Investigation of the Plasma Digitoxin Concentration in Cattle at Different Dosages

Prof. Dr. H. F. Benthe
Pharmakologisches Institut der Universität Hamburg
and
Prof. Dr. Dr. h. c. G. Dirksen; Dr. A. Weissmüller
II Medizinische Tierklinik Universität München Veterinärstr. 13, D-8000 München 22

The stated dosages of digitoxin for treatment of myocardial insufficiency of cattle, as published in the available literature, are few and vary widely from one another. Some of these date back to very old sources (the uncovering of which would require an intensive study of veterinary history), and the others appear to be derived from dosage recommendations for other domestic animals and then have been cautiously set at much lower levels. Thus the amounts of digitoxin suggested for parenteral administration to adult cattle vary from 1.1 mg (manufacturer's recommendation) up to 5-10 mg as initial and 2 mg as maintenance dose (DAVIS and GARB, 1963; ROSSOF, 1974). On the basis of data from the literature and personal communications, DETWEILER (1977) recommends 30.9 µg/kg BW intramuscularly as initial dose, and 1/8 to 1/5 of this amount as daily maintenance dose. As it has now become possible to measure even very low glycoside concentrations in plasma with radioimmunoassay, it seemed desirable to evaluate the previous empirical digitoxin dosage by measuring the plasma levels.

Materials and Methods

Experimental animals: 13 healthy female cattle of different ages and weights were used; the breeds were German Simmental (10), German Brown Swiss (1) and German Black and White (2). Particulars are listed in *table 1*.

Dosage plan: The digitoxin was given intravenously (jugular vein); Digitalis Solution WdT® (0.11 mg/ml) was used for the low dosage ranges (1.1 and 11 mg/animal). The solutions injected at 20 mg/animal were made by dissolving digitoxin in 15 ml of 50% ethanol.

a) *Single administration*
Single injections of digitoxin were carried out in three groups (A, B, C) at 1.1 mg, 11 mg, and 20 mg per animal.

b) *Repeated administrations*
One animal received 20 mg digitoxin i.v. each day for 5 successive days. Another animal received 2 × 20 mg at a dosage interval of 6 hours. Particulars can be found in WEISSMULLER (1982).

Blood sampling: Blood samples were taken from the jugular vein. A pre-injection sample was taken as well as samples at 0.5; 1, 2, 3, 4, 5 and 6 hours post injection. Plasma was separated and frozen until the glycoside determination.

Digitoxin-determination: The plasma digitoxin concentration was determined via RIA (SMITH, 1970); triplicate measurements were made on each sample.

Clinical evaluation: Before the start of the experiment the animals were subjected to a thorough general examination and during the experiment were continually clinically evaluated. The course of the heart rate served as the criterium for effect of the digitoxin. It was determined by auscultation before medication and each time before the blood sampling.

Results

Trial A: Dose of 1.1 mg digitoxin/animal (n=1)

After administering this amount of the glycoside, which corresponded to a dose of 3 µg/kg BW, a blood level of the active substance (1.8 ng/ml) was only demonstrable in the first blood sample, taken 15 min post injection. In all later samples - the next was taken 3 hours later - the glycoside content lay below the detectable level. Heart rate remained uninfluenced.

Trial B: Dose of 11 mg digitoxin/animal (n=4)

This amounted to doses of 17-37 µg/kg (animals 2-3). Half an hour after the injection, plasma levels between 3.5 and 6.7 ng/ml were measured. Within 4 hours however, the plasma digitoxin concentration fell already to values from 2.2 to 1 ng/ml. All three animals showed a slight dose-independent reduction of the heart rate for two to three hours.

Trial C: Dose of 20 mg digitoxin/animal (n=8)

Depending on the body weight the doses varied between 31 and 55 µg per kg. The results of the measurements are graphically demonstrated in figures 1 and 2. The plasma

This paper is published by permission of the Editor, Berliner und Münchener Tierarstliche Wochenschrift.

TABLE 1. List of the experiments and of experimental animals.

