

## PHARMACOKINETIC DISPOSITION OF THEOPHYLLINE IN HORSES

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### Introduction

The effectiveness of theophylline in the horse has been of questionable success in alleviating signs of respiratory distress due to chronic obstructive pulmonary disease (COPD). There have been no studies in the horse that have correlated serum levels of theophylline with efficacy. However, in man the efficacy of theophylline, as determined by pulmonary function tests, has been shown to be well correlated with serum concentrations of theophylline (10-20 µg/ml effective range).<sup>5,11</sup> Coupled with this narrow therapeutic range is the very low therapeutic index of theophylline, since adverse side effects occur at levels slightly above 20 µg/ml. Large fluctuations in serum concentrations do occur after multiple dosings in man and are the result of large interpatient variabilities in half-life (3-20 hrs with a mean of 7.5 hrs in adults).<sup>5,9,11</sup> Therefore, therapeutic monitoring of theophylline in man has been found to be essential to maintain effective blood levels and to avoid toxicity.

The t<sub>1/2</sub> of theophylline has been recently reported in the horse as 3 hrs; unfortunately, no supporting data was included.<sup>2</sup> Even though there have been no studies in domestic animals that have correlated blood levels with efficacy as determined by pulmonary function tests, clinical observations suggest that theophylline is effective at the dose recommended in the dog and cat.<sup>7</sup> It is interesting to note that a dose of 1mg/kg qid in the horse has been recommended, while in man, dog, and cat, the dose is 5 to 10 times higher.<sup>3,5,7</sup> This dose appeared to be extremely low when one considers the short t<sub>1/2</sub> reported previously.<sup>2</sup> In contrast, we have suggested a dose of 3.2-5.6 mg/kg tid-qid based on our clinical impression.<sup>1</sup> Unless the volume of distribution is much smaller and the effective therapeutic concentration range for theophylline is substantially different than other species, a dose of 1 mg/kg would produce serum concentrations far below 10 µg/ml.

This study was designed to determine the basic pharmacokinetic parameters of theophylline (given as aminophylline) in horses following intravenous administration. Preliminary studies were performed in horses with reversible chronic obstructive pulmonary disease to evaluate the efficacy of theophylline with known serum concentrations.

### Theophylline Pharmacokinetics

Six adult horses, weighing from 440 kg to 532 kg, comprising 1 mare and 5 geldings, were used to determine the pharmacokinetics following a single intravenous dose. A dose of 12 mg/kg of aminophylline,<sup>a</sup> equivalent to 9.44 mg of theophylline/kg body weight, was administered over 2-4 minutes into one jugular vein and all subsequent blood samples were collected from the opposite jugular vein. Preliminary studies had indicated this dose to be necessary to

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<sup>a</sup> Aminophylline injection USP, Elkins-Sinn, Inc., Cherry Hill, NY.

produce serum concentrations of theophylline at the lower end of the therapeutic range found in man. Serial blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 15 hours after the beginning of the injection. Horse number 6 was given a second dose of aminophylline one month later to recheck the  $t_{1/2}$ . Blood samples were allowed to clot and the serum collected and stored at  $-20^{\circ}\text{C}$  until assayed. Serum samples were analyzed in duplicate for theophylline by a commercial homogeneous enzyme immunoassay kit.<sup>b</sup> All samples for the IV pharmacokinetic study were within the  $2.5\text{--}40\ \mu\text{g/ml}$  range of the kit. The arithmetic mean  $\pm\text{SD}$  was used in averaging the serum concentrations (Table 1), pharmacokinetic parameters (Table 2), except for the half-lives, and the respiratory parameters. The harmonic mean of half-lives was used since they are reciprocal ( $\ln 2/\beta$ ) values<sup>4</sup>.

Serum concentrations of theophylline following a single intravenous dose of aminophylline are reported for 6 horses in Table 1. The mean concentrations for each sampling time are plotted in Figure 1 with the linear regression lines for the distribution ( $\alpha$ ) and elimination ( $\beta$ ) phase. The data from 5 horses (except horse 3) were best described by a 2-compartment open model. The distribution phase lasted approximately 2 hrs which was much longer than shown in the dog (15 min), cat (15 min) and man (30 min).<sup>6,8,9</sup> The pharmacokinetic parameters for each horse are given in Table 2. The range in  $t_{1/2\beta}$  were very consistent for horses 1-5 (10.4 - 13.0 hr). However, horse 6 had a  $t_{1/2\beta}$  that was somewhat longer (17.1 hr) as compared with the others. A second administration of aminophylline was given to horse 6 and the  $t_{1/2\beta}$  was found to be 17.0 hr, almost identical to the initial result. Thus, we feel confident that 17 hrs is a real finding for this horse and since the  $V'd_{\text{area}}$  was similar to the other horses, we have included horse 6 in calculating the mean values. It should be emphasized that our mean  $t_{1/2}$  of 11.9 hrs was determined in healthy horses and may be quite different in horses with active signs of respiratory disease or some other disease condition. For example, in man the  $t_{1/2}$  is prolonged in patients with acute pulmonary edema, cardiac decompensation, hepatic cirrhosis, etc.<sup>5,11</sup>

