Pharmacokinetics of digoxin-specific Fab: effects of decreased renal function and age

C. Renard,[1] N. Grene-Lerouge,[1] N. Beau,[2] F. Baud[3] & J. M. Scherrmann[1]

[1] *Institut National de la Santé et de la Recherche Médicale U26, Hôpital Fernand Widal, Paris,* [2] *Laboratoire de Bio-Mathématiques, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris V, Paris and* [3] *Service de Réanimation Toxicologique, Hôpital Fernand Widal, Paris, France*

Aims To study the influence of age and renal function on digoxin-specific Fab (DS-Fab) pharmacokinetics.

Methods Sixteen patients (35–91 years) with creatinine clearance ranging from 10.6 to 122.1 ml min^{-1} who had been admitted to hospital with severe digoxin or digitoxin self-poisoning were treated with DS-Fab (80 to 800 mg). Plasma DS-Fab concentrations were determined by radioimmunoassay.

Results The mean ($\pm$s.d.) distribution and elimination half-lives, apparent volume of distribution and total body clearance were 1.1 ± 0.4 h, 20.2 ± 7.3 h, 13.1 ± 5.8 l, and 17.6 ± 10.8 ml min^{-1}, respectively. Interindividual variability of DS-Fab total body clearance was linked linearly with the decrease in creatinine clearance or with the increase in age and DS-Fab distribution volume was not dependent on creatinine clearance or age.

Conclusions The data suggest that DS-Fab should be given to elderly and renal-impaired patients at doses similar to those given to younger or normal renal function patients.

Keywords: digitalis intoxication, specific Fab, renal failure, age, pharmacokinetics

Introduction

Digoxin-specific Fab (DS-Fab) has been successfully used to treat severe cardiac glycoside toxicity [for a review see 1–3]. DS-Fab acts by neutralizing digitalis molecules in peripheral compartments allowing their dissociation from the Na^+K^+ATPase binding sites and their redistribution to the antibody space where DS-Fab can bind them [4].

Up to now, the efficacy of DS-Fab therapy has been evaluated by clinical monitoring of the patient and noting changes in the plasma-free and digoxin-bound Fab pharmacokinetics [4–6]. Although the disposition of DS-Fab is dependent on both renal and nonrenal elimination pathways, renal excretion is the major route of DS-Fab elimination [5]. In consequence, a better understanding of DS-Fab pharmacokinetics is important for effective use of DS-Fab in patients with impaired renal function and in elderly patients. In humans with normal renal function, the elimination half-life of DS-Fab is 16–30 h [1, 4, 5, 7] and a markedly delayed DS-Fab elimination has been reported in patients with end-stage renal disease [8, 9]. In general, most pharmacokinetic information is limited to data from small studies or individual case reports. For example, the existence of a relationship between DS-Fab pharmacokinetic parameters and creatinine clearance or other covariables has never been investigated.

In view of the above, the present study was designed to determine the plasma pharmacokinetics of DS-Fab (Digidot®) in 16 patients treated for cardiac glycoside intoxication and to evaluate the influence of age and renal dysfunction on DS-Fab pharmacokinetics.

Correspondence: Dr J. M. Scherrmann, INSERM U26, Hôpital Fernand Widal, 200 rue du faubourg Saint-Denis, 75475 Paris Cedex 10, France.

