EVALUATION OF THE USE OF ANTIDIGOXIN ANTIBODIES IN THE TREATMENT OF DIGITALIS INTOXICATION (*)

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INTRODUCTION

Digitalis intoxication incidence and mortality

Cardiac glucoside intoxication, and especially digoxin which is currently the glucoside most extensively used, is a frequent medical problem given the very narrow therapeutic range of these compounds. Caspi et al (1) estimate that more than 15% of patients admitted to hospital receive some kind of treatment with digoxin, and almost 35% of these may show signs of intoxication.

The studies published in the 60’s and 70’s, revealed that approximately 20% of those patients who had received maintenance therapy with digoxin showed symptoms or signs of toxicity at some stage during their clinical evolution. However, until the introduction of a sensitive radioimmunoassay test, in 1969, to measure serum digoxin concentrations, it was not possible to accurately diagnose suspected digitalis intoxication. Diagnoses made were based on clinical criteria; this means then that the figures published about incidence rates before that time may have been overestimated (2). Nonetheless, the overall impression is that digitalis intoxication incidence has dropped since the serum digoxin detection tests were made available.

According to Borron et al (3), the death rate associated with digitalis intoxication, before the introduction of antidigoxin (Fab) fragment therapy, was between 14 and 20% and still remains high at between 6 and 29%. A retrospective study carried out by Mahdyoon et al (4) into the digoxin intoxication related death rates, among hospitalised patients from 1980 to 1988 (excluding those cases of acute intoxication either accidental or suicide attempts) found a death rate of 4,6%.

Risk factors

The most common risk factors for digoxin intoxication are: altered renal function, advanced age, male sex and the concomitant administration of other drugs (e.g.; amiodarone, verapamil, quinidine, and propafenone (see fig. 1)). Diuretics may potenciate digoxin intoxication as a result of electrolytic alterations including hypokalaemia, hypomagnesemia and hypercalcaemia.

Other contributing factors to a higher risk of digoxin intoxication are: hyperthyroidism, lung disease with respiratory failure as well as the type and severity of underlying heart disease, acid-base abnormalities and amyloidosis.
Types of digoxin intoxication

There are two types of digoxin intoxication:

1. Intoxication in patients treated with digoxin, as a result of a concomitant pathology, an interaction with other drugs, or other causes which may induce a pathological increase in the serum-digoxin concentrations and the appearance of other symptoms and electrocardiographic signs of intoxication. These are the most frequent and usually the least life threatening.

2. Severe intoxication or digoxin poisoning, resulting from the ingestion of an accidental overdose in children, or attempted suicide. These are usually life threatening and require emergency treatment.

We do not have any figures on the incidence of either of these two types of digoxin intoxication in Andalusia, although we do suspect that the majority of cases fall into the first category.

The aims of this report

This report was initiated following a question formulated by the Pharmaceutical Service at the “Punto de Europa” Hospital (Algeciras, Cadiz) regarding the use of antidigoxin antibodies, especially in cases of digitalis intoxication of the first type previously described. The objective was to review the indications for usage published on this therapeutic technology and evaluate their degree of scientific evidence.

METHODOLOGY

In order to carry out this report extensive bibliographic searches have been made in the following documentary databases using the key words “antidigoxin antibodies”:
I. **Medline (since 1984)**

The search strategy used for Medline was as follows:

1. "Digoxin"/adverse-effects, antagonists and inhibitors, immunology, poisoning, toxicity
2. explode "Digitalis-Glycosides"/ adverse-effects, antagonists-and-inhibitors, immunology, poisoning, toxicity
3. #1 or #2
4. antibod*
5. antibod* and #3
6. TG = "HUMAN"
7. #5 and (TG = "HUMAN")
8. "Poisoning-therapy"
9. "Poisoning-therapy" in MIME
10. "Immunoglobulins,-Fab-therapeutic-use;"
11. "Immunoglobulins,-Fab-therapeutic-use;" in MJME
12. "Immunoglobulins,-Fab-administration-and-dosage"
13. #3 and (#8 or #10 or #12 or (#4 in ti)) and #6
14. PT = "LETTER"
15. #13 and (PT = "LETTER")
16. #13 not #15
17. PT = "CLINICAL-TRIAL"
18. #16 and (PT = "CLINICAL-TRIAL")

