CASE REPORT

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Accidental Digoxin Overdose in an Infant: Postmortem Tissue Concentrations

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ABSTRACT: We report the digoxin concentration in various tissues of a seven-week-old infant who died 45 min after receiving an accidental intravenous overdose of digoxin. The digoxin content of various organs was calculated and expressed as a percentage of dose administered. The literature of accidental massive digoxin overdose in infants has been reviewed. Data on tissue concentrations and distribution of digoxin in this age group is scarce. The concentration of digoxin in myocardium, kidney, liver, and other organs observed in our case rank among the highest ever reported in human tissues.

KEYWORDS: toxicology, digoxin, radioimmunoassay, toxic concentrations in infancy, tissue digoxin levels

Digoxin levels have been determined in tissues from adult patients [*1–6*] and children [*7–9*] at the time of cardiac surgery or postmortem examination. There is still scarce information regarding tissue concentrations associated with fatal digoxin overdosing. We report an infant who accidentally received a very high dose of digoxin intravenously and died shortly thereafter. Tissues from various organs were obtained through the Coroner's office for analysis of digoxin concentration.

Case Report

A one-month-old infant was hospitalized elsewhere with congestive heart failure and a large ventricular septal defect. An oral loading dose of 60 μg/kg of digoxin was given followed by a daily oral maintenance dose of 20 μg/kg. Cardiac failure persisted and was difficult to control. Three weeks following admission, a dose of 2 mg of intravenous furosemide was prescribed; inadvertently, 2.0 mg of digoxin was administered intravenously instead. Ventricular

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fibrillation ensued and the infant expired about 45 min later. The County Coroner's office notified our laboratory about the incident and provided us with samples of several tissues for analysis of the digoxin concentration.

Methods

Fresh tissue fragments from various organs were obtained at the time of the autopsy. The digoxin extraction method has been previously described [*8*]; in brief, tissue samples were homogenized in absolute ethanol and centrifuged; the supernatants were evaporated to dryness and resuspended in phosphate-bovine serum albumin buffer. Digoxin was measured by a radioimmunoassay procedure using tritiated digoxin [*8*], the antibody having an affinity of $3.6 \times 10^9 M^{-1}$ and Sips index of heterogeneity equal to 0.94 (1.00) indicating a single moiety.

Results

The infant was seven weeks old and weighed 4.10 kg at the time of death. A large ventricular septal defect and congestive heart failure were confirmed at autopsy. Organ weights were not available.

The digoxin concentrations in various tissues of the toxic infant are shown in Table 1. They are compared to data obtained in our laboratory on four nontoxic fullterm neonates, ages two to eleven days, and four nontoxic older children, aged one and one half to seven years. Both groups of control patients had received therapeutic doses of digoxin orally before death: the neonates averaged 15 mg/kg/day and the older children 7.5 mg/kg/day. Two control groups were used because the infant described in this report, being seven weeks old, falls in an age and size range intermediate between full term and older infants. Tissue concentrations of digoxin were expressed as nanograms per gram of wet tissue. Blood, vitreous humor, or urine samples were not available for digoxin determination.

Discussion

Tissue concentrations of digoxin have been reported to be higher in newborn infants who receive therapeutic doses of the drug than in older children and adults [*8*]. However, because of the close proximity of the present case to the newborn and organ functional immaturity in infants less than three months of age, in the ensuing discussion we refer to the ratio of the tissue digoxin concentrations between the toxic infant reported and nontoxic neonate controls and not those in older children.

Following intravenous administration, the half-time of digoxin distribution in various tissues including myocardium is 30 min [*10*]. As a result, one would expect 50% of the maximal concentration to be present in the tissue in 30 min, 75% at 60 min, 87.5 % at 90 min, and 94% at 120 min.

Our laboratory [*8*] and others [*6*] have shown that, in general, nontoxic patients have higher digoxin concentrations in ventricular than in atrial myocardium, and that the concentration in left ventricle is usually greater than that of the right ventricle. In older nontoxic children the latter was true but there was no apparent difference in tissue digoxin levels between the atria and the ventricles.

In the infant with accidental digoxin poisoning, the concentrations of digoxin in right and left atrium were 667 and 394 ng/g, and those in the right and left ventricle 1006 and 1252 ng/g, respectively. These concentrations were approximately six times higher than those observed in full term neonates receiving therapeutic doses of digoxin.