Trials	Animal No.	Age in Years	Breed	Weight (kg)
A	1	2	DFV	300
B	2	2,5	DSB	300
	3	2	DFV	650
	4	8	DBV	550
C	3	2	DFV	650
	4	8	DBV	550
	5	3	DFV	440
	6	6	DFV	580
	7	5	DFV	590
	8	5	DFV	640
	9	7	DFV	585
	10	3	DFV	360
	6	6	DFV	580
D	11	2.5	DFV	500
	12	6	DFV	550
E	13	2	DSB	300

DBV = German Brown Swiss
DFV = German Simmental
DSB = German Black and White

levels of both groups show a marked exponential course. An influence of the dose/kg cannot be established. The higher values of the one group (No. 8-10) compared with the other (No. 3-7) are of note. This difference was present both in the early values (30 min.) and the later measurements (1-6 h). Since the dosages were not different, other animal-dependent influences must exist. The two groups were evaluated separately for the statistical analysis *(table 2).*

Heart rate (group C): Immediately following the injection a bradycardia appeared. Since the extent and duration, however, showed no relation to the corresponding plasma digitoxin levels, only the mean values are compared, for which an actual difference exists:

Original value: 65 ± 5.6/min (n=9)

maximal bradycardia: 49 ± 5.6/min

The original values were reached again in the 5th to 6th hour post injection.

Trial D: Dose of 5 × 20 mg digitoxin/animal on five successive days (n=2)

Since no digitoxin was identifiable in some of the measurements made 24 h. following single-dose injection (Trial C), it was decided to conduct repeated injections. Thus

Figure 1. Plasma digitoxin concentration after intravenous injections of 20 mg digitoxin to adult cattle. (Nos. 3-7)

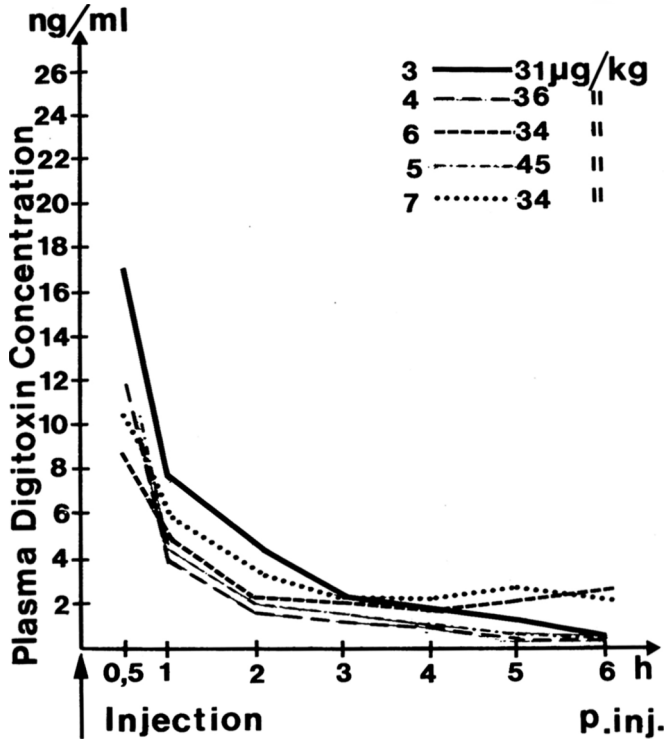

Figure 2. Same as figure 1. (Nos. 6-10)