Horses 3 and 4 did show some signs of agitation and mild excitement within 15 minutes of the infusion and these lasted for over 1-2 hrs. There was no correlation of serum theophylline concentrations with the development of adverse effects.

### Efficacy of Theophylline

Three additional horses (7, 15 and 21 years of age) with reversible COPD were given single intravenous doses of aminophylline (equivalent to 0.8, 2.4, 4.7, 7.1, 9.4 and 11.8 mg theophylline/kg body weight) starting with the lowest dose and all doses were at least 3 days apart. The studies were designed to give a preliminary assessment of the clinical effects of aminophylline on respiratory function in relation to dose. Each horse acted as its own control. These horses were considered to have COPD that was reversible with drug therapy since single intravenous doses of atropine (5-6 mg) reversed most of the signs of respiratory distress. Atropine was given at least 1 month before the start of this study and immediately at the end of study (after largest dose of aminophylline). These horses, with no clinical signs of respiratory disease,

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b Emit-add, Syva, Palo Alto, CA.

TABLE 1. Serum concentrations ( $\mu\text{g/ml}$ ) of theophylline in horses after a single intravenous injection of aminophylline at a dose equivalent to 9.44 mg theophylline/kg body weight.

Time (hr)	Horse Number (age in years)						Mean $\pm$ SD	
	1(14)	2(19)	3(4)	4(4)	5(7)	6(16)		
0.25	15.9	15.1	10.8	15.1	19.3	13.2	14.9	2.83
0.5	12.5	13.3	11.0	12.6	14.0	14.2	12.9	1.18
1.0	11.5	9.8	9.8	12.3	11.7	12.2	11.2	1.14
2.0	9.8	8.8	9.5	9.5	9.7	9.8	9.5	0.38
4.0	9.8	6.3	7.7	7.5	9.0	9.9	8.4	1.43
6.0	7.0	5.4	7.3	5.7	7.1	9.7	6.9	1.19
8.0	6.5	5.1	7.0	5.1	7.3	7.8	6.5	1.14
12.0	5.4	4.1	4.1	4.0	5.3	6.8	5.0	1.10
15.0	4.5	3.5	4.6	4.0	5.0	6.0	4.6	0.86

TABLE 2. Pharmacokinetic parameters of theophylline in horses after a single intravenous injection of aminophylline at a dose equivalent to 9.44 mg theophylline/kg body weight.

Kinetic Parameters	Horse Number (age in years)						Mean $\pm$ SD
	1(14)	2(19)	3(4)	4(4)	5(7)	6(16)	
Body weight (kg)	511	532	507	518	505	440	502 32
$C_p^0$ ( $\mu\text{g/ml}$ ) <sup>†</sup>	17.4	15.9	NA	16.2	23.9	18.2	18.3 3.3
A ( $\mu\text{g/ml}$ )	6.2	7.2	NA	6.6	13.2	7.2	8.1 2.9
$\alpha$ ( $\text{hr}^{-1}$ )	1.95	1.03	NA	0.87	2.18	1.51	1.51 0.57
$t_{1/2\alpha}$ (hr)	0.355	0.673	NA	0.801	0.318	0.460	0.495 <sup>‡</sup> NA
B ( $\mu\text{g/ml}$ )	11.2	8.7	10.4	9.6	10.7	11.0	10.3 0.9
$\beta$ ( $\text{hr}^{-1}$ )	0.0622	0.0638	0.0618	0.0667	0.0534	0.0405	0.0581 0.0097
$t_{1/2\beta}$ (hr)	11.2	10.9	11.2	10.4	13.0	17.1	11.9 <sup>‡</sup> NA
$V_c$ (l/kg)	0.543	0.594	NA	0.583	0.395	0.519	0.527 0.080
$V_d$ (area) (l/kg)	0.822	1.026	0.865	0.910	0.842	0.843	0.885 0.075
$Cl_B$ (ml/kg/hr)	51.1	65.5	53.5	60.9	45.0	34.1	51.7 11.2

<sup>†</sup> $C_p^0$  is the initial serum concentration for a 2-compartment open model where  $A+B = C_p^0$ .

