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Tissue Concentrations at Autopsy in Infants and Children Receiving Therapeutic Digoxin

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ABSTRACT: Therapeutic tissue concentrations of digoxin have been reported for relatively small numbers of infants and children. In forensic medicine, knowledge of these concentration ranges is important for confirming or excluding digoxin overdosage in different age groups. In addition to age and weight, other factors such as dosage, duration of treatment, route of administration, sampling site, time of last dose, and death-autopsy interval may influence tissue concentrations. In this paper we report on tissue concentrations in 36 infants and children who received therapeutic digoxin before death.

KEYWORDS: pathology and biology, toxicology, digoxin, children

Therapeutic tissue concentrations of digoxin have been reported for relatively small numbers of infants and children [*1–6*]. In forensic medicine, knowledge of these concentration ranges is important for confirming or excluding digoxin overdosage in different age groups. In addition to age and weight, other factors such as dosage, duration of treatment, route of administration, sampling site, time of last dose, and death-autopsy interval may influence tissue concentrations. In this paper we report on tissue concentrations in 36 infants and children who received therapeutic digoxin before death.

Materials and Methods

Postmortem analysis of digoxin concentration (C dig) was performed in 36 infants and children, aged 1 day to 18 years. All had received therapeutic doses of the drug until death. Antemortem serum digoxin concentration was measured within several days before death, and autopsy was performed within 24 h of death. The last dose of digoxin was given 1 to 12 h before death. A specific protocol was used for the collection of blood and tissues (Tables 1 and 2). Postmortem blood samples were obtained from within the heart. Samples from the brain, kidneys, and adrenal glands were obtained from the cortical area. The specimens were frozen and subsequent analysis was performed by previously reported methods [*2,3*]. The original method of digoxin radioimmunoassay (RIA) developed in our laboratory was used for most analyses [*2,3*]; more recently, commercially available I^{125} RIA kits were used. Both methods have been extensively tested in our laboratory. Tissue concentrations were expressed as nanograms per gram (ng/g) of wet tissue or nanograms per millilitre (ng/mL) of blood or bile. The

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TABLE 1—*Digoxin concentration in*

	Blood										
	Ante-mortem	Post-mortem	LV	RV	RA	LA	Kid-neys	Skeletal Muscle	Skin	Fat	Liver
Premature infants	3.0	...	103	117	80	...	50	26	7	6	19
	2.3	5.4	323	283	222	172	144	56	22	16	106
	2.2	9.0	69	137	91	52	24	11	6	3	18
	3.9	11.5	...	...	...	...	...	2	2	1	6
Full-term infants	3.7	12.7	372	348	231	213	169	89	24	17	88
	2.0	...	160	65	45	6	121	17	9	4	11
	...	6.5	231	247	160	154	277	31	16	7	60
	2.5	...	173	156	108	96	139	18	11	12	25
	1.8	...	309	587	184	111	120	80	125	13	82
	2.2	5.9	258	218	145	181	229	...	...	...	...
	2.7	...	196	80	169	122	207	26	24	5	15
	1.5	...	234	192	...	...	...	21	39	7	86
Older children	1.0	3.2	150	162	57	79	211	25	14	7	47
>2 years	1.2	...	70	112	81	32	17	9	8	2	36
	0.7	3.0	102	30	75	...	137	16	22	5	27

[a]The patients in each group are shown in Table 3. LV = left ventricle, RV = right ventricle, RA = right atrium, and LA = left atrium.

