Digoxin therapeutic drug monitoring: age influence and adverse events

Suivi thérapeutique pharmacologique de la digoxine : influence de l'âge et effets indésirables

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RÉSUMÉ

Introduction : La digoxine est un glycoside cardiotonique, indiqué dans le contrôle de la réponse ventriculaire rapide dans la fibrillation auriculaire et pour réduire les hospitalisations par insuffisance cardiaque. L'intervalle thérapeutique de la digoxine est étroit. Ainsi, dans le traitement des sujets âgés (≥ 65 ans), il est important de prescrire la dose optimale de digoxine afin de prévenir la toxicité et dans ce cas le suivi thérapeutique pharmacologique (STP) de la concentration résiduelle (C0) de digoxine trouve son intérêt.

Objectif : L'objectif était d'évaluer les C0 de digoxine, l'influence de l'âge sur ses paramètres pharmacocinétiques et de rapporter les évènements indésirables induits.

Méthodes : Il s'agit d'une étude rétrospective. Nous avons inclus les patients adressés au service de pharmacologie clinique pour dosage de la C0 de digoxine par une technique immunoenzymatique par polarisation de fluorescence automatisée. Les intervalles thérapeutiques de C0 de la digoxine étaient : 1 à 2,5 ng.mL-1 pour les enfants, 0,8 à 2 ng.mL-1 pour les adultes et 0,5 à 0,9 ng.mL-1 pour les sujets âgés (≥ 65 ans) dans la fibrillation auriculaire et l'insuffisance cardiaque.

Résultats : Nous avons collecté 183 prélèvements de 132 patients. Le sex-ratio M/F était 0,47. La moyenne d'âge était 60 ans et 57% des patients étaient des sujets âgés. La dose moyenne de digoxine était 0,3 mg.j-1. Chez les sujets âgés, 45% recevaient des doses quotidiennes supérieures à 0,125 mg.j-1. La C0 moyenne de digoxine était 1,6 ng.mL-1. Il y avait plus de C0 supra-thérapeutiques chez les sujets âgés (p<0,0001). Il n'y avait pas de corrélation entre les C0 et les doses quotidiennes de digoxine. Les évènements indésirables, essentiellement cardiaques et digestifs, étaient rapportés chez 47 patients (36%), parmi lesquels 47% étaient des sujets âgés.

Conclusion: Le STP est un moyen utile dans la prévention de la toxicité de la digoxine, surtout chez les sujets âgés où le diagnostic peut être difficile à établir.

Mots clés : Suivi thérapeutique pharmacologique ; digoxine; sujet âgé ; fibrillation auriculaire ; insuffisance cardiaque ; toxicité

SUMMARY

Introduction: Digoxin is a cardiac glycoside, used to control rapid ventricular rates in atrial fibrillation and to reduce the hospitalizations due to heart failure. Digoxin has a narrow therapeutic range. So, in the treatment of older patients (≥ 65 years), it is important to set the optimal dose of digoxin to prevent toxicity and therapeutic drug monitoring of digoxin trough plasmatic concentration (C0) may be useful.

Aim: To assess measured C0, to evaluate age influence on digoxin pharmacokinetic parameters and to report adverse events in patients administered digoxin.

Methods: It consisted in a retrospective study. We included all the patients addressed to the department of clinical pharmacology for digoxin C0 measurement by an automated fluorescence polarization immunoassay. Therapeutic ranges of digoxin C0 were: 1 to 2.5 ng.mL-1 in children, 0.8 to 2 ng.mL-1 in adults and 0.5 to 0.9 ng.mL-1 in older adults (≥ 65 years) in atrial fibrillation and heart failure.

Results: We collected 183 samples from 132 patients. Sex ratio M/W was 0.47. Mean age was 60 years and 57% of patients were older adults. Mean dose of digoxin was 0.3 mg.day-1. In older adults, 45% were administered daily doses over 0.125 mg.day-1. Mean digoxin C0 was 1.6 ng.mL-1. There was more supra-therapeutic C0 in older adults than younger ones (p<0.0001).There was no correlation between C0 and daily dose of digoxin. Adverse events, mainly cardiac and digestive, were reported in 47 patients (36%), among this population 47% were older adults.