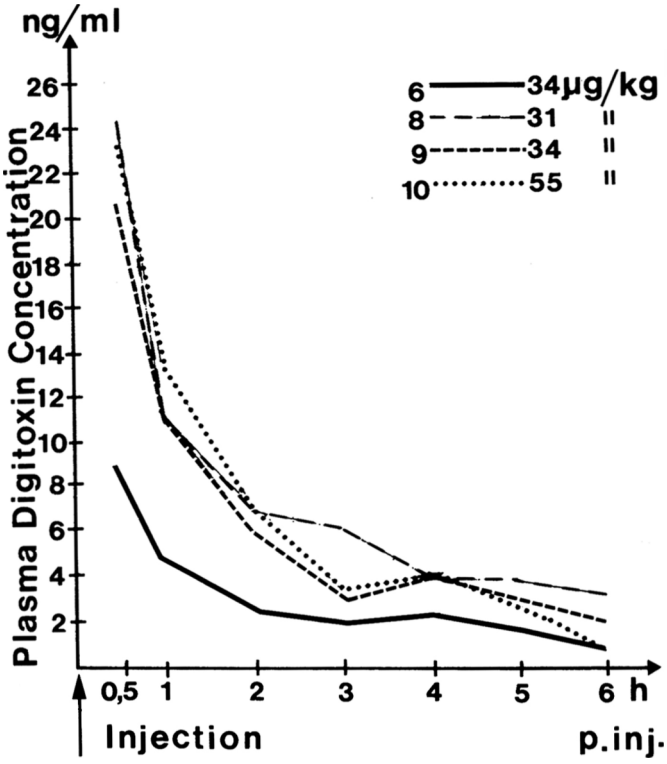

TABLE 2. Heart rate and plasma digitoxin concentration after intravenous injection of 20 mg digitoxin in adult cattle.

Animal Number	3		4		5		6		7		8		9		10		6	
	Dose of Digitoxin (mg/kg bw)																	
	31		36		45		34		34		31		34		55		34	
Hours post inj.	HR	DC	HR	DC	HR	DC	HR	DC	HR	DC	HR	DC	HR	DC	HR	DC	HR	DC
0	60	0	68	0	68	0	60	0	64	0	72	0	56	0	72	0	64	0
0,5	44	17,0	44	12,5	60	12,2	56	8,7	48	10,4	44	25,0	48	21,0	48	24,0	52	9,1
1	44	7,9	44	4,2	60	4,5	56	5,0	48	6,0	44	11,3	48	11,2	52	13,5	48	4,9
2	44	4,9	44	1,7	60	2,0	56	2,3	52	3,5	52	7,0	48	6,0	60	7,3	56	2,7
3	44	2,4	48	1,2	60	1,6	60	2,1	56	2,1	52	6,1	48	3,1	64	3,5	60	2,0
4	48	1,8	48	1,0	64	1,1	60	1,8	56	2,1	60	4,0	48	4,0	72	4,2	60	2,4
5	44	1,3	52	0,3	68	-	60	-	60	2,7	60	3,8	48	2,8	72	2,8	56	1,8
6	56	0,5	56	0,3	68	0,7	60	2,6	60	2,2	60	3,2	52	1,7	72	0,8	60	0,9

- = Not recorded due to technical reasons.
HR = Heart rate
DC = Digitoxin plasma level in ng/ml

any accumulation effect would be observed.

Even after 5 × 20 mg digitoxin no measurable plasma levels built up in either animal (No. 11 + 12). 24 h. after each injection no glycoside could be found. The heart rates also remained unchanged.

Trial E: Dose of 2 × 20 mg digitoxin/animal at an interval of 6 hours (n=1)

Following the results of trial D a dose of 2 × 20 mg/animal at an interval of 6 h. seemed justifiable. 30 mins. after both the first injection and the second injection maximal concentrations of ca. 20 ng/ml were measurable, that is, no glycoside accumulation appeared even with the dosage interval shortened to 6 h. However a marked bradycardia was noticeable following the second injection: original rate 64/min, max. bradycardia 36/min. This marked pharmacodynamic effect did not correspond to an elevated plasma concentration *(table 3).*

Discussion

The pharmacodynamics and -kinetics of digitoxin in the organism are dependent on different influences, such as plasma protein binding, distribution in the body fluids and organs, modification and breakdown by metabolism, and elimination. For example fat tissue takes up digitalis glycosides only minimally (BENTHE, 1975) and therefore does not contribute to the distribution space very considerably (which should be considered in weight related dosing). Furthermore the synergistic inotropic action of digitalis glycosides with calcium ions or with medications or metabolic conditions which reduce the potassium or

TABLE 3. Heart rate and plasma digitoxin concentration after two injections of 20 mg digitoxin 6 hours apart in one adult bovine animal.

Hours after 1st injection	Heart rate per minute	Plasma digitixon conc. mg/ml
0	64	0
0.5	52	21.8
1	44	11.4
2	52	14.8
3	52	5.5
4	52	11.4
5	52	3.8
6	52	3.0
2nd injection of 20 mg digitoxin		
6.5	36	19.7
7	52	15.8
8	56	8.6
9	56	5.2
10	60	7.5
11	60	6.4
12	64	5.9

magnesium levels in the serum should be taken into account (in cattle and other species ACTH, certain corticosteroids, diuretics, laxatives, salicylates, hypomagnesemic tetany, hypokalemia of metabolic alkalosis in post-abomasal obstruction or abomasal reflux syndrome, respiratory insufficiency).

