Treatment of 150 Cases of Life-Threatening Digitalis Intoxication With Digoxin-Specific Fab Antibody Fragments

Final Report of a Multicenter Study

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One hundred fifty patients with potentially life-threatening digitalis toxicity were treated with digoxin-specific antibody fragments (Fab) purified from immunoglobulin G produced in sheep. The dose of Fab fragments was equal to the amount of digoxin or digitoxin in the patient's body as estimated from medical histories or determinations of serum digoxin or digitoxin concentrations. The youngest patient received Fab fragments within several hours of birth, and the oldest patient was 94 years old. Seventy-five patients (50%) were receiving long-term digitalis therapy, 15 (10%) had taken a large overdose of digitalis accidentally, and 59 (39%) had ingested an overdose of digitalis with suicidal intent. The clinical response to Fab was unspecified in two cases, leaving 148 patients who could be evaluated. One hundred nineteen patients (80%) had resolution of all signs and symptoms of digitalis toxicity, 14 (10%) improved, and 15 (10%) showed no response. After termination of the Fab infusion, the median time to initial response was 19 minutes, and 75% of the patients had some evidence of a response by 60 minutes. There were only 14 patients with adverse events considered to possibly or probably have been caused by Fab; the most common events were rapid development of hypokalemia and exacerbation of congestive heart failure. No allergic reactions were identified in response to Fab treatment. Of patients who experienced cardiac arrest as a manifestation of digitalis toxicity, 54% survived hospitalization. Reasons for partial responses and nonresponses, in descending order of frequency, were underlying heart disease that was the true cause of some of the presumed manifestations of suspected digitalis toxicity, too low a dose of Fab, and treatment of patients who were already moribund. Thus, a treatment response can be expected in at least 90% of patients with solid evidence of advanced and potentially life-threatening digitalis toxicity. (Circulation 1990;81:1744–1752)

Advanced digitalis intoxication can have a fatal outcome, particularly in patients with underlying cardiac dysfunction or those who have ingested massive doses of digitalis accidentally or with suicidal intent. Important possible clinical findings after massive digitalis ingestion include hyperkalemia, atrioventricular block, and malignant ventricular tachyarrhythmias. Although hemodialysis or hemoperfusion may help control hyperkalemia, these approaches are generally inadequate for treatment of advanced toxicity because of the extensive tissue distribution of digoxin and are of limited value for prompt reversal of life-threatening toxicity. The need to improve treatment of advanced digitalis intoxication was an important stimulus for the development of a specific means for reversal of established cardiac glycoside effects.

Exogenous antibodies have been used in the management of many disease states, initially including diphtheria and tetanus and more recently including organ transplant rejection. The concept of therapeutic use of specific exogenous antibodies was extended to the treatment of digitalis intoxication by the
development of antibodies with a high affinity and specificity for digoxin. The initial clinical report of the use of purified digoxin-specific Fab fragments for treatment of advanced digoxin toxicity occurred in 1976. Based on several such favorable responses, a multicenter clinical trial using purified digoxin-specific Fab fragments was initiated. Interim reports were published when 26 and 63 patients had been enrolled; the present report is the summary of this prospective multicenter study of 150 patients with life-threatening digitalis intoxication who were treated with purified digoxin-specific Fab fragments.

Methods

Preparation of Purified Fab Fragments of Digoxin-Specific Antibodies

As described previously, sheep were immunized with a digoxin-serum albumin conjugate and antisera were collected from animals that responded with high titers of antibody with high affinity and specificity for digoxin. Intact antibody was cleaved with papain, yielding digoxin-specific Fab fragments. The Fab fragments were isolated and purified by passing the papain digest through an affinity chromatography step. The final purified Fab fragments were determined to be both sterile and pyrogen free by standard tests, and the material was then lyophilized in 40-mg aliquots. Material prepared by this method is stable under recommended storage conditions for at least 3 years (package insert for Digoxin Immune Fab [ovine], Digibind®).

