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Kinetics of the Fab Fragments of Digoxin Antibodies and of Bound Digoxin in Patients with Severe Digoxin Intoxication

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Summary. 17 patients with severe digoxin intoxication were successfully treated with 320 to 480 mg Fab fragments of digoxin-specific IgG from sheep. The infusion period ranged between 0.5 and 7 h. Serum and urine concentrations of digoxin bound to Fab fragments, and in 11 cases unbound Fab fragments in serum, were determined during and after the infusion.

The renal clearance of bound digoxin and therefore of the antibody was 13.6 ml/min. The median extrarenal clearance of the Fab fragments was 10.9 ml/min.

The half-life of the serum concentrations starting at 12 h was 14.3 h, and the value was increased to 25.4 h when regression began at 24 h; the corresponding apparent distribution volumes were 25.9 and 54 l. These figures exceed the volume of the extracellular space and suggest intracellular penetration of the Fab fragments.

The dosage of the antibody should be sufficiently high to bind digoxin in the most severe cases of poisoning. The maximum serum concentrations of bound antibody were 30 mg/l after 3 h and 20 mg/l after 5 h. A loading dose of 160 mg followed by an infusion of 0.5 mg/min was sufficient to absorb digoxin re-diffusing into the serum during the first 8 h. In some cases free digoxin reappeared in the serum 8-12 h after beginning the treatment. This might be prevented by infusing a further ampoule at a rate of 0.1 mg/min or less.

Key words: digoxin intoxication; antibody treatment, pharmacokinetics, clearance, distribution volume

Fab fragments of digoxin antibodies are of proven value in the treatment of life-threatening poisoning with digoxin (Grabensee and Peters 1983; Harenberg et al. 1983; Hess et al. 1978; 1979; Jax et al. 1983; Murphy et al. 1982; Smith et al. 1976, 1982; Smolarz et al. 1984; 1985; Smolarz and Abshagen 1986; Wahl et al. 1983; Weller et al. 1983; Wenger et al. 1985; Zilker et al. 1983; Zucker et al. 1982). A prerequisite for successful treatment is that free antibody is present in the extracellular space as long as the body contains a toxic amount of the glycoside. For the sake of safety large amounts of antibodies are given in a short time. This has the disadvantage that part of the antibody may be cleared from the serum before enough digoxin has become available from the tissues for binding. The following investigations on the kinetics of Fab fragments is intended to contribute to rational treatment of glycoside poisoning.

Material and Methods

Patients

Details of the patients are shown in Table 1. All 17 patients had taken digoxin or its derivatives in attempts at suicide. The serum concentration of digoxin before starting treatment varied between 3.4 and 29 ng/ml (Table 3). Antibody therapy was started between 1.5 and 24 h after ingestion of the glycosides.

Indications for the use of antibody were definite signs of intoxication and life-threatening cardiac arrhythmias. The types of arrhythmia before starting therapy are shown in Table 1. In 4 cases recurrent ventricular fibrillation was seen. In most cases AV-conduction disturbances of different degrees and ventricular extrasystoles were the direct reason for administration of the antibody.

Administration of Fab Fragments

The Fab fragments had a binding capacity of 1 mg digoxin per 80 mg Fab fragments (= 1 ampoule). The

Table 1. Personal data of treated patients. The creatinine clearance in Cases 1-11 was calculated by the equation of Cockcroft and Gault with a minimum age of 40 years, in the other cases from the serum concentration and renal excretion of creatinine

