SUMMARY

Pharmacokinetics of Digoxin and Digitoxin in the Dog and the Influence of Experimental Cholestasis on the Pharmacokinetics

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INTRODUCTION

In 1785, William Withering utilized an extract from the foxglove plant, digitalis, in the treatment of dropsy. Withering also published his now famous book, An Account of the Foxglove and Some of its Medical Uses: With Practical Remarks on Dropsy and Other Diseases. Delabere Blaine, in 1841, presented evidence of favorable effects obtained with digitalis in certain dogs treated for ascites, but also observed that digitalis had no benefical effect on other dogs. Today, more than 200 years after the publication of Withering's famous book, the digitalis glycosides, digoxin and digitoxin, are primarily administered for the treatment of congestive heart failure and for the control of the ventricular rate in patients with atrial fibrillation. In recent years, due to the increased recognition of clinical heart diseases in domestic animals, digitalis glycosides have been used with increasing frequency in veterinary medicine. Rational therapy depends upon the accurate and complete knowlege of the drug's behavior within the body. Digitalis glycosides have relatively narrow margins of safety between their effective therapeutic dosage and toxic dosage and these drugs should be administered with caution to avoid possible toxicity.

A considerable amount of information has been accumulated pertaining to the absorption, distribution, biotransformation and excretion of digitalis glycosides in animals, accompanying advances in clinical pharmacology. The metabolism and excretion of digoxin are more clearly understood than for the other digitalis glycoside, digitoxin. Better understanding of the pharmacokinetics of digoxin may be attributed to the much more extensive use of this drug in clinical practice and animal experiments than for digitoxin. However, there are still many problems concerning digitalis pharmacokinetics in veterinary medicine. It is known that the liver is an important site involved

in the metabolism and excretion of these drugs, but the specific mechanisms and role of the liver pertaining to digitalis pharmacokinetics is not yet completely understood. It is not clear whether liver dysfunction may have a significant influence of digoxin and digitoxin pharmacokinetics in the dog.

The present study was undertaken to evaluate the role of the liver in digoxin and digitoxin metabolism and excretion in dogs that have undergone ligation of the common bile duct, producing experimental cholestasis. Furthmore, the clinical effectiveness of digoxin and digitoxin were also evaluated and compared.

MATERIALS and METHODS

A. Digoxin Evaluation

For this experiment, eighteen apparently healthy dogs were divided into three groups. After the dogs had been anesthetized with pentobarbital sodium, a midline anterior abdominal incision was made. The common bile duct was doubly ligated in seven dogs (L group). A group of three dogs was given phenobarbital for two weeks followed by surgical ligation of the common bile duct (P group). A control group, consisting of eight dogs received abdominal incisions, that were later closed leaving the common bile duct intact (C group).

Digoxin was given by a single intravenous, to exclude the influence of variances in the absorption of the drug. All of the experimental dogs received 25 μg/kg of digoxin, five to six after the surgical operations. Venous blood samples were drawn in heparinized syringes from each animal prior to the operation and at 0.5, 1, 2, 3, 6, 8, 12, 18, 24, 30, 36 and 48 hours post intravenous injection of digoxin. The plasma was separeted and the samples were frozen for later digoxin analysis. The plasma digoxin concentration was

determined in duplicate using a commercially available radioimmunoassay (RIA) kit.

B. Digitoxin Evaluation

For this experiment, fifteen healthy dogs were divided into three groups, as was the procedure digoxin evaluation: a control group (C group) of three dogs, a common bile duct ligation group (L group) of six dogs and a phenobarbital pretreatment group (P group) of six dogs that were given phenobarbital for two weeks prior to surgery involving ligation of the common bile duct.

Digitoxin was given as a single intravenous administration at a dosage of 20 μg/kg. Multiple plasma samples were collected over a period just prior to digitoxin administration through 72 hours. Plasma digitoxin concentrations were also measured using the RIA technique.