Clinical Trial Design

An open-label multicenter clinical trial of Fab treatment for life-threatening digitalis intoxication was then undertaken. In brief, 21 geographically distributed U.S. medical centers ("Appendix") were supplied with Fab (designated BB Investigational New Drug 874 by the U.S. Food and Drug Administration). A common protocol was used that was approved by each institutional committee for the protection of human subjects. The goals of the investigation were to evaluate the ability of Fab fragments to reverse the toxic effects of digitalis and simultaneously provide sufficient safety information to warrant approval of the drug for treating patients with potentially life-threatening digitalis toxicity. Secondary objectives were to define the pharmacokinetics and pharmacodynamics of Fab fragment treatment and to assess the antigenicity of purified polyclonal sheep Fab fragments in humans. The two key inclusion criteria were that patients had actual or potentially life-threatening cardiac rhythm disturbances, hyperkalemia, or both caused by digitalis intoxication and that these conditions were refractory to or likely to be refractory to treatment with conventional therapeutic modalities.

After informed consent was obtained from the patient or next of kin, screening for hypersensitivity was performed by a skin test and a small (1 mg) intravenous test dose. Whenever possible, the Fab fragments were administered intravenously during 2 hours in the early stages of the protocol and later in the study during 15–30 minutes (in isotonic saline) after having been passed through a sterile 0.22-μm membrane filter. The dose of Fab fragments was calculated to be equal on a mole-for-mole basis to the amount of digoxin or digitoxin in the patient’s body, estimated from the medical history or determinations of serum digoxin or digitoxin concentrations (Table 1). Clinical and laboratory data were recorded before, during, and after Fab treatment. Serum glycoside concentrations were measured by immunoassay before and after the administration of Fab as previously described. When clinically feasible, multiple blood and urine samples were obtained for more detailed assessment of the effects of Fab administration on digoxin pharmacokinetics using special procedures to determine total and free glycoside concentrations.

Recorded on each patient’s case report form was the response to Fab treatment for sinus bradycardia, atrioventricular block, ventricular premature depolarizations, asystole, ventricular tachycardia, ventricular fibrillation, supraventricular tachyarrhythmias characteristic of digitalis intoxication, nausea and vomiting, hyperkalemia, and central nervous system disturbances, all signs of digitalis toxicity. An overall response to therapy with digoxin-specific antibody fragments was assigned to each patient using the following scheme. The term “resolved” indicated complete resolution of all signs and symptoms of toxicity; life-threatening cardiac arrhythmias had to

<table>
<thead>
<tr>
<th>Calculation of equimolar dose of digoxin-specific Fab fragments</th>
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<tr>
<td>Calculation of body load of digoxin</td>
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<tr>
<td>Ingested amount (mg)×bioavailability of digoxin tablets =mg×0.8</td>
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<tr>
<td>Serum digoxin concentration (ng/ml)×5.6×weight (kg)</td>
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<tr>
<td>Calculation of dose Fab fragments</td>
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<tr>
<td>MW Fab (50,000) =64×body load (mg)=Fab dose (mg)</td>
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<tr>
<td>MW digoxin (781)</td>
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<tr>
<td>Body load of digoxin (mg) =vials of Fab fragments</td>
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<tr>
<td>0.6 mg neutralized/40 mg vial</td>
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<tr>
<td>*Volume of distribution of digoxin in average adult (U/kg).</td>
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Example

Serum digoxin concentration (SDC)=2 ng/ml on maintenance therapy

Weight=65 kg

Ingested amount=18 mg digoxin (tablets)

Body load= [ingested amount×0.8] + [(SDC×5.6×65)]

=14.4+0.728=15.128 mg

Dose of Fab fragments=64×15=960 mg

Number of vials= 15/0.6 = 25
resolve during an accelerated time course (within minutes to a few hours after treatment). In addition, evidence was sought for rapid resolution of hyperkalemia by frequent measurements of serum potassium levels. The term “improved” was used when some but not all of the signs of suspected toxicity resolved or improved. The term “no response” indicated the failure of any of the signs of toxicity to improve.

Statistics

The data were described by the median plus lower and upper quartiles rather than the mean±SD because in many instances the data were not symmetrically distributed. The lower and upper quartiles describe the 25th and 75th percentiles of the data points; that is, one fourth of the data will be less than or equal to the lower quartile and one fourth will be equal to or more than the upper quartile.

A logistic regression model was used to assess the relation between covariates and the probability of a slow response to Fab. A slow response to treatment was defined as an initial response time of more than 60 minutes after Fab administration, which represented the upper quartile of the sample. Covariates examined were the presence or absence of cardiac disease, setting of digitalis toxicity (long-term therapeutic use vs. acute ingestion), and predefined age categories.

The significance of changes in serum potassium between pretreatment and posttreatment values (4±2 hours after Fab administration) was evaluated with a two-tailed Wilcoxon signed-rank test. Differences were considered significant at p less than 0.05.