Pat. no.	Ident. no.	Sex	Age [years]	Weight [kg]	CR [mg/dl]	CL_{CR} [ml/min]	Kind of arrhythmias	Fab dose [mg]	Infusion time [h]	Clinical results and time of normalisation	
										Rhythm[a]	[h]
1	6	m	20	62	1,0	86	VES, tachycardia	400	0,5	SR	2
2	10	f	67	65	0,9	62	ventricular fibrillation	400	0,5	SR	1
3	15	f	57	68	1,1	61	a-block III°, ventr. flatter	480	0,5	SR	12
4	19	f	16	49	0,8	72	av-block III°, PAT, VES	400	0,5	SR	12
5	12	f	65	64	0,9	63	ventricular fibrillation	480	3	SR	2
6	16	f	69	78	0,93	70	av-block I°, bradycardia	400	3	SR	12
7	2	m	41	57	1,1	71	av-block III°, VES, salves	480	5	SR	1
8	3	m	31	60	0,8	104	ventr. tachycardia, VES	480	5	SR	2
9	4	f	40	68	normal[b]	80	av-block II°, PAT	480	5	SR	1
10	7	f	49	58	0,73	85	ventr. fibrillation	480	5	SR	4
11	14	m	17	78	1,0	108	av-block III°, VES, salves	480	5	SR	8
12	78	m	74	70	1,21	10	av-block II/III°, nodal rhythm	160+160	0,25/7	SR	6
13	79	f	36	50	0,64	43	no arrhythmias	160+160	0,25/7	SR	
14	88	m	84	60	0,93	160	bradyarrhythmia absol., VES	160+160	0,25/7	AA	2
15	91	m	56	72	0,75	232	av-block I°, VES	160+160	0,25/7	SR	7
16	95	f	22	54	0,69	53	av-block II°, VES	160+160	0,25/7	SR	5
17	98	f	20	43	0,45	45	no arrhythmias	160+160	0,25/7	SR	

[a] SR = sinus rhythm, AA = absolute arrhythmia;
[b] 1.0 mg/dl was inserted for calculating creatinine clearance; C_R = serum creatinine, CL_{CR} = creatinine clearance

Table 2. Serum concentrations of free + bound Fab fragments. Concentrations in mg/l

Pat. no.	Time [h]									
	0.5	1	2	5	7	8	12	24	36	48
2	–	72.5	42.0	28.3	–	7.8	4.3	2.4	1.2	0.6
3	133.2	106.4	43.1	13.6	–	5.1	2.4	0.9	0.4	0.4
4	142.1	88.8	41.5	10.3	–	1.1	3.1	1.9	–	–
5	61.8	86.7	–	20.0	–	6.2	–	1.5	0.7	0.5
6	40.0	54.6	56.1	21.8	–	6.9	4.4	2.4	1.1	0.3
12	45.7	40.6	31.4	25.7	21.2	–	8.7	2.4	–	–
13	29.6	39.9	22.6	14.0	10.7	–	3.4	1.0	–	–
14	35.8	25.7	25.2	23.2	16.4	–	10.6	6.8	–	–
15	26.2	19.9	17.5	9.1	7.6	–	2.2	0.8	–	–
16	40.9	25.0	17.7	15.6	14.3	–	3.5	–	–	–
17	41.4	35.8	25.3	17.0	18.9	–	3.3	2.0	–	–

Additional values

Pat.	3		5				6
[h]	72	96	3	13	72	96	33
[mg/l]	0.24	0.22	76.7	3.4	0.23	0.17	1.2

affinity constants determined in several batches were below 3×10^{-9} l/M both for digoxin and digitoxin. The content of dimeric $F(ab)_2$ was less than 0.5%.

At the beginning of the investigations little was known about the optimum dosage and infusion rate. 400–480 mg was given either within 0.5 h or in 3–5 h. After a preliminary evaluation of the results from the first 11 cases, further 6 patients each received 160 mg in 0.25 h, and an additional 160 mg in 7 h.

Determination of Bound and Free Digoxin in Serum and Urine

Blood samples were taken at the times indicated in Tables 2 and 3. The collection periods for urine depended on kidney function and on the facilities in the hospitals involved.

The measurements were carried out according to the method of Smith et al. (1976) with a few modifications. To obtain calibration curves, digoxin was added to pooled human serum at concentrations be-

Table 3. Serum concentrations of bound digoxin and reappearance of free digoxin. Concentrations in ng/ml. Figures at t=0 represent free digoxin before treatment

