CorSalud 2018 Jul-Sep;10(3):211-218

CorSalud

Cuban Society of Cardiology

Original Article

Cardiocentro Ernesto Che Guevara Santa Clara Cuba

Digoxin prescription in geriatric patients of the primary health care

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: January 4, 2018
Accepted: February 10, 2018

Competing interests
The authors declare no competing interests

Acronyms
ACE: angiotensin-converting enzyme
AF: atrial fibrillation
CHF: congestive heart failure
HBP: high blood pressure

ABSTRACT

Introduction: Digoxin is one of the most used drugs in cardiovascular diseases, frequent in the geriatric patient, characterized by its narrow therapeutic margin.
Objectives: To characterize the prescription of digoxin and identify problems related to its prescription in geriatric patients.
Method: A descriptive and cross-sectional study was carried out on the use of drugs, indication-prescription type, in 23 patients with digoxin indication, treated at the Policlínico José Martí in Santiago de Cuba, from April to June 2017.
Results: In the case study, women (78.26%), ages between 70-74 years (26.08%), and patients with one or two associated diseases were more likely to use it. Diagnosis of cardiovascular diseases by Comprehensive General Medicine was prevalent, associated with a greater frequency of diuretics and antiplatelet drugs intervention group. The group with the lowest probability of survival was that of late treatment.
Conclusions: The prescription of digoxin may be considered as rational, although there is a possibility of drug interactions that could lead to toxic effects or therapeutic failure.
Keywords: Digoxin, Drug prescriptions, Geriatric patients, Drug interactions

Prescripción de digoxina en pacientes geriátricos de la atención primaria de salud

RESUMEN

Introducción: La digoxina es un medicamento muy empleado en algunas enfermedades cardiovasculares, que son frecuentes en el paciente geriátrico, y está caracterizada por su estrecho margen terapéutico.
Objetivo: Caracterizar la prescripción de digoxina e identificar problemas relacionados con su prescripción en pacientes geriátricos.
Método: Se realizó un estudio descriptivo y transversal, de utilización de medicamentos, de tipo indicación-prescripción, en 23 pacientes con indicación de digoxina, atendidos en el Policlínico José Martí de Santiago de Cuba, Cuba, desde abril hasta junio de 2017.
Resultados: En la casuística predominó su uso en el sexo femenino (78,26%), entre 70 y 74 años (26,08%), con una o dos enfermedades asociadas. Fue prevalente

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el diagnóstico de las enfermedades cardiovasculares por especialistas de Medicina General Integral, y la indicación de digoxina se asoció con mayor frecuencia a diuréticos y antiagregantes plaquetarios.
Conclusiones: La prescripción de digoxina puede considerarse como racional, aunque existe posibilidad de interacciones medicamentosas, que pudieran conllevar efectos tóxicos o falla terapéutica.
Palabras clave: Digoxina, Prescripciones de medicamentos, Pacientes geriátricos, Interacciones medicamentosas

INTRODUCTION

Among the objectives of health professionals is the rational use of medicines and their promotion. Knowing how medications are used is a necessary step to promote their rational use. Sometimes ineffective drugs are prescribed, the most expensive drug is selected, or a treatment is initiated without due attention to non-pharmacological measures and recommendations. In these cases, we refer to the irrational use of medications[1].

The increase in life expectancy together with a growing decrease in birth rates has led, in recent decades, to a significant increase in the elderly population worldwide. The World Health Organization estimates that in the year 2026, there will be around two million elderly people with dependency problems, which will almost double the current figure, and specifically in Cuba, 17% of the population is 60 years or older[2].

The prevalence and incidence of congestive heart failure (CHF) continues to rise, especially in the elderly, which is an important geriatric problem. In elderly patients, the etiopathogenic, epidemiological and even clinic characteristics of the CHF differ significantly from those found in younger patients, but the treatment applied derives from the result of clinical trials with little involvement of elderly patients. Beyond the heart disease, it is essential to assess the patient as a whole, taking into account the interrelation between the CHF and different characteristic geriatric syndromes of the elderly patient[3].

