

DRUGS USED TO TREAT CARDIOVASCULAR DISEASE IN HORSES

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The treatment of cardiovascular disease in the horse has evolved considerably over the past ten years. Diseases involving the cardiovascular system of horses, which were once considered nontreatable, are now being diagnosed and treated routinely in many progressive equine practices. Common cardiovascular diseases of the horse include a variety of cardiac arrhythmias, particularly atrial fibrillation, acquired heart disease and congenital heart disease. Table 1 lists the common cardiovascular diseases observed in horses in the United States.

TABLE 1: COMMON DISEASES OF THE CARDIOVASCULAR SYSTEM OF THE HORSE

- A. Cardiac Arrhythmias
 - 1. Sinus arrhythmia
 - 2. First degree A-V block
 - 3. Second degree A-V block
 - 4. Interference dissociation
 - 5. Ventricular extrasystoles
 - 6. Atrial fibrillation
 - 7. Ventricular tachycardia

- B. Acquired Heart Disease
 - 1. Mitral insufficiency
 - 2. Tricuspid insufficiency
 - 3. Aortic insufficiency
 - 4. Myocarditis
 - 5. Pericardial disease
 - 6. Myocardial disease

- C. Congenital Heart Disease
 - 1. Ventricular septal defect
 - 2. Patent ductus arteriosus
 - 3. Aortic and pulmonic stenosis

The drugs used for the treatment of cardiovascular disease in horses are principally agents which are designed to improve the quality of life, not necessarily prolong life. Towards this end digitalis glycosides, diuretics and a variety of antiarrhythmic drugs have been advocated. The digitalis glycosides, particularly digoxin, have been extensively studied and are frequently used clinically to treat cardiovascular failure in horses. Table 2 lists pharmacokinetic data reported by various investigators for digoxin in horses.¹⁻⁵

Table 2: PHARMACOKINETICS OF DIGOXIN IN HORSES

| | t _{1/2} (hr) | Vd _{beta} (l/kg) | Vd _{ss} (l/kg) | CL _T ml/min/kg | F (%) | Dose | |
|-------------------------|--------------------------|------------------------------|----------------------------|------------------------------|----------|---------------|------|
| | | | | | | IV (µg/kg) | Oral |
| Frankfort & Shatzman | 23 | 5.0 | | 2.5 | | 5-7 | |
| Button | 23.1 | 4.89 | 4.35 | 2.4 | 19 | 7 | 35 |
| Pedersoli <u>et al.</u> | 16.8 | 4.33 | | 3.8 | 35 | 6.1 | 17 |
| Brumbaugh <u>et al.</u> | 16.9 | 5.0 | | 3.4 | 23 | 4-5 | 20 |

This data indicates that for digoxin to be used safely, it must be administered at least once daily and preferably, twice daily. Digitalis glycosides increase the force of cardiac contraction and improve peripheral perfusion to the gastrointestinal tract and kidney, help to normalize acid/base and electrolyte disturbances, decrease cardiac rate and reduce the ventricular response during atrial fibrillation. Digitalis glycosides are also believed to be useful in the treatment of atrial premature depolarizations, although this claim has not been substantiated in horses. Contraindications for the use of digitalis glycosides include: aortic and pulmonic stenoses, myocarditis, pericarditis, cardiac tamponade and sustained ventricular tachycardia. Signs of digitalis intoxication include: muscle weakness, lethargy, anorexia and diarrhea. In horses, digitalis therapy is most frequently associated with the treatment of atrial fibrillation and of myocardial failure from any cause. The use of digitalis therapy for the treatment of atrial fibrillation has been questioned based upon its known electrophysiologic effects to shorten atrial action potential duration, thereby predisposing to reentrant mechanisms and the perpetuation of atrial fibrillation; digitalis, however, does reduce the number of atrial impulses reaching the ventricles, thereby slowing ventricular rate, and generally improves cardiac output and peripheral perfusion. Extreme caution must be practiced when administering digitalis to horses in that relatively large dosages are usually required and digitalis toxicity is a potential side effect.

