Treatment of 63 Severely Digitalis-Toxic Patients With Digoxin-Specific Antibody Fragments

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Digitalis intoxication is among the most common adverse drug reactions in clinical medicine. Severe episodes may be fatal, particularly in patients with advanced cardiac disease or in patients who have ingested massive doses of digitalis accidentally or with suicidal intent. Treatment of digitalis intoxication has been limited by the absence of a specific antagonist and by the fact that standard therapeutic modalities are of limited effectiveness when toxicity is severe. The need to improve treatment of digitalis toxicity stimulated interest in finding a specific means for reversing the effect of this group of drugs.

Development of Antigen-Binding Fragments (Fab)

Antibodies to digoxin were successfully produced in 1967 with the hope that they could be used to measure digoxin concentrations in body fluids and also to reverse digitalis toxicity in human beings (1). The serum digoxin radioimmunoassay employing these antibodies was first reported in 1969 (2). Intravenous use of the antibodies to reverse experimentally induced digoxin toxicity was demonstrated in dogs in 1971 (3). The mechanism by which they reverse toxicity appears to be by binding digoxin in extracellular fluid, causing a decrease in the effective free extracellular drug concentration. A concentration gradient is thus created that promotes release of digoxin from receptor sites.

Use of these whole heterologous antibodies, derived initially from rabbits and subsequently from sheep, was limited by the known incidence of immediate and delayed hypersensitivity when such foreign proteins are administered to human beings. Advances in the knowledge of antibody structure and purification methods during the 1960s and early 1970s allowed modification of these antibodies to render them less immunogenic. Digestion of the antibody with papain yields two antigen-binding fragments (Fab), each having a mass of 50,000 daltons, and one crystalline fragment (Fc) from each gamma-G globulin molecule (mass = 150,000 daltons) (4). Digoxin-specific Fab can be isolated and purified by passing papain-digested hyperimmune animal serum through a column containing a digitalis glycoside attached to an inert support matrix (5). This process is referred to as immunoadsorption and is closely analogous to affinity chromatography. Only the digoxin-binding frag-
ments adhere to the column, from which they are eluted as purified digoxin-specific Fab.

This purified Fab eluate has numerous advantages over whole antibody. The smaller size of these fragments permits them to distribute more rapidly and into a larger distribution volume within the body (6), resulting in more rapid and effective reversal of toxicity (7,8). They also can be excreted rapidly by glomerular filtration (6) in contrast to the whole antibody, which is degraded slowly by the reticuloendothelial system. Elimination of the antigenic determinants and complement-binding site of the Fe portion renders the Fab portion less immunogenic than intact antibody (6). In addition, the smaller size of the fragments, their more rapid excretion and the absence of other protein impurities further reduce the antigenicity of the preparation.

The ability of digoxin-specific antibodies and antibody fragments to reverse toxicity in experimental preparations in vitro and in intact animals has been amply demonstrated. In erythrocytes with established digoxin-induced inhibition of sodium and potassium transport, the inhibition was reversed by subsequent incubation with digoxin antibody and antibody fragments (9,10). Digoxin induces an increase in developed tension in isolated guinea pig atrial muscle strips. The addition of digoxin antibody fragments reverses this effect and restores muscle tension to pre-digoxin levels (10). Addition of toxic levels of digoxin to canine Purkinje fibers in a tissue bath can cause electrical inexcitability. When digoxin antibodies are added to the bath, membrane characteristics return to normal (11). Also, prolongation of rabbit atrioventricular node effective and functional refractory periods and conduction time caused by digoxin are rapidly reversed by digoxin antibodies (11).

Intact animal studies of digoxin toxicity have shown that lethal doses of digoxin in control dogs can be reversed after the onset of toxic rhythm disturbances by digoxin antibodies (3) and antibody fragments (7). When an adequate neutralizing dose is given, advanced toxicity can be reversed, and this occurs more rapidly with Fab fragments than with the whole antibody (7). The inotropic effects of digoxin are also reversed with more rapid reversal using Fab fragments than with whole antibody (8), but this occurs over a slower time course than does arrhythmia reversal. These in vitro and in vivo studies clearly demonstrate the ability of digoxin-specific antibodies and antibody fragments to reverse the toxic and inotropic effects of digoxin, and also demonstrate the advantage of the purified digoxin-specific Fab portion over the intact gamma-G globulin antibody.

On the basis of these experimental findings, digoxin-specific Fab fragments were prepared in a form suitable to treat patients suffering from severe and potentially life-threatening digitalis intoxication. The first patient treated in this trial was described in 1976 (12). Experience with the first 26 patients was reported in 1982 (13). The present article summarizes our experience to date.

