, the upslope of depolarization is slowed and the QRS complex widens.

The greater the degree of blockade, the wider the resulting QRS complex.

Most of the literature analyzing QRS prolongation due to sodium channel blockade comes from the experience with tricyclic antidepressant poisoning.

However, other drugs that produce sodium channel blockade (e.g. Class IA antidysrhythmics) can cause prolonged QRS duration, with or without other ECG findings characteristic of TCA overdose.
Sodium Channel Blockade

Electrocardiographic manifestations

- Tricyclic antidepressant
  1. This aVR lead shows a prominent R wave, a hallmark of sodium channel blockade in TCA overdose
  2. A prospective study demonstrated that a QRS duration of < 100 ms was an indicator of good prognosis
  3. While those with a QRS > 100 ms presented with seizures in one third of cases
  4. A QRS complex over 160 ms was associated with ventricular dysrhythmias

Flecainide is an increasingly used class 1C antiarrhythmic drug used for the management of both supra-ventricular and ventricular arrhythmias.

It causes rate-dependent slowing of the rapid sodium channel slowing phase 0 of depolarization and in high doses inhibits the slow calcium channel.\(^\text{a}\)
Potassium channel blockade interrupts the rectifying potassium current produces an increased duration of phase 2 and phase 3 of the myocardial action potential and translates to the ECG primarily as a prolonged QT interval.

Blockade of the rectifying potassium channels may also cause T-wave abnormalities or the presence of U-waves.

The presence of a long QT represents slowed repolarization, which produces the myocardial substrate for the development of polymorphic ventricular tachycardia, or torsades de pointes.

Potassium Efflux Blockade

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Potassium Efflux Blockade</th>
<th>Potassium Efflux Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuteol</td>
<td>Erythromycin*</td>
<td>Pratermineme</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Esolopram</td>
<td>Phenylephrine</td>
</tr>
<tr>
<td>Amiodarone*</td>
<td>Feneolamine</td>
<td>Phenylpropanolamine</td>
</tr>
<tr>
<td>Amtriptyline</td>
<td>Flucenazole</td>
<td>Pecosamine*</td>
</tr>
<tr>
<td>Dextromethorphanine</td>
<td>Fluoresin</td>
<td>Prettripryline</td>
</tr>
<tr>
<td>Amphotamine</td>
<td>Florafine</td>
<td>Pseudophedrine</td>
</tr>
<tr>
<td>Arsenic trioxide*</td>
<td>Fosphenytin</td>
<td>Quinaprice</td>
</tr>
<tr>
<td>Atenolol*</td>
<td>Gatlenzox</td>
<td>Quinidine*</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Gemfibrozil</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Haloperidol*</td>
<td>Ritodrine</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Imipramine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Chloroquine*</td>
<td>Isopretenerol</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Chlorpromazine*</td>
<td>Itraconazole</td>
<td>Sertindole</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ketoconazole</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Clonazapamide*</td>
<td>Levotiroxide</td>
<td>Sotalol*</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Levofoxazic</td>
<td>Sparfloxacin*</td>
</tr>
<tr>
<td>Clonazepam*</td>
<td>Lithium</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Cloralpine</td>
<td>Methadone*</td>
<td>Temozolimide</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Methylbupropionate</td>
<td>Telithromycin</td>
</tr>
<tr>
<td>Desolamine</td>
<td>Meperidine</td>
<td>Tertbutaline</td>
</tr>
<tr>
<td>Desmethylfenflurine</td>
<td>Mexiletine</td>
<td>Trenadine*</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Midodrine</td>
<td>Triacetazide*</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Metribolizna</td>
<td>Ticamidin</td>
</tr>
<tr>
<td>Dopemidine*</td>
<td>Nicardipine</td>
<td>Tracezolone</td>
</tr>
<tr>
<td>Dornazepine</td>
<td>Nepentephrine</td>
<td>Trimethoprim-Sulfa</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Nortripryline</td>
<td>Trimipramine</td>
</tr>
<tr>
<td>Dofuspin</td>
<td>Ofloxacin</td>
<td>Vandamifil</td>
</tr>
<tr>
<td>Droperidol*</td>
<td>Onodansetron</td>
<td>Ventinzolname</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Pantopozide</td>
<td>Ziperazidone</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Pentamidine*</td>
<td></td>
</tr>
</tbody>
</table>