Very few drugs have withstood the test of time and are still used today for more than a century: within cardiovascular medication, no doubt, the digitalis compounds. The use of digital is documented since 1785. The infusions of foxglove leaves, *Digitalis purpurea* according to its official taxonomy, gave way to the preparations of the dust of those leaves, to the extraction and purification of the digitalis glycosides, among which the digitoxin, the digoxin and the lanatoside C, and, to a lesser extent, the ouabain, obtained from another plant, had more success. The digoxin is one of the most used drugs in heart disease, given its indications and demonstrated effectiveness in some of these episodes for the reduction of the ventricular rhythm. This drug is characterized by the narrow therapeutic margin and is considered among the three drugs that can cause the most adverse effects, regardless of the dose used[4].

In the elderly, the adequacy in the dose, frequency and route of administration of medications is of utmost importance for a rational use. To a large extent, the need for adequacy lies in the multiple physiological changes that patients present and their impact on the pharmacokinetics and pharmacodynamics of medications; example: the increase in volume of distribution, the decrease in blood perfusion and lower biotransformation, as well as elimination[5].

As part of the recommendations on the use of drugs, the so-called Beers criteria include a list of drugs whose use is limited in the geriatric population, or whose dosage must be modified. Relevant for elderly patients is in this case the digoxin[6]. It is the responsibility of the physician to maintain a good doctor-patient relationship, which will take time for an adequate explanation of the importance of treatment, its benefits and risks, including adverse reactions, to allow appropriate drug prescriptions[7].

With the present research, we set out to characterize the prescription of digoxin and identify problems related to the indication of this drug in geriatric patients, in primary health care.

METHOD

A descriptive and observational study was carried out, concerning the use of indication-prescription medications in geriatric patients, who were pre-

scribed digoxin. The population was constituted by 39 patients with digoxin prescription, controlled and registered in the *Farmacia U- 646*, located in the *Bloque H* of the *Policlínico José Martí*'s health area in Santiago de Cuba, from April to June 2017. A sample of 23 patients belonging to the Family Doctor's Office # 37 of this town was selected; all the medical certificates of the National Program of Medications were reviewed, and the medical records of family and individual health, from where the necessary data were extracted, were registered in a survey made for such purpose, as an empirical research method.

Variables

The chosen variables were: age, sex, associated diseases, diagnoses of cardiovascular diseases performed by specialties, risk of therapeutic failure or toxic effects, and groups of prescribed drugs. These variables were properly classified and conceptualized. The risks of therapeutic failure or toxicity associated with the use of digoxin were identified according to the disease for which it was indicated and the comorbidities, dose and interval of prescribed dose, as well as individuality of the prescription; in the same way, there was taken into account any other medication used by the patient.

Analysis ad statistical processing of data

The statistical package SPSS version 23.0 was the one used and also the percentage and the arithmetic mean as summary measures of information. In order to test if there was an association among the characteristics of interest, the X^2 statistician was applied. All data were expressed in contingency tables and figures, and for report writing, theoretical analysis and synthesis and inductive-deductive methods were employed.

Bioethical parameters

All research participants agreed and showed their agreement by signing the informed consent model. The study met the ethical criteria in accordance with institutional policy and the principles of the Declaration of Helsinki.

RESULTS

The female sex (18, for 78.26%) was predominant, as well as the age group of 70-74 years (6, for 26.08%), followed by that of 65-69 (5, for 21.73%) (**Table 1**). It is worth noting that in patients under the age of 64, the number of prescriptions is lower, for both sexes they were made in those with more advanced ages. These differences between the two groups were not statistically significant (p= 0.378).

As shown in **table 2**, there was a predominance of patients with only one (43.48 %) or two (39.13 %) associated diseases, who received pharmacological treatment for them, together with digoxin, meaningless from a statistical standpoint regarding sex (p= 0.062).

Diagnoses made by the Comprehensive General Medicine specialty for all cardiovascular diseases (**Table 3**) prevailed, and it is worth noting that the Cardiology specialty only made it for one patient, for whom digoxin was not a primary indication (6.3%), being a cardiomyopathy without CHF. There were no statistically significant differences among the diseases described (p=0.105). It is also worth noting that in total, there were 4 patients diagnosed with CHF, 9 with high blood pressure (HBP) and 16 with

Table 1. Patients with digoxin prescription according to sex and age.