<sup>‡</sup>Harmonic mean.

were brought in from the pasture and placed in the barn until they showed signs of respiratory distress (12-24 hrs). They were given aminophylline as described for the pharmacokinetic experiment. The effect of increasing doses was correlated with serum theophylline and clinical signs (at preinjection, 0.25, 0.5, 1, 2, 3, 4, and 6 hrs). Each horse was assessed subjectively by 2 people who were aware of the dose given. The clinical signs evaluated were respiratory rate, heart rate, effort of breathing, effort of expiration, nostril flare, presence of wheezes in the lungs, trachea or at the nostrils, crackles in the lungs and the presence of coughing. The paired t-test was used to evaluate the respiratory changes determined in the COPD horses after aminophylline.

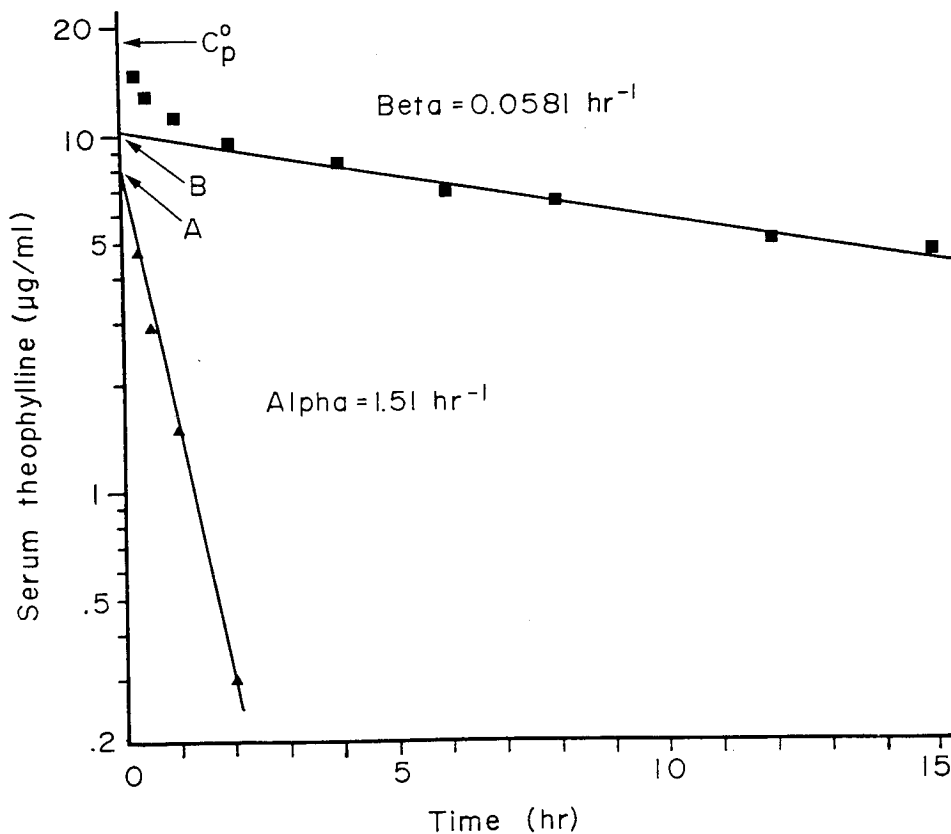


Figure 1. Mean serum concentrations of theophylline (■) in 6 healthy horses after a single intravenous dose of 12 mg/kg of aminophylline (equivalent to 9.44 mg/kg of theophylline) are graphically displayed on a semi-logarithmic plot. The straight lines represent the distribution (alpha) and elimination phase (beta) of a 2-compartment open model and were plotted from the mean parameters (A, B,  $\alpha$  and  $\beta$ ) in Table 2. The points in the alpha phase (▲) were calculated by "featherings."