II. **The Cochrane Library**

The terms “digoxin, antibody, antidigoxin” were used for the search done at the Cochrane Library

III. **The Iowa Drug Information Service (IDIS), (1966-98 June)**

IV. **CADIME files (Centro Andaluz de Información sobre el Medicamento, Andalusian Drug Information Service)**

V. **ÍNDICE MÉDICO ESPAÑOL (Spanish Medical Index)**

To conduct the search in the Spanish Medical Index the terms “ANTICUERPOS ANTIDIGOXINA” were used.

CADIME have lent their services for consultation of documentary sources 3 and 4 and for source 5 the Library of the Regional Health Authority (Consejería de la Salud) also collaborated.

The selected articles were reviewed and classified by the level of evidence according to the Jovell A, and Navarro Rubio MD classification (5).

Ensuing from the searches conducted the abstracts of 245 articles were reviewed. Out of these, 33 articles were selected ranging from bibliographic reviews of the use of antidigoxin antibodies to those describing the use of antidigoxin antibodies and those which described cases of their clinical use.
The evaluation of the scientific evidence from the reviewed articles was done in 9 articles, these being the case series, those with an innovative methodological design, and those designed with an adequate level of quality. (See fig. 2)

THE CURRENT STATE OF DIGOXIN (& DIGITALIS) INTOXICATION TREATMENT

Currently there are two treatment options for digitalis intoxication, these are, conventional treatment and (Fab) antidigoxin-specific antibody fragment treatment

Conventional treatment

1. Gastric decontamination (gastric lavage, activated charcoal). If the patient is seen within the first two hours following ingestion, and when there is no life-threatening arrhythmia, as gastric lavage may precipitate ventricular fibrillation or asystole. For this reason gastric lavage is considered to be ineffective and also associated to a number of complications.


3. Anti-arrhythmic drugs. Atropine is the initial treatment of choice for sinal bradycardia and to block VA.

4. Cardioversion in digoxin intoxication patients may cause severe disrrhythmia or asystole. That is why, when deemed necessary, electroshock treatment must be given at the lowest voltage possible (3).

5. Ventricular pacemakers. Unfortunately during a digoxin intoxication, heart rate reduces the fibrillation threshold and thus increases the risk of serious dysrhythmia, especially during the placement of pacemakers.

Regarding possible complications during the placement of pacemakers, Taboulet P, et al (6), in a non-randomised retrospective study compared the safety and efficacy of the use of pacemakers versus immunotherapy with Fab antidigoxin. They concluded that immunotherapy is far safer than the pacemakers (given the 36% of yatrogenic accidents, 13% of which are fatal). For this reason they recommend immunotherapy as the first line of treatment in acute digitalis intoxication. Should this measure fail to control severe bradycardia then revert to the use of a pacemaker.

In summary, it can be said that conventional treatment of digoxin intoxication is complicated and slow although recovery is possible, but is non-specific and can sometimes exacerbate other problems.

Fab antidigoxin antibody fragment therapy

Although these are antidigoxin specific antibodies, they have also been used to treat intoxication from other drugs of the digitalis family (digitoxin, oleander leaf, and other
plants containing D. lanata) obtaining similar results, although much slower, to those obtained in the treatment of digoxin intoxication. Likewise it is also known that immunotherapy is more effective when given at an early stage and at carefully calculated doses.

Taboulet P, et al (7) have proposed the use of antidigoxin Fab antibody fragments for two situations:

1. **Alterations which are directly life-threatening**: ventricular arrhythmia such as ventricular taquicardia or ventricular fibrillation, bradynrhythmia including sinoatrial bradycardia below 40 beats per minute refractory at 1mg of atropine, second or third degree atrioventricular block with a low ventricular rate or ventricular asystole, hyperkalaemia greater than 5 mEq/l (6mEq/l in children), mesenteric infarct or cardiogenic shock. In these patients a curative dose of Fab should be administered as rapidly as possible (equimolar neutralisation).

