THE USE OF DIGOXIN-SPECIFIC Fab FRAGMENTS FOR SEVERE DIGITALIS INTOXICATION IN CHILDREN

ALAN D. WOOLF, M.D., M.P.H., THOMAS WENGER, M.D., THOMAS W. SMITH, M.D., AND FREDERICK H. LOVEJOY, JR., M.D.

Abstract *Background.* Because life-threatening digitalis intoxication is unusual in children, treatment with digoxin-specific–antibody Fab fragments (Fab) has rarely been reported. We describe the efficacy of Fab in the treatment of children with severe digitalis intoxication.

Methods. Twenty-nine children with intoxication due to digoxin (28) or digitoxin (1) received Fab at 21 participating hospitals between 1974 and 1986. Data were gathered about the patients' medical illnesses, doses and serum concentrations of digitalis, responses to Fab therapy, and outcomes.

Results. In the infants and young children with acute digoxin intoxication, the digoxin doses ranged from 0.30 to 0.96 mg per kilogram of body weight; two adolescents had severe intoxication after doses of only 0.20 and 0.26 mg per kilogram. The serum digoxin concentrations ranged from 3.0 to >100 ng per milliliter (mean, 13.8). Atrioventricular block (present in 22 patients [76 percent]) was the most common sign of toxicity. All the patients in this series had severe disturbances of cardiac rhythm, hyperkalemia (mean serum potassium concentration, 5.4 mmol per liter), or both. In 27 patients (93 percent), digitalis toxicity resolved after the administration of Fab. Of the 19 patients for whom data were available on the timing of the response to Fab, 15 responded within 180 minutes. Three patients required retreatment with Fab. Seven died of complications unrelated to the administration of Fab.

Conclusions. We recommend that Fab be used in the treatment of digitalis poisoning in infants and young children who have ingested ≥0.3 mg of digoxin per kilogram, who have underlying heart disease, or who have a serum digoxin concentration of ≥6.4 nmol per liter (≥5.0 ng per milliliter) in the elimination phase; and who also have a life-threatening arrhythmia, hemodynamic instability, hyperkalemia, or rapidly progressive toxicity. Adolescents, who are more sensitive to the toxic effects of digoxin than younger children, may require treatment with Fab after ingesting lower doses. (N Engl J Med 1992;326: 1739-44.)

DIGITALIS preparations, widely prescribed for children and adults with heart disease,[1-4] are potent medications that in excessive doses may have cardiac, gastrointestinal, neurologic, and metabolic effects. Although there are case series of digitalis poisoning in children,[5-8] few exposures result in severe toxicity. Lewander et al.[9] reported on 41 cases of digoxin poisoning in children that represented the combined experience of three pediatric academic medical centers over a 10-year period. None of these acutely poisoned children, whose serum digoxin concentrations ranged from 3.8 to 14.1 nmol per liter (3 to 11 ng per milliliter), had life-threatening dysrhythmias or died.[9]

In 1976, Smith et al. reported the successful use of digoxin-specific–antibody Fab fragments (Fab) to treat an adult with digoxin intoxication.[10] There have been numerous subsequent reports of adults successfully treated with Fab,[11-20] and there are reviews outlining indications for its use in adults.[21-25]

Although there are case reports of pediatric digitalis poisoning in which Fab therapy was used,[26-35] indications for the treatment of children with Fab remain unclear. The purpose of this article is to describe the characteristics and outcomes of 29 children and adolescents with digitalis intoxication who received Fab in a multicenter study and to offer recommendations for the use of Fab in children.

From the Department of Medicine, Children's Hospital, the Department of Pediatrics, Harvard Medical School, and the Massachusetts Poison Control System, all in Boston (A.D.W., F.H.L.); the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (T.W.S.); and the Burroughs Wellcome Company, Research Triangle Park, N.C. (T.W.).

Presented in part at the annual meeting of the American Association of Poison Control Centers, Tucson, Ariz., September 14, 1990.