Conclusion: TDM is useful to prevent toxicity, mainly in older adults where diagnosis may be difficult to establish.

Key words: Therapeutic drug monitoring; digoxin; elderly; atrial fibrillation; heart failure; toxicity

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INTRODUCTION

Digoxin is a cardiac glycoside used to control rapid ventricular rates in atrial fibrillation and to reduce hospitalizations due to heart failure (HF). Digitalis, first introduced to clinical cardiology by William Withering in Birmingham around 1785, has widely been used as a positive inotrope in HF and for its negative chronotropic activity in atrial fibrillation [1, 2]. Digoxin is incompletely absorbed when taken orally. Distribution follows a 2-compartment model: the first is plasma and other rapidly equilibrating tissues and the second being more slowly equilibrating tissues including the myocardium. Half-life of digoxin is 36 hours that can be prolonged in case of renal dysfunction [3-5].

Digoxin nowadays is not a drug of choice to control heart rate in atrial fibrillation but remains a useful agent for the adjunctive treatment of HF due to impaired left ventricular systolic function in patients of all ages [6]. Digoxin has no influence on survival but may decrease morbidity.

In older patients (≥65 years) [7], it is important to set the optimal dose, considering age, gender, renal function, concomitant diseases and medications used [8]. For adult, recommended doses are 0.125-0.25 $mg.day^{-1}$[9]. Lesauskaitė et al suggested that the recommended daily dose of digoxin for elderly is 0.125 $mg.day^{-1}$ [10]. Digoxin presents a complex pharmacokinetic profile, a narrow therapeutic range (TR) and multiple drug interactions [6,11]. Then therapeutic drug monitoring (TDM) of its trough plasmatic concentration (C_0) may be useful to prevent toxicity. In fact, Rathore et al noted that patients with digoxin C_0 between 0.5 to 0.8 $ng.mL^{-1}$ had a 6.3% lower mortality rate compared with patients receiving placebo. Whereas patients with digoxin C_0 superior to 1.2 $ng.mL^{-1}$ had an 11.8% higher absolute mortality rate than patients receiving placebo [12]. Lewis has shown that the therapeutic effect is near maximal at 1.48 $ng.mL^{-1}$ and that the incidence of toxicity increases dramatically at concentrations over 2.8 $nmol.L^{-1}$ [3]. Values above 2.5 $ng.mL^{-1}$ are generally considered toxic [4]. Digoxin adverse reactions incidence consist in cardiac and extra-cardiac toxicity.

Aim: We aimed through this study to assess measured C_0, to evaluate age influence on digoxin pharmacokinetic parameters and to report adverse events in patients administered digoxin.

METHODS

- **Patients and samples**

It consisted in a retrospective study (January 2009 to July 2018). We included all the patients addressed to the department of clinical pharmacology for a digoxin C_0 measurement. Blood was collected just before the administration of digoxin when steady state was established. Blood samples were addressed with an information form including patient identity, digoxin indication, posology and date of administration onset, associated medications and adverse events. In this study, we excluded all the patients in whom age wasn't reported.

- **Therapeutic drug monitoring of digoxin**

The samples were analyzed, at the same day of blood collection, by an automated fluorescence polarization immunoassay until 2013 then by an automated antibody conjugated magnetic immunoassay (Axsym® then Architect® from Abbott® laboratories). The lower limit of detection was 0.3 ng.mL-1. Linearity was assessed between 0.3 and 4 ng.mL- with a correlation coefficient ≥ 0.9. TR of digoxin C0 were considered 1 to 2.5 ng.mL-1 in children, 0.8 to 2 ng.mL-1 [6] in adult and 0.5 to 0.9 ng.mL-1 in older adults (≥65 years) in atrial fibrillation and HF [10]. We used statistical tests as following: Mann Whitney test to compare quantitative variables and Chi2 test to compare percentages of qualitative variables.