Pat. no.	Time [h]													free digoxin	
	0	0.5	1	2	5	7	8	12	24	36	48	72	96	reapp. [h]	max. [ng/ml]
1	13	152	176	161	48.8	27.2	19.2	13.9	5.6	2.7	2.5	1.3	1.1	3.5	6.8
2	10	–	17	135	127	–	97	53.7	29.7	15.1	7.5	–	–	10	2.3
3	7.4	78	67	68	88	–	57	29.8	10.6	5.2	4.4	3	2.7	10	2.8
4	13	151	142	130	129	–	14.3	39	23.8	–	–	–	–	6.5	5.0
5	29	334	356	–	250	–	77.7	–	18.3	9.2	5.8	2.9	2.1	6.5	7.4
6	9.4	182	183	158	89	–	86	55.5	30.1	13.2	4.3	–	–	10	1.9
7	6.7	40	42	38	28	–	58	33.2	13.5	8.2	6.1	3.5	2.0	10	1.5
8	3.4	37.2	39.5	43	46.8	–	41.8	59.3	17.0	–	6.4	3.3	2.0	3.5	5.2
9	11	96	87	98	74	–	48	27	12.1	8.5	5.7	–	2.6	10	2.0
10	13	–	–	176	131	–	109	45	18.9	–	7.5	2.9	1.8	10	3.0
11	6.1	–	–	–	–	–	–	–	–	–	–	–	–	11	0.8
12	14	227	224	206	169	151	–	110	34	–	–	–	–	12	3.8
13	20	205	332	283	175	80	–	44	15	–	–	–	–	12	2.0
14	19.5	193	223	200	164	163	–	132	86	–	–	–	–	24	0.6
15	11	116	112	116	114	84	–	31	14	–	–	–	–	12	4.4
16	4.9	72	73	77	79	75	–	45	–	–	–	–	–	12	1.7
17	–	18	18	20	24	24	–	23	19	–	–	–	–	24	0

Additional values

Pat.	1				5		6	8			9	10	
[h]	0.17	17.1	41.1	45.1	3	13	33	39	101	149	75	0.58	1.08
[ng/ml]	1.27	9.2	2.1	0.6	379	42.6	14.8	9.8	1.8	1.1	2.9	94	144

Pat.	11											
[h]	1.1	1.6	1.8	3.1	6.1	9.1	13.8	24.9	36.8	48.9	60.8	84.8
[ng/ml]	2.0	75	91	87	73	59	35.3	17	9.2	6.8	4.8	2.8

tween 0.6 and 20 ng/ml. Standards and serum samples from patients were diluted 1:1 with physiological saline, and urine samples with pooled human serum heated for 1 hour at 95 °C and centrifuged. The digoxin concentration in the protein-free supernatant was measured by RIA. Bound Fab fragments were calculated from bound digoxin multiplied by the binding capacity.

To determine the concentration of free digoxin, serum or urine were subjected to equilibrium dialysis at 22 °C for 20 h, in the Dianorm dialysis system (Dianorm Company). Serum was dialysed against pooled serum and urine against physiological saline. The digoxin concentration in 0.1 ml dialysate was determined by RIA. Dialysates from the urine samples were previously diluted 1:10 to 1:20 with pooled serum.

Determination of Bound and Free Fab Fragments in Serum

The concentration of bound Fab fragments was calculated from the concentration of bound digoxin multiplied by the binding capacity of 80 mg Fab fragments/1 mg digoxin. For the determination of free Fab fragments, ^{3}H-digoxin was added to the serum samples in quantities that exceed the binding capacity of the free Fab fragments. The serum samples were then dialysed as for the determination of free digoxin. The concentration of bound ^{3}H-digoxin was calculated from the concentrations of radioactivity and the volumes on each side of the dialysis membrane. This was multiplied by the binding capacity of the Fab fragments.

Determination of the Renal Clearance of Bound and Free Digoxin

Free digoxin was found in the urine of some patients at times when only Fab-bound digoxin was detectable in the serum. This can only be due to a change in the binding properties of the antibody after filtration in the kidney or during the processing of the urine. The renal clearance of Fab-bound digoxin was therefore calculated from the total quantity of digoxin in the urine in those collection periods during which the serum contained no or only a low concentration of free digoxin.

Table 4. Renal clearance and excretion of bound digoxin. Amount in urine = excretion of bound digoxin during the collection period