The other ten dogs were given tritium labeled (^{3}H-) digitoxin. Eight of these dogs were divided into three groups, the C, L and P groups, as per the conditions described above. In the remaining two dogs (F group), an external biliary fistula was prepared 5 to 6 hours prior to this study. All of these dogs received a single intravenous dose of 50 μCi/14 kg of ^{3}H-digitoxin and 20 μg/kg of cold digitoxin, as a carrier. In these four groups, blood samples from each animal were obtained just prior the operation and at 1, 3, 6, 12 and 24 hours after the intravenous injection of the drug. Urine specimens for these four groups and the bile sample from the F group were collected at 12 hour intervals following the administration of digitoxin and the total volume was also measured. The plasma, urine and bile samples were frozen to be analyzed later.

The plasma, urine and bile were extracted using dichrolomethane (CH_2Cl_2) to separate the cardioinactive water soluble metabolites from the CH_2Cl_2-soluble cardioactive metabolites and the parent compound. The radioactivity of the CH_2Cl_2-soluble and -insoluble fractions was counted using a liquid scintillation counter. Quenching was corrected using an automatic external standardization.

C. Pharmacokinetic Analysis

The natural logarithms of the plasma drug concentration, plotted on the Y axis, were plotted against time on the X axis. The drug concentration-time curve for each individual experimental group and for the group mean data were best fitted by a one- or two-compartment open model. Therefore, the plasma concentration of the drug, as a function of time, may be calculated by one exponential or the sum of two exponentials as in the following equation:

$$Ct=Co\cdot e^{-k\cdot t} \qquad \text{(Equation 1)}$$

$$Ct=A\cdot e^{-\alpha\cdot t}+B\cdot e^{-\beta\cdot t} \qquad \text{(Equation 2)}$$

where, Ct=the concentration of the drug at any time t

Co=the concentration of the drug at time 0

k=the first-order rate constant for the overall elimination of drug from the body

α=distribution (fast) phase rate constant

β=elimination (slow) phase rate constant

A=Y-axis intercept of the extrapolated distribution phase

B=Y-axis intercept of the extrapolated elimination phase

The concentration-time data was subjected to least squares regression analysis and the coefficient of correlation between the theoretical value from the equation and measured concentrations by RIA were calculated. The hybrid

constants, A, B, α and β were estimated and used to calculated various pharmacokinetic parameters as follws:

Elimination half-life (hr.)

$t_{1/2}k = (\ln 1/2)/k$

Distribution phase half-life (hr.)

$t_{1/2}\alpha = (\ln 1/2)/\alpha$

Elimination phase half-life (hr.)

$t_{1/2}\beta = (\ln 1/2)/\beta$

Distribution rate constant ($hr.^{-1}$)

(from the peripheral into the central compartment)

$k_{21} = (A \cdot \beta + B \cdot \alpha)/(A + B)$

Elimination rate constant ($hr.^{-1}$) (from the central compartment)

$k_{e1} = \alpha \cdot \beta / k_{21}$

Distribution rate constant ($hr.^{-1}$)

(from the central into the peripheral compartment)

$k_{12} = \alpha + \beta - k_{21} - k_{e1}$

Area under the drug concentration-time curve (ng·hr/ml)

$AUC = Co/k$, or $A/\alpha + B/\beta$

Volume of the central compartment (l/kg)

$Vd_{central} = Dose/(A + B)$

Volume of the peripheral compartment (l/kg)

$Vd_{peripheral} = Vd_{central} \cdot k_{12}/k_{21}$

Total volume of the distribution (l/kg)

$Vd = Dose/Co$, or $Vd_{central} + Vd_{peripheral}$

Total volume of the distribution using the area method (l/kg)

$Vd_{area} = Dose/AUC \cdot \beta$

Total body clearance (ml/min/kg)

TBCL = Dose / AUC

RESULTS

A. Digoxin Evaluation

The plasma digoxin concentration of the individual dogs, after a single intravenous digoxin injection, decreased rapidly (distribution phase) dering the first few hours and then more slowly (elimination phase) for the following 6 to 8 hours. This concentration-time curve fits a two compartment open model. Therefore, the kinetics of the concentration-time data for individual subjects and for the average data from each group was best described by a bi-exponential function (Equation 2). The mean correlation coefficients between digoxin assayed using RIA and the calculated digoxin value from the equation were 0.997 or more for each of the three groups, indicating an excellent fit.