Age groups (years)	Sex				Total	
	Female		Male			
	Nº	%	Nº	%	Nº	%
55 – 59	-	-	1	4.35	1	4.35
60 – 64	2	8.70	-	-	2	8.70
65 – 69	3	13.04	2	8.70	5	21.73
70 – 74	6	26.08	-	-	6	26.08
75 – 79	2	8.70	-	-	2	8.70
80 – 84	3	13.04	1	4.35	4	17.39
85 – 90	2	8.70	1	4.35	3	13.04
Total	18	78.26	5	21.74	23	100

Source: Survey
p=0.378

Table 2. Patients with digoxin prescription, according to sex and number of associated diseases with pharmacological treatment.

Number of associated diseases	Sex				Total	
	Female		Male			
	Nº	%	Nº	%	Nº	%
1	7	30.43	3	13.04	10	43.48
2	7	30.43	2	8.7	9	39.13
3	3	13.04	-	-	3	13.04
More than 3	1	4.35	-	-	1	4.35
Total	18	78.26	5	21.74	23	100

p=0.062

Table 3. Patients with digoxin prescription, according to diagnosis and specialty that prescribed it.

Specialty	Diagnóstico					
	CHF		HBP		Other CVD	
	Nº	%	Nº	%	Nº	%
CGM	3	75.0	8	88.9	13	81.2
Internal Medicine	1	25.0	1	11.1	2	12.5
Cardiology	-	-	-	-	1	6.3
Total	4	100	9	100	16	100

p=0.105
CGM, Comprehensive General Medicine; CHF, congestive heart failure; CVD, cardiovascular diseases; HBP, high blood pressure.

other cardiovascular diseases. Digoxin was prescribed to treat CHF (17.3 %) and to control heart rate in patients with atrial fibrillation (AF) (13.04%), diseases for which use it is indicated. It was also indicated in patients with ischemic heart diseases (39.13%) and hypertensive heart diseases (21.7 %).

The prescribed doses of digoxin were 0.25-0.125 mg/day, with a general dosage range of 24 hours. No diseases, that compromised the effect of this drug, were detected; however, 100% of the sample was exposed to drug interactions that could lead to toxic effects or therapeutic failure in 30.4% (7 patients), associated with irregular intervals dosing, 2 days at the week of rest and doses above the recommended therapeutic guidelines (**Figure**).

Among the most used pharmacological groups for the control of the diseases presented by the studied patients (**Table 4**), in general, antiplatelet agents (69.5%) and diuretics (65.2%) predominated. It draws attention that only in 1 patient of 4 with CHF, the diuretics and angiotensin-converting enzyme inhibitors (ACE inhibitors) are used. A 12.5% of antiplatelet agents and 71.4% of calcium channel blockers were used in patients with HBP.

DISCUSSION

Older adults present a series of physiological changes that determine alterations in the pharmacokinetic and pharmacodynamic processes of many medications of frequent prescription. This population also has a high prevalence of comorbidities, polypharmacy and prescription of potentially inappropriate medications. Aging is a natural process that involves degenerative changes, which can affect the efficacy and safety of the drugs that the patient uses[6]. There are two important factors when choosing the best treatment: the time from the onset of symptoms and the age of the patient. This latter is of great importance, in order to contribute to reducing adverse effects and rates of hospitalization[8].

Lo Presti *et al*[9] suggested that several concomitant cardiovascular diseases increase the risk of in-

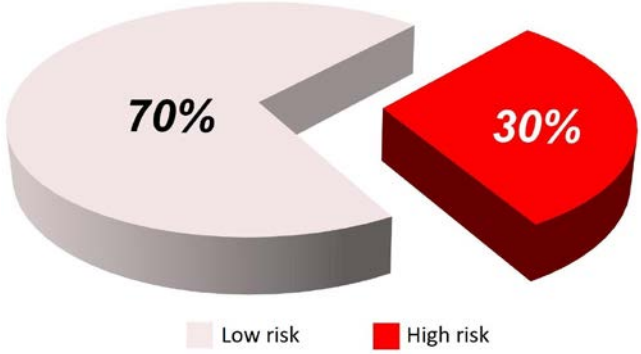

Figure. Patients at risk of treatment failure or toxic effects when considering the dosing interval and the prescribed dose of digoxin.

