PHARMACOLOGY AND PHARMACOKINETICS OF ANTIARRHYTHMIC DRUGS

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The need to develop and test new antiarrhythmic drugs is essential if morbidity and mortality rates associated with cardiac arrhythmias are to be reduced. New antiarrhythmic drugs should demonstrate negligible toxicity, excellent efficacy against a variety of arrhythmias, convenient dosing regimens and be devoid of drug toxicity and interactions. The "ideal" antiarrhythmic drug has yet to be developed, although a wide variety of chemical compounds are currently being evaluated for clinical use. Theoretically, the development and use of antiarrhythmic drugs should be based upon a complete understanding of those mechanisms responsible for the production of cardiac arrhythmias. Regrettably, the mechanisms responsible for the production of many experimentally induced cardiac arrhythmias are incompletely understood while mechanisms responsible for the spontaneous development of cardiac arrhythmias are largely speculative. Recent advances in electrophysiologic testing procedures are helping to elucidate potential causes for the development of cardiac arrhythmias.[1] Table 1 lists basic cellular electrophysiologic mechanisms believed responsible for arrhythmia development. Among these, abnormal automatic mechanisms and reentry are believed to be responsible for the development of most spontaneously occurring arrhythmias.

Table 1. Cellular Mechanisms Responsible for Producing Cardiac Arrhythmias

1.	Enhancement or depression of impulse generation
	a. Enhanced or depressed normal automaticity from the SA node, peri AV nodal or Purkinje system.
	b. Abnormal automaticity developing in atrial or ventricular myocardium.
	c. Triggered activity developing from normally quiescent cardiac tissue due to
	1. early afterdepolarizations
	2. late afterdepolarizations
2.	Abnormal conduction of the cardiac impulse
	a. Conduction block
	b. Delayed conduction
	c. Unidirectional block and reentry or reflection

Supraventricular or ventricular abnormal automatic mechanisms are produced by exposure to catecholamines, reduced potassium concentrations, acidosis, low calcium concentrations, hypoxia, inhalation anesthetics, digitalis glycosides and trauma. Abnormal automaticity develops when one or a combination of these factors leads to impulse generation in tissues which may or may not normally exhibit automatic activity. Afterdepolarizations, for example, may become responsible for impulse generation in tissues which are normally automatic. Reentry is a unique mechanism which is dependent upon unidirectional conduction block and delayed conduction. Basically, a normal or abnormally generated impulse is slowed in its electrical activation of myocardium and has the opportunity to recirculate and re-excite tissues which have had time to undergo repolarization. This mechanism has been referred to as a circus movement. Ischemia, hypoxia, acidosis and drug overdosage are believed to be the most common causes for reentry.

The reason for being concerned with the various cellular mechanisms responsible for the development of cardiac arrhythmias is based upon the belief that drugs can be developed which will specifically effect one or a number of these mechanisms.[2,3] Tremendous strides have been made during the past 10 years in developing methods to detect cardiac arrhythmias and producing experimental arrhythmia models to test antiarrhythmic drugs. Table 2 lists those experimental arrhythmia modeling techniques used most frequently for testing the efficacy of antiarrhythmic drugs.

One question that must be answered before proceeding further with a general discussion of antiarrhythmic drugs is why treat cardiac arrhythmias at all? The answer to this question is somewhat intuitive and is based upon the electrical and mechanical abnormalities which cardiac arrhythmias produce. Supraventricular and ventricular arrhythmias frequently lead to a degeneration in hemodynamic status.[4] Physiologically, this may include abnormal ventricular contraction, leading to a reduced stroke volume, cardiac output and arterial blood pressure. Peripheral vascular resistance may increase, thereby causing an abnormal distribution of blood flow. Table 3 lists the pharmacologic effects of many conventional and new antiarrhythmic drugs.[5,6] Electrically, cardiac rhythm disturbances may predispose to more malignant forms of arrhythmia and, in many instances, have been shown to increase cardiac excitability and reduce ventricular fibrillatory threshold.[7] Whether or not these latter effects are due to hemodynamic deterioration leading to hypoxia or ischemia or a direct cellular effect is not certain. Clinically, arrhythmias lead to lethargy, depression and syncopy. Occasionally, convulsions are observed. The occurrence of sudden death, secondary to the acute onset of arrhythmias, has been speculated to occur in animals, although the significance of this problem in the general population is unknown.