Results

Clinical Characteristics of Patients

Between December 1974 and April 1986, 150 patients received digoxin-specific antibody fragments. Because patients were often treated under urgent clinical circumstances, complete data were not always available for every patient. Seventy-seven patients were female, 69 were male, and one infant had ambiguous genitalia. Gender was not recorded in three cases. Twenty-five of the patients were children between the ages of 1 day and 4 years (median age, 3 months). The remaining 125 patients were 16 years old or older (median age, 65 years). One fourth (lower quartile) of the adults were 54 years old or younger, and one fourth (upper quartile) were 75 years old or older. The youngest patient treated in the protocol received Fab fragments within several hours of birth, and the oldest patient was 94 years old. One hundred twenty-one patients (81%) had concurrent cardiac disease.

One hundred thirty-nine patients (93%) suffered from digoxin intoxication, and five (3%) suffered from digitoxin intoxication; the type of glycoside was unspecified in the remaining patients. Seventy-five patients (50%) were receiving long-term digitalis therapy, 15 (10%) had taken a large overdose of digitalis accidentally, and 59 (39%) had ingested an overdose of digitalis with suicidal intent. In 53 cases of single overdoses (accidental or suicidal), the ingested dose could be estimated from the clinical information; the median ingested dose of digoxin was 12.5 mg (range, 0.14–62.5 mg) and of digitoxin was 12.0 mg (range, 2.0–40.0 mg).

The cardiovascular manifestations of digitalis toxicity were known in 148 cases and consisted of second- or third-degree atrioventricular block in 79 patients (53%), ventricular tachycardia in 68 patients (46%), ventricular fibrillation in 49 patients (33%), ventricular asystole in 16 patients (11%), and hyperkalemia in 56 patients (37%) (Figures 1 and 2). Attempted conventional therapeutic interventions included ventricular pacing in 72 patients (48%), DC cardioversion in 31 patients (21%), cardiopulmonary resuscitation in 38 patients (26%), antiarrhythmic drug therapy in 81 patients (54%), atropine in 33 patients (22%), calcium channel antagonists in six patients (4%), and β-adrenoceptor blockers in 11 patients (7%). In addition, standard measures for treatment of hyperkalemia were used, including glucose and insulin, bicarbonate infusions, and enemas with potassium-binding resins.

At the time of enrollment into the study, the median serum digoxin concentration of the patients was 8.0 ng/ml (lower quartile, 5.0; upper quartile, 13.1). The median serum digitoxin concentration was 156 ng/ml. The median digoxin-specific Fab fragment dose was 200 mg (120–480 mg); the highest dose given was 1,600 mg (40 vials). Fab fragments were administered intravenously during a median of 20 minutes (20–30 minutes). The median time from ingestion of glycoside to initiation of Fab treatment was 12 hours (7–25 hours).

In 121 patients, serum creatinine measurements were available before initiation of Fab treatment. Based on a definition of 1 mg/dl or less in infants and children and 1.5 mg/dl or less in adults, 48 patients (40%) had normal function and 73 (60%) had abnormal function. Of 18 children who had a baseline serum creatinine, 11 had abnormal values ranging...
from 1.2 to 3.1 mg/dl (median, 2.2 mg/dl). In 62 adults with an abnormal baseline creatinine, the median was 2.8 and the upper quartile had levels of 4.1 or more. Five patients were on dialysis when Fab was administered.

Response to Treatment With Digoxin-Specific Fab Fragments

Although intradermal and intravenous sensitivity testing before Fab infusion were recommended, clinical circumstances did not always permit these screening maneuvers. The results of skin testing were reported in 94 cases and were nearly uniformly negative; only one patient had erythema but without wheal or induration. None of the 77 patients who underwent intravenous testing exhibited a reaction, including the patient who had erythema on intradermal testing. No allergic reactions were identified during or after administration of the therapeutic dose of Fab fragments.

The clinical response to Fab was unspecified in two cases, leaving 148 patients who were evaluated (Figure 1). One hundred nineteen patients (80%) resolved all signs and symptoms of digitalis toxicity, 14 (10%) improved, and 15 (10%) showed no response. All of the five patients with digitoxin toxicity were complete responders. Four of the five patients on dialysis were complete responders, and the fifth improved after Fab administration.