For the digoxin pharmacokinetics of the C group, the mean biological half-life of plasma digoxin in the distribution phase ($t_{1/2\alpha}$) was about 1 hour and in the elimination phase ($t_{1/2\beta}$) was approximately 20 hours. The mean volume of the distribution by extrapolation (Vd) was 6.6 l/kg body weight. The apparent distribution volume for the central compartment ($Vd_{central}$) was 1.5 l/kg and for the peripheral compartment ($Vd_{peripheral}$) was 5.1 l/kg. Calculated from the area under the drug concentration-time curve, the distribution volume (Vd_{area}) was 9.4 l/kg. The total body clearance (TBCL) was 5.65 ml/min/kg for the C group.

For the L group, the plasma digoxin concentration did not, at any time, differ significantly from observed values of the C group. There was no significant difference between the observed value obtained from this group and the C group, regarding the pharmacokinetic parameters of the distribution phase.

However, the $t_{1/2\beta}$ of about 25 hours, the Vd and $Vd_{peripheral}$ tended to be prolonged or increased for the L group compared with the C group. The k_{12}, as the rate constant for the distribution from the central into the peripheral compartment was significantly larger for the L group than for the C group. The k_{el}, K_{21}, Vd_{area} and $Vd_{central}$ were not significantly different between these two groups. The TBCL for the L group was lower than for the C group, although the difference failed to be statistically significant.

For the P group, the pretreated with phenobarbital appeared to increase the activity of the hepatic microsomal enzymes. Despite this increased activity, however, the pharmacokinetic parameters for the distribution phase did not vary significantly from the values obtained from the C and L groups. The $t_{1/2\beta}$ for this group, in spite of the common bile duct ligation, was not prolonged and the rate constants, Vd, $Vd_{central}$, $Vd_{peripheral}$ and Vd_{area} were not increased. There was no significant difference between the P and C groups for these parameters. In contrast, the Vd and $Vd_{peripheral}$ of the P group were significantly different when compared to the L group. Furthermore, the k_{el}, as the elimination rate constant from the central compartment, tended to be significantly increased than for the L group. Although the TBCL for the P group was higher than for the C and L groups, there was no statistically significant difference.

B. Digitoxin Evaluation

The plasma digitoxin concentration-time curve after a single intravenous digitoxin administration was also best described by a bi-exponential (Equetion 2), the same as for the digoxin pharmacokinetics. The mean correlation of the coefficients between the digitoxin values obtained by RIA assay and the theoretical digitoxin values derived from the equation were 0.986 or more for

individual animals from each group.

For the digitoxin pharmacokinetics of the C group, the mean value of $t_{1/2\alpha}$ was about 1 hour. The $t_{1/2\beta}$ was calculated by using a least squares linear regression analysis from the plasma concentrations over the 48 hour period after the digitoxin dose, because the plasma digitoxin concentrations after 48 hours were not detectable. This mean value was approximately 8 hours. The Vd was 0.808 l/kg body weight. The $Vd_{central}$ and $Vd_{peripheral}$ were 0.404 l/kg and 0.403 l/kg, respectively. The Vd_{area} was 0.906 l/kg. The TBCL of this drug was 1.57 ml/min/kg body weight for the C group.

For the L group, the plasma digitoxin concentration maintained a significantly higher level than that did the C group during all of the sampling periods. However, the pharmacokinetic parameters of the distribution phase were not staistically different between the L group and the C group. The $t_{1/2\beta}$ of the L group was about 24.5 hours this value was significantly longer than for the C group. Although the k_{el} of the L group was lower than the C group, the difference observed for this parameter and also for the other two rate constants failued to achieve statistical significance. The Vd and Vd_{area} were significantly smaller for the L group than for C group. The $Vd_{central}$ and $Vd_{peripheral}$ of the L group did not differ significantly from the C group, but the $Vd_{peripheral}$ value for the L group was lower than the C group. The TBCL for the L group tended to be less than for the C group.