Methods

Patients

Sixteen patients (12 females and 4 males) aged from 35 to 91 years and weighing 49 to 93 kg were admitted to Fernand Widal hospital with severe digoxin ($n = 5$) or digitoxin ($n = 11$) self-poisoning. Signs of intoxication were: nausea, vomiting, arrhythmia (first-degree atrioventricular block: $n = 7$; third-degree atrioventricular block: $n = 5$; tachycardia: $n = 3$; ventricular extrasystoles: $n = 3$) and hyperkalaemia ($K^+ > 5.5$ mmol l^{-1}, $n = 9$). Plasma digoxin concentrations before starting the DS-Fab treatment ranged from 3.6 to 40.3 mmol l^{-1} and plasma digitoxin concentrations from 131 to 397 mmol l^{-1}. All patients were treated with DS-Fab (Digidot®, Boehringer, Mannheim, RFA). DS-Fab doses ranging from 80 to 800 mg according to the ingested dose were infused over 0.25 to 2 h. The DS-Fab dose given was that required for equimolar neutralization of the total body load of glycoside or for half equimolar neutralization if the patient's condition was not critical and if no poor prognostic factors were present. Briefly, these prognostic factors were: 1) age (> 55 years); 2) male sex; 3) underlying heart disease; 4) high-degree atrioventricular block (first-degree atrioventricular block is not a poor prognostic factor); 5) peak potassium level above 5.5 mmol l^{-1} [10].

Collection and analysis of plasma samples

Blood samples were taken for digitalis monitoring following patient admission and for determination of plasma creatinine and DS-Fab concentrations. Additional blood samples were collected just before DS-Fab administration, at infusion midpoint, at the end of infusion, 6 h afterwards and then every day until recovery. All blood samples were centrifuged at $+4^{\circ}$ C immediately after collection and plasma was stored at -20° C until analysis. Creatinine clearance was determined using the Cockroft and Gault equation [11]. Plasma concentrations of DS-Fab were determined by radioimmunoassay as previously described [12].

DS-Fab pharmacokinetic analysis

Plasma concentration-time data were analyzed using the Siphar Software (SIMED, Créteil, France). The log-linear plasma concentration-time data were fitted by linear regression analysis to obtain distribution and terminal disposition rate constants. The distribution ($t_{\frac{1}{2}\lambda,1}$) and terminal ($t_{\frac{1}{2},z}$) half-lives were calculated as $0.693/\lambda_z$. The area under the plasma DS-Fab concentration-time curve from zero to infinity (AUC) was determined by linear trapezoidal estimation from 0 to the last measured time, with extrapolation to infinity (less than 20% of total AUC) by adding the value of the last measured plasma concentration divided by the terminal disposition rate constant. Total body clearance (CL) was calculated by the ratio between the DS-Fab dose and the AUC. The volume of distribution at steady-state (V_{ss}) was calculated using the following equation [13]:

$$V_{ss} = (D \times \mathrm{AUMC}/\mathrm{AUC}^2) — (D \times t)/(2 \times \mathrm{AUC})$$

where D is the DS-Fab dose, t the infusion duration and AUMC the area under the first moment-time curve from time zero to infinity.

Statistical analysis

All data are given as mean $\pm$ s.d. Standard linear regression was used when errors in measurements occurred in only one dependent variable (GraphPad Prism®, San Diego, USA). When errors could occur in both sets of data, linear regression analysis was performed using the method of Deming [14]. Significance was set at $P<0.05$.

Results

Reversal of digitalis-induced dysrhythmias, hyperkalaemia and myocardial depression was observed within 4–8 h of the DS-Fab administration. No adverse effects were noted and all patients recovered from the digitalis toxicity.

Post-infusion plasma DS-Fab kinetics were characterized by a biexponential decline in all patients. Distribution and terminal half-lives ranged from 0.5 to 1.9 h and from 11.0 to 34.5 h, respectively. The volume of distribution ranged from 6.0 to 28.2 l and total body clearance from 4.5 to 39.2 ml min^{-1} (Table 1). The decrease in DS-Fab total body clearance was linearly related to the creatinine clearance decrease. Linear regression calculated with the Deming method gave $\mathrm{CL} = 12.63 + 0.11 \times \mathrm{CL_{CR}}$ ($r^2 = 0.56$) (Figure 1). A similar analysis for the distribution volume gave $V_{ss} = 11.71 + 0.03 \times \mathrm{CL_{CR}}$ ($r^2 = 0.05$).