For many years, the only antiarrhythmic drugs that were available to veterinarians were quinidine, procainamide and lidocaine. Digitalis, a drug used to increase myocardial contractile activity, has also been advocated as an antiarrhythmic but has found limited use for this purpose in veterinary medicine. Classically, pharmacologists have attempted to categorize antiarrhythmics based upon their cellular membrane effects.[7] The classification takes into account historical concepts that antiarrhythmics alter cardiac excitability, conduction and refractoriness. Based upon these effects, antiarrhythmic drugs have been categorized into four basic groups (Table 4).

Table 2. Common Methods Used to Produce Cardiac Arrhythmias

1. Chemical
   a. Irritants
      1) Aconitine
      2) Veratrine
      3) Barium
   b. Pharmacologic
      1) Digitalis
      2) Catecholamines
      3) Halogenated fluorocarbons
   c. Ionic
      1) Hyperkalemia
      2) Hypercalcemia

2. Ischemia
   a. Limited-flow
   b. No flow
   c. Reflow (reperfusion)

3. Electrical
   a. Electrical shock
   b. Timed stimulation
   c. Programmed electrical stimulation (PES)

4. Electrical
   a. Discrete CNS lesions
   b. Sympathetic nerve stimulation
   c. Parasympathetic nerve stimulation
   d. Chemical modulation of autonomic tone

5. Surgical Ablation
   a. Crushing (SA & AV node)
   b. Cauterizing
   c. Freezing

Table 3. Electrocardiographic and Hemodynamic Effects of Antiarrhythmic Drugs*

Drug	Electrocardiographic			Hemodynamic				Undesirable Effects Upon Cardiac Rhythm
	PR	QRS	QT_c	Heart Rate	Cardiac Contractility	Cardic Output	Arterial Blood Pressure	
Quinidine	↓↑	↑	↑	↑	↓	↓	↓	"Atropine-like" effect; pacemaker suppression; sinus arrest; asystole; ventricular tachycardia; ventricular fibrillation; 1st, 2nd or 3rd degree heart block
Procainamide	↓↑	↑	↑	↑	↓	↓	↓	
Disopyramide	↓↑	↑	↑	↑	↓	↓	↓	
Lidocaine	o↓	o	↓	o	o↓	o↓	o↓	Pacemaker suppression Asystole Sinus arrest
Phenytoin	o↓	o	↓	o	o↓	o↓	o↓	
Mexiletine	o↑	o	↓	o	o↓	o↓	o↓	
Tocainide	o	o	↓	o	o↓	o↓	o↓	
Aprindine	↑	↑	↓	↓	↓	↓	↓	
Flecainide	o	↑	o	↓	o	o	o↓	
Propranolol	o↑	o	o	↓	↓	o↓	↓	Pacemaker suppression, atrio-ventricular block; asystole; Note: may aggravate or produce heart failure
Amiodarone	↑	↑	↑	o	↓	↓	↓	
Bretylium	↑	o↑	↑	o	↑↓	↑↓	o	
Verapamil	o	↑	↑	o↓	↓↓	↓	↓	Pacemaker suppression; asystole; Note: potent negative contractile effect

o - no change; ↑- increase; ↓- decrease

* Electrocardiographic and Hemodynamic Depressant Effects are Dose Dependent

Table 4. Classification of Antiarrhythmic Drugs

Class I	Class II	Class III	Class IV
Class IA			
Quinidine	Propranolol	Bretylium	Verapamil
Procainamide	Nadolol	Amiodarone*	Diltiasem
Disopyramide	Timolol	Bethanidine*	Nifedipine
Acecainide (NAPA)*	Pindolol	Sotalol*	D-600*
Pirmenol*	Metoprolol		Nisoldipine*
	Atenolol		Tiapamil*
	Practolol*		
Class IB			
Lidocaine			
Phenytoin			
Mexiletine*			
Tocainide*			
Lorcainide*			
Ethmozin*			
Class IC			
Encainide*			
Flecainide*			
Aprindine*			