METHODS

A study of the use of Fab (Digibind, Burroughs Wellcome) was instituted in 1974 with 21 participating medical centers (see Appendix). Children were enrolled if they had evidence of severe digoxin or digitoxin toxicity from one-time exposure or long-term dosing. Each patient's underlying cardiac disease, if any, and the medications with which the patient was being treated were recorded. Clinical evidence used to define digitalis intoxication included the presence of nausea and vomiting, mental alteration, sinus bradycardia, atrioventricular block, ventricular extrasystoles, asystole, ventricular tachycardia, ventricular fibrillation, supraventricular arrhythmias, and hyperkalemia. Fab was given to patients who had a clinical history compatible with digoxin poisoning, evidence of progressive symptoms and signs, and severe bradycardia, conduction defects, dysrhythmias, or digitalis-induced hyperkalemia (as manifested by a serum potassium concentration that was higher than 5.0 mmol per liter or was rising rapidly).

Base-line measurements of electrolytes, blood urea nitrogen, creatinine, and serum digoxin levels were obtained when circumstances permitted. If the serum digoxin concentration was reported to be "greater than" a given value, that value was used in calculations.

The dose of Fab was based on a stoichiometric ratio of the amount of Fab needed for a total-body burden of digoxin; the pediatric dose was extrapolated empirically from experience in adults.[36] For digoxin intoxication, the following formula was used: dose of Fab in milligrams = (serum digoxin concentration in nanograms per milliliter × 5.6 × the body weight in kilograms/1000) × 64. For digitoxin intoxication, the following formula was used: dose of Fab in milligrams = (serum digitoxin concentration in nanograms per milliliter × 0.56 × the body weight in kilograms/1000) × 64. If the steady-state serum digoxin concentration was unknown but there was reliable information on the amount ingested, the dose of Fab was based on the fact that 40 mg (one vial) of Fab binds approximately 0.66 mg of digoxin. Fab was infused intravenously; skin testing for hypersensitivity reactions was advised before admin-

istration. The time that Fab therapy began was noted, and when possible in the case of acute intoxications, the length of time from digoxin exposure to the initiation of Fab therapy was also recorded. Serum potassium levels were monitored for 48 to 72 hours after Fab therapy. Each patient's subsequent course and survival were also described.

Data were analyzed with both descriptive and inferential statistics. Univariate statistics for categorical data used the chi-square test or Fisher's exact test, and continuous variables were compared with use of Student's t-test.[37] All analyses consisted of two-tailed tests, with an alpha level of 0.05 used to demonstrate statistical significance. Informed consent for participation in the study was obtained from a parent of each child before enrollment; the study was approved by the investigational review board of each participating institution.

Results

Twenty-one medical institutions reported that 29 children were treated with Fab from 1974 through 1986. Information on three patients in this series (Patients 1, 2, and 16) has been published as case reports.[26,27,29]

Age, Sex, and Underlying Cardiac Problems

The age and sex of the children and the presence or absence of underlying heart disease are shown in Table 1. The median age was 1.5 years. Four patients were receiving other cardiac medications at the time of the intoxication (two propranolol, one isosorbide dinitrate, and one quinidine).

Dose and Serum Concentration of Digoxin

Eighteen exposures to digitalis (17 to digoxin and 1 to digitoxin) were classified as single-dose poisonings (resulting from the use of someone else's medication in 13 cases and from overdose with the patients' own medication in 5); in the other 11 cases, the patients were intoxicated during long-term use of their own medication. In 10 of the 17 acute digoxin intoxications, the amount taken was known (mean dose, 0.4 mg per kilogram of body weight). In two poisonings in adolescents, doses of 0.20 and 0.26 mg per kilogram were taken. In the six younger children without underlying heart disease (excluding Patient 12, whose case was complicated by quinidine intoxication), the doses of digoxin ranged from 0.30 to 0.96 mg per kilogram. The mean (±SD) serum digoxin concentration in 27 patients was 17.7±23.2 nmol per liter (13.8±18.1 ng per milliliter); 15 of the 16 children with underlying cardiac disease had serum digoxin concentrations above 6.4 nmol per liter (5.0 ng per milliliter).