Standard linear regression analysis of the influence of patient age on DS-Fab total body clearance and volume of distribution gave $\mathrm{CL} = 40.22 - 0.33 \times \mathrm{age}$ ($r^2 = 0.29$, $P = 0.03$) (Figure 1) and $V_{ss} = 16.23 - 0.04 \times \mathrm{age}$ ($r^2 = 0.02$, $P = 0.61$), respectively.

Furthermore, age and creatinine clearance were linearly correlated according to the equation $\mathrm{CL_{CR}} = 157.20 - 1.62 \times \mathrm{age}$ ($r^2 = 0.79$, $P < 10^{-3}$).

Discussion

Today, DS-Fab is successfully used in digitalis intoxication treatments [1, 2]. Patients who receive DS-Fab are characterized by an extremely wide variability in terms of age, renal function, cardiac failure, and severity of digitalis intoxication. The influence of these inter-patient variability factors can be evaluated by following DS-Fab pharmacokinetics and searching for some degree of correlation between pharmacokinetic parameters and physiological variables. The few studies on DS-Fab pharmacokinetics concern either patients with normal renal function [4, 5] or end-stage renal disease [5, 8, 9, 15]. Most of these studies are limited to a small number of patients, which precludes assessment of any relationship between variables.

The 16 patients included in our study consisted of 11 elderly patients (aged 70–90 years) and five adults (aged 35–63 years). Their creatinine clearance spanned a wide range (10.6 to 122.1 ml min^{-1}). The use of the Cockroft and Gault formula to assess creatinine clearance in ill elderly patients could be questioned, despite reports that found the formula appropriate in healthy or ambulatory individuals over 65 years of age [16]. As our patients were not affected by obesity, severe muscle wasting, or severe liver disease, and as creatinine clearance was stable in all patients during the pharmacokinetic study, we used the Cockroft and Gault formula as a guide to renal function.

Pharmacokinetic parameters calculated in our study were within the range of those previously reported by Schaumann *et al.* [5] where elimination half-life, volume of distribution, and total body clearance ranged respectively from 6.5 to 27.2 h, 8.4 to 55 l, and 10.2 to 37.3 ml min^{-1}. However, our volumes of distribution were lower than the body extracellular fluid, as also found by Ujhelyi [9] who reported volumes of distribution ranging from 10.3 to 23.8 l.

Our study demonstrates a wide intersubject variability in pharmacokinetic parameters characterized by a 9- and 5-fold difference between extreme values for total clearance and volume of distribution, respectively. Among the factors that could explain such variability, age and creatinine clearance were investigated and we found a linear decrease in DS-Fab total body clearance when creatinine clearance decreased. Linear regression analysis using the Deming method showed that DS-Fab total body clearance was linked linearly to renal function, whereas DS-Fab volume of distribution was not. We found a linear decrease of DS-Fab total body clearance when age increased and no linear link between DS-Fab volume of distribution and age. The concomitant influence of age and creatinine clearance on DS-Fab total body

Table 1 Pharmacokinetic parameters of DS-Fab.

Patient	CL_{CR} (ml min^{-1})	$t_{\frac{1}{2},\lambda 1}$ (h)	$t_{\frac{1}{2},z}$ (h)	V_{SS} (l)	CL (ml min^{-1})
1	10.6	0.6	25.7	10.8	5.2
2	16.8	1.7	19.7	6.0	6.2
3	18.8	1.2	27.9	20.6	19.5
4	21.8	1.9	22.0	8.9	12.5
5	22.6	0.6	27.7	10.7	4.5
6	24.8	1.7	26.0	7.6	8.5
7	29.0	1.4	23.9	14.6	19.7
8	31.6	1.1	13.1	7.7	13.1
9	32.4	1.2	34.5	28.2	28.2
10	40.3	0.8	12.5	15.1	26.2
11	42.9	0.8	13.7	9.1	11.1
12	57.5	1.1	16.4	11.3	9.3
13	66.5	1.1	12.1	9.8	23.4
14	79.9	1.1	24.0	18.4	18.1
15	100.5	0.5	11.0	15.6	36.2
16	122.1	0.9	12.4	15.4	39.2
Mean	44.9	1.1	20.2	13.1	17.6
s.d.	32.2	0.4	7.3	5.8	10.8
Range	10.6–122.1	0.5–1.9	11.0–34.5	6.0–28.2	4.5–39.2

CL_{CR}, creatinine clearance; $t_{\frac{1}{2},\lambda 1}$, $t_{\frac{1}{2},z}$ half-lives of distribution and elimination phases, respectively, V_{SS}, steady-state volume of distribution; CL, total body clearance.