Table 4. Patients with digoxin prescription, according to found diagnosis and other prescribed pharmacological groups.

Pharmacological groups	Diagnosis					
	CHF		HBP		Other CVD	
	Nº	%	Nº	%	Nº	%
Diuretics (n=15 [65.2%])	1	6.7	5	33.3	9	60.0
Nitrates (n=9 [39.1%])	1	11.1	1	11.1	7	77.8
CCB (n=7 [30.4%])	1	14.3	5	71.4	1	14.3
ACE inhibitors (n=7 [30.4%])	1	14.3	3	42.8	3	42.8
Antiplatelet agents (n=16 [69.6%])	3	18.8	2	12.5	11	68.7
Beta-blockers (n=2 [8.7%])	-	-	1	50.0	1	50.0
Antiarrhythmic agents (n=1 [4.3%])	-	-	-	-	1	100

ACE, angiotensin-converting enzime; CCB, calcium channel blockers; CVD, cardiovascular diseases; HBP, high blood pressure; HCF, congestive heart failure.

teractions, and they found that the acute coronary syndrome (68.9%) and high blood pressure (12.6%) were the most frequent conditions, which was similar to a research that evaluated interactions among medications prescribed at discharge in an internal medicine department, where HBP and CHF predominated. This last, in its acute phase, is one of the most frequent causes of hospitalization and leads to difficulties in choosing the best treatment. As indicated by international guidelines, the usual therapeutic approach aims at the improvement of signs and symptoms, to correct volume overload and to improve cardiac hemodynamics in order to increase perfusion to vital organs. The recommended treatment is characterized by the use of diuretics and vasodilators, which, although alleviate symptoms, do not have a favorable influence on mortality at short and long terms[10].

The digoxin acts on the sodium-potassium/ATPase pump, which increases the intracellular concentration of sodium and calcium. With the highest concentration of calcium, they improve the interaction of actin-myosin and ventricular contraction. Another mode of action of digoxin that improves ventricular function is its effect on the autonomic nervous system; the reduction of sympathetic stimulation decreases tachycardia and improves ventricular filling and myocardial contraction. The control of potassium levels minimizes the toxicity potential of digoxin[11].

The correct selection of a drug must be made taking into account the criteria of efficacy, safety, convenience and cost, by a qualified staff. The consumption of drugs has increased associated with the development of the pharmaceutical industry over the last 50 years and, therefore, the likelihood of unwanted effects, as well as iatrogenies caused for its misuse[7]. On the other hand, there is a great interindividual variability in the response to drugs, due to physiological and pathological changes observed in older adults. In this sense, some authors have described that, in older ages, there is a decrease in the cerebral expenditure and regional blood flow to different organs, mainly brain, kidney and liver. Consequently, decreasing the blood flow and the hepatic mass, as well as the activity of its enzymes, can cause a fall in the metabolic capacity of the organ[9]. Likewise, the CHF can increase this liver dysfunction. Moreover, there are drugs, such as digoxin, captopril, enalapril, atenolol and furosemide whose renal elimination may be decreased in the elderly, which may favor more intense adverse reactions in this age group[12].

The main indication of the digital was the CHF since its start. A better use of the drug, the background about interactions with other drugs and the need to reduce the dosage in patients with failure of the renal function, the ability to determine blood levels, disappearance of digitoxin, and obviously, decreased use of digoxin, have determined a clear

decrease in the incidence of digitalis toxicity[4]. During the last decades, the treatment of CHF in adults was more aimed to treat it as associated neurohormonal changes than to improve the contractile function of the myocardium, and most recommendations are based in randomized multicenter studies[8]. The digoxin is currently indicated in frequency controls for supraventricular tachyarrhythmias, refractory CHF to treatment with diuretics and angiotensin-converting enzyme inhibitors (ACE inhibitors) and cardiac failure[13]. Practice guidelines relegated digital symptomatic control of CHF in patients that do not respond to other drugs that have shown themselves survival benefits. According to Scheuermeyer *et al*[14], the US guideline on CHF, of 2013 establishes, as a class IIa recommendation, that digoxin may be beneficial unless contraindicated in patients with CHF and low ejection fraction to reduce hospitalizations.