2. **Potentially lethal intoxications**: Mild bradycardia below 60 bpm (in adults), not taking into account conduction problems, especially in patients with factors associated with bad prognosis. In these patients, when atropine does not increase bpm above 60, half the equimolar or “prophylactic” dose is administered and the patient remains under observation, because not all cases require a full dose of Fab. It is always used the equimolar dose in children.

Krisanda (8) also recommends the use of Fab antidigoxin antibody fragments in cases of:
- Ingestion of excessive quantities of digital (in children, more than 4mg or more than 0.1mg/kg weight; in adults more than 10mg).
- Constant serum digitalis levels above 5ng/mL in children or 6ng/mL in adults.

In summary, the generally accepted indications for Fab fragment therapy are:

1. The presence of changes in heart rate which potentially threaten the patients life
2. Hyperkalaemia, or
3. The two previous symptoms, whenever these are caused by digitalis intoxication and the patients are refractory to conventional treatment.

On the other hand, no clinical trials have been done to evaluate the usefulness or the safety of the use of Fab antidigoxin antibodies in the treatment of suspected digitalis intoxication of a severity from mild to moderate. This in part is due to the fact of the low incidence rate of digoxin toxicity in patients on digitalis therapy. However, the unique specificity of the antibody preparations and their high level of safety in cases of patients with more sever intoxications, support their use in patients who have suspected intoxication of a more moderate nature (2).

Regarding the administration of the habitual dose, this is usually given by 20 to 30 min intravenous infusion. Nonetheless, Schaumman et al (9) have suggested that this dose be administered in two equal parts, the first half in 15 min, and the second in about 7 hours, in order to reduce the risk of intoxication recurring.

**Adverse effects of the use of antidigoxin Fab antibodies.**

In general these are rare (7).
1. In 0.8% of cases there was a hypersensitive reaction. This is the only contraindication for this therapy.

2. It could cause heart failure by annulling the beneficial effect of the digoxin, although this is difficult to prove.

3. The recurrence of signs of toxicity some time after immunotherapy, from the remnant free digoxin. This usually occurs after massive intoxications in which the initial neutralisation was lower than the estimated neutralisation. This has been observed in between 1.3 and 2.8% of cases.

4. Rapid control of hyperkalaemia with Fab fragments may lead to hypokalaemia in the first four hours. Said hypokalaemia reflects the efficiency of the treatment and occasionally calls for the administration of potassium chloride.

Because neutralisation with Fab fragment therapy is so expensive, and not always available in smaller hospitals, it is sometimes delayed until there is a serious arrhythmia. On the contrary however, Fab therapy is simple and can be given in any hospital. Nonetheless, the indication for Fab therapy should be very carefully given on a case by case basis, seeing as there are no unequivocal criteria which make it possible to predict the course of a digitalis intoxication.

In summary, antidigoxin Fab fragments are currently indicated in digoxin or digitoxin intoxications when these are life threatening or may be life threatening for the patient. (7). Its efficacy has been proven in these cases. The potential role of Fab fragments in less severe intoxications or as a means of helping to diagnose digitalis intoxications requires still more research.

Annex 1 represents the criteria for the use of antidigoxin antibodies as used by the Virgen del Rocio Teaching Hospital in Seville.

AN APPRAISAL OF THE MAIN STUDIES

Fig. 2 lists the main studies which have been consulted, their methodology, results and conclusions and the level of evidence they provide.

In the reviewed bibliography no controlled, randomised trials were found. This may be explained by the fact that Fab fragments are recommended in those cases where the patient’s life is under threat and therefore, for ethical reasons, this prevents this type of study from being conducted.

Most of the papers reviewed are descriptions of case series or single cases which have been treated with antidigoxin Fab fragments and bibliographic reviews which describe digoxin intoxication and the indications for the use of Fab fragments. This type of study provides little or no scientific evidence. However, amongst these mention should be made, given that it has the greatest number of patients, the multicentre, prospective, nonrandomised study of 150 cases published by Antman EM et al (10) and the follow-up study by Hickey AR et al (11), of 717 cases.