Clinical Toxicity and Early Treatment

Table 2 lists the patients who had each of the 10 clinical symptoms and signs of digitalis toxicity. Atrioventricular block, manifested in 22 of the 29 patients (76 percent), was the most common sign of digitalis toxicity. Twenty-seven of the 29 patients had two or more signs of toxicity in addition to nausea and vomiting.

Of the 24 patients for whom data were available, all received antiarrhythmic medications, ventricular pacing, or both before Fab therapy. Four patients were reported to have received only ventricular pacing; six received only antiarrhythmic medications; three received both antiarrhythmic drugs and ventricular pacing; five received direct-current cardioversion, cardiopulmonary resuscitation, and antiarrhythmic medications; four received cardioversion, cardiopulmonary resuscitation, antiarrhythmic medications, and ventricular pacing; and two received both cardiopulmonary resuscitation and antiarrhythmic drugs.

Table 1. Demographic and Clinical Characteristics of 29 Children with Digitalis Poisoning.*

Patient No.	Age/Sex	Heart Disease†	Type of Intoxication	Digoxin Dose	Serum Digoxin Level‡
				mg	*ng/ml*
1	18 mo/M	None	Acute	11.0	17.1
2	30 mo/M	None	Acute	10.0	>100
3	18 yr/F	None	Acute	10.0	15.2
4	24 mo/M	None	Acute	6.0	25.0
5	30 mo/M	None	Acute	4.5	9.5
6	24 mo/M	None	Acute	6.25	13.2
7	2 mo/F	CA, PDA	Chronic	NA	5.2
8	11 days/F	Carotid AVM	Chronic	NA	>6.0
9	3 mo/F	Unspecified	Acute	NA	10.8
10	44 days/F	PDA	Chronic	NA	13.5
11	14 days/F	ASD, VSD	Chronic	NA	>5.0
12	24 mo/F	None	Acute	2.25	6.2
13	7 days/F	AS, HLV, CA	Chronic	NA	9.4
14	1 day/F	Myocarditis	Acute	NA	7.8
15	22 mo/M	None	Acute	NA	7.7
16	5 days/NA§	PDA	Chronic	NA	6.5
17	16 yr/F	None	Acute	12.5	>5.0
18	28 mo/M	None	Acute	NA	12.0
19	10 days/NA	AVM	Chronic	NA	8.0
20	18 days/M	CA	Chronic	NA	>5.0
21	2 days/F	PAT	Chronic	NA	17.9
22	16 yr/F	PAT	Acute	NA	14.0
23	48 mo/M	TA	Chronic	NA	9.0
24	18 yr/M	None	Acute	NA	6.5
25	30 mo/F	None	Acute	5.0	23.0
26	1 day/NA	PAT	Acute	NA	NA
27	24 mo/M	None	Acute	2.0¶	NA
28	3 days/M	DORV, IAA, SI	Acute	0.14	10.0
29	9 mo/F	Myocarditis	Chronic	NA	3.0

*NA denotes not available.

†CA denotes coarctation of the aorta, PDA patent ductus arteriosus, AVM arteriovenous malformation, ASD atrial septal defect, VSD ventricular septal defect, AS bicuspid aortic stenosis, HLV hypoplastic left ventricle, PAT paroxysmal atrial tachycardia, TA tricuspid atresia, DORV double-outlet right ventricle, IAA interrupted aortic arch, and SI situs inversus.

‡To convert digoxin values to nanomoles per liter, multiply by 1.28.

§The patient had ambiguous genitalia.

¶The patient received digitoxin.

Dose of Fab

Table 2 shows the doses of Fab in the 29 patients. In 10 patients with acute intoxication, the mean interval between the last dose of digoxin and Fab treatment was 20±23.5 hours (range, 6 to 84).

Efficacy of Fab

Tables 2 and 3 summarize the effectiveness of Fab therapy in resolving the manifestations of digitalis toxicity in the patients. In 27 patients (93 percent), all

Table 2. Fab Treatment in 29 Children with Digitalis Poisoning.