The times to initial improvement in signs and symptoms of toxicity and to complete response were analyzed in 80 patients for whom information was available. Therapeutic responses noted during Fab infusion were assigned a 0-minute response time. The time to initial response was 19 minutes (0–60 minutes) from termination of the infusion. The time to complete response was 88 minutes (30–360 minutes). Thus, most patients who responded had clinically evident improvement by 1 hour after termination of infusion and complete response by 4 hours. The time to initial response was analyzed to determine whether the presence of concurrent cardiac disease, type of digitalis intoxication (long-term dosing vs. single overdose), and age (≤70 vs. >70 years and ≤12 vs. >12 years) were associated with a particularly slow response (>60 minutes after Fab administration; i.e., the upper quartile of the sample). None of the above three factors was significantly associated with a particularly slow initial response.

Partial responders and nonresponders were carefully evaluated for causes of less-than-complete resolution. Of the 14 patients classified as improved but in whom not all of the potential signs of putative toxicity resolved, two were moribund at the time of treatment, two received an inadequate dose of Fab due to limited supplies of the drug, two had concomitant toxicities with other cardiovascular drugs, and eight had coincident medical conditions that caused signs and symptoms initially ascribed to digitalis. Of the 15 cases of failure to respond to Fab, five were moribund at the time of treatment (one also received an inadequate dose of Fab), four were believed in retrospect to definitely not be suffering from digitalis toxicity, five were believed in retrospect to probably not be suffering from digitalis toxicity, and one was classified as a true nonresponder. The true nonre-
sponder was a 71-year-old, 40-kg woman on long-term digoxin treatment who developed intermittent high-grade atrioventricular block and malignant ventricular tachyarrhythmias in association with a serum digoxin concentration of 9.7 ng/ml. She was given 130 mg Fab (calculated dose, 148 mg), but high-grade atrioventricular block recurred 1 hour after the infusion. Her signs of digitalis toxicity resolved during a time course consistent with the natural history of her condition, not during the accelerated time course observed in the patients who were classified as responders.

Of the 150 patients, 107 (71%) survived to hospital discharge. Of the 43 who died, 20 had complete resolution of toxicity, 12 had improvement in signs of toxicity, and 11 had no response to Fab. The majority of the 43 deaths could be ascribed to underlying heart disease still present after resolution of digitalis toxicity or to other medical illnesses. Of the patients who were moribund before treatment with Fab fragments, the majority ultimately died of the consequences of neurologic and cardiovascular complications of their protracted pretreatment cardiac arrest or low output status. However, several of these patients demonstrated remarkable resolution of both their digitalis toxicity and their apparently moribund state. Notably, of the 56 patients whose digitalis toxicity culminated in cardiac arrest, 30 (54%) survived hospitalization after treatment with Fab fragments.

**Laboratory Evidence of Response to Fab Fragments**

A dramatic fall in serum potassium concentration can occur after reversal of severe digitalis toxicity because reversal of Na,K-ATPase inhibition tends to reestablish rapidly the normal transmembrane potassium gradient. Serum potassium concentrations before and 2 and 6 hours after treatment were available in 82 cases and indicated a significant reduction from a median of 5.0 to 4.1 meq/l (p=0.0001). This reduction occurred despite concomitant administration of potassium chloride in some cases. The time course of decline in serum potassium concentration was consistent with the rapid time course of arrhythmia response; that is, declines in serum potassium were often noted within 1 hour and appeared complete within 4 hours (Figure 3).

**Adverse Responses to Treatment With Digoxin-Specific Fab Fragments**

Adverse events related to Fab administration were initially raised as a possibility in 32 of the 150 patients. In only 14 of these 32 patients were the reported adverse events judged to be possibly or probably caused by Fab. Relatively rapid development of hypokalemia was observed in six of the 150 patients (4%). Four patients (3%) experienced exacerbations of congestive heart failure after Fab treatment; this was thought possibly to have been caused by loss of inotropic support from digitalis therapy. However, because many patients with poor ventricular function also received multiple other treatments, it is not possible to determine a true incidence of decompensation with emergence of overt heart failure in this patient population. Two patients suffered mild hypotensive episodes; each had been hemodynamically unstable before the Fab infusion. Another patient complained of nausea just after Fab treatment; this patient also had nausea as a clinical manifestation of digitalis toxicity before treatment. A neonate, several hours old, developed transient apnea during the Fab infusion.