* Investigational

Class I antiarrhythmic drugs block sodium entry into cardiac cells. Class II antiarrhythmic drugs are beta-adrenoceptor blocking agents. Their antiarrhythmic membrane ionic activity is uncertain. Class III antiarrhythmic drugs exhibit their activity by prolonging action potential duration and refractoriness. Class IV antiarrhythmic drugs inhibit calcium entry into cardiac cells. Because of the rapid and intense development of Class I antiarrhythmic drugs, this group has been sub-categorized into groups IA, IB, and IC. Group IA antiarrhythmic drugs are typified by quinidine, procainamide, and disopyramide and other drugs that depress phase-0 of the action potential, have moderate effects upon conduction of the electrical impulse and prolong repolarization. Class IB antiarrhythmic drugs are represented by lidocaine, mexiletine and tocainide and demonstrate mild effects on phase-0 of the action potential and conduction velocity, but shorten repolarization. Class IC antiarrhythmic drugs are represented by encainide and flecainide and are known to profoundly depress phase-0 of the action potential and conduction, but

demonstrate little or no effect on repolarization. It is clear that many of the cellular electrophysiologic effects of the drugs listed in table 3 overlap and that a precise distinction between the electrophysiologic effects of antiarrhythmic drugs is impossible. This point becomes increasingly important when considering the fact that electrophysiologic mechanisms responsible for drug effects may not be identical in normal and diseased tissues. Antiarrhythmic actions in the central and autonomic nervous systems and indirect drug actions upon the peripheral vasculature may also play a role in a specific drug's antiarrhythmic activity. Regardless of the many experimental and clinical studies that have been completed, no foolproof method has evolved for determining which antiarrhythmic drugs are specifically indicated for a given arrhythmic situation. For example, although beta-adrenoceptor blocking drugs have proven efficacy in the treatment of catecholamine-induced arrhythmias, lidocaine, a drug that does not possess beta-adrenoceptor blocking activity, is an excellent antiarrhythmic in this situation. It seems reasonable to conclude, therefore, that one method or means of categorizing antiarrhythmic drugs is based upon their ability to eliminate one or a number of the various types of spontaneously occurring arrhythmias.[8] Such clinical efficacy studies have been performed, but a great many more need to be completed before conclusive evidence will be available. Those studies that have been conducted using several antiarrhythmic drugs in different animal species indicate that quinidine is by far the most effective antiarrhythmic therapy for the treatment of supraventricular arrhythmias in dogs, cats and horses. Difficulties with the use of quinidine in small animals, however, include poor patient acceptability and the frequent occurrence of toxic side effects.

Lidocaine is by far the most efficacious drug available for the treatment of ventricular arrhythmias, although it has the practical disadvantage of requiring intravenous administration. The intramuscular use of lidocaine, although potentially beneficial, has not proven to be particularly effective. The development of several new antiarrhythmic drugs, which offer a longer duration of action, thereby reducing the frequency of daily administrations, has not been as rewarding from the standpoint of efficacy. One drug, amiodarone, demonstrates a long duration of action and excellent antiarrhythmic effects, although clinical experience in veterinary medicine at this time is sparse. The calcium antagonists, verapamil and nifedipin, were initially thought to possess unique antiarrhythmic properties for the treatment of supraventricular arrhythmias. The ability of these drugs to depress transarcolemmal calcium flux, however, may lead to severe cardiac depression and profound hypotension mandating the discontinuance of therapy. One last comment that must be made regarding the development of antiarrhythmic drugs is that many, if not all, antiarrhythmic drugs have the potential to induce cardiac arrhythmias. Although not normally noted for this ability, recent studies in humans and animals has verified that many, if not all, antiarrhythmic drugs can be arrhythmogenic. Non-sustained ventricular tachycardia, multifocal ventricular tachycardia and ventricular fibrillation have been produced by the administration of quinidine, procainamide and lidocaine to dogs with ventricular rhythm disturbances. Although this type of response to antiarrhythmic therapy is rare, it warrants close scrutiny and careful monitoring of all patients receiving antiarrhythmic drugs.