Patient No.	Dose of Fab*	Resolution										Outcome
		Sinus bradycardia	Atrioventricular block	Extrasystoles	Asystole	Ventricular tachycardia	Ventricular fibrillation	Supraventricular dysrhythmia	Nausea and vomiting	Hyperkalemia	Loss of consciousness	
	mg											
1	810	Yes	Yes								Yes	Alive
2	1000	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Alive
3	760			Yes				Yes	Yes	Yes	Yes	Alive
4	600		Yes						Yes	Yes		Alive
5	200	Yes	Yes					Yes	Yes		Yes	Alive
6	360	Yes	Yes					Yes	Yes		Yes	Alive
7	5	No	No		No		No			No	No	Died
8	40		Yes	Yes		Yes	Yes			Yes	Yes	Died
9	80	Yes				Yes	Yes			Yes		Alive
10	110	Yes	Yes		Yes						Yes	Died
11	15		Yes	Yes		Yes	Yes	Yes	Yes	Yes		Alive
12	120	Incomplete		Incomplete		Incomplete					No	Died
13	6		Yes			Yes				Yes		Alive
14	9		Yes					Yes				Died
15	28	Yes	Yes						Yes		Yes	Alive
16	160	Yes		Yes		Yes	Yes			Yes		Died
17	320		Yes				Yes		Yes		Yes	Alive
18	120	Yes	Yes						Yes		Yes	Alive
19	NA		Yes									Alive
20	50	Yes	Yes	Yes		Yes	Yes			Yes		Alive
21	25		Yes									Alive
22	240		Yes	Yes					Yes	Yes		Alive
23	80					Yes	Yes	Yes			Yes	Alive
24	200	Yes	Yes					Yes	Yes			Alive
25	80	Yes	Yes			Yes	Yes	Yes	Yes	Yes	Yes	Alive
26	40		Yes			Yes				Yes		Alive
27	160		Yes	Yes	Yes	Yes	Yes		Yes		Yes	Alive
28	NA			Yes			Yes	Yes		Yes		Died
29	20					Yes	Yes	Yes				Alive

*NA denotes not available.

symptoms and signs attributable to digitalis intoxication resolved. One child (Patient 12) improved but did not have a complete response; she had a concomitant quinidine overdose and a traumatic attempt at out-of-hospital resuscitation. Her dysrhythmias improved but were not abolished; she died one week later after failing to improve neurologically. One child (Patient 7) appeared to have no response to Fab; she had severe underlying heart disease. Three patients required a second dose of Fab within 4 to 16 hours after the initial dose. In one of these, the physicians mistakenly believed that Fab needed to be divided into two doses given four hours apart. In the second, initial improvement in cardiac toxicity after the administration of Fab was not sustained; this patient also had concomitant quinidine intoxication that complicated treatment. In the third patient, cardiac toxicity resolved after the administration of Fab, but 24 hours later the patient had an episode of ventricular fibrillation without explanation. Although conversion to normal sinus rhythm was quickly achieved, a second dose of Fab was administered empirically.

In 18 patients the serum potassium concentrations were known both before Fab was given and within four hours after its administration. The mean serum potassium concentration after Fab treatment (4.3±1.2 mmol per liter) was significantly lower than the concentration before treatment (5.4±1.6 mmol per liter; range, 3.5 to 10.3; $P<0.001$).

Fourteen patients had impaired renal function (defined as a serum creatinine level of 88 μmol per liter [1.0 mg per deciliter] or higher in children at least one year old and a level of more than 62 μmol per liter [0.7 mg per deciliter] for younger children) that was not associated with a higher serum digoxin concentration ($P = 0.17$) or increased mortality ($P = 0.34$), but

Table 3. Clinical Manifestations of Digitalis Poisoning in 29 Children and Resolution with Fab Treatment.