Methods

The design of the multicenter trial has been described previously (13). Briefly, this was a study in 20 geographically distributed medical centers in the United States in which digoxin-specific Fab fragments were given in an unblinded fashion to patients with potentially life-threatening cardiac rhythm disturbances or hyperkalemia, or both, caused by digoxin or digitoxin intoxication. These patients had failed conventional therapeutic efforts to treat digitalis toxicity or, in a few cases, were judged unlikely to respond to standard measures because of massive intoxication.

Digoxin-specific Fab fragments derived from sheep were administered intravenously, generally over a 15 to 30 minute period. The dosage of Fab fragments was calculated to be equimolar to the amount of digoxin in the patient’s body. Estimates of total digoxin load were derived from the medical history or from determinations of serum digoxin concentrations, or both.

Therapy with digoxin-specific antibody fragments was considered effective if life-threatening cardiac arrhythmias resolved over an accelerated time course, that is, within minutes to a few hours after treatment. In addition, evidence was sought for resolution of hyperkalemia caused by toxicity-induced inactivation of the cellular Na⁻-K⁺ adenosine triphosphatase (ATPase) pump. Total and free plasma digoxin concentrations were determined when possible.

To assess safety, skin testing and intravenous challenge with a small dose of purified digoxin-specific antibody fragments were undertaken along with standard laboratory tests. Patients were observed carefully for immediate and delayed hypersensitivity reactions. Clinical circumstances sometimes limited the ability to collect data from laboratory tests.

Results

Patients. After informed consent was given by the patient or a responsible relative, 63 patients received digoxin-specific antibody fragments. Fifty-nine had digoxin toxicity and 4 had digitoxin toxicity. Thirty-seven were male, 25 were female and 1 was a true hermaphrodite. The mean age was 50.6 years (range 3.5 days to 85 years).

Twenty-eight patients ingested massive amounts of digitalis with suicidal intent. Seventeen of these were patients receiving long-term digitalis therapy, whereas the other 11 had no underlying heart disease. An additional five patients, previously in good health, ingested large amounts of digoxin as a result of error or accident. Toxicity occurred in 30 patients as a result of error, accident or misadventure in an effort to treat their underlying heart disease.

Manifestations of digitalis toxicity included nausea and vomiting in 37 patients, hyperkalemia in 29 patients, second or third degree atrioventricular block in 41 patients, high grade ventricular ectopic activity in 46 patients, ventricular
tachycardia in 41 patients, ventricular fibrillation in 23 patients and ventricular asystole in 1 patient.

Previous attempts to reverse digitalis toxicity included ventricular pacing in 39 patients, direct current cardioversion in 15 patients and administration of atropine in 16 patients, lidocaine in 34 patients and phenytoin in 23 patients. Twenty-four patients required closed chest cardiopulmonary resuscitation.

Serum digoxin concentrations of patients at the time of entry into the study ranged from 2.4 to greater than 100 ng/ml, with an average concentration of greater than 14.1 ng/ml (in cases where the pretreatment serum digoxin concentration was reported only as greater than a stated amount, that stated amount was used to calculate the mean). All but 9 of the 63 patients had serum digoxin concentrations greater than 5 ng/ml.

The administered dose of digoxin-specific antibody fragments averaged 520 mg (range 4.0 to 1,600).

Twenty of the patients in this study had normal renal function before Fab administration. Thirty-one patients had evidence of abnormal renal function. Renal function was not reported in 12. The mean (± SD) blood urea nitrogen and creatinine levels in those patients with abnormal renal function were 43 ± 20 mg/100 ml (n = 28) and 2.7 ± 1.2 mg/100 ml (n = 30), respectively.

Clinical response. Our overall experience is summarized in Figure 1. Seven of these 63 patients who received digoxin-specific antibody fragments were excluded from the evaluation of efficacy. Two of these patients received doses of Fab fragments less than one-tenth the amount calculated to be needed. Both of these patients died before an adequate dose was given. An additional three patients were excluded because they received their digoxin-specific antibody fragments after they were already agonal (which we defined as no functioning ventricular rhythm for longer than 5 minutes before initiation of digoxin antibody fragments, or resuscitation efforts discontinued and death pronounced less than 15 minutes after administration of a therapeutic dose). Two other patients were excluded because they did not have clear evidence of digitalis toxicity. One of these was a patient receiving therapeutic doses of digoxin who took a suicidal overdose of furosemide; he was also agonal before antibody fragments were administered. The second patient had ventricular arrhythmias and a history of digoxin use, but no other clinical evidence in favor of the diagnosis of digitalis toxicity. This patient had no response to the antibody fragments and a pretreatment serum digoxin concentration measurement returned from the laboratory later in the day showed a low therapeutic concentration.