RESULTS

In this study, we collected 183 samples from 132 patients with a mean of 1.4 sample per patient varying from one to 12 samples per patient (table 1). Sex ratio men/women was 0.47. Mean age was 60 years (SD = 23 years). Among patients, 75 (57%) were older adults (87 samples). In older adults, the ratio men/women was 0.51.

Patients were addressed from different departments: 38 (29%) from cardiology, 38 (29%) from emergency and intensive care departments and 56 (42%) from other departments.

Digoxin was indicated in 50 patients for atrial fibrillation, 25 for HF and nine took digoxin for a suicide attempt, in the other cases digoxin indication wasn't specified. There was a mean of two years between digoxin onset and digoxin

first TDM. Renal insufficiency was noted in 15 patients: nine women and six men (creatinine values were not reported).

Mean dose of digoxin was 0.3 mg/day (SD = 0.16 mg/day) and mean digoxin C_0 was 1.6 ng.mL-1 (SD =1.5 ng.mL^{-1}). There was no association between C_0 and digoxin posology, r = 0.08 (figure 1). In this study, C_0 were in the therapeutic range in 23.5%, sub-therapeutic in 33.5% and supra-therapeutic in 43%.

Among patients, 20 presented an involuntary digoxin intoxication (37 samples) and nine (25 samples) took digoxin for a suicide attempt (table 2). Mean age was, respectively 64 and 25 years, significantly different in the two groups (p=0.001). Mean first C_0 wasn't significantly different in the two groups (p=0.13). First C_0 was supra-therapeutic in 12 cases among 20 in involuntary intoxication and in six cases among nine in voluntary intoxication. In 13 patients, digoxin C_0 was assessed to control compliance.

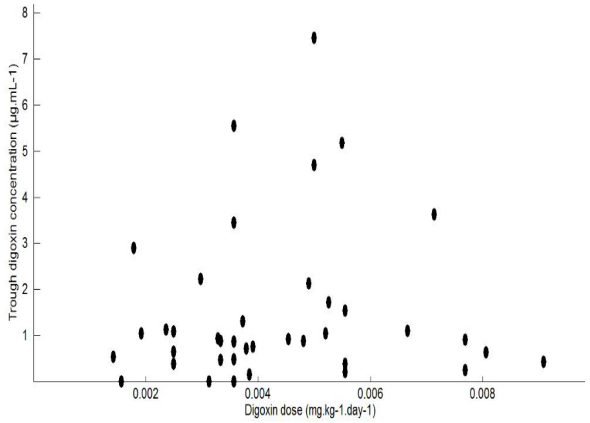

Figure 1. Distribution of trough digoxin concentrations in function of digoxin doses

Mean digoxin C_0 was 1.7 ng.mL^{-1} in older adults (SD = 1.8 ng.mL^{-1}) and difference wasn't significant between these C_0 in older adults and the other patients (p=0.13). In older adults, mean dose of daily digoxin was 0.27 mg.day^{-1}. In 45% of cases (39 samples) administered daily doses were higher than 0.125 mg.day^{-1}. The distribution of C_0 and C_0/Dose (C_0/D) and comparisons of the results are summarized in table 3. There wasn't significant difference in C_0/D in the two groups of concern (p =0.2). There was a significant difference in C_0 with more supra- therapeutic C_0 in older adults than younger ones if Chi2 test was applied (p<0.0001).

Adverse events were reported in 47 patients (36%) from whom 64 samples were collected: 51 in 35 women and 13 in 11 men (sex ratio men/women = 0.31). Among these patients, adverse events were reported in 22 older adults (47%). The adverse events consisted in cardiac events in 29 patients and 45 samples (dysrhythmia, bradycardia and conduction disorders), digestive troubles in 28 patients and 39 samples (vomiting, nausea and diarrhea), visual disturbances in six women and paresthesia in a man (table 4). In these patients, digoxin C_0 was supra therapeutic in 30% of case varying from 22% in case of one adverse event report per patient to 50% in those presenting three adverse events.