TABLE 2—*Digoxin concentration in*

	Blood										
	Ante mortem	Post mortem	LV	RV	RA	LA	Kid-neys	Skeletal Muscle	Skin	Fat	Liver
Premature infants	2.2	4.2	169	238	...	...	39	30	19	13	82
	2.0	...	212	197	...	...	96	38	13	7	59
	1.6	...	220	228	...	...	102	54	20	3	76
	3.5	14.1	245	247	84	168	166	21	43	...	147
	4.0	12.0	185	149	105	115	50	14	11	15	55
	1.3	...	142	109	...	...	53	18	6	...	31
	1.2	...	250	205	173	154	234	30	16	16	105
	2.6	6.0	456	431	273	203	416	55	...	...	129
Full-term infants	2.8	6.1	450	231	232	169	106	35	10	5	56
	3.2	...	201	183	224	164	242	40	54	12	163
	1.8	4.3	238	...	175	...	166	62	40	9	90
Children	1.4	3.0	181	212	160	166	884	127	66	32	189
<2 years	0.9	...	226	117	44	67	...	45	...	9	...
	1.5	...	78	61	59	32	152	8	31	2	42
	1.2	3.3	...	...	...	...	78	11	6	4	32
	0.8	...	21	...	9	31	51	...	18	7	38
Children	1.0	4.2	69	64	54	51	251	11	45	1	35
>2 years	1.2	...	114	71	60	...	213	81	7	10	77
	0.5	...	19	10	9	7	30	2	1	0	21
	0.9	2.7	142	78	...	...	32	30	0	3	34

[a]The patients in each group are shown in Table 3.

tissues (ng/mL or ng/g) for acute group.[a]

Spleen	Lungs	Brain	Adrenal	Pancreas	Stomach	Small Intestine	Large Intestine	Gall Bladder	Urinary Bladder	Thymus	Thyroid	Gonad
8	18	...	2	41	12	28	1	27	...	10	23	...
13	32	3	31	34	24	87	82	29	20	18	30	8
13	26	2	18	19	17	25	11	19	10	8	31	17
...	...	...	...	...	28	21	2	...	...	...	...	...
42	70	15	75	27	46	259	101	78	...	37	75	54
10	16	5	...	12	11	16	12	64	7	9	11	13
21	42	2	31	45	15	80	52	...	28	18	48	28
18	28	1	35	27	25	49	66	47	21	14	39	15
14	61	...	20	...	22	1438	81	59	...	...	23	...
...	...	...	...	...	...	...	...	...	...	...	...	...
10	20	6	...	...	48	112	84	67	...	...	...	4
16	26	...	45	43	26	98	57	169	23	20	38	17
20	44	6	73	427	24	43	30	320	16	145	27	19
9	12	0.3	...	6	11	47	6	...	16	...	8	...
14	27	10	26	44	26	52	32	254	...	...	21	17

tissues (ng/mL or ng/g) for chronic group.[a]

Spleen	Lungs	Brain	Adrenal	Pancreas	Stomach	Small Intestine	Large Intestine	Gall Bladder	Bile	Urinary Bladder	Thymus	Thyroid	Gonad
10	...	...	32	18	33	109	98	106	...	...	20	25	...
13	31	3	30	23	36	26	87	28	75	11	...	...	...
10	35	5	...	...	38	58	45	...	34	...	...	...	...
15	32	8	38	39	48	70	320	267	215	...	26	55	17
12	21	4	28	26	16	83	96	103	31	...	25	19	...
...	...	...	...	15	2	45	62	1	...	...	...	...	4
26	28	10	31	51	36	44	141	...	...	18	29	32	28
...	47	9	...	69	70	648	...	...	...	47	...	...	...
7	16	...	12	18	16	30	16	31	...	...	9	...	14
26	44	5	39	110	62	150	31	144	...	36	30	56	62
21	...	34	26	76	50	164	133	81	...	...	...	46	...
44	94	57	82	134	120	304	259	180	...	50	83	...	59
...	...	...	...	...	...	...	...	...	...	...	...	...	...
4	12	30	12	18	14	12	21	45	...	5	6	11	10
...	...	8	12	4	13	40	42	299	205	11	5	8	4
7	7	...	8	8	7	12	18	...	...	...	9	8	...
6	13	...	9	24	149	40	37	17	...	...	...	...	...
13	20	30	22	...	56	178	78	2	...	...	...	34	...
0.3	2	3	5	3	4	16	4	7	...	...	...	3	...
7	9	...	...	...	8	30	7	46	...	5	...	19	3

infants and children were classified according to the duration of digoxin administration into an acute group, 16 subjects who received the drug for 3 days or less, and a long-term therapy or chronic group, 20 who received the drug for longer than 3 days.

