Safety Pharmacology Society Webinar:

Cardiac Physiology and Chronobiology

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Overview

- Basics of heart conductive system
- ECG 101
- Diurnal variability in different species
Cardiac conduction system

- Impulse initiated by the **Sinus Node**.
- It travels to the atriums and to the **Atrioventricular (AV) Node** located between the chambers.
- The **AV Node** slows the impulse down and passes it through to the AV Bundle (or **Bundle of His**).
- **Bundle of His** divides itself into two tracts through the ventricles and the Purkinje Fibers, which stimulate muscle of the ventricles.
ECG and Cardiac Activity

- Electrocardiogram (ECG) is a representation of the heart's electrical activity
- The P wave, represents atrial depolarization
- The QRS complex represents ventricular depolarization
- The ST segment represents the repolarization of the ventricles
- The QT interval represents ventricular depolarization and repolarization
AV Node

P wave

pause

atrial contraction

AV Node depolarization slows down

AV valves
Normal ECG

Normal duration and amplitude of ECG waves, complexes, and segments is variable in different species

E.g. QT/RR ratio in normal conditions
human > monkey > dog
How to Think about Heart Rhythm

Electrical Impulse Formation

Site of Origin
- Sinus Node
- Atrium
- AV node
- Ventricle

Rate
- Normal
- Fast
- Slow

Regularity
- Regular
- Irregular
Sinus arrhythmia

- Common finding, more prominent in dogs
Sinus bradyarrhythmia

- Common finding, more prominent in dogs, especially during night hours (vagal prevalence)
Sinus arrhythmia with ventricular escape complex

- Less common finding, still can be observed in healthy animals
AV block

- First degree AV block – prolongation of PR interval
- Second degree AV block
  - Type 1 (aka Mobitz 1 or Wenckebach): Progressive prolongation of PR interval with dropped beats
  - Type 2 (aka Mobitz 2 or Hay): PR interval remains unchanged prior to the P wave which suddenly fails to conduct to the ventricles.
- Third degree AV block, also known as complete heart block, condition when impulse generated in the sinus node does not propagate to the ventricles
2nd Degree AV Block, Type 2

- Common finding in healthy animals, more frequent in dogs
3rd degree AV block

- Impulse generated in the sinus node, conducts to atria but does not propagate to the ventricles
- If impulse for ventricles generated at AV node or His Bundle before bifurcation, QRS complex can be of normal shape
Single PVC

- Ventricular cell may initiate an impulse and cause a premature ventricular contraction (PVC)
- A single occurrence is seen quite often and does not cause any serious problems
Multiple polytopic PVC

- Abnormal finding, may suggest myocardial damage and/or issues with repolarization
- Frequent PVC dramatically increase probability of polymorphic ventricular tachycardia aka Torsades de Pointes (TpD)
Torsades de Pointes

- Torsades de pointes (TdP) – is a polymorphic ventricular tachycardia that can cause sudden death
- Although uncommon, TPD is one of the most severe cardiac side effects
Chronopharmacology

Chronokinetics of Indomethacin (Human data)

Other examples:
- Amitriptylin
- Diasepam
- Digoxin
- Propranolol
- Verapamil
- Nidedipin
- Theophyllin
...

Clench et al., 1981
Chronopharmacology

Same amount of drug given at a different time of the days may result in different exposure (Cmax, Tmax, AUC…)
- Chronopharmacokynetics

Same amount of drug given at a different time of the days may result in different pharmacodynamic response
- Chronopharmacodynamics

v. Mayersbach, 1976
Diurnal Variability in HR

Sato et al, 1995; Soloviev et al, 2006; Stubbman et al 2008

Difference between nocturnal and diurnal species
Diurnal Variability in BP

Sato et al, 1995; Soloviev at al, 2006; Stubbann et al 2008
Diurnal Variability in Temperature

- Stubbam et al. 2008;
- Soloviev et al. 2003;
- Soloviev et al. 2006

- Rat, activity
- Rat, temperature
- Minipigs

Stubbam et al. 2008; Soloviev et al. 2003; Soloviev et al. 2006
Diurnal Variation of QT interval

Difference up to 32 msec (12.7%)
Suggested Literature

- Dubin D. Rapid Interpretation of EKG's. 2000.
Suggested Literature

Thank you!

Questions?