For the P group, the plasma digitoxin concentration-time curve, after the intravenous digitoxin injection, for 4 of the 6 dogs and for the mean data were best descrived by a bi-exponential function (Equation 2). However, the data from the other two dogs in the P group was best fitted by a one compartment open model (Equation 1), because the plasma digitoxin concentration decreased in a

mono-exponential pattern and was not observed to be splitting into two phases (α and β phases). Therefore, for these two dogs, the pharmacokinetic parameters concerning the distribution phase could not be calculated. In spite of the fact that the dogs in the P group had the common bile duct ligated, as did the L group, the P group, with phenobarbital pretreatment, had significantly lower plasma digitoxin concentration than were found in the L group. There was no significant difference in plasma digitoxin concentration observed between the P and C groups. All of the pharmacokinetic parameters calculated in this study did not demonstrate a statiatically significant difference between the P and C groups. In comparison with the L group, the pharmacokonetic parameters of the distribution phase for the P group were not significantly different. The $t_{1/2\beta}$ was significantly shorter for the P group than the L group. The k_{el} of this group tended to be higher than the L group. The Vd and Vd_{area} were significantly larger and $Vd_{peripheral}$ tended to be larger for this group than the L group. The P group had a significantly larger TBCL than did the L group.

In this experiment using ^{3}H-digitoxin, the plasma radioactivity of the CH_2Cl_2-soluble fraction (digitoxin and its cardioactive metabolites) was higher for the L group than for the C, P and F groups at 12 and 24 hours after the administration of the ^{3}H-digitoxin. The plasma concentrations decreased grdually, after digitoxin administration, for all of the groups. These results were comparable to the results obtained from digitoxin evaluation data from RIA assays.

In the radioactive analysis of the first 24 hours urine samples, 15～20 % of the radioactive intravenous digitoxin dose was excreted from the C, L and F groups, during the first 24 hour period. Of the radioactive digitoxin excreted into the urine, 95 % was the CH_2Cl_2-insoluble fraction (cardioinactive water

soluble metabolites). On the other hand, the mean urinary radioactive excretion of the P group, pretreated with phenobarbital, was 35 % of the intravenous digitoxin dose. This larger percentage of radioactive urinary excretion demonstrated by the P group, compared with the three other groups, was almost entirely composed of the CH_2Cl_2-insoluble fraction. The $t_{1/2\beta}$ of the CH_2Cl_2-soluble fraction was calculated from the plasma concentration at 6, 12 and 24 hours after the single intravenous administration of ^{3}H-digitoxin by employing the least square regression analysis. For the C, P and F groups, the mean $t_{1/2\beta}$ ranged from 9.7 to 11.0 hours and was much shorter than the mean value for the L group of 15.4 hours.

In the F group, 7 % of the ^{3}H-digitoxin dose was excreted in the bile within the first 24 hours after the intravenous injection and 85 % of the radioactive material excreted into the bile was the CH_2Cl_2-insoluble fraction. Therefore, most of the ^{3}H-digitoxin excreted into the urine by the four groups and into the bile of the F group was in the aqueous form.

C. Biochemical Data and Histological Findings from Liver Examination

For all of the groups in the digoxin and digitoxin experiments, the renal function, estimated from the plasma creatinine concentration and the blood urea nitrogen (BUN) were maintained within normal ranges during the entire experimental period.

For the liver function tests during the preoperative period, 24, 48 and 72 hours after the digoxin or digitoxin dose, tje total bilirubin (T-Bil), alkaline phosphatase (ALP) and glutamic pyruvic transaminase (GPT) levels were determined using standard clinical laboratory techniques. In the digoxin evaluation, these liver function parameters increased gradually, following the common bile duct

ligation and reached higher levels in the L and P groups than in the C group at 24 and 48 hours after the digoxin dose.