The groups were further subdivided into age and weight groups; there were twelve preterm and twelve full-term neonates, five children under two years, and seven over two years of age. The route of digoxin administration was intravenous in twelve, oral in seventeen, and intramuscular in seven patients.

Results

Table 3 shows the clinical data. Digoxin tissue concentrations in the acute group are shown in Table 1, and in the chronic group in Table 2. Individual measurements made for each organ are shown.

Values of C dig were higher in postmortem than antemortem blood. Both the antemortem and postmortem levels were higher in premature than in full-term infants and older children. In preterm infants antemortem blood levels ranged from 1.2 to 4.0 and postmortem levels from 4.2 to 14.1 ng/mL. In full term neonates antemortem concentrations ranged from 1.5 to 3.7 and postmortem levels from 4.3 to 12.7 ng/mL. In older children the range for antemortem levels was 0.5 to 1.5 and for postmortem concentrations 2.7 to 4.2 ng/mL. No significant difference was observed between the acute group and the chronic group.

Ventricular myocardial C dig levels tended to be higher than atrial myocardium levels in all age groups. These concentrations were greater in preterm and full term neonates than in older children in both the acute and chronic group. In neonates the C dig in ventricular myocardium ranged from 69 to 587, and in atrial myocardium from 45 to 273 ng/g. In older children the C dig in ventricular myocardium ranged from 18 to 226, and in atrial myocardium from 7 to 166 ng/g. Values of C dig in the right and left ventricles and atria were not significantly different.

The C dig in kidney tissue was variable. A distinct pattern could not be observed for different age groups or modes of administration. Values ranged from 17 to 416 ng/g.

In skeletal muscle, the C dig did not vary significantly among age groups or with the duration of administration. The range was from 2 to 127 ng/g. The C dig levels in the gastrointestinal tract, including the hollow organs, liver, and pancreas, were generally high regardless of the route of drug administration. They showed marked variability, especially in the small and large intestines and gall bladder. The C dig levels were generally lower in the stomach wall than in the walls of other hollow viscera. In the liver, C dig levels were higher in premature and full term infants than in older children, but there was considerable variability. In neonates the C dig ranged from 60 to 163, and in older children from 21 to 189 ng/g.

In lung tissue, there was considerable variation in range of digoxin concentrations. The C dig levels appeared to be higher in premature and full term neonates compared to older children in the chronic group. In the acute group, this age difference was not apparent.

In cortical brain tissue, C dig levels were low and no significant difference was observed among age groups relating to duration of drug administration. The C dig values for other organs are shown in Table 2.

Discussion

The digoxin concentration of different organs in infants and children receiving therapeutic digoxin is of importance in forensic medicine for the recognition of drug overdose. Previous information regarding digoxin tissue concentrations in these age groups has been fragmentary [*1–6*].

Several investigators have shown differences between serum and blood C dig or both obtained antemortem and postmortem. In addition, samples from different sites, for example