Of the remaining 56 patients, digitalis toxicity responded to digoxin-specific antibody fragment therapy in 53. In one of these patients, recovery was followed by a return of toxic manifestations due to a lack of sufficient supply of Fab fragments. This patient received about half the dose expected to neutralize the amount of digoxin believed to be in the patient’s body. However, his suicidal ingestion was massive (25 mg) and he ultimately died from digoxin-induced ventricular fibrillation before more antibody fragments could be obtained. Toxicity resolved completely in the other 52 patients including the 4 patients with digitoxin toxicity.

In each of the three patients who showed no response to the digoxin-specific antibody fragments, the diagnosis of digitalis toxicity was uncertain. Two of these patients had an elevated serum digoxin concentration, but also had very severe underlying heart disease and documented severe ventricular arrhythmias before the serum digoxin concentration became elevated. A third patient developed a prolonged episode of ventricular fibrillation after a combined digoxin and tricyclic antidepressant overdose. She was successfully resuscitated to a regular rhythm with complete heart block, but without return of brain function. Digoxin antibody fragments were then administered but had no effect on her heart block, which in retrospect was considered most likely to be due to the tricyclic overdose.

Time course of response. Patients usually responded to the antibody fragments within 30 minutes of administration. The onset of response was probably affected by such factors as the speed of administration of the antibody fragments, the amount of Fab fragments given in relation to the amount of digoxin ingested and other less well defined factors. Infants and young children sometimes responded within minutes.

The response of an adult patient is shown in Figure 2. He was given 520 mg of digoxin-specific antibody fragments
after three episodes of ventricular tachycardia requiring direct current cardioversion. This patient also manifested ventricular ectopic beats, atrial fibrillation, nausea and vomiting, a serum potassium concentration of 6.2 mEq/liter and a serum digoxin concentration of 4.7 ng/ml. No episodes of ventricular tachycardia occurred after the Fab fragments were given. He averaged two ventricular ectopic beats/min until treatment with the antibody fragments, after which ventricular ectopic activity completely resolved. As can be seen in Figure 2, his ventricular response was 90 beats/min before Fab was administered. During Fab infusion, the ventricular rate increased to 120 beats/min, indicating partial reversal of digoxin effects on atrioventricular conduction. Response was complete by 3 ½ hours after Fab administration.

Laboratory evaluation. Laboratory evidence for binding of digoxin or digitoxin by digoxin-specific antibody fragments was seen in the postadministration serum drug concentrations. In all six patients in whom it was measured, the concentration of free and, therefore, active digoxin or digitoxin decreased to zero or near zero within 1 to 2 minutes after administration of the antibody fragments. Total serum digoxin concentration increased rapidly after administration of the antibody fragments to values typically 10- to 20-fold higher than pretreatment levels. Essentially, all of this digoxin was bound to the antibody fragments and was, therefore, pharmacologically inactive. A typical serum digoxin response to administration of digoxin-specific antibody fragments is shown in Figure 3.

Serum potassium concentration. The mean potassium concentration before treatment with antibody fragments was 5.5 mEq/liter (range 2.4 to 10.3). In 31 patients for whom serum potassium concentrations were known both before and after Fab administration, the average pretreatment potassium concentration was 5.8 mEq/liter and the average posttreatment level (usually obtained about 4 hours after start of treatment) was 4.4 mEq/liter (p < 0.01). In all patients who had elevated serum potassium concentrations, treatment with digoxin antibody fragments reversed the hyperkalemia. Some of these patients received other treatment for hyperkalemia before administration of the antibody fragments. There was no relation between pretreatment hyperkalemia and outcome (Fig. 4). There were no significant changes in other laboratory variables measured.

Adverse reactions. There were no obvious reactions to Fab treatment in any of the patients in this trial. One patient had slight erythema at the site of skin testing, but no systemic reaction to the therapeutic dose. Several patients developed fever at various times after administration of the antibody fragments, but in no case was the timing or the clinical setting suggestive of a Fab-induced or endotoxin-induced fever. In all febrile patients, clear evidence of infection existed. There was no evidence of renal deterioration caused by antibody fragment therapy. No acute hypersensitivity reaction or delayed serum sickness was seen in any of the patients.

Six patients had clinical evidence of some degree of impaired ventricular function several hours to 1 day after treatment. Although withdrawal of the inotropic support of digoxin may have added to their preexisting low cardiac output state, numerous adjustments in fluid volume, diuretic drug and vasodilator therapy, as well as the frequent occurrence of cardiac arrest occurring about the time of treatment in this group, make assessments of causality impossible. In contrast, most patients responded to digoxin antibody treatment with obvious improvement in their hemodynamic state coincident with resolution of refractory arrhythmias.
Our clinical experience to date confirms and extends the data previously reported in 1982 (13). Treatment of digoxin and digitoxin toxicity with digoxin-specific antibody fragments is rapid and appears to be safe. The antibody fragments had no demonstrable effects other than reversal of the action of digitalis.