Potassium Efflux Blockade

Electrocardiographic manifestations

A rhythm strip showing Torsade de Pointes: a rapid polymorphic tachycardia with characteristic "twisting" of the QRS complexes around the baseline.

Digoxin and Other Cardioactive Steroid Toxicity

Box 1. Na+/K+ ATPase blocking agents and substances

- Bufadienolides
- Digoxin
- Digitoxin
- Foxglove
- Lily of the valley
- Oleander
- Red squill
Digitalis effect manifesting with abnormal inverted or flattened T waves coupled with ST segment depression, frequently described as a sagging or scooped ST segment/T wave complex.

Other findings include:
1. QT interval shortening: as a result of decreased ventricular repolarization time
2. PR interval lengthening: as a result of increased vagal activity
3. and increased U-wave amplitude.

These electrocardiographic manifestations are seen with therapeutic digoxin levels and do not correlate with toxicity.
Electrocardiographic abnormalities with cardiac glycoside toxicity are the result of the propensity for increased automaticity (from increased intracellular calcium) accompanied by slowed conduction through the AV node.

As a result, cardiac glycoside toxicity may result in a wide array of dysrhythmias

**Excitant activity**
1. atrial,
2. Junctional
3. ventricular premature beats
4. Tachydysrhythmias

**Suppressant activity**
1. sinus bradycardia
2. bundle branch blocks
3. first-, second-, and third-degree AV blocks

**Any combination of excitant and suppressant activity**
1. Atrial tachycardia with AV block,
2. second-degree AV block with junctional premature beats

Digoxin and Other Cardioactive Steroid Toxicity

- The most common dysrhythmia associated with toxicity induced by these agents is frequent premature ventricular beats.
- Paroxysmal atrial tachycardia with variable block or accelerated junctional rhythm is highly suggestive of digitalis toxicity.
- Marked slowing of the ventricular response in a patient who has atrial fibrillation who is on digoxin should suggest the possibility of toxicity.
- Bidirectional ventricular tachycardia is stated to be specific for digitalis toxicity, but rarely is seen.
Calcium channel blocker toxicity

All cardiac CCBs inhibit the voltage sensitive L-type calcium channel within the cell membrane.

The inhibition of this channel prevents movement of calcium from extracellular sites through the cell membrane to intracellular sites.

Decreased intracellular calcium within the myocardial cells results in:
1. slowing of conduction,
2. decreased contractility,
3. and decreased cardiac output.

The dihydropyridine class of drugs have a higher affinity for the peripheral vascular smooth muscle cells, less effect on the cardiac calcium channels, and is associated more often with hypotension with a resulting reflex tachycardia.

Verapamil and diltiazem, on the other hand, have strong affinity for cardiac and vascular calcium channels and subsequently the combination of hypotension with bradycardia may be seen.

Calcium channel blocker toxicity

**Electrocardiographic manifestations**

- CCB toxicity initially causes a **sinus bradycardia** (may or may not be symptomatic)

- As levels of CCB increase, may develop **various degrees of AV block** (first-, second-, and third-degree) and **junctional and ventricular bradydysrhythmias** on ECG

- A **widening of the QRS complex** may be encountered.
  1. This may be caused by **ventricular escape rhythms** or by **CCB-induced sodium channel blockade** causing a delay of phase 0 of depolarization.
  2. This delay and subsequent QRS complex widening also **increases the potential for dysrhythmias**
Beta-adrenergic blocker toxicity

- BBs competitively inhibit various $\beta$-adrenergic receptors.