The retrospective, nonrandomised study carried out by Taboulet P et al (7), is interesting, it presents a fair level of evidence which compares three treatment groups, although the sample is small, as well as a cost-effectiveness analysis.
published by Mauskopf JA and Wenger TL (12). This analysis offers an interesting approach to the evaluation of possible indications for this therapy.
### Fig 2. - An assessment of the main studies consulted

<table>
<thead>
<tr>
<th>Publication</th>
<th>Methodology</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| **Ujhelyi et al (13)** | **Nº of cases:** 14 cases from two hospital, over an 18 month period  
**Population:** Adults  
**Type of study:** Observational of the pharmacokinetics and pharmacodynamics | • Following the administration of antidigoxin Fab, the total digoxin is rapidly increases and is eliminated in two phases. The first of $11.6 \pm 4.1$ hrs, & the second of $118 \pm 57$ hrs  
• Free digoxin levels drop rapidly after administration of Fab antidigoxin, at $0.6 \pm 1.1$ nmol/mL, but bounce back up to a mean concentration of free digoxin of $1.7 \pm 1.3$ nmol/mL en unas $77 \pm 46$ horas  
• All patient's completely or partially improve their signs and symptoms with the administration of antidigoxin Fab. | 1. The elimination of digoxin following administration antidigoxin Fab is delayed in patients con renal dysfunction  
2. The pick up of free digoxin levels is usually delayed in anephric patients  
3. It is important to monitor free digoxin levels following Fab fragment administration in some patients so as to guide additional doses, to confirm possible new outbreaks toxicity, or decide to recommence digoxin therapy. | VIII (poor) |
| **Taboulet P et al (6)** | **Nº of cases:** 92 cases treated in the ICU  
**Population:** Adults  
**Type of study:** Retrospective nonrandomised (on 51 patients who did not improve with conventional treatment)  
Three groups:  
1. – only pacemakers (n=23)  
2. – only Fab anti-digoxin (n=12)  
3. – both treatments (n=16) | • 41 patientes survived with only conventional treatment (gastric lavage, activated charcoal & atropine)  
• 51 patients were given pacemakers and antidigoxin Fab, and the death rate was 13%  
(digoxin intoxication = 14; digitoxin intoxication = 36; mixt = 1)  
• The prevention of life-threatening arrhythmia failed in 8% of the cases treated with Fab, and in 23% of those given a pacemaker (no significant difference)  
• Yatrogenic accidents with pacemakers were frequent (14/39, 36%), & often fatal (5/39, 13%)  
• Immunotherapy was not associated to any serious adverse effects (0/28, 0%) and was safer than the pacemaker ($p < 0.05$) | 1. In digitalis intoxication, pacemakers can have some preventive and even curative effects although limited; they are hard to handle and exposes the patients to severe yatrogenic accidents.  
2. Fab fragments act as a powerful antidote and are safer and easier to use than a pacemaker.  
3. Fab fragments should be use as first line therapy for digitalis intoxications.  
4. Should immunotherapy fail to work then a pacemaker would be used. | V (fair) |
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<th>Publication</th>
<th>Methodology</th>
<th>Results</th>
<th>Conclusions</th>
<th>Nivel de evidencia científica</th>
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| Mauskopf JA and Wenger TI. (12) | Population: 3 groups of adults (A) with hearth disease, intoxication during therapy; (B) with heart disease, suicide attempt; (C) no heart disease, suicide attempt y (D) 1 group of children < 5 yrs. no heart disease, accidental ingestion. Each group was subdivided into two: those who presented some kind of immediately life-threatening heart problems, and those whose problems were only potentially life-threatening. **Type of study:** Cost-effectiveness study with estimations of costs and benefits from non-controlled clinical trials conducted for other purposes as well as from expert opinions. | • The probability of survival was higher in the group treated with Fab fragments  
• The hospital cost per patient (not including the Fab fragments) are lower for all children who have accidentally ingested & also for groups A, B y C with potential life-threatening clinical manifestations because the survivors need less aggressive therapy and stay less time in the ICU.  
• In these groups there are savings made in spite of the fact that this means additional costs to the hospital having saved their lives using Fab fragments. The savings are made even if we consider the cost of the Fab fragments, because the net cost of treatment for these groups is negative .  
• To the contrary, for groups A, B & C with immediate life-threatening heart disease, the additional hospital costs are generated by the use of Fab fragment, by the patients whose lives are saved, are higher than the reduction in cost for the survivors. So, the net cost of treatment in these patients, including Fab fragments, is positive. | 1. For those Patients with immediate life-threatening heart problems and for those for whom the net costs are not positive, the cost per year of life saved is somewhere between 1.912 & 5.400 dollars.  
