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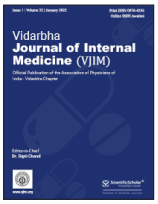

Review Article

Digoxin Holiday

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ABSTRACT

Digoxin is used in clinical practice for two major purposes: To improve ventricular performance in heart failure with reduced ejection fraction and to control the ventricular rate in atrial fibrillation. It is a cardiac glycoside with a positive inotropic effect and causes atrioventricular nodal inhibition through vagomimetic effect. It also decreases the sympathetic drive generated by the failing circulation, which provides a rational in using the drug in congestive heart failure (CHF) with sinus rhythm. The use of this drug is a standard therapy in the treatment of CHF with atrial fibrillation. However, the dose adjustment of this drug is difficult because of the variation in its pharmacokinetic characteristics, the variability in its clearance, and the lack of a good relationship between the dose and the desired effect and its narrow therapeutic range. This creates difficulty for clinicians to choose the appropriate dosage of the drug to get the desired benefit without the risk of toxicity. In many countries, serum concentration monitoring is not always possible, so it is common in clinical practice to drop the medication for 1 or 2 days a week, giving the drug a 'holiday,' to avoid the risk of toxicity. This is contrary to the use of this drug without interruption in countries where routine serum concentration monitoring is possible. This review provides a summary of the evidence relating to the rationale behind using digoxin holiday and the therapeutic implications of digoxin holiday. Much of the information is available from prospective crossover clinical trials. There are no randomised control trials of digoxin holiday in patients with heart failure and/or atrial fibrillation.

Keywords: Drug holiday, Digoxin, Heart failure, Atrial fibrillation

INTRODUCTION

Drug holiday – concept, definition and rationale

A drug holiday is the deliberate interruption of pharmacotherapy for a defined period and for a specific clinical purpose followed by a resumption of full strength dosing.[1] It is also referred to as medication holiday/drug, vacation/structured treatment, interruption/strategic treatment, interruption/tolerance and break/treatment break. It is the conscious decision to stop using a regularly prescribed medication for days or even years. The purpose of drug holiday is

- To diminish the unwanted side effects of the medication (e.g., digoxin) or
- To decrease tolerance to the drug or
- To assess the need for continued medication (e.g., drugs to treat ADHD in summer vacation) or
- To reduce a long-term risk associated with medication (e.g., bisphosphonates).[2]

The risks involved in using drug holiday can be

- A period without effective drug action (e.g., digoxin)[3] or
- Rebound effects when dosing is suddenly stopped (e.g., clonidine and beta-adrenoceptor antagonist)[3] or
- Relapse of the disease (e.g., lung cancer) or
- Loss of the effectiveness of the medication or poor medication adherence.

DIGOXIN HOLIDAY

Introduction

Digoxin is a cardiac glycoside, derived from the foxglove plant known as digitalis purpurea and has played a prominent role in the therapy of congestive heart failure (CHF) since William Withering codified its use in his classic monograph on the efficacy of the leaves of the foxglove plant in 1785.[4] It is the oldest compound in cardiovascular medicine and continues to be used in contemporary clinical practice by most clinicians in the management of heart failure due to various causes.[5] It is used in heart failure with reduced ejection fraction (HFrEF) and also for heart rate control in atrial fibrillation. It does not provide a mortality benefit in

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heart failure.[6] However, it reduces the risk of recurrent hospitalisations in patients with heart failure without atrial fibrillation.[7-9] The widespread availability of digoxin, its low cost, and continued confidence in the usefulness of the drug based on long years of experience are some of the reasons for its continued use. The use of this drug without interruption is practiced in countries where monitoring of the drug is possible. Interrupting the use of digoxin for 1 or 2 days in a week or 'digoxin holiday' is commonly practiced in many countries, especially in those, where routine serum digoxin concentration monitoring is not available or is not feasible. To understand the rationale behind using 'digoxin holiday,' it is important to understand the drug's mechanism of action, pharmacokinetics, metabolism, drug interactions, and its toxicity, considering the narrow therapeutic range.

MECHANISM OF ACTION

Digoxin has two principal mechanisms of action – it increases the force of myocardial contractions and reduces conduction velocity at the atrioventricular (AV) node. It thus has a positive inotropic and electrophysiological effect on the heart.[6]

Positive inotropic

It increases the force of contraction of the heart by reversibly inhibiting the activity of the myocardial Na-K ATPase pump on the extracytoplasmic site of the α-subunit.[4] This binding causes an increase in intracellular sodium which, in turn, causes an increase in the availability of activator Ca^{++} in heart cells, either through enhanced Ca^{++} entry, decreased expulsion of $Ca^{++,}$ or both, through Na^{+}-Ca^{++} cation exchanger and increases the force of contraction.[4,6,7] The cardiac output increases with a subsequent decrease in the ventricular filling pressures.[6]

AV nodal inhibition through vagomimetic effect

It acts on the AV node by stimulating the parasympathetic nervous system and slows AV nodal conduction which, in turn, reduces the heart rate. In addition, the increased intracellular calcium levels prolong Phases 4 and 0 of the cardiac action potential, thus increasing the refractivity of the AV node.[6]

PHARMACOKINETICS

Absorption of digoxin is 70% on oral administration and about 25% is serum albumin bound.[7] Digoxin has a high volume of distribution due to extensive binding to the muscle, and hence, lean body weight should be considered while dosing.[4,7] The renal excretion of digoxin is mostly unchanged and is directly proportional to the glomerular filtration rate (GFR).[6] Digoxin cannot be cleared by dialysis.[7]