A variety of antiarrhythmic drugs have been proposed as potential therapy for the treatment of supraventricular and ventricular arrhythmias in horses. To date, however, only digitalis and quinidine have demonstrated efficacy in the treatment of cardiac arrhythmias in horses.⁶ Quinidine produces a variety of direct electrophysiologic effects upon the atrial and ventricular myocardium which decrease conduction velocity and cardiac excitability, but which increase cardiac refractoriness. These electrophysiologic properties are no doubt responsible for its efficacy in the treatment of supraventricular arrhythmias including atrial fibrillation and ventricular tachycardia. Several studies have reported a greater than 70% conversion rate of atrial fibrillation to normal sinus rhythm following the administration of quinidine.⁶ Alternative antiarrhythmics, including procainamide, lidocaine and propranolol, have not demonstrated antiarrhythmic activity comparable to that of quinidine. The

reason for this discrepancy may be due to their pharmacokinetic values in horses. Table 3 indicates that the clearance and volume of distribution of lidocaine in horses is extremely large leading to a relatively short biological half-life and the rapid deterioration in plasma concentration with time.

Table 3: PHARMACOKINETIC VALUES OF ANTIARRHYTHMIC DRUGS IN HORSES

| Drug | Dose | Route | Cl_T (ml/min/kg) | V_{dss} (l/kg) | V_d (l/kg) | V_c (l/kg) | $t_{1/2}$ (hr) |
|--------------|---------|-------|-----------------------|---------------------|-----------------|-----------------|-------------------|
| Lidocaine | 2 mg/kg | IV | 64.4 | 8.2 | 1.7 | 2.2 | 3.1 |
| Procainamide | 1 mg/kg | IV | 3.91 | 2.1 | 2.4 | 0.7 | 7.0 |
| Quinidine | 5 mg/kg | IV | 5.49 | 2.8 | 2.9 | 1.1 | 6.7 |
| Propranolol | 1 mg/kg | IV | 12.1 | 1.4 | | | 1.7 |

This response is more clearly depicted in Figure 1 which illustrates the rapid decline in plasma lidocaine concentration with time following intravenous administration of 2 mg/kg to a 473 kg horse. This figure illustrates that extremely low concentrations of lidocaine occur within a relatively short period of time following intravenous administration. If the minimum effective concentration for antiarrhythmic therapy in horses is similar to that in other species, a minimum of 0.5-1.0 $\mu\text{g/ml}$ of lidocaine is required to produce antiarrhythmic effects. This concentration could not be produced safely unless a constant infusion was administered. Constant infusion techniques are not possible under most field circumstances in horses.

Procainamide is another antiarrhythmic drug frequently used in small animal patients but which finds limited usefulness in horses because of the relatively rapid decrease in plasma concentration with time (Figure 2, Table 3). Interestingly, n-acetyl procainamide is produced following the intramuscular administration of procainamide to horses (Figure 3). N-acetyl procainamide retains antiarrhythmic properties similar to procainamide. Regardless of the presence of both parent compound and active metabolite, their plasma concentration remains relatively low and possibly outside the therapeutic range. An important practical disadvantage of the use of procainamide in horses is its expense.

Propranolol, a nonspecific beta-adrenoceptor blocking drug has been advocated as potential antiarrhythmic therapy for use in horses. Figure 4 illustrates the plasma concentration time curve for propranolol in horses and Table 3 lists relevant pharmacokinetic values. Although this drug should be useful in the treatment of a variety of cardiac arrhythmias initiated or perpetuated by increases in sympathetic tone, it is difficult to justify its use based upon frequent intravenous administration and high first pass effects, if given orally.