In the digitoxin evaluation, the ALP and GPT levels gradually increased in the L and P groups and were higher in these groups than in the C group at 24 and 72 hours after the digitoxin dose. The T-Bil of the P group increased as did the other liver function test parameters. Both the C and L groups had almost the same T-Bil values, although the dogs from the L group had undergone common bile duct ligation.

The histological examination was conducted using a light microscope after the conclusion of the experiment. The morphological features of a normal liver were observed in tissue speciemens taken from the dogs of the C group. In the L and P groups, including the L group from the digitoxin expoeriment, bile plugs were found in the intrahepatic ducts and canaliculi. The Kupffer cells and hepatocytes contained bile pigment and indications of bile stasis was detected.

Furthermore, for dogs from the P group, pretreated phenobarbital, an inducer of hepatic microsomal drug metabolizing enzyme activity, in both of these experiments, the liver preparations demonstrated varying degrees of liver-cell hypertrophy or what are called "induction cells" under the light microscope.

DISCUSSION

A. Digoxin Evaluation

The digoxin pharmacokinetics for the control group, C group, are in agreement with data that has been previously reported.

In humans, digoxin is excreted after administration primarily by the kidney and also in the bile. The largest fraction of the drug and its metabolites that

were excreted into the urine and into the bile were the unchanged, original glycoside and also its lipid soluble cardioactive metabolites. The water soluble cardioinactive metabolites of digoxin composed only a small fraction of the compounds that were excreted. The concomitant administration of phenobarbital, as an inducer of hepatic microsomal drug metabolizing enzyme activity, did not affect the digoxin $t_{1/2\beta}$ for humans. Therefore, digoxin undergoes insignificant metabolism in humans, the influence of the liver on digoxin metabolism and excretion in humans appears to be limited. Furthermore, it has been repoted by many authors that in patients with hepatic diseases (alcoholic cirrhosis, acute and chronic hepatitis), the blood digoxin concentration and the urinay excretion of digoxin were unaltered. Therefore, digoxin can be administered with relative safety in patients if their renal function is normal.

In the dog, digoxin is excreted both in the urine and in the bile, as is the case in humans. Moreover, the excretion volume of digoxin and its metabolites into the urine and bile is almost the same for both species. However, the ratio of the cardioinactive water soluble metabolites of digoxin to the total excreted volume of digoxin and all of its metabolites was much higher in dogs than in humans. For the dogs, the excretion volume of the bile was almost totally composed of cardioinactive water soluble metabolites of digoxin, in contrast to humans. The liver is a primary site involuved in the metabolism of many drugs. It is known that phenobarbital induces hepatic microsomal drug metabolizing enzyme activity. There are some reports that in normal dogs, phenobarbital pretreatment has shortened the digoxin $t_{1/2\beta}$, because the metabolism and excretion of the digoxin in dogs may be affected by the liver. Therefore, the influence of liver diseases on the digoxin pharmcokinetics for dogs appeares to be greater than in humans.

In the present study of digoxin in the dog, the apparent volume of distribution was increased and the $t_{1/2\beta}$ tended to be prolonged for dogs had undergone experimental cholestasis, due to common bile duct ligation. Furthermore, the $t_{1/2\beta}$ in dogs with phenobarbital pretreatment followed by the common bile duct ligation was shortened, because of the enhancement of the hepatic microsomal drug metabolizing enzyme activity. Althought there are some studies that suggest the pharmacokinetics of digoxin appears to be less susceptible to liver influence, the results from this experiment that the liver can significantly influence the metabolism and excretion of digoxin in dogs. However, the effect of the liver may be less than the kidney, as plasma digoxin concentrations did not vary significantly between dogs, whether or not they had undergone surgical cholestasis, throughout this experiment.