Relation of pretreatment potassium concentration to outcome. Digitalis toxicity can cause a net loss of potassium from cells by inactivating the cell membrane Na\(^+\)-K\(^+\) ATPase pump. When toxicity is severe, serum potassium concentration rises. A clear relation between hyperkalemia and fatal outcome was demonstrated in patients who ingested large amounts of digitalis accidentally or with suicidal intent and who received standard therapy for their toxicity (14). Bismuth et al. (14) reviewed 91 episodes of acute digitalis poisoning at the Paris Poison Control Center. They excluded patients who were receiving therapy with diuretic drugs at the time of ingestion and those who died more than 4 days after the ingestion. Their results are summarized in Figure 4.

In the present study, no correlation existed between potassium concentration before treatment and outcome. In fact, most of the patients with hyperkalemia survived as a result of treatment with digoxin antibody fragments. To compare the results of our study with the experience of Bismuth et al. (14), 38 patients from our study were excluded from the analysis in Figure 4. Nine patients lacked a pretreatment serum potassium concentration determination, 23 patients developed toxicity in the course of clinical management with digitalis and diuretic drugs and 6 patients died more than 4 days after ingestion of digitalis. By comparing the outcome of the patients of Bismuth et al. with our results, it is evident that digoxin-specific antibody fragments had a pronounced effect on survival in our patients.

Response time. As suggested by the large volume of distribution of Fab fragments compared with the intact gamma-G globulin molecule in baboons (6), and in keeping with other experimental studies in animals, clinical response to digoxin-specific antibody fragments has been reasonably rapid in almost all cases. One would expect response time to be even faster with more rapid administration or use of a larger dose of Fab fragments. On the other hand, administration of a larger dose subjects the recipient to a larger and more prolonged antigenic stimulus and greater exposure to potentially coadministered impurities, such as bacterial endotoxins that might arise in processing of the Fab fragments. Such impurities are minimized by the manufacturing process, and detailed sterility and pyrogenicity testing is done before clinical use. Where speed of action is essential to the life of the patient, bolus administration of an ample neutralizing dose seems a reasonable way to accelerate the effect.

Safety of ovine Fab. From the inception of this effort to develop a specific therapeutic agent for digitalis intoxication, special attention was given to the potential problems associated with intravenous use of heterologous antibody fragments in human beings. Thus far, there has been no evidence of acute hypersensitivity or delayed serum sickness after use of ovine Fab fragments. We do not yet have any experience with reexposure to purified digoxin-specific Fab fragments.

Elimination of Fab fragments. Although the toxic and pharmacologic actions of digoxin are neutralized by binding to the antibody fragment whether or not this digoxin-Fab fragment complex is removed from the body, elimination of both digoxin and the antibody fragments is a matter of concern. If the digoxin-Fab complex remains for a prolonged period in the body, immune degradation of the heterologous Fab might lead to re-release of free digoxin over a period of a few days, with possible recrudescence of overt toxicity.

In patients with good renal function, the digoxin-Fab complex appears to be eliminated fairly rapidly by glomerular filtration, usually with a half-life of about 16 to 20 hours. We were unable to obtain adequate serum samples in patients with severe renal impairment to define the half-lives of elimination of either digoxin or the Fab fragments in such patients. However, with the exception of one patient who received an inadequate Fab dose, we did not observe
any recurrence of toxicity after response to the antibody fragments. Many of our patients with abnormal renal function had excellent responses to antibody fragment treatment. Experience with these Fab fragments in patients without renal function is insufficient to permit comment.

Once the antibody fragments have been given, it is not possible to follow the patient’s serum digoxin concentration using routine radioimmunoassay methods (12,15). An accurate determination of total digoxin concentration can be obtained by first boiling the serum, but this measure does not reflect the concentration of free and, therefore, active digoxin in the body. Free digoxin concentrations can be measured by equilibrium dialysis (12).

The presence of digoxin-specific antibody fragments in the patient’s blood also complicates the process of repeat administration of digoxin to these patients. Elimination of Fab fragments from the body may require a week or longer, depending, as noted, on renal function, after which redigitalization and use of standard serum digoxin concentration assays for follow-up study can be instituted as needed.

**Further experience.** The digoxin antibody fragments used in this study were supplied by Wellcome Research Laboratories, United Kingdom. Additional experience with this material in other countries and with digoxin-specific antibody fragments made by others support our conclusions. A total of 40 such patients treated worldwide has been reported (15–23), with apparent good response and no evidence of hypersensitivity or other adverse reactions. If further experience confirms the safety of the clinical use of digoxin-specific antibody fragments, their use might be expanded to first line therapy for any patient who requires definitive treatment. Use of digoxin-specific Fab fragments for both diagnostic and therapeutic purposes in patients in whom the diagnosis of digitalis toxicity is uncertain must await further evidence supporting their safety and usefulness in this setting.

**References**