Manifestation	Before Fab	After Fab
	no. (%) with manifestation	*no. (%) with resolution*
Atrioventricular block	22 (76)	21 (95)
1st degree	3 (10)	3 (100)
2nd degree	10 (34)	9 (90)
3rd degree	9 (31)	9 (100)
Sinus bradycardia	14 (48)	12 (86)
Ventricular tachycardia	13 (45)	12 (92)
Ventricular fibrillation	13 (45)	12 (92)
Supraventricular arrhythmia	11 (38)	11 (100)
Ventricular extrasystoles	10 (34)	9 (90)
Ventricular asystole	3 (10)	2 (67)
Extracardiac		
Altered mental status	15 (52)	13 (87)
Hyperkalemia	14 (48)	13 (93)
Nausea and vomiting	13 (45)	13 (100)

that was associated with underlying cardiac disease ($P<0.001$) and was marginally associated with higher serum potassium levels ($P = 0.06$).

There were seven deaths among the children in this series. One child (Patient 28) died of renal failure, progressive sepsis, and necrotizing enterocolitis nine days after the administration of Fab; another (Patient 14) died with candidal myocarditis and sepsis; a third (Patient 10) died six days after Fab therapy of respiratory arrest, renal failure, and complications of the original cardiac arrest. A fourth child (Patient 12), the only one to die who did not have heart disease, was declared brain-dead from a cardiac arrest that occurred before the administration of Fab; this patient had concomitant quinidine toxicity (serum quinidine concentration, 22 μg per milliliter). A fifth child (Patient 16), who had multiple congenital defects, died after an intracerebral hemorrhage from a congenital arteriovenous malformation seven days after Fab therapy. A sixth child (Patient 8), with high-output cardiac failure caused by a cavernous hemangioma and arteriovenous malformation of the carotid artery, died five days after Fab therapy from sepsis that occurred during peritoneal dialysis to treat renal failure sustained early in life. The seventh child who died (Patient 7) had a history of perinatal asphyxia, ischemic encephalopathy, respiratory distress syndrome, renal failure, and cardiac arrest, all of which preceded the diagnosis of digoxin toxicity. She died after a persistently downhill course marked by disseminated intravascular coagulation and possible sepsis. No new toxicity related to digitalis was noted in any of these patients after the completion of therapy with Fab.

Time to Response

Fifteen of the 19 patients (79 percent) for whom response times were available had a complete resolution of digitalis toxicity within 180 minutes of Fab therapy; the median time to a complete response was 90 minutes (range, 1 to 2160). The median time to an initial response after Fab (in 16 patients) was 25 minutes (range, 1 to 240).

Adverse Effects of Fab Therapy

Fourteen patients received sensitivity testing before Fab treatment; no allergic reactions to Fab were reported. No patient had an exacerbation of dysrhythmia or worsening heart failure due to the abrupt withdrawal of digitalis. One patient had both hypokalemia (potassium level, 2.0 mmol per liter) and an associated dysrhythmia that were related to Fab therapy and resolved with supplemental intravenous potassium. One neonate had transient apnea that may have been related to Fab treatment or to the insertion of the needle before the administration of Fab.

Discussion

Severe digitalis poisoning is uncommon in children and adolescents, although cases continue to be seen sporadically. The intoxication differs from that in adults because children with healthy hearts seem more resistant to the toxic effects of digitalis.[9,38] Few children become ill with life-threatening symptoms; those who do either have taken massive overdoses or have severe preexisting cardiac disease. Whereas in adults ventricular ectopy is often the earliest cardiac sign of digitalis toxicity,[20] serious toxicity in the children in our series was more often heralded by sinus bradycardia or varying degrees of atrioventricular conduction block. Although the overall mortality rate of the children in this series and their rate of response to Fab therapy were similar to those in adults,[20] it is possible that young children, with more resilient hearts, can be successfully revived with Fab much later in the course of digitalis intoxication than can adults.

In contrast to the children studied by Lewander et al.,[9] some children in the present study had chronic digoxin intoxication. Our patients were also more severely intoxicated and frequently had other incapacitating medical problems; it is not surprising that we observed a 24 percent mortality rate, whereas Lewander et al. observed no deaths.[9] Our enrollment protocol and the time needed to obtain Fab for a patient in the early years of the study explain the sometimes long interval between the diagnosis of digitalis intoxication and Fab therapy.