Table 1. Distribution of the samples per patients

Samples	1	2	3	5	6	7	12
Patients	111	13	2	1	2	1	1
% patients	84%	10%	1,5%	1%	1,5%	1%	1%

Table 2. Characteristics of intoxicated patients

	Voluntary intoxication	**Involuntary intoxication**	**p**
Number	9	20	_
Men/women	0.29	0.33	_
Elderly patients	0	11	_
Mean age (years)/ Standard deviation (years)	25/8	64/22	0.001
Samples mean number per patient	3	1.8	_
Mean first C_0 (ng.mL^{-1}) /standard deviation (ng.mL^{-1})	3.3/1.7	2.3/2.5	0.13

Table 3. Distribution of doses, C_0 and C_0/D according to age

Means and percentages	< 65 years old (57 patients, 96 samples)	≥ 65 years old (75 patients, 87 samples)	p
Mean dose (mg.day^{-1})/SD	0.35/0.2	0.27/0.1	0.31
Mean dose (mg.kg^{-1}.day^{-1})	0.004	0.004	0.87
Mean C_0 (ng.mL^{-1})/SD	1.38 / 1.3	1.74 / 1.76	0.13
C_0/Dose	361 (14 patients)	426 (26 patients)	0.2
% Sub therapeutic C_0	46%	19%	<0.0001
% Supra therapeutic C_0	29%	59%	
% C_0 out of the TR	75%	78%	_

Table 4. Adverse drug reactions

	One	Two	Three	Total of patients
Number of adverse drug reactions	32	13	2	47
Number of patients aged <65 years	18	6	1	25
Number of older adults	14	7	1	22
Number of patients with supra therapeutic C_0 (%)	7 (22%)	6 (46%)	1 (50%)	14 (30%)

C_0: trough plasmatic digoxin concentration

DISCUSSION

Digoxin has historically been one of the most commonly prescribed drugs for treatment of chronic HF with reduced ejection fraction, but its use has declined over the past two decades since the publication in 1997 of results of the Digitalis Investigation Group (DIG) trial. In fact, DIG trial showed that digoxin had a neutral effect on all-cause mortality [13].

Whereas, this drug use had proven its interest. In the one hand, digoxin is advantageous in terms of cost, in terms of effectiveness when given once daily and in terms of avoidance of harmful adverse reactions as increased blood pressure, renal or potassium disorders. Such factors, may limit application of other effective drugs in HF. In the other hand, a strong association emerged between the safety and efficacy of digoxin and C_0. This suggested that therapeutic digoxin C_0 optimizes its therapeutic benefit and avoids toxicity.

In this study, we aimed to assess measured C_0, to evaluate age influence on digoxin pharmacokinetic parameters and to report adverse events in patients administered digoxin.

We collected 183 samples from 132 patients with a mean of 1.4 sample per patient. Sex ratio men/women was 0.47. Among patients, 57% were older adults.

Digoxin is commonly prescribed in elderly patients. The percentage of older patients administered digoxin in 528 elderly patients in an academic geriatrics clinic was 17% [14].

In our study, assessment of digoxin C_0 showed that supra therapeutic C_0 was significantly higher in older adults (59% vs 29%) despite a lower administered dose of digoxin in older patients (0.27 vs 0.35 mg.day^{-1}) showing a higher bioavailability of digoxin in older adults.