2. The cost per year of life saved with Fab fragments is small if compared to the other treatments aimed at increasing life-expectancy by reducing risk of death from coronary heart disease.  
3. Therefore, the use of Fab fragments in patients with life-threatening digitalis intoxication could be considered fairly cost-effective. | V (regular) |
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<th>Publication</th>
<th>Methodology</th>
<th>Results</th>
<th>Conclusions</th>
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| Smolarsz et al (14) | **No of cases:** 34  
**Population:** From 2 to 80 yrs (average age = 44)  
**Type of stud:** Case Series | - The best results from Fab fragment therapy have been seen in patients presenting ventricular fibrillation or other severe arrhythmia, whose heart rate was stabilised within 0.5-13 hrs (mean 3.2 hrs)  
- Fab fragment infusion tolerance was good, no hypersensitivity reactions were observed. | 1. Conventional therapy for digitalis intoxication according to the literature is not specific, not very efficient & complicated. On the contrary Fab fragment therapy is highly specific and rapid.  
2. Fab fragment therapy is simple and can be given at any hospital.  
3. The indications for Fab fragment therapy should be carefully considered case by case, given that there are no unequivocal criteria which make it possible to predict the course of digitalis intoxication. | VIII (poor)                                                                                                  |
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<th>Methodology</th>
<th>Results</th>
<th>Conclusions</th>
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| Wenger et al (15) | Nº of cases: 63 Adults (average age 50.6 yrs) Population: Adults (average age 50.6 yrs) Type of study: Case series (multicentre study) | 7 patients were excluded from the trial (2 due to inadequate doses, 2 because of incorrect diagnoses, & 3 in agonic state)  
Of the 56 remaining Patients, 53 had a positive response to Fab fragment therapy.  
One of the Patients who had responded positively relapsed because the dose received was insufficient and subsequently died.  
The 52 remaining, including two with digitoxin intoxication, made a complete recovery.  
In the three who did not respond positively the diagnosis of digitalis intoxication was wrong: 2 had severe heart disease with previous ventricular arrhythmia when his/her plasma digoxin levels were raised; and the third developed a ventricular fibrillation following an overdose of a combinations of digoxin & tricyclic anti-depressants.  
The onset of response to Fab fragment therapy was usually 30 mins after administration.  
There were no adverse reactions, with the exception of one mild erythema at the site where the skin-prick test had been done, but there were no systemic reactions. | 1. The treatment of digoxin or digitoxin intoxication with antidigoxin-specific antibodies is swift and appears to be safe.  
2. Antibody fragments do not appear to have any effects other than of counteracting the action of the digitalis.  
3. Potentially life-threatening digitalis intoxications can be treated quickly and safely with digoxin-specific Fab fragments. | VIII (poor) |
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<th>Results</th>
<th>Conclusions</th>
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| Woolf AD et al (16) | Nº of cases: 29 (28 Digoxin intox. & 1 Digitoxin) | • In 27 (93%) all the signs and symptoms of digitalis intoxication were resolved.  
• One patient got a partial response; but also suffered a concomitant quinidine intoxication and had also undergone traumatic resuscitation prior to admittance to hospital, dying a week later..  
• Another child with severe underlying heart disease, seemed not to respond to Fab fragment therapy.  
• Three Patients required a second dose of Fab 4-16 hrs after the first dose.  
• 15 of the 19 Patients whose response times were registered, recovered completely in the 180 following Fab fragment therapy.  
• No allergic responses to Fab fragments were observed. | 1. The use of Fab fragments is recommended for the treatment of digitalis intoxications in infants and small children when there has been an ingestion of digoxin of 0.3 mg or more, per kilogram of weight, where there is underlying heart disease, or if the digoxin concentration in plasma is greater than or equal to 6.4 nmol per litre (≥ 5.0 ng per millilitre) in the elimination phase; and if there has also been life-threatening arrhythmia, haemodynamic instability, hyperkalaemia, or rapidly progressive toxicity.  
2. Adolescents are more sensitive to the effects of digoxin than young children, they may require Fab fragment treatment at lower doses of digoxin. |