There is no doubt that the digital decreases ventricular rate and thus, improves cardiac output of the tachycardic patient. The AF is the most prevalent arrhythmia in hospital emergency, which is a disease with severe implications for double mortality and morbidity and it has a high, primarily relation with the CHF and arterial thromboembolism. Drugs that block the atrioventricular node are used as a general strategy of heart rate control, such as beta-blockers, calcium channel blockers or digoxin[15]. According to Bonino *et al*[16], a study conducted by García López *et al,* in 2013, revealed that digoxin was the most used drug (42%) at the emergency department of the Hospital Obispo Polanco de Teruel, in patients with AF and CHF for the heart rate control. However, it has also been used in patients without CHF (21%), although studies suggest, as first choice, the beta-blockers or calcium channels. It is also noted that there is no evidence that the use of digoxin in patients without clinical CHF reduces morbidity and mortality of AF.

According to Scheuermeyer *et al*[14], the AF guidelines of the American College of Cardiology, American Heart Association and Heart Rhythm Society recommend, as indication I, digoxin or intravenous amiodarone for rapid control of heart rate in patients with CHF, in the absence of preexcitation; they indicate that digoxin is effective in controlling the resting heart rate in patients with CHF and reduced ejection fraction, and that it may be considered, as a class IIb recommendation, the administration of amiodarone or digoxin to slow a rapid ventricular response in patients with acute coronary and AF syndromes, associated with severe left ventricular dysfunction and CHF or hemodynamic instability. Other publications, derived from the AFFIRM[17] and TREAT-AF[18] studies, show opposite conclusions, since the first one found that the administration of digoxin in patients with AF can increase mortality; and the second, quite the opposite.

The dosage of this drug should be individualized according to age, renal function, severity of the condition and other factors; sometimes, it is necessary to rest two days a week for the risk of digitalis toxicity. In general, the dose in the elderly is usually lower than in younger adults. For these reasons, its contraindications, precautions, situations where it is necessary to control the blood levels and electrolyte, and drug interactions[19,20] must be well known.

The gastrointestinal absorption in the geriatric patient is very similar to that of the young patient; however, the maximum plasma digoxin time lasts from 38 to 69 hours, which prolongs the time required to reach a steady state of 7 to 12 days. Likewise, it usually requires a 20% decrease in dose. For this reason, the evaluation of treated patients requires not only measurement of the plasma levels of the drug, but also an evaluation of renal function and body weight; as the renal dysfunction, reduced muscle mass and the high percentage of presenting another cardiac disorder, present in the elderly, may increase the susceptibility to the effects of this drug and the risk for digitalis toxicity[6].

Ortega López*et al*[4] highlighted the importance of the interaction of digoxin with loop diuretics and ACE inhibitors with potassium-sparing diuretics, which can promote the occurrence of serious adverse drug reactions. Moreno Pérez *et al*[6] associate this drug with ophthalmological manifestations such as dyschromatopsia (yellow-green), blurred vision and flashes, photophobia and amblyopia. On the other hand, Montoya *et al*[11] state that in the SOLVD study, digoxin, together with other medications such as ACE inhibitors, diuretics and beta-blockers, contributed to improve the survival of these patients.

Some recently published studies suggest that digoxin is not associated with an increase in mortality for any reason, regardless the presence of underlying cardiac failure[9]. All medications carry a risk of causing adverse effects. However, there are some that have a greater potential to cause problems when used by the elderly. It has been shown that inappropriate prescription in elderly people is highly prevalent but preventable.

CONCLUSIONS

The digoxin prescription is considered as rational, although there is a possibility of drug interactions, which may lead to toxic or therapeutic failure.

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