We observed a significant decrease in the serum potassium concentration after the administration of Fab. The inhibition of the membrane-bound–sodium pump by digitalis results in a loss of intracellular potassium to the extracellular space, whence it is excreted by the kidney, causing elevated serum potassium concentrations but an overall depletion.[39] When toxicity is rapidly reversed by Fab, the total-body potassium deficit is reflected as hypokalemia. This should prompt clinicians to monitor their patients' serum potassium concentrations serially, beginning immediately after the administration of Fab. No allergic reactions to Fab were noted, but this does not eliminate the need for vigilance when Fab is used in children.

Clinicians are cautioned that measurements of serum digoxin concentrations in children do not necessarily correlate with the effects of the drug. Also, the distribution of digoxin dictates that there must be sufficient time (four to six hours after a dose) for equilibration between compartments before serum levels are meaningful. After Fab is given, the serum digoxin concentration cannot be used to judge continuing tissue-level exposure to the drug, since digoxin that has been bound by Fab contributes to the level. Newer techniques of measuring unbound digoxin may be more useful,[40] but decisions are more rationally based on the patients' clinical characteristics, particularly the seriousness of their rhythm disturbances.

We suggest that Fab be reserved for children in

whom severe overdosing with digoxin is known with reasonable certainty to have occurred and that both clinical and laboratory measures be incorporated to assess the urgency of the clinical situation. It has been suggested that in young children without heart disease the ingestion of more than 4 mg of digoxin is likely to be life-threatening.[41] On the basis of these published results and our own experience (involving six young children who became extremely ill after digoxin doses of 0.30 to 0.96 mg per kilogram), we suggest that the ingestion of 0.3 mg of digoxin or more per kilogram by a young child without heart disease portends serious toxicity. Adolescents, perhaps more similar to adults in their cardiac sensitivity to digoxin, may become symptomatic at even lower doses. In 15 of the 16 children with underlying heart disease in our series, serum digoxin levels were higher than 6.4 nmol per liter; these levels were also accompanied by signs of substantial digitalis toxicity.

Given the success of Fab therapy in this study, we support its earlier use, perhaps before cardiac pacing or treatment with antiarrhythmic agents, in children with confirmed digitalis intoxication who present with potentially life-threatening dysrhythmias, hemodynamic instability, or rapidly rising serum potassium levels, and in those with massive ingestions. Children require close monitoring after Fab therapy; a second dose may be necessary if toxicity attributable to digitalis recurs or fails to resolve.

Appendix

The institutions (and chief investigators) participating in the study were as follows: University of Alabama at Birmingham (V.J. Plumb); Health Sciences Center, University of Arizona at Tucson (F.I. Marcus); Veterans Affairs Health Center, Little Rock, Ark. (J.E. Doherty); UCLA School of Medicine, Los Angeles (K.I. Shine); Moffitt Hospital, San Francisco (K. Chatterjee and W.W. Parmley); Health Sciences Center, University of Colorado, Denver (A.S. Nies); Yale University School of Medicine, New Haven, Conn. (D. Rutlen); University of Miami School of Medicine, Miami (R.J. Myerburg); Emory University School of Medicine, Atlanta (R.C. Schlant); University of Chicago, Chicago (H.A. Fozzard); Indiana University School of Medicine, Indianapolis (A. Watanabe); Sinai Hospital, Baltimore (R. Veltri); Brigham and Women's Hospital, Boston (T.W. Smith); Massachusetts General Hospital, Boston (E. Haber and H. Garan); Washington University School of Medicine, St. Louis (A.S. Jaffee); College of Physicians and Surgeons, Columbia University, New York (V.P. Butler, Jr.); Duke University Medical Center, Durham, N.C. (R.M. Califf); University of Cincinnati Medical Center, Cincinnati (R.J. Toltzis); University of Pennsylvania Hospital, Philadelphia (F.E. Marchlinski); Baylor College of Medicine, Houston (R.J. Luchi); and University of Texas Health Sciences Center, Dallas (J.T. Willerson).