In skeletal muscle, the concentration of digoxin in the toxic infant was 373 ng/g versus an average of 32 ng/g in nontoxic neonates. This twelvefold difference is of importance because of the role of skeletal muscle as a repository of digoxin. Assuming a skeletal muscle mass of

TABLE 1—*Digoxin tissue concentrations of the present infant compared to those of two group of controls (infants*

	Myocardium								
	Right Atrium	Left Atrium	Right Ventricle	Left Ventricle	Skeletal Muscle	Kidney	Liver	Fat	Brain
Present case	667	631	1006	1252	373	1683	501	90	24
Controls									
(1) Full term neonates ($n = 4$)	95 ± 59	138 ± 23	180 ± 84	196 ± 36	32 ± 17	198 ± 69	50 ± 34	6 ± 2	14 ± 15
(2) Older infants and children ($n = 4$)	67 ± 18	77 ± 37	60 ± 14	74 ± 37	8 ± 6	232 ± 27	41 ± 25	4 ± 4	21 ± 12

22% of the infant's body weight, that is, 902 g, the total digoxin content in skeletal muscle was 337 μg, approximately 17% of the total fatal dose of 2.0 mg of digoxin that the infant received. Even if a skeletal muscle digoxin store as a result of earlier treatment is taken into consideration, the calculated amount of the fatal terminal dose that accumulated in skeletal muscle is considerable. The ratio of digoxin concentration in skeletal muscle to ventricular myocardium was 1:3, contrasted to a ratio of 1:6 in nontoxic neonates.

The concentration of digoxin in kidney tissue reflects (1) the amount of digoxin reaching this organ and (2) the ability of the kidney to excrete the drug. In past studies, the renal concentration of digoxin was found to be lower in neonates than in older children and even less in premature infants [*8*]. This appeared to reflect the lesser excretory ability of the more immature kidney. The renal digoxin concentration in the toxic infant was about nine times higher than that found in nontoxic neonates, suggesting good renal function. Assuming a combined weight for the kidneys of 39 g, the total digoxin content in renal tissues was 66 μg, or 3.3% of the administered dose.

The digoxin concentration in liver tissue is of interest because a significant fraction of the drug is excreted with bile and enters the entero-hepatic cycle; a small fraction of the administered drug is metabolized in liver. In the infant reported, the concentration of digoxin in the liver was 501 ng/g, about ten times the average concentration of nontoxic neonates. Assuming a liver weight of 160 g, the total calculated content of digoxin in the liver is 80 μg, 4% of the total administered dose.

Despite the massive overdose of digoxin, the concentration in the brain (cerebral cortex, exact site unknown) was not significantly different from that observed in nontoxic neonates and older children. The relative inability of digoxin to concentrate in brain tissue is well known, and is attributed to its low liposolubility and slow or absent passage through the blood-brain barrier. Recent studies suggest increased concentrations of digoxin in selected areas of brain, such as the choroid plexus of the fourth ventricle [*11*]. In the present study, vitreous humor was not available for digoxin analysis. Note that the concentration of digoxin in adipose tissue in the toxic infant was 15 times higher than that observed in nontoxic neonates.

The concentration of digoxin in the adrenal cortex of the toxic infant was very high, 377 ng/g, or 15 times that observed in nontoxic neonates. The digoxin concentration in the thymus gland, spleen, lung, and skin was of similar magnitude, ranging from 250 to 278 ng/g, corresponding to 11 to 17 times those observed in nontoxic neonates. These tissues tend to have low concentrations of digoxin under therapeutic conditions. This is especially true of organs with a very rich blood supply such as the spleen.

and children who received therapeutic doses of digoxin). Tissue concentrations are expressed in ng/g.

Adrenal Cortex	Thymus	Spleen	Skin	Lung	Pancreas	Stomach	Small Intestine	Large Intestine	Gall Bladder
377	250	268	265	278	124	200	1359	962	862
25 ± 7	15 ± 5	16 ± 6	22 ± 3	26 ± 14	61 ± 22	31 ± 21	93 ± 62	70 ± 51	71 ± 9
14 ± 7	21 ± 18	8 ± 5	38 ± 30	17 ± 5	21 ± 4	71 ± 67	75 ± 69	52 ± 22	70 ± 107

The amount of digoxin in the wall of the small and large intestine was very high, measuring 1359 and 962 ng/g, respectively. It was also very high in the bile, 862 ng/g. The high intestinal content has two explanations: (1) therapeutic administration of oral digoxin and (2) the appearance of the drug in the intestinal tract even when given intravenously [*12*]. Following an intravenous injection of digoxin, approximately 7% is excreted in the bile within 1 h [*12*]. The very high concentration in intestinal wall may suggest that under toxic conditions, excretion through the intestine may occur [*13*]. The concentration in intestinal wall and bile was 12 to 15 times that observed in nontoxic neonates, while that in gastric wall and pancreatic tissue were relatively low, that is, 200 and 124 ng/g, respectively, or, six and two times the average observed in nontoxic full term neonates.