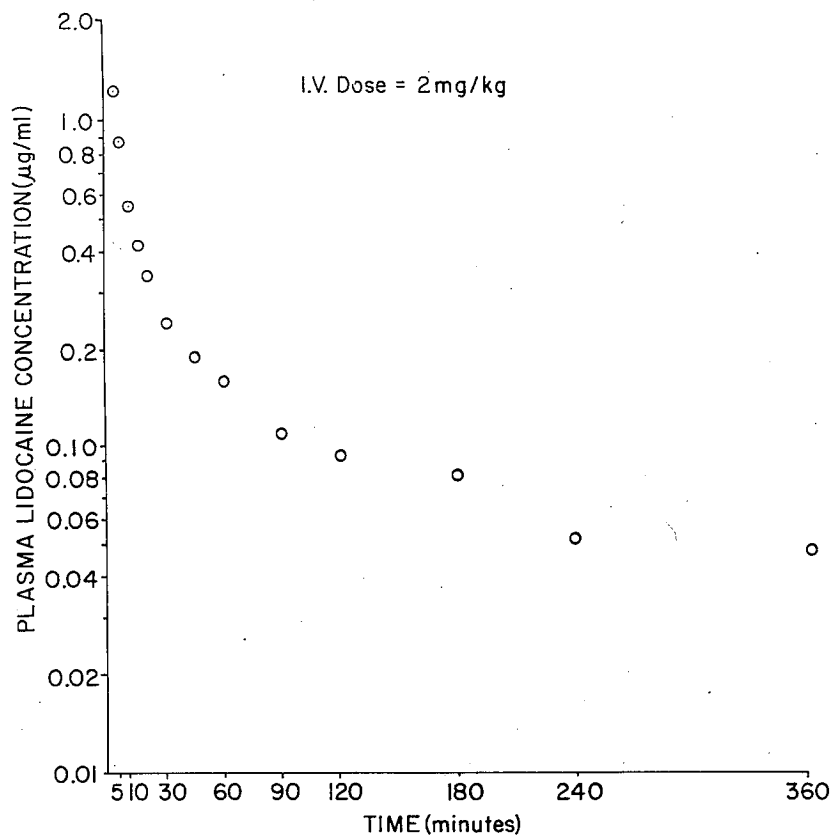


Figure 1 Plasma elimination time curve following the IV administration of lidocaine to a horse.