A Canadian study concerning 1000 nursing home residents showed that 32% of elderly HF patients were treated with digoxin and that C_0 were higher than toxic levels in 30% of them Ageing results in prolonged elimination half-life because of lower reported digoxin clearance [16] and decreased volume of distribution for digoxin explained by low lean body mass [17]. Cusack et al reported a longer half-life (37 to 70 hours), higher bioavailability (90 to 145 nmol.mL^{-1}.hr^{-1}), lower absorption (84% to 76%), decreased volume of distribution (5.3 to 4.1 L.Kg^{-1}) and slower plasma clearance (106 to 37 mL.min^{-1}) for the older cohort [18].

In our study, 45% of older patients received digoxin dose higher than recommended.

In a Canadian study, 80% of older patients received doses higher than recommended [15]. Because of pharmacokinetic changes due to age and the difficulty to differentiate pharmacokinetic changes resulting from aging as coexisting diseases and other medications, it is recommended to start medication at a low dose and to increase it slowly with close clinical monitoring [19,20]. In this case, TDM of digoxin C_0 may be helpful.

In our study, adverse events were reported in 47 patients and sex ratio men/women was 0.31. In a study of Budnitz et al, made from 2007 to 2009, in emergency hospitalized older american adults, digoxin was the seventh inducing drug of adverse events [21].

Among these patients, adverse events were reported in older adults in 47% of cases. They were mainly cardiac and digestive. Barron et al reported that digoxin adverse reactions may occur in 48 to 80% be cardiovascular, neurological or gastrointestinal disturbances [8]. Passmore and al reported that anorexia was a particularly common sign of digoxin toxicity among the elderly [22].

Extra-cardiac toxic effects of digoxin during long term therapy may go undiagnosed because of their gradual onset or nonspecific nature [8].

Visual disturbances were reported in six women. The mechanism underlying ocular symptoms is presumed to be related to Na+ K+ATPase inhibition but remains speculative [23,24].

Ophthalmologic tests considered most useful to support a diagnosis of digoxin intoxication.

Studies reported that impaired color vision is not associated to high digoxin C_0 [25].

Dally et al reported that digoxin induced mortality was significantly higher in patients over 55 years (p= 0.0001) [26]. No case of mortality was reported in our study.

In our patients presenting adverse events, digoxin C_0 was supra therapeutic in 30% of case varying from 22% in case of one adverse event report per patient to 50% of cases in case of three adverse events report per patient.

Ehle et al [27] and Hack [28] reported an association between high digoxin C_0 and digoxin induced adverse events as bradydysrythmia, nausea or vomiting, abdominal pain, diarrhea and neuropsychiatric symptoms as altered mental status, headache, hallucinations and convulsions.

Risk factors in case of digoxin intoxication are: male sex, hyperkaliemia, advanced atrioventricular block, underlying cardiac disease and drug interactions [8]. In this study, sex ratio men/women was 0.47 but no other risk factors were cited. Digoxin therapeutic monitoring should prevent digoxin intoxication.

In this study, we evaluated age influence on digoxin pharmacokinetic parameters and assessed adverse events in patients administered digoxin. Age influence was reported in term of TDM indication and the proportion of supra therapeutic digoxin C_0.

In this study, we encountered some limits:

- the number of patients was limited: this showed the under prescription of TDM of digoxin and the fact that digoxin prescription is limited;
- the adverse reaction probability scales were not assessed of a lack of information;
- a lack of information about clinical and biological parameters, evolution, drug interactions in patients.

CONCLUSION

Digoxin nowadays is not a drug of choice in atrial fibrillation but remains a useful agent for the adjunctive treatment of chronic HF. Many factors contribute to increase risk of digoxin toxicity

in older adults and diagnosis can be difficult in this group. TDM is useful mainly to prevent toxicity, mainly in older adults.