The 3 horses with signs of COPD had the following changes:

1. Decrease in severity of clinical signs after aminophylline doses of 9, 12 or 15 mg/kg that lasted from 1-6 hours.

↓ wheezing, crackles and respiratory effect

2.  $P_{aO_2}$  at 0.5 hr. -  $75.6 \pm 11.1$  to  $70.5 \pm 8.4$  mm Hg (NS)
3.  $P_{aCO_2}$  at 0.5 hr -  $43.6 \pm 5.5$  to  $39.4 \pm 6.7$  mm Hg, ( $P < 0.001$ )
4. pH at 0.5 hr -  $7.38 \pm 0.017$  to  $7.41 \pm -0.023$ , ( $P < 0.001$ )
5. Heart rate - No change (45.7 - 47.4 per min)
6. Respiratory rate - No change (19.7 - 20.7 per min)
7. Two horses showed signs of apprehension at 15 min to 1 hr following the 12 and 15 mg/kg dose of aminophylline.

Doses of 1, 3 and 6 mg/kg of aminophylline (equivalent to 0.8, 2.4 and 4.7 mg/kg of theophylline, respectively) used in our study did not improve the clinical signs, whereas doses from 9 to 15 mg/kg showed slight improvement that did not increase over that range. The serum concentration of theophylline (0.5 hr post dosing) produced at doses of 1, 3 and 6 mg/kg of aminophylline were all below  $10 \mu\text{g/ml}$  whereas the 9, 12, and 15 mg/kg doses corresponded to concentrations between 10 and  $20 \mu\text{g/ml}$ .

Our data for the therapeutic range in horses are preliminary but do suggest a range similar to that found in man. Therefore, assuming a therapeutic range of theophylline from 10 to  $20 \mu\text{g/ml}$  and using our pharmacokinetic parameters (Table 2), dosages of theophylline have been calculated to produce average steady-state serum concentrations ( $C_p^{\infty}$ ) of 10 and  $15 \mu\text{g/ml}$  (Table 3). The doses are somewhat underestimated for oral administration since the drug would probably not have 100% bioavailability. However, in the dog, cat, and man, bioavailabilities greater than 90% are obtained.<sup>5,8,9,11</sup> No data are available for the horse. (See comment by Dr. Desmond Baggot, during panel discussion, for unpublished bioavailability data in horses.) It is interesting to note that our previously recommended oral doses of 3.2 to 5.6 mg/kg of theophylline given 3 to 5 times daily would correspond to our calculated doses for 3 to 4 times a day therapy (Table 3). These numbers are only approximations to help one in planning a chronic dosage regimen and should not be relied upon until further studies have substantiated the blood levels produced after chronic oral dosings and the degree of therapeutic efficacy.

As with other drugs (e.g. cardiac glycosides and anticonvulsants) with a low therapeutic index and variable rates of elimination, measurement of individual drug concentrations may be necessary to optimize the efficacy of theophylline.<sup>5,10,11</sup>

TABLE 3. Intravenous and oral doses of theophylline (mg/kg) to produce average serum concentrations of 10 and 15  $\mu$ g/ml at steady-state ( $\bar{C}_p^\infty$ ).\*

$\bar{C}_p^\infty$	Dosing Interval (hr)		
	6	8	12
10	3.1	4.1	6.2
15	4.6	6.2	9.3

\*The doses were calculated from  $\bar{C}_p^\infty T V' d_{(area)} / (1.44 F t_{1/2}^\beta)$  where T is the dosing interval and F represents the fraction of theophylline bioavailable. The bioavailability was set at 1.0 for both IV and PO because no data for oral administration were available.

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#### Points raised during discussion

Question: What is the minimum dose of atropine to produce an effect on the respiratory parameters of the horse and what is the duration of action of the 5 mg dose in the horse?

Dr. Kowalczyk: I really do not have experience giving doses lower than 5-7 mg of atropine. Duration of effects is up to 2 hrs.

Question: On the half-life of theophylline in the horse?

Dr. Kowalczyk: It was actually fortunate that Dr. Davis' group reported a 3 hour half-life because if they had reported a longer half life we probably would not have done the study. It was really the report on that short half-life that gave us the impetus to carry out our study.

Dr. Baggot: We also did a study and came up with the same i.v. data. In addition we dosed aminophylline with essentially 100% bioavailability, and ended up with recommending an oral dose of aminophylline of 5 mg/kg at 12 hour intervals which is exactly the same as for the cat, because the clearance in the horse and the cat is 40 ml/hr/kg compared to the dog which is 100 ml/hr/kg. So for the horse and cat we end up with 5 mg/kg at 12 hour intervals whereas for the dog 10 mg/kg at 8 hour intervals. So it agrees exactly with what you found.