There have been reports of five infants who died following accidental massive overdose of intravenous digoxin (Table 2). The 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 and analysis of blood at autopsy showed digoxin levels ranging from 30 to 150 ng/mL.

Conclusion

In summary, the concentrations of digoxin in the toxic infant were highest in the kidney, small intestine, ventricular myocardium, large intestine, bile, and atrial myocardium. Markedly elevated levels were also found in liver, skeletal muscle, and adrenal cortex tissue. The skin, lung, spleen, thymus gland, and stomach wall had moderately elevated concentrations. As expected, the concentration of digoxin was considerably less in adipose tissue. In the brain, it was not significantly different from that observed in nontoxic states.

Karjalainen et al [*1*] and Reissel et al [*14*] studying adults, suggested that myocardial concentrations above 250 ng/g were toxic as were those with more than 8 ng/mL in postmortem blood. It is difficult to establish and predict a fatal myocardial concentration of digoxin. From our earlier studies of ventricular myocardial concentrations in infants and children who received therapeutic dosages of digoxin, and from those of others [*7–9*], it appears likely that ventricular myocardial concentrations above 500 ng/g represent toxicity and carry a high probability of fatality. The high values reported by Gorodischer et al [*15*], that is, 519, 643, and 975 ng/g, in some infants receiving therapeutic doses of digoxin are disproportionately higher than those reported by others. They can probably be explained by the short dose administration/autopsy interval which ranged from 0.75 to 6 h. Furthermore, two of these reported cases had received large digitalizing doses.

TABLE 2—*Autopsy blood and tissue concentrations of previously reported infants with massive digoxin overdoses.*[a]

Reference	Patient Age	Last Dose of Digoxin Administered Intravenously, mg	Dose to Death, Time Interval	Digoxin Blood Level at Autopsy, ng/mL	Tissue Concentration, ng/g	
Steentoft [*17*][b]	11 d	0.7	30 to 60 min	150	myocardium	200 (100)
					liver	230 (300)
					kidney	680
					lung	100
					urine	380
Phillips [*18*]						
Case 5	11 w	0.5	8 hr	31		
Case 11	2 mo	0.8	6 hr	38		
Dickson and Blazey [*19*][c]	10 w	0.8	20 min	148-(200)	liver	190 (210)
					pericardial fluid	112 (120)
Selesky et al [*20*]	3 d	3.0	5.5 h	30.3	brain	0.9
					lung	45
					liver	35
					kidney	130

[a] Abbreviations: d = days, w = weeks, mo = months, min = minutes, h = hours.
[b] Fluorometric or colorimetric assay (the latter is shown inside parentheses).
[c] Radioimmunoassay with extraction or direct assay (the latter is shown inside parentheses); for liver tissue, single and double extraction were used.

The content of digoxin in various organs of the toxic infant in this report was calculated using assumed organ weights from standard tables [*16*]. The organ content of digoxin was expressed as a percentage of the dose administered and was compared to that present in four nontoxic infants who received therapeutic doses of the drug (these values are indicated inside parentheses). In the toxic infant, skeletal muscle contained 16.8% of the digoxin dose administered (12.2% in nontoxic infants), the kidney 3.3% (versus 2.9%), myocardium 1.5% (versus 2.7%), lungs 1.0% (versus 0.9%), and the brain 0.6% (versus 2.9%). The other organs contained significantly smaller amounts ranging from 0.1 to 0.2% of the digoxin dose administered in both the toxic and nontoxic infants.

The forensic pathologist, when faced with the dilemma of trying to ascertain whether or not death can be attributed to digoxin overdose (and in the absence of blood levels of digoxin) may have to rely heavily on the concentration of digoxin in selected tissues. It appears to us, on the basis of our knowledge of these concentrations of digoxin in autopsied infants and children who had received therapeutic doses of this drug, and the limited experience with these concentrations in massive overdoses of the drug, that in the absence of blood, myocardium, liver, and skeletal muscle are probably the tissues of choice for toxicologic analysis of digoxin. Spiehler et al [*11*] suggested recently that the digoxin content of the medulla, under the obex, may be useful in confirmation of elevated blood digoxin concentrations.

References

[*1*] Karjalainen, J., Ojala, K., and Reissel, P., "Tissue Concentrations of Digoxin in Autopsy Material," *Acta Pharmacologica et Toxicologica. Supplementum*, Vol. 34, No. 5, May 1974, pp. 385–390.

[*2*] Doherty, J. E., Perkins, W. H., and Flannigan, W. J., "The Distribution and Concentration of Tritiated Digoxin in Human Tissues," *Annals of Internal Medicine*, Vol. 66, No. 1, Jan. 1967, pp. 116–124.