Investigations with humans and a variety of domestic animals have shown in addition, that considerable quantitive differences exist between species with regard to the pharmacokinetics of digitoxin. While humans eliminate only 7% daily (AUGSBERGER, 1954; R. KREBS, 1976), resulting in a half-life of 2.4 to 16.4 days (and the danger of accumulation), dogs eliminate about 70% per day (ELWERS, 1981) with a half-life of 10 to 14 hours (LEHMANN, 1980; ETTINGER, 1980). On the other hand elimination in cats occurs similarly slowly as in man (BENTHE, 1980).

From the results of these trials cattle seem to be one of the species which break down or eliminate digitoxin very quickly. As a rule only very minimal concentrations of the active substance were measurable in plasma after the fifth hour post injection; even following a repeated dosing after 6 hours (*trial E).* The drug half-life was 2 to 3 hours. Because of this the danger of drug accumulation in cattle is hardly a real danger and the risk of intoxication is relatively small, except in extreme circumstances. Probably the elimination mechanism is the decisive factor for the rapid decrease of the drug in the blood and the quick fading of its cardiac effect. Presumably the liver can bind unmodified digitoxin to glucuronic acid on a large scale, following which this water-soluble metabolite is eliminated via the feces.

As mentioned previously in the description of methods, the development of digitalis-effect on the cardiac muscle and the tolerance of the drug were judged simply by the course of the heart rate; i.e. by the inception and duration of the slowing of the rate following the injection. As far as it is justifiable to interpret this vagal effect as an indication of a positive inotropic reaction, it can be concluded from the results that the digitoxin effect was already present 30 min. after intravenous injection of an adequately high dose. This time period lies within that estimated by LARBIG (1975) for the appearance of digitoxin effect in humans, namely 30 to 120 minutes.

The most important result of this trial is no doubt the finding that the recommended therapeutic digitoxin dose for cattle found in the available literature is too low and the recommended treatment interval too long. The digitoxin concentration established as the "therapeutically effective plasma level" for humans is in the range of 9-30 ng/ml (PETERS, 1980), and the recommendations for the dog and cat run in the same order of magnitude (BENTHE, 1980). This range seems relatively large if one considers that the lowest threshold of positive inotropic effect is estimated at 6 ng/ml (AUST and BELZ, 1980), while on the other hand toxic side effects can already be seen in some patients (human) at 15 ng/ml (FORTH et al., 1977). JAHRMÄRKER (1977) therefore calls attention to the fact that the determination of the blood glycoside level is only fully usable when considered with the clinical effects due to the individual variation in sensitivity.

Plasma digitoxin concentrations over 9 ng/ml (see above) were first achieved in these trials when doses between 31 and 55 μg glycoside per kg BW were administered intravenously. The blood level fell back to 6 ng/ml below within one to three hours, but the slowing of the heart rate lasted six hours and possibly longer in some of the experimental animals (without a recognizable strong correlation to the dose administered in this connection).

The therapeutically effective (for cardiac insufficiency) plasma digitoxin level for cattle is probably around 20 ng/ml. In order to reach this range, intravenous initial doses of 60 μg/kg body weight would be required with treatment intervals of less than 6 hours needed to maintain this level. What must be considered, however, is that the effects of the actual plasma levels can be influenced by interactions of the digitalis glycosides with other substances or metabolic states of the animal. These include, for example, interactions between digitalis glycosides and calcium ions or medications and metabolic conditions which reduce the potassium or magnesium content of the serum (in cattle as in other animals - ACTH, certain corticosteroids, saliuretics, laxatives, salicylate hypomagnesemic tetany, hypokalemia/metabolic alkalosis of post-abomasal obstruction, respiratory insufficiency.

For this reason and also because of the well known difficulties of diagnosis, it seems advisable until further investigative results are available, to introduce therapy under practice conditions with a dose of 50 μg digitoxin/kg BW (intravenously) and to continue the medication at intervals of 5 to 6 hours with the same dose or one adjusted to effect.