References

1. Smith TW. Should digoxin be the drug of first choice after diuretics in chronic heart failure? II. Protagonist's viewpoint. J Am Coll Cardiol 1988; 12:267-71.
2. Doherty JE. Clinical use of digitalis glycosides: an update. Cardiology 1985;72:225-54.
3. Smith TW. Digitalis: mechanisms of action and clinical use. N Engl J Med 1988;318:358-65.
4. Soyka LF. Pediatric clinical pharmacology of digoxin. Pediatr Clin North Am 1981;28:203-16.
5. Fowler RS, Rathi L, Keith JD. Accidental digitalis intoxication in children. J Pediatr 1964;64:188-200.
6. Hastreiter AR, van der Horst RL, Chow-Tung E. Digitalis toxicity in infants and children. Pediatr Cardiol 1984;5:131-48.
7. Duke M. Atrioventricular block due to accidental digoxin ingestion treated with atropine. Am J Dis Child 1972;124:754-6.
8. McNamara DG, Brewer EJ Jr, Ferry GD. Accidental poisoning of children with digitalis. N Engl J Med 1964;271:1106-8.
9. Lewander WJ, Gaudreault P, Einhorn A, Henretig FM, Lacouture PG, Lovejoy FH Jr. Acute pediatric digoxin ingestion: a ten-year experience. Am J Dis Child 1986;140:770-3.
10. Smith TW, Haber E, Yeatman L, Butler VP Jr. Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. N Engl J Med 1976;294:797-800.
11. Smith TW, Butler VP Jr, Haber E, et al. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. N Engl J Med 1982;307:1357-62.
12. Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. J Am Coll Cardiol 1985;5:Suppl A:118A-123A.
13. Smolarz A, Roesch E, Lenz E, Neubert H, Abshagen P. Digoxin specific antibody (Fab) fragments in 34 cases of severe digitalis intoxication. J Toxicol Clin Toxicol 1985;23:327-40.
14. Schaumann W, Kaufmann B, Neubert P, Smolarz A. Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. Eur J Clin Pharmacol 1986;30:527-33.
15. Clarke W, Ramoska EA. Acute digoxin overdose: use of digoxin-specific antibody fragments. Am J Emerg Med 1988;6:465-70.
16. Spiegel A, Marchlinski FE. Time course for reversal of digoxin toxicity with digoxin-specific antibody fragments. Am Heart J 1985;109:1397-9.
17. Cooper DM, Maloney JD, Cooper LA, Hodgman JR, Castle LW. Immunological reversal of digitalis toxicity by Fab fragments of digoxin-specific antibodies. Cleve Clin J Med 1987;54:43-8.
18. Desantola JR, Marchlinski FE. Response of digoxin toxic atrial tachycardia to digoxin-specific Fab fragments. Am J Cardiol 1986;58:1109-10.
19. Wieland JM, Marchlinski FE. Electrocardiographic response of digoxin-toxic fascicular tachycardia to Fab fragments: implications for a tachycardia mechanism. PACE Pacing Clin Electrophysiol 1986;9:727-38.
20. Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: final report of a multicenter study. Circulation 1990;81: 1744-52.
21. Zalcberg JR. Monoclonal antibodies to drugs: novel diagnostic and therapeutic reagents. Pharmacol Ther 1985;28:273-85.
22. Hursting MJ, Raisys VA, Opheim KE. Drug-specific Fab therapy in drug overdose. Arch Pathol Lab Med 1987;111:693-7.
23. Martiny SS, Phelps SJ, Massey KL. Treatment of severe digitalis intoxication with digoxin-specific antibody fragments: a clinical review. Crit Care Med 1988;16:629-35.
24. Stolshek BS, Osterhout SK, Dunham G. The role of digoxin-specific antibodies in the treatment of digitalis poisoning. Med Toxicol Adverse Drug Exp 1988;3:161-71.
25. Digoxin antibody fragments for digitalis toxicity. Med Lett Drugs Ther 1986;28:87-8.
26. Murphy DJ Jr, Bremner WF, Haber E, Butler VP Jr, Smith TW, Gaum WE. Massive digoxin poisoning treated with Fab fragments of digoxin-specific antibodies. Pediatrics 1982;70:472-3.
27. Zucker AR, Lacina SJ, DasGupta DS, et al. Fab fragments of digoxin-specific antibodies used to reverse ventricular fibrillation induced by digoxin ingestion in a child. Pediatrics 1982;70:468-71.
28. Rossi R, Leititis JU, Hagel KJ, Smolarz A, Brandis M. Severe digoxin intoxication in a child treated by infusion of digoxin-specific Fab-antibody-fragments. Eur J Pediatr 1984;142:138-40.
29. Presti S, Friedman D, Saslow J, et al. Digoxin toxicity in a premature infant: treatment with Fab fragments of digoxin-specific antibodies. Pediatr Cardiol 1985;6:91-3.
30. Autret E, Chantepie A, Bloc D, et al. Utilisation des anticorps anti-digoxine au cours d'une intoxication digitalique chez un nourrisson. Arch Fr Pediatr 1985;42:803-4.
31. Hussain MI, Murray R, Williams BP. Purified digoxin specific Fab fragments: their use in preventing serious complications of digoxin toxicity. Indiana Med 1985;78:780-1.
32. Rose SR, Gorman RL, McDaniel J. Fatal digoxin poisoning: an unsuccessful resuscitation with use of digoxin-immune Fab. Am J Emerg Med 1987; 5:509-11.
33. Kearns GL, Moss MM, Clayton BD, Hewett DD. Pharmacokinetics and efficacy of digoxin specific Fab fragments in a child following massive digoxin overdose. J Clin Pharmacol 1989;29:901-8.
34. Nollet H, Verhaaren H, Stroobandt R, Belpaire F. Delayed elimination of digoxin antidotum determined by radioimmunoassay. J Clin Pharmacol 1989;29:41-5.