Pat. no.	Coll. period [h]	Amount in urine [μg]	AUC (Coll.) [ng·h/ml]	CL_R [ml/min]	$\frac{CL_R}{CL_{CR}}$ [%]	$AUC_{(0-\infty)}$ [ng·h/ml]	Renal excretion [μg]
1	0- 5	779	623	20.8	24.2	1060	1323
2	0-12	1856	1120	27.6	44.5	2132	3531
3	0-12.5	789	765	17.2	28.2	1334	1377
4	0- 5.25	418	670	10.4	14.4	1908	1191
5	0- 7	1379	2012	11.4	18.1	2849	1949
6	0- 5	201	680	4.9	7.0	2134	627
8	12-48	704	731	16.1	15.5	1523	1471
9	12-60	536	504	17.7	22.1	1472	1563
10	0-12	1968	1366	24.0	28.2	2260	3254
11	0-22	1213	1049	19.3	17.9	1303	1509
12	0-12	223	1920	1.9	19.4	2939	355
13	0- 7	1047	1440	12.1	28.1	2175	1579
14	2- 9	1080	1187	15.2	9.5	5617	5123
15	0- 7	527	746	11.8	5.1	1336	946
16	0- 7	254	518	8.2	15.3	1716	844
17	0- 7	63	146	7.2	15.9	1709	738
Mean				14.1	19.6	2092	1711
±SEM				1.7	2.4	271	312
Median				13.6	18.0	1812	1424

$AUC_{(Coll.)}$ = AUC of bound digoxin during the collection period; $AUC_{(0-\infty)}$ = total AUC under the serum concentrations of bound digoxin; CL_R = renal clearance of bound digoxin; CL_{CR} = creatinine clearance; Renal excretion = total excretion of bound digoxin calculated from $AUC_{(0-\infty)}$ multiplied by CL_R

In Patients 1, 2, 3, 5, 9 and 10, the serum contained some free digoxin during the urine collection periods. The excretion of free digoxin calculated from the creatinine clearance multiplied by the AUC of free digoxin was subtracted from the total amount excreted during those periods. The renal clearance of free digoxin is almost the same as the creatinine clearance (Betzien et al. 1980). The creatinine clearance (Table 1) was obtained from the equation of Cockcroft and Gault (1976). Fourty years was taken as the minimum age, as the age-dependent reduction in creatinine clearance only starts at that age (Shock 1958). The amounts of free digoxin were 24 μg in Patient 1, 300 μg in Patient 9 and less than 1% of the total in the other 4 patients. Only the net amounts of bound digoxin in the urine are given in Table 4.

Pharmacokinetic Parameters

The raw data for the serum concentrations are presented in Tables 2 and 3. For the first 12 h, the areas under the serum concentration curves were calculated by the trapezoidal rule. The rate constant λ_z for the terminal elimination phase was calculated from the serum concentrations from 12 h onwards. The extrapolated $AUC_{(12-\infty)}$ was obtained from the serum concentration after 12 h as read from the regression line divided by λ_z. The total body clearance was obtained by dividing the infused dose by $AUC_{(0-\infty)}$.

Results

Success of Treatment

The patients are arranged in the order of increasing duration of infusion of the antibody in Table 1.

The ECG was monitored during and after administration of the antibody. The most convincing results of the treatment were seen in patients with ventricular fibrillation or other severe arrhythmias. Sinus rhythm returned within 1 to 12 h (Table 1), except for Patient 14 who was in absolute arrhythmia. Differences in antiarrhythmic efficacy depending on the infusion rate of Fab were not seen. In two patients there were no severe arrhythmias at the time of starting the infusion. There were, however, definite signs of the ingestion of massive digitalis doses. The clinical outcome was good in all 17 patients and ended in full recovery.

Table 5. Pharmacokinetic parameters of the Fab fragments. Evaluation of the serum concentrations in Table 2. AUC = area under the serum concentrations of bound + free Fab fragments; CL = total body clearance, CL_R and CL_{NR} = renal and nonrenal clearance; λ_z = rate constant for the terminal elimination phase; V_z = apparent distribution volume

Pat. no.	$AUC_{(0-12)}$ [mg·h/l]	$AUC_{(0-\infty)}$ [mg·h/l]	CL [ml/min]	CL_R [ml/min]	CL_{NR} [ml/min]	λ_z [h^{-1}]	V_z [l]
2	277	358	18.6	27.6	− 9.0	0.0549	20.4
3	296	343	23.3	17.2	6.1	0.0255	55.0
4	262	338	19.7	10.4	9.3	0.041[2]	28.8
5	373	411	19.5	11.4	8.1	0.0350	33.4
6	272	345	19.4	4.9	14.4	0.0707	16.4
12	276	358	14.9	1.9	13.0	0.1070	8.4
13	171	206	25.9	12.1	13.8	0.0979	15.9
14	230	521	10.2	15.2	− 4.9	0.0363	16.9
15	118	143	37.3	11.8	25.5	0.0862	26.0
16	172	244	21.9	8.2	13.7	0.0484	27.1
17	215	295	18.1	7.2	10.9	0.0419	25.9
Mean	242	324	20.8	11.6	9.2	0.0596	24.9
±SEM	21	31	2.1	2.1	2.8	0.0092	3.7
Median	262	343	19.5	11.4	10.9	0.0484	25.9