**Inhibition of $\beta_1$ receptors results in**
1. a decrease in the force and rate of myocardial contraction
2. a decrease in AV nodal conduction velocity
3. a decrease in renin secretion

**Inhibition of $\beta_2$-receptors results in**
1. a decrease in glycogenolysis, decrease in gluconeogenesis,
2. decrease in relaxation of smooth muscles in blood vessels, bronchi, and the gastrointestinal tract.

Box 3. Beta-adrenergic blocking drugs

- Acebutolol
- Atenolol
- Betaxolol
- Bisoprolol
- Carvedilol
- Esmolol
- Labetalol
- Metoprolol
- Nadolol
- Pindolol
- Propranolol
- Sotalol
- Timolol

In acute overdose, the most pronounced effects of BBs are on the cardiovascular system:

- **Bradycardia** (from decreased sinoatrial node function), varying degrees of AV block, and hypotension are generally the hallmarks of significant beta-blocker toxicity.

- **Propranolol** is unique because of its Na+ channel blocking activity in overdose that can result in a prolonged QRS interval (>0.10 seconds).

- Propranolol overdose has been associated with a higher mortality rate compared with other BBs.
Issues We Will Address Today

Role Of The ECG in Drug intoxication

How To Approach The ECG In The Overdose Patient

Various Drugs Related ECG Manifestations

Summary: Toxicologic Algorithm
Poisoned patients presenting with a sinus rhythm should be assessed for subtle ECG signs of cardiotoxicity such as AV block, a long QTc or signs of sodium channel blockade (e.g. R in aVR).

Summary

- AV block
- R in aVR, S in I and avL
- Depressed level of consciousness
- Cholinergic symptoms
- Long QTc
- Normal intervals

- Beta adrenergic antagonists
- Tricyclic antidepressants
- Other sodium channel blockers
- Opioid symptoms
- Normal exam and vital signs
- Organic phosphates
- Antidepressants
- Antipsychotics
- Erythromycin co-trimoxazole, quinolones azoles others

- Calcium channel blockade
- Opioids
- Sedative-hypnotics
- Ethanol GHB/GBL
- Methadone
Bradycardic patients should also be assessed for sodium and potassium channel blockade (i.e. R in aVR and long QTc).

Summary

Toxicologic Bradycardia

- Lithium
- Beta adrenergic antagonists (possible hypoglycemia)
- Ca channel blockade (possible hyperglycemia)
- AV block
- Enhanced automaticity (e.g., PVC)
- Opioid drugs
- Organo-phosphates
- Sedative hypnotics
- Alcohol
- R lead aVR, S leads I and aVL, Brugada, RBBB
Summary

Tachycardia is a common presenting rhythm in poisoned patients. The ECG of tachycardic patients should be assessed for wide QRS complexes and other ECG signs that might suggest sodium channel blockade (e.g. R wave in aVR) as well as for QTc prolongation and ischemia.
Conclusion

- Toxicologic, medication- and drug-induced changes and abnormalities on the 12-lead electrocardiogram (ECG) are common.

- A wide variety of electrocardiographic changes can be seen with cardiac and noncardiac agents and may occur at therapeutic or toxic drug levels.

- In many instances, however, a common mechanism affecting the cardiac cycle action potential underlies most of these electrocardiographic findings.

- Knowledge and understanding of these mechanisms and their related affect on the 12-lead ECG can assist the physician in determining those ECG abnormalities associated with specific toxidromes.
Electrolytes in thew Aging

The ECG Changes

Presented by, Wei-Ren Lan
Cardiovascular Medicine
Internal Medicine
Mackay Memorial Hospital
Taipei
Introduction

With aging there are degenerative changes in many organs and the kidney is no exception.