TABLE 3—*Clinical data.*

Age Group	Case	Age	Weight, kg	Body Surface Area (BSA), m^2	Route of Administration[a]	Duration of Administration, days	Digoxin Dose, μg/kg per day
				ACUTE GROUP			
Premature infants	1	3 days	2.32	0.18	IM	1	9
	2	2 days	1.14	0.11	IM	1	35
	3	4 days	2.05	0.16	IV	1	17
	4	1 days	1.69	0.14	PO	1	20
Full-term infants	1	3 days	3.30	0.22	IM	2	72
	2	9 days	2.50	0.18	IM	3	31
	3	2 days	3.60	0.23	IV	1	33
	4	1 day	2.75	0.20	IV	1	22
	5	16 days	3.14	0.21	IV	2	48
	6	7 days	3.28	0.22	IV	3	37
	7	7 days	3.63	0.24	IV	1	66
	8	4 days	3.10	0.21	PO	1	29
	9	10 days	3.67	0.24	PO	2	37
Older children	1	9 years	19.5	0.74	IV	2	33
(>2 years)	2	10 years	26.6	1.00	IV	2	9
	3	10 years	26.0	0.99	IV	1	10
				CHRONIC GROUP			
Premature infants	1	10 days	1.91	0.15	IM	6	7
	2	12 days	1.53	0.13	IM	8	5
	3	13 days	1.44	0.13	IM	5	7
	4	12 days	.89	0.09	IV	10	2
	5	11 days	.63	0.07	IV	6	2
	6	24 days	1.49	0.13	PO	9	3
	7	12 days	1.89	0.15	PO	5	5
	8	11 days	1.35	0.12	PO	5	5
Full-term infants	1	17 days	2.70	0.19	IV	4	10
	2	9 days	4.20	0.26	PO	6	21
	3	11 days	3.77	0.24	PO	7	21
Children <2 years	1	1½ months	3.20	0.21	PO	26	22
	2	3 months	3.69	0.21	PO	8	16
	3	12 months	5.90	0.33	PO	8 months	17
	4	18 months	8.01	0.40	PO	4½ months	18
	5	24 months	8.85	0.42	PO	6 months	17
Children >2 years	1	7 years	17.8	0.57	PO	1½ months	9
	2	7 years	18.6	0.80	PO	6 months	13
	3	11 years	25.7	0.98	PO	18	10
	4	18 years	42.0	1.39	PO	14 years	6

[a] IM = intramuscular, IV = intravenous, PO = oral.

the heart, jugular, subclavian, or femoral veins, had different C dig levels [*7–9*]. Some studies have shown no differences between antemortem and postmortem blood obtained during the first 30 min after death [*9*]; other studies show no useful correlation between longer postmortem intervals and blood C dig levels [*7, 9*]. A new equilibrium between tissue and blood digoxin has been postulated to occur after death.

Many workers have reported myocardial C dig values, especially in adults. Some of these studies were performed in conjunction with surgery, and others with postmortem specimens [*10–17*].

In 1969, Hernandez et al analyzed the pharmacodynamics of tritiated digoxin in infants [*1*]. Our own laboratory reported tissue concentrations obtained at surgery in 1974 [*2*] and at autopsy in 1975 in infants and children [*3*]. Andersson et al described C dig levels in 12 infants and 17 adults [*4*]. Lang et al described additional tissue C dig data in preterm and full term neonates and older infants [*5*].

The above studies revealed higher plasma and tissue C dig values in premature and full term neonates than in more mature infants, but no significant difference in the myocardium-to-plasma digoxin ratio was found. Renal C dig was lower in premature than mature neonates, while other tissue concentrations were similar in these age groups.

Gorodischer et al in 1976 reported C dig values in myocardium, skeletal muscle, and plasma in children [*6*]. Their values were considerably higher than those obtained by other investigators, possibly because of the short dose-death interval and larger doses administered.

In the present study, C dig values tended to be lower in the acute group than the chronic group in preterm and full term infants, but not in older children. Neonates, both premature and full term, had higher tissue concentrations than older children, especially in the blood, myocardium, liver, and gastrointestinal tract. No significant differences were observed in any age group with respect to the routes of administration or dosage.

With regard to the C dig in brain tissue, Andersson et al reported high concentrations in the choroid plexus [*14*] and Spiehler et al described concentration of the drug by the choroid plexus of the fourth but not the lateral ventricles [*18*]. These authors also showed the presence of the drug in the area postrema (chemoreceptor trigger zone) and the nucleus of the vagus with toxic but not with therapeutic digoxin administration. Digoxin was not found in significant concentration in other areas of the brain.