Table 6. Elimination rate of Fab fragments from 24 h on

Pat. no.	λ_z [h^{-1}]
1	0.0174
2	0.0573
3	0.0171
5	0.0293
6	0.0809
7	0.0255
8	0.0222
9	0.0222
10	0.0334
11	0.0290
Mean	0.0334
±SEM	0.0064
Median	0.0273

Renal Clearance and Renal Excretion of Bound Digoxin

In Patients 12–17, the creatinine clearance was determined together with that of bound digoxin. In Patients 12, 13, 16 and 17 the creatinine clearance was low, although serum creatinine was not elevated, suggesting an acute decrease in clearance due to the digoxin poisoning. This may also have occured in patient 6 on whom CL_{CR} was calculated according to the equation of Cockcroft and Gault (1976). The median of 18.0% for the ratio CL_R/CL_{CR} (Table 4) suggests that only part of the Fab fragments are filtered, which is to be expected with a molecular weight of about 50,000.

To calculate the total excretion of bound digoxin via the kidneys, the renal clearance of bound digoxin was multiplied by the total area under the curve for bound digoxin. The median was about 1.4 mg (Table 4).

Kinetics of the Fab Fragments

Table 5 summarizes the results from those 11 patients in whom the concentration of bound + free antibody was determined. The extrarenal clearance CL_{NR} was calculated by deducting CL_R from CL. In two cases a negative figure resulted, which is probably due to an experimental error in determining CL_R. These extremes are eliminated when the median of 10.9 ml/min is used for further evaluation. Adding this median for CL_{NR} from Table 5 to the median of 13.6 ml/min for CL_R from Table 4 one obtains a total body clearance of 24.5 ml/min. This figure is only slightly different from the median in Table 5. Since it has a broader experimental basis it will be used for interpreting the results.

The median of λ_z in Table 5 corresponds to a half-life of 14.3 h. Surprisingly the apparent distribution volume of 25.4 l was greater than the extravascular space. In patients 1–11 the concentrations of bound digoxin were measured until the detection limit was reached. From the figures in Table 3 λ_z was calculated for these patients from 24 h on. The median in Table 6 corresponds to a half-life of 25.4 h and, together with the total body clearance of 24.5 ml/min, to an apparent distribution volume of $V_z = 54$ l.

Proposed Dosage Schedule

The dosage schedule must find a compromise between a too rapid infusion leading to clearance of

Table 7. Percentage of the infused Fab fragments bound to digoxin.
$AUC_B = AUC_{(0-\infty)}$ of bound Fab fragments; $AUC_T = AUC_{(0-\infty)}$ of bound + free Fab fragments.
AUC_B was calculated from the $AUC_{(0-\infty)}$ of bound digoxin in Table 4 multiplied by the binding constant of 80 mg Fab fragments/1 mg digoxin. AUC_T was taken from Table 5.
Patients 2–6 and 12–17 were evaluated separately because of the different infusion rates

Pat. no.	AUC_B [mg·h/l]	$100 \times \frac{AUC_B}{AUC_T}$	
2	171	47.6	
3	107	31.1	
4	153	45.2	
5	228	55.5	
6	171	49.6	
12	235		65.7
13	174		84.7
14	449		86.3
15	107		74.7
16	137		56.3
17	137		46.3
Mean	188	45.8	69.0
±SEM	29	4.0	6.5
Median	171	47.6	70.2

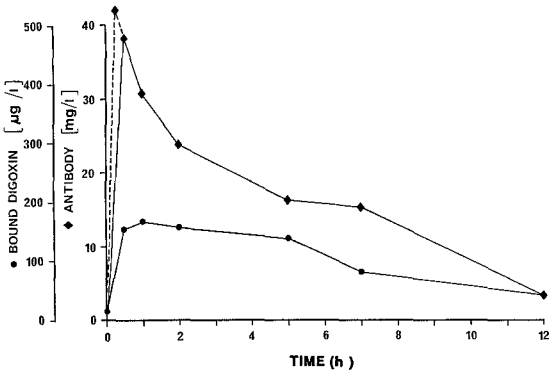

Fig. 1. Medians of the serum concentrations of the Fab fragments and of bound digoxin in Patients 12 to 17
The concentrations of bound digoxin also represent those of the bound antibody read from the right ordinate. The concentration after 0.25 h was extrapolated from those after 0.5 and 1 h

unbound antibody and a dosage which would be insufficient in the most severely intoxicated patients who urgently need an adequate treatment.