REFERENCES

1. Yang EH, Shah S, Criley JM. Digitalis toxicity: a fading but crucial complication to recognize. Am J Med. 2012;125(4):337-43.
2. Ziff OJ, Lane DE, Samra M, Griffith M, Kirchhof P, Lip GYH et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ. 2015;351:h4451.
3. Lewis RP. Digitalis. In: Leier CV, editor. Cardiotonic drugs: a clinical survey. New York: Marcel Dekker, 1987:85-150.
4. Ellenhorn MJ, Barceloux DG. Medical toxicology: diagnosis and treatment of human poisoning. New York: Elsevier, 1988.
5. Ritschel WA, Kearns GL. Handbook of basic pharmacokinetics ... including clinical applications. 6th ed. Washington, DC: American Pharmacists Association; 2004.
6. 2Cheng JW, Rybak I. Use of Digoxin for Heart Failure and Atrial Fibrillation in Elderly Patients. Am J Geriatr Pharmacother. 2010;8(5):419-27.
7. http://www.who.int/ageing/publications/active_ageing/en/
8. Barron SW, Bismuth C, Muszynski J. Advances in the Management of Digoxin.
9. Currie GM, Wheat JM, Kiat H. Pharmacokinetic Considerations for Digoxin in Older People. Open Cardiovasc Med J. 2011;5:130-5.
10. Lesauskaitė V, Jankauskas T. Use of digoxin in older patients. Gerontologica 2010; 11(2): 120–3.
11. Rich MW, Mc Sherry F, Williford WO, Yusuf S; Digitalis Investigation Group. Effect of Age on Mortality, Hospitalizations and Response to Digoxin in Patients with Heart Failure: The DIG Study. J Am Coll Cardiol. 2001;38(3):806-13.
12. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003;289(7):871-8.
13. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–533.
14. Fishkind D, Paris BE, Aronow WS. Use of digoxin, diuretics, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers in older patients in an academic hospital-based geriatrics practice. J Am Geriatr Soc.1997;45:809–12.
15. Misiaszek B, Heckman GA, Merali F, et al. Digoxin prescribing for heart failure in elderly residents of long-term care facilities. Can J Cardiol 2005; 21: 281-6.

16. Ewy GA, Kapadia GG, Yao L, Lillin M, Marcus FI. Digoxin metabolism in the elderly. Circulation. 1969; 39: 449-53.
17. Marquet P. Suivi thérapeutique des digitaliques. In : Marquet P. Suivi thérapeutique pharmacologique pour l'adaptation de posologie des médicaments. Paris: Elsevier 2004: 324-30.
18. Cusack BJ, Kelly J, O'Malley K, Noel J, Lavan J, Horgan J. Digoxin in the elderly: pharmacokinetic consequences of old age. Clin Pharmacol Ther. 1979; 25: 772-6.
19. Durnas C, Loi CM, Cusck BJ. Hepatic drug metabolism and aging. Clin Pharmacokinet. 1990; 19:359-89.
20. Wynne H. Drug metabolism and ageing. J Br Menopause Soc. 2005; 11:51-6.
21. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007;147:755–65.
22. Passmore AP, Johnston GD. Digoxin toxicity in the aged: characterizing and avoiding the problem. Drugs& Aging. 1991;1(5): 364-79.
23. Closson RG. Visual hallucinations as the earliest symptom of digoxin intoxication. Arch Neurol. 1983;40(6):386.
24. Aronson JK, Ford AR. The use of colour vision measurement in the diagnosis of digoxin toxicity. Q J Med. 1980;49(195):273–82
25. Lawrenson JG, Kelly C, Lawrenson AL, Birch J. Acquired colour vision deficiency in patients receiving digoxin maintenance therapy. Br J Ophthalmol. 2002;86(11):1259–61.
26. Dally S, Alperovitch A, Lagier G, Bismuth C, Fournier E. Facteurs pronostiques de l'intoxication digitalique aigue. Presse Med. 1981;10(27):2257-60.
27. Ehle M, Patel C, Giugliano RP. Digoxin: clinical highlights: a review of digoxin and its use in contemporary medicine. Crit Pathw Cardiol 2011;10(2):93-8.
28. Hack JB. Cardiac steroids. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. Goldfrank's toxicologic emergencies. 9th ed. New York, NY: McGraw-Hill Medical; 2011. p. 936-45.