In clinical situations, it has been speculated that digoxin concentrations in blood and tissues may increase gradually and the incidence of digitalis toxicity caused by high concentrations may be increased in dogs that have liver diseases during their digoxin maintenance therapy. Accordingly, dogs who require digoxin should be evaluated carefully regarding not only their renal function but also their liver function, and precautions should be taken when digoxin is administered to patients with cholestasis or other hepatic disorders.

B. Digitoxin Evaluation

The digitoxin pharmacokinetics for the control group of dogs, C group, from the present study are in agreement with data that has been previously reported.

In humans, although digitoxin excreted into the urine and bile, the ratio of the cardioinactive water soluble metabolites of digitoxin to the total excreted volume is less for both the urine and bile. Furthermore, almost all of

the previous studies concluded that the blood concentrations and $t_{1/2\beta}$ of digitoxin in patients are not affected by various liver diseases (cirrhosis, acute and chronic hepatitis). It has also been suggested that patients with chronic active hepatitis have a shortened $t_{1/2\beta}$ compared with control subjects, because of the enhansment of the digitoxin metabolism and excretion. It can be stated from these results that the influence of the liver on digitoxin pharmacokinetics for humans does not appeare to be significant and the digitoxin elimination is not impaired by various forms of hepatic diseases, although the concomitant administration of phenobarbital may reduce the $t_{1/2\beta}$ of digitoxin.

In the dog, digitoxin is excreted into the urine and bile, as is the case in humans. However, the volume of digitoxin and its metabolites excreted in dogs is much greater than in humans. Moreover, for dogs the largest percentage of the excreted total volume is comprised of the cardioinactive water soluble metabolites of digitoxin. It appears that digitoxin that is administered to dogs undergoes a significant degree of hepatic biotransformation and, thereafter, the unchanged original glycoside and its cardioactive and cardioinactive metabolites are excreted into the urine and the bile. Therefore, the influence of the liver on digitoxin metabolism and excretion in the dog seems to be much greater than in humans. On the other hand, there are some reports that the $t_{1/2\beta}$ of digitoxin in dogs, even with the most severe liver disease, is not prolonged and also that the pretreatment with phenobarbital, as an inducer of hepatic microsomal enzymes, does not alter the $t_{1/2\beta}$ of the dogs.

In the present study of digitoxin in the dog, the plasma digitoxin concentration maintained a significantly higher level in the group of dogs that had the common bile duct ligation than for the control group, throughout the experiment. The $t_{1/2\beta}$ was about three times longer for the dogs with

experimental cholestasis than for the control dog group. Furthermore, the dogs that received phenobarbital pretreatment, followed by the common bile duct ligation, did not havae increased plasma digitoxin levels or a longer $t_{1/2\beta}$ than the control dog group. For the group of dog that was pretreated with phenobarbital, the volume of the cardioinactive water soluble digitoxin metabolites that were excreted into the urine was increased. These results indicate that the liver can significantly influence digitoxin metabolism and excretion in dogs. Although liver damage plays a role in the alteration of the pharmacokinetics of digitoxin in dogs, the influence of biotransformation might differ depending on the type of liver disease and the degree of liver damage.

In clinical situations, blood and tissue digitoxin concentrations may be expected to increase even more in dogs with liver diseases during maintenance therapy and digitalis toxicity is a serious concern. Accordingly, prior to digitoxin therapy, patients should be evaluated carefully, specifically focusing on the status of their liver function. Digitoxin should be used with caution in dogs with cholestasis or other liver diseases.

C. Comparison Between Digoxin and Digitoxin

Digitalis glycosides consist of the basic steroid-type nuleus (cyclopentanoperhydrophenanthrene nucleus) to which is attached an unsaturated lactone ring at carbon atom 17 (C-17) and three glucose molecules at C-3.