<p>| Nivel de evidencia científica | VIII (poor) |</p>
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<th>Methodology</th>
<th>Results</th>
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| Antman EM et al (11) | **Nº of cases: 150**  
**Population:** 25 cases were children (average age three months) & 125 were over 16 (average age 65)  
**Type of study:** Cases series, multicentre study of 21 USA hospitals (139 patients Digoxin intox. & 5 digitoxin, & rest type of glycoside unknown) | • In 94 a skin-prick sensitivity test was carried out and only one case of localised erythema was observed with no swelling or, induration  
• The response to Fab fragment was not registered in two cases and only 148 were assessed  
• 119 Patients (80%) resolved all their signs and symptoms of digitalis intoxication.  
• 14 (10%) improved and  
• 15 (10%) did not respond at all  
• The 5 patients with digitoxin intoxication were among those who got a complete response  
• In most of the patients who responded there was a clinical improvement an hour after completing infusion, and the improvement was complete by 4 hrs.  
• Of the 15 cases which did not respond to Fab fragment therapy, 5 were dying when the treatment was given, four, in a retrospective analysis, were clearly considered to not be suffering from digitalis intoxication , five were probably not digitalis intoxications, and one was classified as a true non-responder.  
• Of the 32 Patients who presented adverse effects, in only 14 was this attributed to the Fab fragment therapy.  
• Six patients (4%) very rapidly developed hypokalaemia.  
• In four cases (3%) there was an exacerbation of their congestive heart failure following Fab fragment therapy.  
• Two patients suffered mild episodes of hypertension.  
• Another patient had nausea, and  
• A neonate, only a few hours old, developed a transitory apnoea during Fab fragment infusion.  
• Recurrence of toxicity was seen in only two patients | 1. The nature and severity of digitalis intoxications observed, the poor prognosis with conventional treatment, and the dramatic improvements seen in the initial clinical experiences, would pose some very serious ethical considerations if we were to deny critically ill patients treatment with antibodies.  
2. A clinical response can be expected from at least 90% of patients with solid evidence of advanced and potentially life-threatening digitalis intoxications. | VIII (poor) |
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| Wenger TL (17) | Nº of cases: 28 Population: Adults altered renal function Type of study: Cases series | • Patients with poor renal function neither effectiveness nor safety of the Fab fragment therapy was diminished in terms of response percentage, onset of response or evidence of a worsening of the intoxication.  
• In 27 cases the disease did not worsen.  
• Only in one case did intoxication recur 10 days after treatment, and lasted another ten days | 1. Worsening of toxicity in patients with renal dysfunction is rarely seen, even in patients with advanced renal failure however it can happen and make be late in onset and long lasting.  
2. The combination of a high dose of digitalis and a low dose of Fab fragments and a very deteriorated renal functions are the clinical parameters most frequently associated with a worsening of the intoxication. | VIII (poor) |