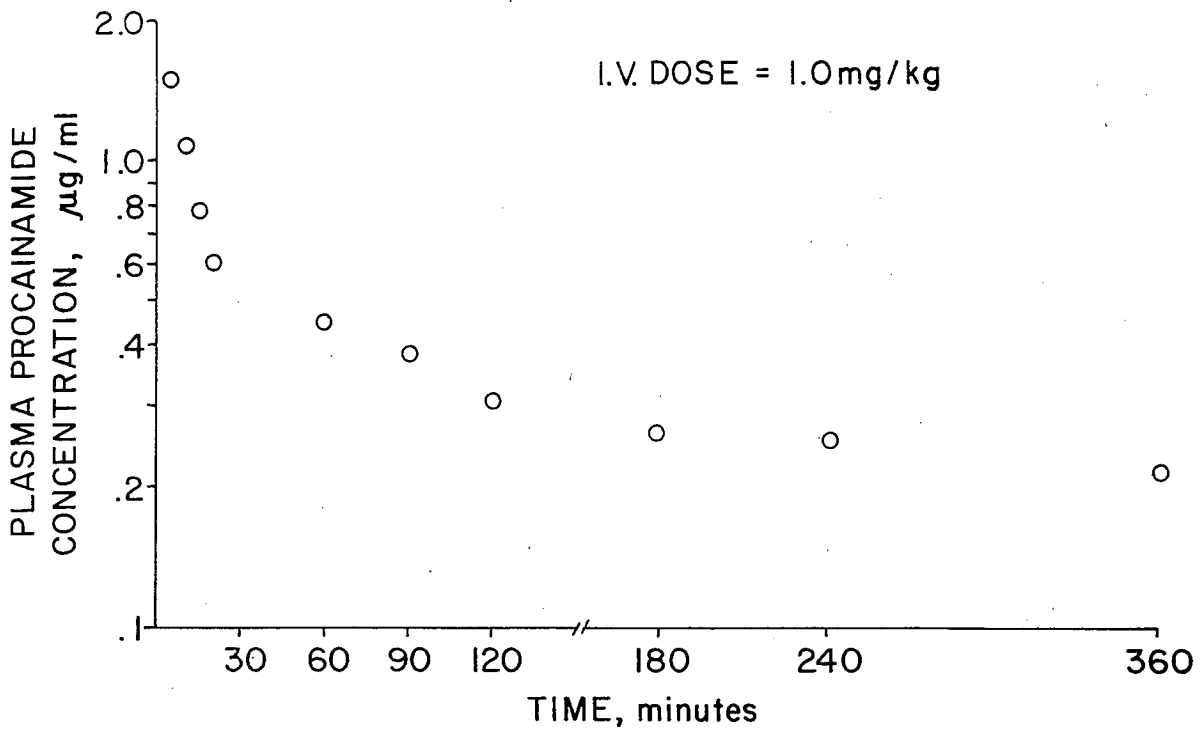


Figure 2 Plasma elimination time curve following the IV administration of procainamide to a horse.

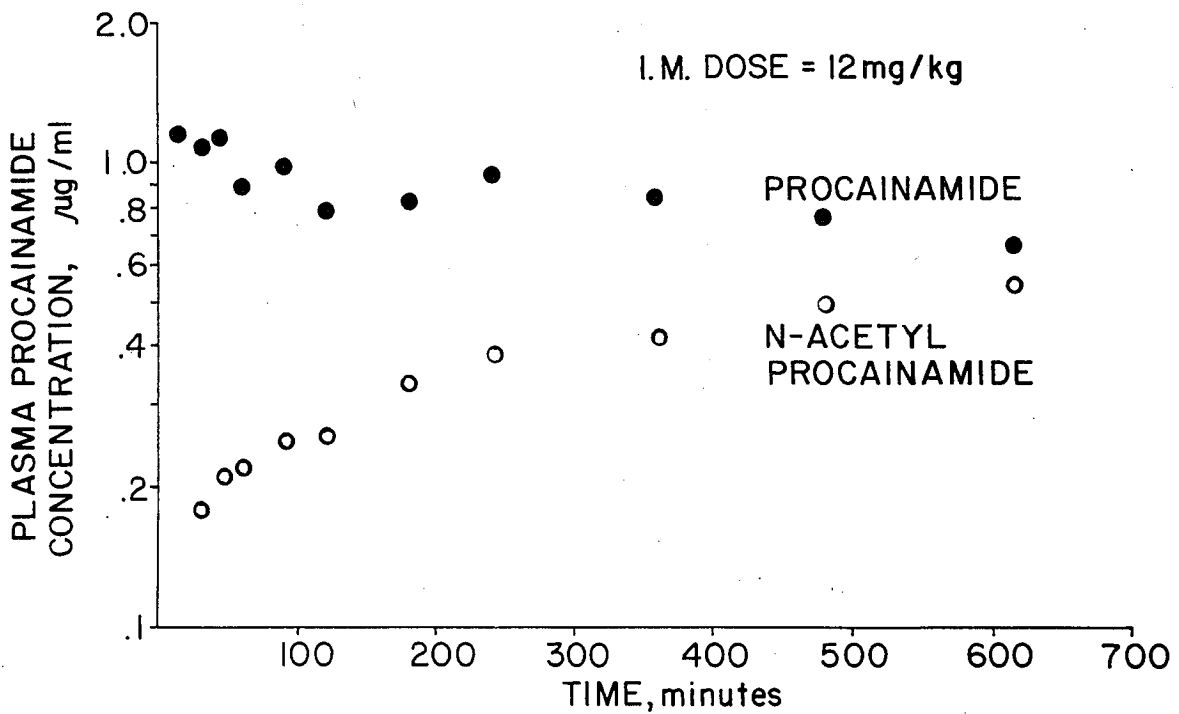


Figure 3 Plasma elimination time curve following the IM administration of procainamide to a horse. Note the appearance of n-acetyl procainamide.