The digoxin and digitoxin molecules differ only in one position as digoxin has a hydroxyl (OH) group at C-12 in the steroid-type nucleus, while digitoxin lacks OH group at this position. This small difference in the structure significantly influences the water and lipid solubility, the extent of plasma protein binding and the rate of gastrointestinal absorption. Digoxin, with the

OH group at C-12 and C-14 in a steroid-type nucleus, is more polar, less successfully bound to the plasma proteins and is absorbed to a lesser degree. On the other hand, digitoxin, with a OH group only at C-14, is a relatively nonpolar digitalis glycoside and is therefore nearly completely absorbed across the gastrointestinal menbrane after oral administration. Also digitoxin binds much more successfully to the plasma proteins.

It has been demonstrated that there are significant differences between digoxin and digitoxin pharmacokinetics. In the dog, the $t_{1/2\beta}$ for digoxin is approximately 20 to 30 hours and the $t_{1/2\beta}$ for digitoxin is significantly shorter, from 6 to 14 hours. The results from the present study concerning the relationship between the $t_{1/2\beta}$ of digoxin and digitoxin are in agreement with previously published experimental results. The dog had a longer $t_{1/2\beta}$ for digoxin than for digitoxin. The $t_{1/2\beta}$ for digoxin for humans and dogs are almost the same. However, in humans the $t_{1/2\beta}$ of digitoxin is from 4 to 10 days, and for humans the $t_{1/2\beta}$ for this drug is much longer than for digoxin. The pharmacokinetics of digitalis, especially digitoxin, in the dog are significantly different from those in humans.

Concerning the volume of distribution, there are differences between these two digitalis glycosides. The volume of digoxin distribution is about 10 times greater than for digitoxin.

In clinical practice both digoxin and digitoxin have both benefits and disadvantages. The comparative study of digoxin and digitoxin is very important for the evaluation of suitable digitalis therapy. There have been few clinical evaluations reported concerning digitoxin and also very few clinical and experimental comparisons between these two digitalis drugs.

In this section, a comparisons between the influence of the liver on

digoxin and digitoxin pharmacokinetics will be discussed. The influence of experimental cholestasis on digoxin pharmacokinetics differs from digitoxin. Consequently, it appears that there are differences in the role of the liver and its effect on these two drugs. The $t_{1/2\beta}$ of both digoxin and digitoxin for dogs was prolonged due to the experimental cholestasis and the $t_{1/2\beta}$ was shortened for dogs that had experienced cholestasis elicited by pretreatment with phenobarbital which increased the activity of the hepatic microsomal drug metabolizing enzymes. However, the prolongation of the $t_{1/2\beta}$ was much larger for digitoxin than for digoxin. Furthermore, the plasma digitoxin concentration was significantly higher in dogs with cholestasis than in the group of control dogs. In the digoxin experiment, there was no statistically significant difference the plasma digoxin concentrations observed between these two groups.

From the data, the influence of the liver on digitoxin pharmacokinetics appears to be much more significant than the liver's effects on digoxin in canines. It has been postulated that digitoxin, which is a highly bound plasma protein and also lipid soluble, may undergo more complicated pharmacokinetics in canines as a result of various pathological conditions. These conditions can influence the plasma protein concentration, e.g., hypoproteinemia caused by the exacerbation of congestive heart failure or liver diseases, or plasma protein movement due to ascites, in addition to the direct influence of liver disorders. Therefore, for the clinical selection of a specific digitalis glycoside, it is suggested that digoxin may be preferable to digitoxin for attainment of optimal digitalis therapy in dogs with cholestasis or other hepatic diseases.

The pharmacokinetics of digoxin and digitoxin in dogs are very complex as is the case n humans. Comparative studies of these two drugs are scant and confusion may result from the extrapolation of the pharmacokinetic data obtained

from human experimental evaluations and then applied to dogs, due to species differences. Increased clinical and experimental investigations focusing on these two digitalis glycosides during maintenance therapy is suggested, evaluating both normal, healthy canines and comparing these results with data obtained from dogs exhibiting various stages of differing pathological conditions. This additional data will assist in establishing optimal digitalis doseage schedules and to determine the clinical usefulness of both of these drugs. Future studies should include comparisons between digoxin and digitoxin pharmacokinetics, since these drug's biotransformation and excretion in canines is very complex and differs significantly from humans.