Summary

Thirteen healthy, female cattle weighing 300 to 650 kg, and of the German Simmental, German Brown Swiss, and German Black and White breeds, received intravenously administered digitoxin in doses from 3 μg to 66 μg/kg BW in experimental trials. Blood samples were taken at intervals corresponding to the respective investigatory purpose, and the plasma digitoxin concentration was ascertained via radioimmunoassay. At the same time the heart rate was evaluated.

Results: Only after the administration of 31 to 55 μg digitoxin/kg BW (10 trials on 9 animals) did the drug content in plasma rise after 30 min. to levels of 6.7 to 25 ng/ml, which is the therapeutically effective range in man, dog and cat (6/9 - 30 ng/ml). The plasma levels declined within 6 hours to 0.3 to 3.2 ng/ml. Heart rates decreased in the first hour post injection by 7 - 39% of the beginning values, but climbed again markedly therafter.

With administration of 66 μg digitoxin/kg BW twice at an

interval of 6 hours (1 animal), the following concentrations existed each time at 30 min. and 6 hours post injection: 21.8 and 3.0 ng/ml; 19.7 and 5.9 ng/ml. Immediately following the second injection, a pronounced bradycardia appeared momentarily. With administration of 40 or 36 μg digitoxin/kg BW five times at intervals of 24 hours (2 animals), no measurable drug levels were determinable 24 hours post injection, with the exception of one sample.

Conclusions

The digitoxin dosages put forth in the available literature are too low and the treatment intervals too long. Until further investigative results are available it is recommended, in a practice situation, to introduce therapy with a digitoxin dose of 50 μg/kg body weight intravenously and to continue the medication with the same dosage or one adjusted to therapeutic effect.

English translation by Franklyn Garry, D.V.M., II. Medizinische Tierklinik, Universität München, Veterinärstr. 13, D-8000 München 22

References

1. Augsberger, A. (1954) Quantitatives zur Therapie mit Herzglykosiden. II. Mitteilung: Kumulation und Abklingen der Wirkung. Klin. Wschr. *32*, 945-951. - 2. Benthe, H. F. (1975) Organverteilung verschiedener Herzglykoside. In: Jahrmärker, H. (Hrsg.): Digitalistherapie. Springer-Verlag, Berlin Heidelberg New York, S. 19-37. - 3. Benthe, H. F. (1980) Mündl. Mitteilung. - 4. Davis, L. E. und S. Garb (1963) Treatment of a cow with congestive heart failure. J. Am. Vet. Med. Ass. 142, 255-257. - 5. Detweiler, D. K. (1977) Cardial drugs. In: Meyer, Jones, L., N. H. Booth und L. E. McDonald (Hrsg.): Veterinary pharmacology and therapeutics (4. Aufl.) The Iowa State University Press, S. 496-542. - 6. Elwers, W. (1981) Persönl. Mitteilung. - 7. Ettinger, S. J. (1980) Cardiovascular diseases. In: Kirk, R. W. (Hsrg.): Current veterinary therapy 7. Aufl. W. B. Saunders Co., Philadelphia London Toronto, S. 293-390. - 8. Forth, W., D. Henschler und W. Rummel (1977) Allgemeine und spezielle Pharmakologie und Toxikologie. 2. Aufl. Bibliographisches Inst. Mannheim Wien Zürich. - 9. Jahrmärker, H. (1977) Wann lohnt eine Digitalis-Blutspiegelbestimmung? Münch. med. Wschr. 119, 1101-1102. - 10. Krebs, R. (1976) Modifizierende Faktoren in der Glykosidtherapie. Med. Klin. 71, 1759-1770. - 11. Lehmann, H. D. (1980) Zur experimentellen und veterinär-Klinischen Pharmakologie der Herzglykoside. Prakt. Tierarzt 61, 579-588. - 12. Peters, U. (1980a) Klinische und pharmakologische Grundlagen für eine kontrollierte Digitalistherapie. Z. Kardiol. 68, 247-261. - 13. Peters. U. (1980b) Digitoxin und Chinidin. Medica 1, 786-787. - 14. Rossof, J. S. (1974) Handbook of veterinary drugs. Springer publishing company, New York, S. 173. - 15. Weissmüller, A. (1982) Untersuchungen über die Digitoxin konzentration im Blutplasma des Rindes bei unterschiedlicher Dosierung. Vet. Diss. München.