[*3*] Coltart, J., Howard, M., and Chamberlain, D., "Myocardial and Skeletal Muscle Concentrations of Digoxin in Patients on Long-term Therapy," *British Medical Journal*, Vol. 2, No. 6, May 1972, pp. 318–319.

[*4*] Gullner, H. G., Stinson, E. B., Harrison, D. C., and Kalman, S. M., "Correlation of Serum Concentrations with Heart Concentrations of Digoxin in Human Subjects," *Circulation*, Vol. 50, No. 4–6, Oct. 1974, pp. 653–655.

[*5*] Jusko, W. J., and Weintraub, M., "Myocardial Distribution of Digoxin and Renal Function," *Clinical Pharmacology and Therapeutics*, Vol. 16, No. 3, Part 1, Sept. 1974, pp. 449–454.

[*6*] Biddle, T. L., Weintraub, M. and Lasagna, L., "Relationship of Serum and Myocardial Concentration to Electrocardiographic Estimation of Digoxin Concentration," *Journal of Clinical Pharmacology*, Vol. 18, No. 1, Jan. 1978, pp. 10–15.

[*7*] Andersson, K. E., Bertler, A., and Wettrell, G., "Postmortem Distribution and Tissue Concentrations of Digoxin in Infants and Adults," *Acta Paediatrica Scandinavica*, Vol. 64, No. 3, May 1975, pp. 497–504.

[*8*] Kim, P. W., Krasula, R. W., Soyka, L. F., and Hastreiter, A. R., "Postmortem Tissue Concentrations in Infants and Children," *Circulation*, Vol. 52, No. 4–6, Dec. 1975, pp. 1128–1131.

[*9*] Lang, D., Hoffstetter, R., and von Bernuth, G., "Postmortem Tissue and Plasma Concentrations of Digoxin in Newborns and Infants," *European Journal of Pediatrics*, Vol. 128, No. 3, March 1978, pp. 151–161.

[*10*] Doherty, J. E., de Soyza, N., Kane, J. J., Bissett, J. K., and Murphy, M. L., "Clinical Pharmacokinetics of Digoxin Glycosides," *Progress in Cardiovascular Diseases*, Vol. 21, No. 2, Sept./Oct. 1978, pp. 141–158.

[*11*] Spiehler, V. R., Sedgwick, P., and Richards, R. G., "The Use of Brain Digoxin Concentrations to Confirm Blood Digoxin Concentrations," *Journal of Forensic Sciences*, Vol. 25, No. 4, Oct. 1981, pp. 645–650.

[*12*] Caldwell, J. H., and Cline, C. T., "Biliary Excretion of Digoxin in Man," *Clinical Pharmacology and Therapeutics*, Vol. 19, No. 4, April 1976, pp. 411–415.

[*13*] Caldwell, J. H., Caldwell, P. B., Murphy, J. W., and Beachler, C. W., "Intestinal Secretion of Digoxin in the Rat," *Naunyn-Schmiedeberg's Archives of Pharmacology*, Vol. 312, No. 3, July 1980, pp. 271–275.

[*14*] Reissel, P., Alha, A., Kaijalainen, J., Nieminen, R., and Ojala, K., "Digoxin Intoxication Determined Postmortem," presented at 6th International Congress of Pharmacology, Helsinki, 1975 (abstract).

[15] Gorodischer, R., Jusko, W. J., and Yaffe, S. J., "Tissue and Erythrocyte Distribution of Digoxin in Infants," *Clinical Pharmacology and Therapeutics*, Vol. 19, No. 3, March 1976, pp. 256-262.
[16] Schulz, D. M., Giordamo, D. A., and Schulz, D. H., "Weight of Organs of Fetuses and Infants," *Archives of Pathology*, Vol. 74, No. 3, Sept. 1962, pp. 244-250.
[17] Steentoft, A., "Fatal Digitalis Poisoning," *Acta Pharmacologica et Toxocologica Supplementum*, Vol. 32, No. 5, April 1973, pp. 353-357.
[18] Phillips, A. P., "Case Experience with Digoxin Analysis in Postmortem Blood," *Journal of the Forensic Science Society*, Vol. 14, No. 2, April 1974, pp. 137-140.
[19] Dickson, S. J., and Blazey, N. D., "Postmortem Digoxin Levels. Two Unusual Case Reports," *Forensic Science*, Vol. 9, No. 2, March/April 1977, pp. 145-150.
[20] Selesky, M., Spiehler, V., Cravey, R. H., and Elliott, H. W., "Digoxin Concentration in Fatal Cases," *Journal of Forensic Science*, Vol. 22, No. 2, April 1977, pp. 409-417.

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