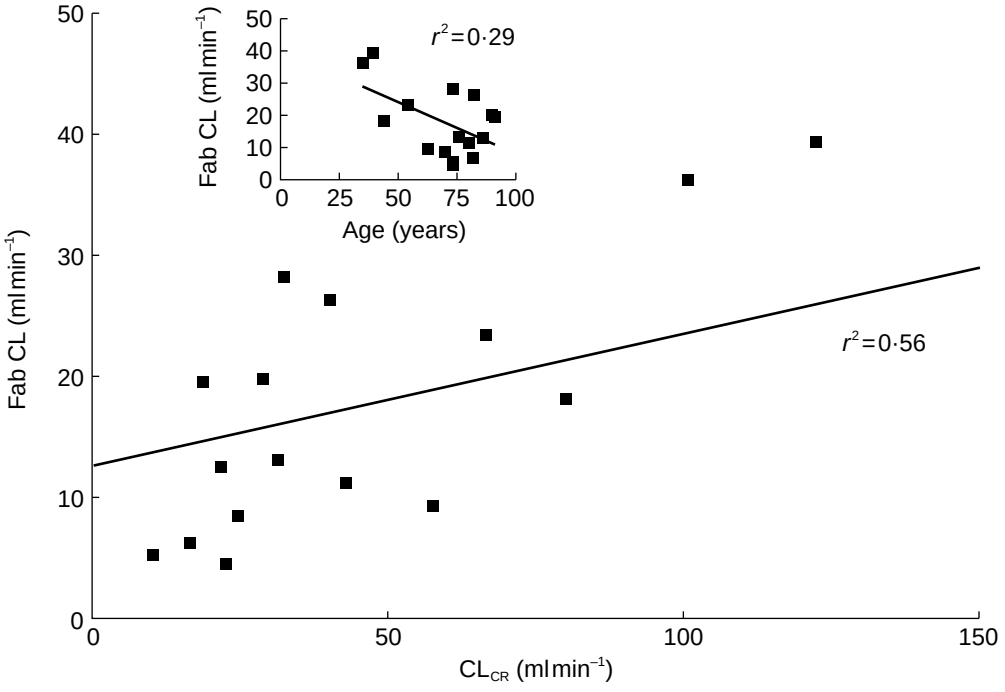

Figure 1 Linear regression (Deming method) of DS-Fab total body clearance with creatinine clearance and linear regression (classical method) of DS-Fab total body clearance with age (insert).

clearance was not surprising because age and creatinine clearance were correlated.

In our study these variations in DS-Fab total body clearance and volume of distribution resulted in plasma terminal half-lives ranging from 11.0 to 34.5 h. In other studies, more pronounced increases in DS-Fab terminal half-life were observed mainly in end-stage renal disease. A terminal half-life of 96 h with a systemic clearance of 1.8 ml min^{-1} has been reported in an elderly female patient infused with 80 mg of DS-Fab [15]. Allen [8] described elimination half-lives for DS-Fab of 25–73 h in four patients with moderate to severe renal impairment. Similarly, Ujhelyi [9] reported terminal half-lives ranging from 59 to 137 h in five digoxin-intoxicated patients, four with end-stage renal disease receiving long-term haemodialysis, and one with severe renal dysfunction.