Wenger TL (17)
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| Hickey AR et al (10) | Nº of cases: 717  
Population: Adults  
(average age in males = 75 yrs & in women =72 yrs)  
Type of study: case series | - The average dose applied was 120 mg and the most frequent was 80 mg.  
- 357 Patients (50%) recovered completely from their signs and symptoms of intoxication,  
- 172 (24%) made a partial recovery and  
- 98 (12%) did not respond to treatment  
- In 99 Patients (14%) the response was uncertain.  
- The non-responses to Fab fragment therapy was found in: 14% of the patients on maintenance treatment when the intoxication took place; 20% of those intoxicated after and initial dose or undergoing hospital treatment; and in 15% of the heart patients who had overdosed.  
- No patient without heart disease who had overdose was found in the non-responders group.  
- Six patients (0.8%) had probable allergic reactions during the Fab fragment therapy, half of whom had a previous history of allergic reaction to antibiotics.  
- 20 (2.8%) patients worsened, and this was attributed to the an inadequate initial dose.  
- In 7% of patients there was some adverse reaction to Fab fragment therapy | 1. The results of this study suggest that antidigoxin-specific antibodies, even in elderly patients in a deteriorated clinical state due to digitalis intoxication and with underlying heart disease, provides substantial benefits and is has a very low incidence of treatment related adverse effects. | VIII (poor) |
CONCLUSIONS

1. There is a very high level of concordance among the studies reviewed with regards to the indications for the use of the antidigoxin antibody Fab fragments compared to traditional treatment in severe acute accidental digoxin intoxications and in suicide attempts.

2. Regarding those intoxications which result from different factors, in patients undergoing digitalis therapy and which tend to be of a less severe nature, the usual therapeutic approach is traditional treatment, and the assessment of the patient just in case it might prove to be necessary to use Fab fragments.

3. According with the literature consulted, it would seem that the digoxin intoxication death rates have not decrease as much as might have been desired following the appearance of a drug so highly specific as Fab fragments.

4. Several authors suggest that in high risk patients a more active approach in the use of Fab fragments is required in order to reduce the treatment failure rates and the digoxin intoxications high death rates which are still observed.

5. Nonetheless, it is important to emphasise that none of the treatment regimes with antidigoxin antibody Fab fragments so far proposed have proven to be valid in a controlled, randomised clinical trial.

6. What are needed are clinical trials to evaluate the effect of dose and the pattern of administration on the pharmacokinetics of the Fab fragments, and which also look into it’s use at different degrees of severity of digitalis intoxication.

7. In the same vein, cost-effectiveness studies on the two therapeutic options would also be useful in cases of less severe intoxications in patients on digitalis therapy; and should not be confined to the analysis of the high cost of Fab fragments when deciding on the clinical indications for this drug.

8. In any event, a protocol is necessary for the use of this drug and it must be consensuated by the practitioners at each hospital.

ACKNOWLEDGMENTS

We wish to acknowledge CADIME and the Library at the Consejería de Salud (Health Care Authority) for their very generous and speedy collaboration in the bibliographic searches and in obtaining the articles selected.
CRITERIA FOR THE USE OF ANTIDIGOXIN ANTIBODY FAB FRAGMENTS (VIRGEN DEL ROCIO TEACHING HOSPITAL)

The use of Antidigoxin Antibodies (Fab fragments) is indicated only in the cases of life-threatening Digoxin or Digitoxin intoxications which do not respond to conventional therapy. If the following symptoms are seen then a severe intoxication may be suspected:

- severe ventricular arrhythmia (taquicardia or ventricular fibrillation)
- progressive bradyprrhythmia
- second or third degree block nonrespondant to Atropine
- Hiperkalaemia greater than 5mEq/l
- ingestion of digoxin in healthy subjects (over 10mg and 4mg in adults and children respectively); or when the ingestion of digoxin causes serum concentrations in stable state of more than 10 nanogrammes/ml.

It is estimated that 40mg of antidigoxin antibodies (Fab fragments) can neutralise 0.6 mg of Digoxin or Digitoxin. The calculation of the dose is made based on the amount of digoxin ingested or ideally based on the serum concentrations when stable.

Administration by IV infusion for 20 to 30 minutes. If there is heart failure then an IV bolus should be given. An additional dose may be given if the signs of intoxication persist.

An initial response is usually seen 30 mins after the infusion has finished and up to a maximum of 3 to 4 hours.

The main reasons why the treatment fails or their is only a partial response are:
- incorrect diagnosis of digitalis intoxication
- an inadequate dose of antidigoxin antibodies

A few adverse responses have been described such as mild allergic reactions (erythema, hives, facial tumefaction and rashes).
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