A decline in both glomerular filtration rate and renal plasma flow may be associated with an inability to excrete a concentrated or a dilute urine, ammonium, sodium, or potassium.

Hypernatremia and hyponatremia are the most common electrolyte abnormalities found in the elderly and both are associated with a high mortality.

Under normal conditions the elderly are able to maintain water and electrolyte balance but this may be jeopardized by an illness, a decline in cognitive ability, and with certain medications.

Therefore, it is important to be aware of the potential electrolyte abnormalities in the elderly that can arise under these various conditions in order to prevent adverse outcomes.

Sodium

Hypernatremia

- Hypovolemia most common cause

- Also consider diabetes insipidus
  1. Central (deficient production of AVP)
  2. Nephrogenic (diminished response to AVP)

Commonly Prescribed Medications Associated with Hypernatremia in the Elderly

1. Lithium \(\rightarrow\) Decrease AQP-2
2. Vasopressin V2 receptor antagonists \(\rightarrow\) Decrease cAMP
3. Loop diuretics \(\rightarrow\) Decrease diluting capacity
4. Mannitol \(\rightarrow\) Osmotic diuresis

Hyponatremia

Commonly Prescribed Medications Associated with Hyponatremia in the Elderly:

1. Prostaglandin-synthesis inhibitors → *Impair water excretion*
2. Phenothiazines → *Release of ADH*
3. Tricyclics → *Release of ADH*
4. Serotonin-reuptake inhibitors → *Release of ADH or Potentiates renal ADH effect*
5. Opiate derivatives → *Release of ADH*
6. Carbamazepine → *Release of ADH*
7. Cyclophosphamamide → *Potentiates renal ADH effect*
8. Thiazides → *Na loss, decrease distal fluid delivery, ADH release*
9. Desmopressin → *V2R agonist*
Hyponatremia

Sodium

Length of stay (days)  | In-hospital mortality (%)  | Post-discharge mortality (%)  | Death or rehospitalization since discharge (%)
--- | --- | --- | ---
6.4  | 6.0  | 12.4  | 42.5
5.5  | 3.2  | 7.1  | 34.8

Na < 135 mEq/L  | Na ≥ 135 mEq/L

P < .0001

Hyperkalemia

Most common life-threatening electrolyte abnormality

<table>
<thead>
<tr>
<th>TABLE. Common Causes of Hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous Causes</strong></td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Metabolic acidosis (e.g., diabetic ketoacidosis)</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism type II (also known as Gordon’s syndrome; familial hyperkalemia and hypertension)</td>
</tr>
<tr>
<td>Chemotherapy causing tumor lysis</td>
</tr>
<tr>
<td>Muscle breakdown (rhabdomyolysis)</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Hemolysis</td>
</tr>
<tr>
<td>Hypoaldosteronism (Addison’s disease, hyporeninemia)</td>
</tr>
<tr>
<td>Hyperkalemic periodic paralysis</td>
</tr>
<tr>
<td><strong>Exogenous Causes</strong></td>
</tr>
<tr>
<td>Medications: K⁺-sparing diuretics, ACE inhibitors, nonsteroidal anti-inflammatory drugs, potassium supplements, penicillin derivatives, succinylcholine, heparin therapy (especially in patients with other risk factors), β-blockers</td>
</tr>
<tr>
<td>Blood administration (particularly with large transfusions of older “bank” blood)</td>
</tr>
<tr>
<td>Diet (rarely the sole cause), salt substitutes</td>
</tr>
<tr>
<td>Pseudohyperkalemia (due to blood sampling or hemolysis, high white blood cell count, high platelets, tumor lysis syndrome)</td>
</tr>
</tbody>
</table>

Circulation. 2005;112:IV-121-IV-125.)
Potassium

Hyperkalemia: ECG Changes

- T wave in hyperkalemia is typically tall and narrow, but does not have to be tall (may be just narrow and peaked pulling ST segment)

- Tall T means
  1. > 2 big boxes in the precordial leads or
  2. >1 small box in limb leads, or
  3. T wave taller than QRS.