The last two studies clearly show that end-stage or severe renal disease can markedly reduce DS-Fab elimination and amplify our finding on the link between DS-Fab total body clearance and renal function. In patients with renal impairment the longer body residence of DS-Fab raises the problem of monitoring digoxin or digitoxin after DS-Fab administration. As DS-Fab interferes with most competitive clinical immunoassays [6] it does not give reliable values of

digoxin or digitoxin concentrations as long as DS-Fab is circulating in the body, thus special care must be taken when assaying digitalis in patients with reduced renal function.

Furthermore, our study raises the question of the influence of reduced DS-Fab clearance on Fab dosage in patients with poor renal function. In clinical practice, the dose of DS-Fab administered varies depending on the amount of digoxin to be neutralized, assuming that a stoichiometric Fab dose versus digoxin body load is required. In fact, the effect of renal failure on the reduction of DS-Fab total clearance is a longer body residence time of the DS-Fab-digoxin complexes which could be potentially beneficial. The longer DS-Fab fragments circulate, the greater the probability that digoxin molecules in deep compartments will be neutralized by DS-Fab [17]. Moreover, as long as digoxin molecules remain tightly bound to the DS-Fab, no further digoxin toxicity would be expected from a longer circulation time of DS-Fab-digoxin complexes. Our data suggest that DS-Fab should be given to the elderly and patients with renal impairment at the same dose as for younger or normal renal function patients.

References

1 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. *Circulation* 1990; **81**: 1744–1752.

2 Hickey AR, Wenger TL, Carpenter, *et al*. Digoxin immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Col Cardiol* 1991; **17**: 590–598.

3 Ujhelyi M, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; **28**: 483–493.

4 Smith TW, Haber E, Yeatman L, Butler VP. Reversal of advanced digoxin intoxication with Fab fragments of digoxin specific antibodies. *N Engl J Med* 1976; **294**: 797–800.

5 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**: 527–533.

6 Ujhelyi M, Green P, Cummings D, Robert S, Vlasses P, Zrowitz B. Determination of free serum digoxin concentrations in digoxin toxic patients after administration of digoxin Fab antibodies. *Ther Drug Monit* 1992, **14**: 147–154.

7 Smolarz A, Roesch E, Lenz E, Neubert H, Abshagen P. Digoxin specific antibody (Fab) fragments in 34 cases of severe digitalis intoxication. *Clin Toxicol* 1985; **23**: 327–340.

8 Allen NM, Dunham GD, Sailstad JM, Findlay JWA. Clinical and pharmacokinetic profiles of digoxin immune Fab in four patients with renal impairment. *DICP* 1991; **25**: 1315–1320.

9 Ujhelyi MR, Robert S, Cummings DM, *et al*. Disposition of digoxin immune Fab in patients with kidney failure. *Clin Pharmacol Ther* 1993; **54**: 388–394.

10 Bismuth C, Gaultier M., Conso F. Hyperkalemia in acute digitalis poisoning : Prognostic significance and therapeutic implications. *Clin Toxicol* 1973; **6**: 153–162.

11 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.

12 Vo Thanh-Barthet C, Urtizberea M, Sabouraud AE, Cano NJ, Scherrmann JM. Development of a sensitive radioimmunoassay for Fab fragments: Application to Fab pharmacokinetics in humans. *Pharm Res* 1992; **10**: 692–696.

13 Gibaldi M, Perrier D. *Pharmacokinetics 2nd ed*. Marcel Dekker, New-York, 1982.

14 Deming WE. *Statistical adjustment of DATA*. John Wiley and Sons, New-York, 1943.

15 Sinclair AJ, Hewick DS, Johnston PC, Stevenson IH, Lemon M. Kinetics of digoxin and antibody fragments during treament of digoxin toxicity. *Br J Clin Pharmacol* 1989; **28**: 352–356.

16 Nicoll S, Sainsbury R, Bailey R, *et al*. Assessment of creatinine clearance in healthy subjects over 65 year of age. *Nephron* 1991; **59**: 621–625.

17 Scherrmann JM. Antibody treatment of toxin poisoning. Recent advances. *Clin Toxicol* 1994; **32**: 363–375.

(*Received 25 April 1996, accepted 14 April 1997*)