Furosemide is a loop diuretic that produces a prompt diuresis in horses and has been used in the treatment of edematous states associated with congestive heart failure. Furosemide may be particularly effective in the initial treatment of pulmonary edema, ascites, subcutaneous edema and reduced urine formation due to poor renal blood flow. Its use in the treatment of congestive heart failure has been questioned based upon its ability to produce a prompt diuresis, thereby decreasing the effective circulating blood volume and venous return resulting in reductions in cardiac output.⁸ Providing that fluid volume can be appropriately maintained, the diuresis by furosemide is usually not detrimental to cardiac output. Additional advantages of furosemide therapy may be an improvement in gas exchange and the mobilization of fluids or redistribution of fluids away from the central compartments to peripheral capacitance vessels. These effects may help to unload a stressed heart, thereby improving general cardiac performance and peripheral blood flow. The most beneficial use of furosemide from a practical standpoint is in treating pulmonary edema. The removal of pulmonary congestion can be life saving to a horse in which pulmonary fluid accumulation has led to a dramatic reduction in gas exchange, resulting in hypoxia. Potential problems with the overzealous use of furosemide include: reductions in cardiac output as stated previously, dehydration, and acid/base and electrolyte disorders. Hypokalemic/hyponatremic metabolic alkalosis can be produced with frequent or overzealous furosemide administration. Hypokalemia is important from a clinical standpoint because digitalis toxicity is more likely to occur during hypokalemia and antiarrhythmic drugs are less effective. Close patient monitoring and relatively frequent serum potassium determinations are required during the administration of furosemide to horses with congestive heart failure. Table 4 lists the dosages of drugs commonly used to treat cardiovascular diseases in horses. Of these drugs only digitalis, quinidine and furosemide appear to be beneficial from a practical standpoint at the present time.

Table 4: DOSAGES OF DRUGS USED TO TREAT CARDIOVASCULAR DISEASES IN HORSES

| | Intravenous | Intramuscular | Oral |
|--------------|--|----------------|------------------------------------|
| Digitalis | 0.25-0.35 mg/100 lb (loading) 0.1-0.2 mg/100 lb (maintenance) | | 1 mg/100 lbs |
| Quinidine | 20 mg/100 lbs total 2 g | | 1 g/100 lbs q 2 hrs, total 70 g |
| Procainamide | 20 mg/100 lbs total 2 g | 0.5 mg 100 lbs | |
| Lidocaine | 25 mg/100 lbs total 2 g | | |
| Propranolol | 5-10 mg/100 lbs twice daily | | |
| Furosemide | 25 mg/100 lbs | 30 mg/100 lbs | |