The dominant pattern of serial serum creatinine measurements was one of stable or improved renal function after Fab therapy. Three patients with pretreatment serum creatinine levels in the normal range had posttreatment values of 1.5 mg/dl or more. In all three cases, the rise in serum creatinine was clearly ascribable to decreased renal perfusion before Fab. One patient was described as oliguric, and the other two had cardiac arrests before Fab treatment.

**Serum Digoxin Measurements After Fab Treatment**

Laboratory evidence for the binding of digoxin or digitoxin by the Fab fragments was available in the posttreatment serum drug concentrations in 11 patients studied early in the trial. In all cases, the concentration of free, pharmacologically active digoxin or digitoxin in the serum fell to near-zero levels within 1–2 minutes of administration of Fab fragments. The total serum digoxin concentration, reflecting pharmacologically inactive antibody-bound drug, rose rapidly to values 10- to 20-fold those before treatment (Figure 4). Equilibrium dialysis or ultrafiltration are required to measure the free digoxin concentration after treatment because in a patient’s serum, Fab interferes with conventional assay techniques.12,13

**Discussion**

Based on a substantial body of experimental evidence demonstrating antibody-mediated reversal of
cardiac glycoside effects in experimental models extending from isolated membrane Na,K-ATPase preparations to intact animals, it was predicted nearly two decades ago that an immunochemical approach might be clinically successful in reversing digitalis toxicity. The advantages of the smaller size of the Fab fragment (molecular weight, 50,000) include a more rapid onset of action due to enhanced diffusion into the interstitial space and, in patients with normal renal function, relatively rapid clearance of digoxin bound to Fab fragments in the urine (half-life, ~16 hours). The latter point minimizes the chance of late release of bound digoxin and reemergence of toxicity. Although the average intrinsic affinity constant for digoxin is 30- to 100-fold that for digitoxin, the affinity for the latter was still considered high enough to permit evaluation of the clinical efficacy of digoxin-specific Fab antibody fragment treatment for life-threatening intoxication with either digoxin or digitoxin. This was confirmed by our observations in the five patients suffering from digitoxin toxicity.

The proposed sequence of events that occurs after infusion of digoxin-specific Fab fragments includes rapid binding of intravascular digoxin and diffusion of the Fab fragments into the interstitial space with binding of free digoxin. The decreased extracellular free digoxin creates a concentration gradient that promotes egress of tissue stores of digoxin into the extracellular fluid, where it is also rapidly bound. Thus, the free digoxin molecules that dissociate from membrane receptors are subsequently rapidly bound and cannot reassociate with the inhibitory site on the α-subunit of Na,K-ATPase. This dissociation event and the subsequent step of binding to Fab are critically important processes in the reversal of digitalis toxicity. Characteristically, the total extracellular digoxin concentration rises dramatically, but such digoxin is pharmacologically inactive because only the unbound form can associate with myocardial receptor sites.

Experience in the multicenter trial reported here indicates that purified Fab fragments of high affinity and specificity for digoxin rapidly and safely reverse advanced digitalis toxicity in humans. An initial response was usually seen within 60 minutes in patients suffering from digitalis toxicity, and complete reversal of glycoside effects was usually evident within 4 hours of administration. True nonresponders were rare, and lack of response should raise the suspicion that too low a dose of Fab fragments
was given or, alternatively, that the clinical signs and symptoms are not caused by digitalis toxicity. No acute allergic reactions or serum sickness–type illnesses were recognized in conjunction with Fab fragment treatment. The anticipated adverse reactions caused by relatively rapid reversal of the effects of digitalis, such as worsened left ventricular function or hypokalemia, were noted in less than 10% of treated patients. It should be noted, however, that excretion through renal mechanisms and therapeutic maneuvers to reduce hyperkalemia before Fab administration may result in total body potassium depletion with persisting high or normal serum potassium concentrations. In this clinical context, rapid onset of hypokalemia should be anticipated when toxicity is reversed by digoxin-specific Fab fragments. Serum potassium levels should be monitored and potassium supplementation used as needed to avoid hypokalemia. As previously noted, after Fab treatment, the standard immunoassay and other methods for measurement of serum digoxin concentration usually give unreliable results that are likely to be misleading as estimates of the state of digitalization. Furthermore, unless absolutely required for inotropic support or arrhythmia management, “back titration” with digoxin is usually unnecessary and should not be attempted for at least 7 days or possibly longer in patients with impaired renal function.