(Circulation. 2005;112:IV-121-IV-125.)
Hypokalemia:

- The major consequences of severe hypokalemia result from its effects on nerves and muscles (including the heart).

- The myocardium is extremely sensitive to the effects of hypokalemia, particularly if
  1. the patient has coronary artery disease or
  2. is taking a digitalis derivative.

Symptoms of mild hypokalemia are

1. weakness,
2. fatigue,
3. paralysis,
4. respiratory difficulty,
5. constipation,
6. paralytic ileus,
7. leg cramps

- more severe hypokalemia will alter cardiac tissue excitability and conduction

Hypokalemia can ventricular arrhythmias.

- Pulseless electrical activity or asystole may develop.
Potassium Hypokalemia: ECG Changes

- T progressively flattens
- U wave more and more prominent (looks like T)
- ST-segment more and more depressed
- A prolonged “QT” interval (actually QTU)

Flat T

ST depression with prominent T (actually U) and prolonged QT when K<2.5-3

Circulation. 2005;112:IV-121-IV-125.)
Hypokalemia: ECG Changes

ECG changes of *digoxin effect* (digoxin therapy) simulate the changes seen with hypokalemia (U wave and ST depression), *except* that with digoxin therapy QT is not prolonged.

*Circulation. 2005;112:IV-121-IV-125.*)
Calcium

Hypocalcemia: ECG Changes

- Reduced PR interval
- Narrowing of the QRS complex
- Prolonged ST and ST-depression
- T wave flattening and inversion
- Prolongation of the QT-interval
- Prominent U-wave
Calcium

**Hypercalcemia**

- **Cardiovascular symptoms** of hypercalcemia are **variable**.

- Myocardial contractility **may initially increase** until the calcium level reaches >15 mg/dL when **myocardial depression** occurs.

- Hypercalcemia **can worsen digitalis toxicity** and may **cause hypertension**.

- In addition, many patients with hypercalcemia **develop hypokalemia**. Both of these conditions **contribute to cardiac arrhythmias**.

(Circulation. 2005;112:IV-121-IV-125.)
Calcium

Hypercalcemia: ECG Changes

Hypercalcemia, high blood calcium, speeds repolarization

- **Mild:** broad based tall peaking T waves
- **Severe:** extremely wide QRS, low R wave, disappearance of p waves, tall peaking T waves
- short QTc <390 ms. when the serum calcium is >13 mg/dL
- **Atrioventricular block** may develop and progress to complete heart block
- even **cardiac arrest** when the total serum calcium is **15 to 20 mg/dL.**
Magnesium

Hypermagnesemia

- Hypermagnesemia can produce vasodilation
- **Severe** hypermagnesemia can produce hypotension
- Extremely high serum magnesium levels may produce
  1. a depressed level of consciousness,
  2. bradycardia,
  3. cardiac arrhythmias,
  4. hypoventilation,
  5. cardiorespiratory arrest
Magnesium

Hypermagnesemia

Cardiac Findings in Hypermagnesemia

- Hypotension
- ECG Changes begin at Mg >10 mg/dL
  - Bradycardia
  - Prolonged PR
  - Prolonged QRS
  - Prolonged QT
- Complete heart block (at 30 mg/dL)
- Asystole (at 34-40 mg/dL)
Magnesium

Hypomagnesemia: ECG Changes

- Prolonged PR
- Widened QRS
- Prolonged QT
- Decrease T wave
- Atrial / ventricular arrhythmias (especially if on digoxin)
Conclusion

Electrolyte abnormalities are among the most common causes of cardiac arrhythmias.

They can cause or complicate attempted resuscitation and postresuscitation care.

A high degree of clinical suspicion and aggressive treatment of underlying electrolyte abnormalities can prevent these abnormalities from progressing to cardiac arrest.