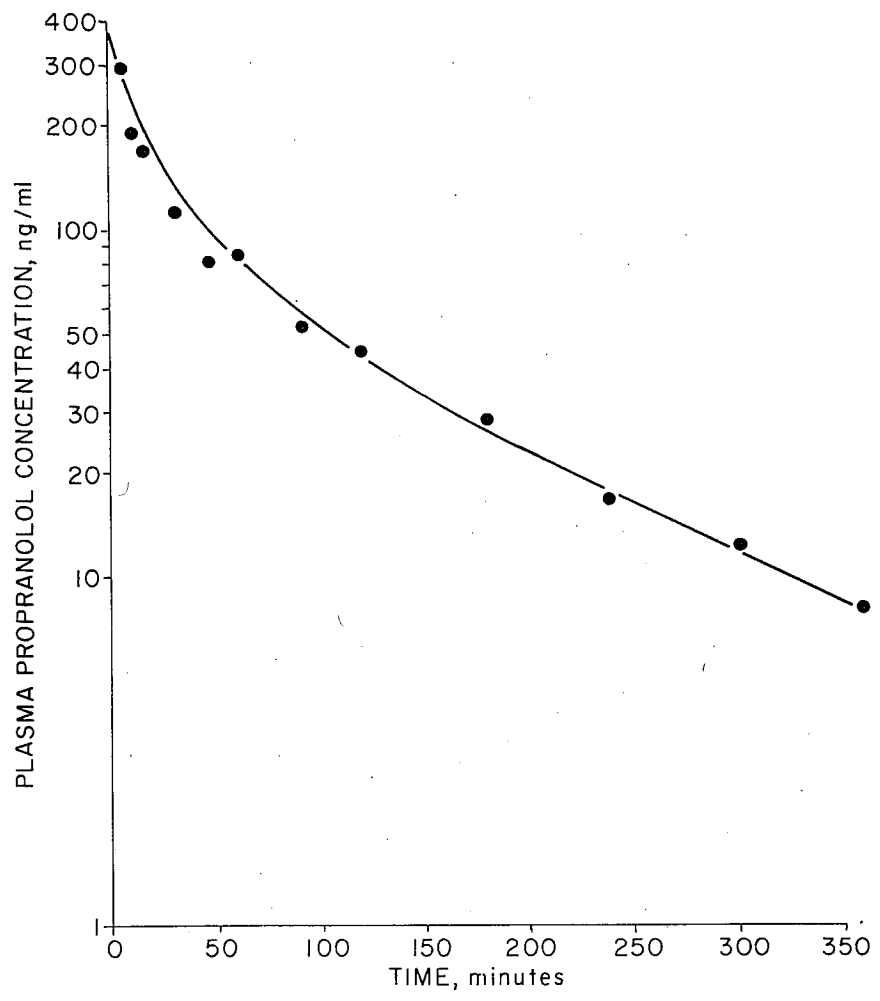


Figure 4 Plasma elimination time curve following the IV administration of propranolol to a horse.

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Points raised during discussion

Question: Would our cardiologist colleagues please indicate what work they feel should be done at the basic science level in support of clinical activities and where they might see the needs?

Dr. Knauer: The first thing that becomes immediately obvious here, as several people have mentioned so far, you have got 100 years of work ahead of you. You can clearly see the empiricism of many of the treatments in the clinical setting and we have had so many new drugs come to the fore just in the decade of the 80's. There was nothing in the 60's or 70's that changed much. The decade of the 80's has produced many new promising drugs and we need to work out the pharmacokinetics of these drugs, as Dr. Muir has been able to do for some of the antiarrhythmic agents. For all the species in which they might be useful you could all take these on as projects with your graduate students and it would take you all a lifetime just to do the ones that are available right now let alone the ones that are going to be available in the next 5 to 6 years.

Dr. Harris: Another approach that I think would be valuable is in the veterinary colleges where we should encourage more communication from the basic sciences to the clinical areas and getting more of the basic science people into the clinic and functioning as part of the clinical teaching staff. I think this is one of the most important things that would help us in teaching and would help the students in acquiring what knowledge they need to know about these drugs and all the interactions and reactions that can occur with them.

Dr. Knauer: Some of the best discussions that we have during rounds is when some of the basic science people come over to the teaching hospital and sit in on our daily rounds or offer consultation on a particular case. I would encourage this kind of interaction.

Dr. Adams: There is a tremendous amount of basic research being done with many of these drugs across the country and the world. Where I think we are lacking in veterinary medicine is in the documentation of drug effectiveness under "clinical conditions" and I think that charge needs to be issued to clinicians, whether as a school, by themselves, or hopefully with interaction with the basic science departments. That is where I think we are lagging behind. When you go to look for these drugs, and we are talking about empiricism in many cases, we do not have the documentation of objective-type data in clinically relevant spontaneous disease conditions. And that is where I think that a significant charge needs to be issued and it seems like that the interaction of clinicians with basic scientists would be an excellent way to do that.

Dr. Harris: The problem with veterinary schools and being able to do what is needed is the clinical load most schools put on their clinicians. There is no time to really sit down and statistically analyze or to have a controlled research study with drugs and therapy. You are spending all your time teaching, generating income for the hospital and doing other things that really are quite time consuming and are not scientific. In order for clinicians to get into the scientific field of clinical research the schools are going to have to supply some support in the form of more personnel. One thing about being in a medical school, every faculty member has a technician. We also all have secretaries available. When I taught 15 years in a veterinary college, technicians were not available for anyone, and getting any secretarial help was next to impossible. Until we get some support, it is going to be very difficult, I think.