Because of its importance in forensic medicine, C dig in vitreous humor has been studied by several investigators. Sturner and Garriott [*19*] found a mean C dig in vitreous humor of 1.9 ± 1.1 ng/mL versus a blood C dig of 3.2 ± 1.6 ng/mL, the mean ratio being 0.67 ± 0.32 ng/mL (range 0.39 to 1.20). In two toxic subjects, these ratios were 0.07 and 0.70, respectively. These authors postulated that at equilibrium, which occurs within a few hours after death, vitreous C dig is approximately equivalent to that of blood, the ratio being 0.7 to 0.8 because of the 25% protein binding of the drug. Ratios of more than 1.0 were only observed in non-overdosed subjects; they were explained as being a result of a lag in re-equilibrating after a blood level decline caused by excretion. DiMaio et al [*20*] suggested that ratios of less than 1.0 reflect rising and ratios of more than 1.0. falling blood C dig levels. From a forensic medicine standpoint, a wide difference between blood and vitreous humor C dig is thought to reflect a short dose-death interval, while C dig equilibration between blood and vitreous humor indicates a long interval. According to Vorpahl and Coe [*7*], the vitreous humor C dig is usually lower than the antemortem serum C dig. These authors suggest that it is possible that in most individuals, C dig in vitreous humor will equilibrate with that of blood. However, significant increases in vitreous humor C dig correspond to toxic antemortem serum levels.

There have been reports of six infants who died following accidental massive overdosage of intravenous digoxin [*21–25*]. Their ages ranged from three days to two months and the amount of digoxin given was from 0.5 to 3.0 mg. Death ensued from 20 min to 8 h following administration. Postmortem blood levels ranged from 30 to 150 ng/mL. The C dig in the myocardium in two cases ranged from 200 ng/g (determined by using a fluorometric assay) to

1252 ng/g; liver C dig in four cases ranged from 35 to 501 ng/g; C dig in the kidneys (three cases) was from 130 to 1683 ng/g; and C dig in the lungs (three cases) was from 45 to 278 ng/g. In addition, there have been a number of cases of accidental fatal overdosage with digoxin in young children who ingested the medication in tablet form. The low tissue levels observed in some of the above reports appear to be incompatible with massive digoxin toxicity, unless death occurred before penetration of the drug into the tissues. Doherty et al [*26*] have shown the halftime of digoxin distribution in tissues to be 30 min following intravenous administration and 50 min following oral ingestion in liquid form. As a consequence one would expect, following an intravenous dose, 50% of the maximal concentration to occur in the tissues by 30 min, 75% by 1 h, and 94% by 2 h.

The selection of tissues for postmortem analysis of digoxin concentration is a controversial issue. In the absence of blood samples, most investigators would probably select liver tissue, proper sections of the brain, or vitreous humor for confirmation of digoxin toxicity. Myocardial tissue has shown great variation in toxic cases; it has been especially distressing to find low myocardial concentrations in cases with known massive overdose. However, high myocardial concentrations of digoxin are consistent with digoxin toxicity [*25*]. Skeletal muscle may be, in some instances, the only accessible or available tissue, for example in previously autopsied exhumed bodies; therefore it may be of significance. Renal and lung tissue digoxin concentrations are not reliable indicators of digoxin toxicity.

In adults, Reissel et al [*27*] proposed toxic levels for blood and myocardium of 8 ng/mL and 250 ng/g, respectively. The present study shows that maximal therapeutic concentrations observed in infants and children are higher than in adults. We propose that toxic levels for postmortem blood concentration be 15 ng/mL for neonates, 10 ng/mL for children less than two years old, and 8 ng/mL for older children and adults. For ventricular myocardium, toxic concentrations are respectively 450, 300, and 250 ng/g for the three age groups. While liver concentrations above 100 ng/g are probably toxic for older children and adults, the toxic threshold may be as high as 200 ng/g for infants and young children. Our data do not show significant age variability for digoxin concentration in skeletal muscle; levels of 100 ng/g or higher are probably toxic in any age group.

Caution should be used in interpreting toxic levels in any tissue and age group because of such variables as dosage, time of last dose received, death-autopsy interval, and other pathophysiologic characteristics of the patient before death. Because of the high prevalence of digoxin toxicity in therapeutic, accidental, or suicidal administration of the drug (including younger age groups), it is important to recognize that therapeutic tissue concentrations differ in infants and children from those established for adults.

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