35. Kaufman J, Leikin J, Kendzierski D, Polin K. Use of digoxin Fab immune fragments in a seven-day-old infant. Pediatr Emerg Care 1990;6:118-21.
36. American Hospital Formulary Service. Digoxin immune Fab. In: AHFS drug information 90. Bethesda, Md.: American Society of Hospital Pharmacists, 1990:1885-9.
37. Colton T. Statistics in medicine. Boston: Little, Brown, 1974.
38. Wenger TL, Smith TW. Lethal dose of digoxin in humans without heart disease. Circulation 1986;74:Suppl II:II-38. abstract.
39. Hougen TJ, Lloyd BL, Smith TW. Effects of inotropic and arrhythmogenic digoxin doses and of digoxin-specific antibody on myocardial monovalent cation transport in the dog. Circ Res 1979;44:23-31.
40. Hursting MJ, Raisys VA, Opheim KE, Bell JL, Trobaugh GB, Smith TW. Determination of free digoxin concentrations in serum for monitoring Fab treatment of digoxin overdose. Clin Chem 1987;33:1652-5.
41. Wenger T, Butler V, Haber E, Smith T. Life-threatening digoxin toxicity in children: treatment with digoxin specific Fab fragments. J Am Coll Cardiol 1986;7:Suppl A:74A. abstract.

IMAGES IN CLINICAL MEDICINE

Images in Clinical Medicine, a new *Journal* feature, presents a variety of clinically important visual images, emphasizing those a doctor might encounter in an average day at the office, the emergency ward, or the hospital. If you have an original unpublished, high-quality color or black-and-white photograph of a typical image that you would like considered for publication, send it with a brief descriptive legend to Kim Eagle, M.D., Massachusetts General Hospital, Cardiac Unit, ACC 4, 15 Parkman St., Boston, MA 02114. Two 5-by-7-inch prints should be sent. If you submit a slide, please send a 5-by-7-inch print along with it. No more than two persons will receive credit for submitting an image.