For estimating the percentage of the antibody which actually binds digoxin, the ratio of bound Fab fragments to the total amount infused was calculated from the areas under the serum concentrations of bound and total Fab fragments (Table 7). In the first series with variable doses and infusion rates, the fraction of bound Fab fragments was always below 50% of the total.

Figure 1 shows the serum concentrations of total and bound Fab fragments in the last 6 patients in whom the dose of the antibody was reduced to 320 mg and the withdrawal of blood samples followed a fixed schedule. This improved the percentage of bound Fab fragments from 47.6 to 70.2% (Table 7).

The highest serum concentrations of bound digoxin were found in Patient 5. They corresponded to 30 mg/l of antibody after 3 h and 20 mg/l after 5 h. No free digoxin was found in Patient 5 at these times but the concentrations are above the medians in Fig. 1. The loading dose of 160 mg must therefore be considered to be the minimum. With a total body clearance of about 25 ml/min, a serum concentration of 20 mg/l will be maintained with an infusion rate of 0.5 mg/min making a total of 240 mg = 3 ampoules in 8 h.

In many cases free digoxin reappeared after 10 h. The maximum of 6.8 ng/ml (Table 3) is highly toxic. To be on the safe side another ampoule may be infused at 0.1 mg/min or less.

Discussion

In calculating the clearance of the Fab fragments, no distinction was made between free and bound antibody. Considering the 80-fold difference in molecular weight it is unlikely that the binding of digoxin has an appreciable influence.

Our data do not allow to decide whether and to what extent the extrarenal clearance was due to elimination of active antibody or to metabolic inactivation in the sense that it loses its capacity to bind digoxin. The area under the concentrations of bound antibody AUC_B multiplied by the extrarenal clearance of 10.9 ml/min results in an extrarenal excretion of 1.1 mg digoxin. Together with the renal excretion of 1.4 mg this adds up to a maximal total excretion of 2.5 mg digoxin in bound form.

The apparent distribution volumes after 12 h or more of equilibration are clearly above the volume of the extracellular space suggesting intracellular penetration of the antibody. Several facts indicate that the Fab fragments penetrate the cells in spite of their high molecular weight. IgG with a molecular weight 3 times that of the Fab fragments has been found within cells (Ring and Duswald 1980). In baboons, the distribution volume of Fab fragments was 8.7 times greater than that of IgG (Smith et al. 1979). The distribution volume of IgG cannot be less than the plasma volume. As the extracellular space is only 4 times greater than the plasma volume, it follows from the high factor that the distribution volume of Fab fragments is greater than that of the extracellular space. Kaul et al. (1984) found antibody inside hu-

man fibroblasts after incubation in vitro. With dimeric $F(ab')_2$ fragments, Ring et al. (1978) found in dogs 24 h after administration concentrations in the tissue which could only be explained by intracellular penetration. Vollerthun et al. (1977) found $F(ab')_2$ fragments in the cytoplasm of mice. As the monomeric Fab fragments have only half the molecular weight, an even greater uptake by the cells is to be expected.

The present rationale for the dosage of digoxin antibodies is to infuse an amount stoichiometric to the ingested digoxin. The latter is either estimated from the number of tablets swallowed or from the serum concentration. The assumption behind this recommendation is that all the antibody will be available for binding digoxin. The present results show that this is not the case. If the antibody is infused during a short time period (Smolarz and Abshagen 1985; Wenger et al. 1985) about half is cleared before enough digoxin has re-diffused from the tissue for binding (Table 7). This ratio may be improved by adhering to the dosage schedule recommended above. One should not try to improve the ratio of bound/total Fab fragments by a further decrease in dose because this would render the serum concentrations insufficient to bind digoxin in particularly severe cases of poisoning where an adequate treatment is most important.

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