In conclusion, it is clear that many veterinary clinicians are gaining a greater appreciation for the frequency of cardiac arrhythmias and their potential for increasing mortality. It is also clear that a wide variety of antiarrhythmic drugs with varying efficacy and toxicity profiles are emerging. The pharmacokinetic and pharmacologic properties of these drugs must be carefully scrutinized in domestic animals before any of these compounds can be advocated as safe and effective therapy for the treatment of cardiac arrhythmias.[9] Tables 5 to 8 list the pharmacokinetic profiles of several antiarrhythmics in the dog, cat, horse and cow. It is hoped that future research and committments by industry will help to develop a variety of antiarrhythmic drugs specific for the many clinical arrhythmias observed and possessing a reasonably long duration of action with little or no toxic side effects.

References

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Table 5. Pharmacokinetic Properties of Antiarrhythmic Drugs in Dogs

Drug	Vd l/kg	Cl_T ml/min/kg	Cl_R ml/min/kg	$t_{1/2}$ hr	Therapeutic Range	F	Protein Binding %	Dose Oral	Dose I.V.
Quinidine	2.9	6.0	N/A	5.6	3-5 µg/ml	N/A	85	12 mg/kg/6h	10 mg/kg
Procainamide	2.1	12.5	$0.5-0.7Cl_T$	2.0	4-10 µg/ml	N/A	N/A	up to 50 mg/kg per day given in 6-8 doses	100 mg stat; 10-40 µg/kg/min
Disopyramide	3.0	25.0	$0.15Cl_T$	1.2 (2.0 p.o)	3-8 µg/ml	0.7	20	7-30 mg/kg q 2h	N/A
Lidocaine	5.7	62	$<0.05Cl_T$	1.0	2-6 µg/ml	low	N/A	N/A	4 mg/kg stat; 40-60 µg/kg/min
Phenytoin	1.2	4.0	$<0.05Cl_T$	3.3	10-16 µg/ml	0.40	65	30 mg/kg/8h	10 mg/kg*
Mexiletine**	N/A	N/A	N/A	N/A	0.5-2.0	high	N/A	?	N/A
Tocainide**	1.7	4.2	$0.3Cl_T$	4.7 (8-12 p.o.)	6-10 µg/ml	0.85	N/A	50-100 mg/kg q 12h	N/A
Aprindine**	10?	11.6	$<0.1Cl_T$	10	1-3 µg/ml	high	N/A	5 mg/kg/day	N/A
Propranolol†	3.3-6.5	34-70	$<0.1Cl_T$	1.1	40-120 ng/ml	low	N/A	5-40 mg q 6h	<1.5 mg/kg
Verapamil†	4.5	65	low	0.8	N/A	low	N/A	?	?

* Administer slowly
† Any other beta blocker can be used as a substitute for propranolol
N/A Data not available
** Investigational drug

Table 6. Pharmacokinetic Properties of Antiarrhythmic Drugs in Cats

Drug	Vd l/kg	Cl_T ml/min/kg	Cl_R ml/min/kg	$t_{1/2}$ hr	Therapeutic Range	F	Protein Binding %	Dose
Phenytoin	N/A	low	N/A	<24 hr	10-16 µg/ml	good	N/A	2-3 mg/kg p.o./day
Quinidine	2.22	14.8	N/A	1.9	3-5 µg/ml	N/A	85	10 mg/kg IV

N/A Data not available

Table 7. Pharmacokinetic Properties of Antiarrhythmic Drugs in Horses

Drug	Vd l/kg	Cl_T ml/min/kg	Cl_R ml/min/kg	$t_{1/2}$ hr	Therapeutic Range	F	Protein Binding %	Dose
Quinidine	3.12	5.5	N/A	6.65	3-5 µ g/ml	0.5	80	12 mg/kg IV to load and 6 mg/kg IV q 6h
Propranolol	2.3	21	N/A	1.25	40-120 ng/ml	N/A	N/A	0.05 mg/kg/IV

N/A Data not available

Table 8. Pharmacokinetic Properties of Antiarrhythmic Drugs in Cattle

Drug	Vd l/kg	Cl_T ml/min/kg	Cl_R ml/min/kg	$t_{1/2}$ hr	Therapeutic Range	F	Protein Binding %	Dose
Quinidine	3.8	19	N/A	2.3	0.5-2.0 µg/ml	0.23	N/A	48 mg/kg IV loading and 42 mg/kg IV 1 6h

N/A Data not available