There were 18 patients with a pretreatment serum creatinine concentration of more than 4.0 mg/dl, including five who were on dialysis. These patients responded to Fab treatment in a manner similar to patients with normal renal function. However, a theoretic possibility exists that digoxin could be re-released with recurrence of toxicity when excretion of the Fab-digoxin complex is slowed by renal failure. Whereas the absence of this phenomenon in the present study suggests that recurrence of toxicity will be uncommon, it remains a possibility under certain circumstances (e.g., very large digitalis load, very poor renal function, low Fab dose). One such case occurred after commercial release of Fab. A dialysis patient developed third-degree atrioventricular block from digitalis toxicity, responded rapidly and completely within 4 hours of Fab treatment, but had recurrence of second- and third-degree block 10 days later. No further Fab was given, and the block resolved during an additional 10 days of observation (Burroughs Wellcome Company, data on file).

Recurrence of toxicity occurred in two of the 150 patients. Neither had renal failure, and each received less than fully neutralizing doses of Fab. In each case, resolution of toxicity was followed within 4–8 hours by recurrent signs and symptoms of toxicity. In one case, no further Fab was available, and the patient died within 24 hours of a massive ingestion of digoxin.

Although not a randomized clinical trial, this trial provides abundant evidence of a pronounced effect of Fab treatment on survival of patients with life-threatening digitalis toxicity. The nature and severity of the clinical digitalis toxicity encountered, the poor prognosis with standard treatment, and the dramatic successes in early clinical experiences present important ethical concerns regarding denial of antibody therapy to critically ill patients. The present study reports relatively good survival rates of patients with elevated serum potassium before treatment; this contrasts to the observations of Gaultier and Bismuth, who reported a mortality rate of 55% for conventionally treated patients who were not on diuretic therapy, did not have prior cardiac insufficiency, and had pretreatment serum potassium concentrations of 5.0 meq/l or more (Table 2).

Further evidence of a striking effect on outcome can be found in the survival rates of patients with digitalis-induced cardiac arrest. Whereas survival after standard therapy in this setting is uncommon (Table 3), more than one half of the patients treated with Fab survived to discharge. In addition, the rapid time course of resolution of toxicity during 1–4 hours instead of several days not only serves as evidence of response but also improves substantially the ease of patient care.

The digoxin-specific antibody fragments used in this trial were supplied by Wellcome Research Laboratories, UK. Favorable experience with a similar preparation in other countries as well as with digoxin-specific antibody fragments from other suppliers may be considered supportive of the conclusions of this trial.

In 1986, the U.S. Food and Drug Administration approved the marketing for clinical use of purified digoxin-specific Fab fragments (Digibind®) as an orphan drug. A postmarketing surveillance study is underway and is anticipated to provide data on more than 700 additional patients treated with Fab. Preliminary review of these data supports our observations in this 150-patient multicenter trial.

Clinical Implications

Although less elegant than reversal of opiate overdose with the competitive antagonist naloxone,
digoxin-specific Fab fragment treatment has gained a place as established therapy for life-threatening digitalis toxicity. An initial treatment response can be expected within 1 hour in 75% of such cases. Important treatment-related side effects such as exacerbation of congestive heart failure, increased ventricular response in atrial fibrillation, or hypokalemia occur in less than 10% of patients, and idiosyncratic adverse reactions such as allergic manifestations occur in less than 1% (preliminary results of post-marketing surveillance study). Although serum digoxin measurements are not reliable for 1–2 weeks after Fab treatment, this is generally not an important clinical problem. A trial is underway examining the clinical usefulness of digoxin-specific Fab fragments for the simultaneous diagnosis and treatment of digitalis toxicity that has not advanced to an overtly life-threatening stage.

Besides demonstrating effectiveness as an antidote to digitalis toxicity, this trial supports the theoretic advantages of using Fab fragments rather than whole antibodies in humans. Future developments could, in principle, include the production of even smaller immunoglobulin fragments with reduced immunogenicity in humans by recombing the variable regions of the light and heavy immunoglobulin chains to form a 23,000-Da Fv fragment with framework regions of human immune specificity. Such measures could lead the way to antibody reversal of toxicity from other drugs or endogenous substances.

Appendix

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KEY WORDS • digitalis • antibodies • Fab fragments
Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study.

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_Circulation_. 1990;81:1744-1752
doi: 10.1161/01.CIR.81.6.1744

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/6/1744