DETERMINANTS OF METABOLISM

Age

Elderly patients have an increased risk of toxicity and dosing should be judicious.[10]

Gender

Females have been shown to have more mortality with use but studies are lacking with more women needed to be enrolled in trials.[10]

Race

Apart from a few studies showing increased morbidity in underrepresented ethnicities, almost no studies are available.[10]

Body weight

Lean body weight is more important for loading due to high binding to muscle.[7] The changes in body composition due to obesity are of little significance. Lower range doses of 0.75–1 mg and higher doses of 1–1.5 mg should be used for the lean body weight of 45–70 kg and 71–90 kg, respectively, for loading. A body weight of <45 kg should be given half the dose.[11]

Renal function

Since 70–80% of digoxin is excreted unchanged, renal insufficiency requires the loading and maintenance doses to be reduced. The loading dose is decreased by half to one-third in CKD. For Stage 5 CKD on renal replacement therapy, other agents (beta-blockers and calcium channel blockers) are preferred or a 10–25% of normal dose of digoxin is indicated.[11]

Drug interactions

Interactions are mainly due to the P-glycoprotein efflux transporter which is located in the intestinal epithelium and pumps out digoxin from the intracellular space into the lumen and thus decreasing the serum levels.[12] Inhibitors of P-glycoprotein increase serum digoxin levels, for example, amiodarone, dronedarone, quinidine, and propafenone. Inducers of P-glycoprotein reduce the levels, for example, phenytoin, rifampin, etc. Bupropion also reduces levels of digoxin by 60%.[11] Diuretics reduce GFR and may result in digoxin toxicity. They may induce hypokalaemia which may precipitate digoxin toxicity when coadministered. Tetracycline and erythromycin can interfere with the hydrolysis of digoxin, leading to increased levels.[11]

Hypokalaemia and digoxin both inhibit sodium-potassium ATPase and increase the risk for arrhythmias and toxicity.

Hypomagnesaemia is also associated with digoxin toxicity.[10]

IMPLICATIONS OF DETERMINANTS

Due to the narrow therapeutic range of digoxin, toxicity is a major concern.[11] This is particularly important in the elderly, renal insufficiency, electrolyte abnormalities, multiple drugs, lean body mass, and female sex. There is an increased risk of all-cause mortality with digoxin levels of more than 1.6–2 ng/ml.[10] Thus, monitoring of the serum levels is essential and blood samples should be taken optimally every 12 h.[11]

DIGOXIN TOXICITY

The most common symptoms of digoxin toxicity are gastrointestinal and include nausea, vomiting, abdominal pain, and diarrhoea. The cardiac manifestations are the most concerning and can be fatal. The classic arrhythmias due to digoxin include atrial tachycardia with a 2:1 conduction, bidirectional ventricular tachycardia, and atrial fibrillation with a slow ventricular response. In a literal sense, its toxicity can induce every arrhythmia except for rapidly conducted atrial arrhythmias (atrial fibrillation and atrial flutter). In AF, an increase in the dose can result in AV block and regular junctional rhythm. Arrhythmias can occur at both therapeutic and subtherapeutic concentrations.[11] Neurological symptoms include lethargy, confusion, and vertigo altered mental status/delirium in the absence of hypoperfusion of the brain. Ocular manifestations include xanthopsia or seeing a yellow, blurred vision, and diplopia.[4]

CURRENT INDICATIONS FOR THE USE OF DIGOXIN

AHC/ACC guidelines for the use of digoxin in heart failure

According to the ACC/AHA 2013 guidelines,[13] digoxin can be used for symptomatic relief, improved quality of life (QoL), and exercise tolerance irrespective of sinus rhythm in mild-to-moderate heart failure. It is used as an add-on drug to guideline-directed medical therapy.

AHC/ACC guidelines for the use of digoxin in atrial fibrillation

According to the ACC/AHC 2014 guidelines,[14] digoxin is not a first-line agent for ventricular rate control and is not an optimal agent for rapid rate control due to the slow onset of action. It decreases the resting heart rate with chronic use but not with exercise. It may be combined with beta-blockers or non-dihydropyridine calcium channel blockers for rate control during exercise.

ESC guidelines for the use of digoxin in acute and chronic heart failure

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalisation (both all-cause and HF hospitalisations) although its effect on top of beta-blockers has never been tested. The effects of digoxin in patients with HFrEF and AF have not been studied in RCTs, and recent studies have suggested a potentially higher risk of events in patients with AF receiving digoxin. However, this remains controversial, as another recent meta-analysis concluded on the basis of non-RCTs that digoxin has no deleterious effect on mortality in patients with AF and concomitant HF, most of whom had HFrEF. In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with the rapid ventricular rate when other therapeutic options cannot be pursued.[15]

ESC guidelines for the use of digoxin in atrial fibrillation

Digoxin is mostly indicated in patients with AF and rapid ventricular rate (>110 bpm) and given in boluses of 0.25–0.5 mg IV if not used previously (0.0625–0.125 mg may be an adequate dose in patients with moderate-to-severe renal dysfunction).[15]

RATIONALE BEHIND DIGOXIN HOLIDAY

Digitalis should always be prescribed under specialist supervision. Given its distribution and clearance, caution should be exerted in females, the elderly, and patients with reduced renal function.[15] The patients who would benefit most from the addition of digoxin are also those at greatest risk of exhibiting the toxic effect of the drug.[4] Based on clinical trial data, the therapeutic range of digoxin would be about 0.5–1.5 ng/ml.[4,16] For heart failure patients, the targeted steady state serum digoxin level is between 0.5 and 0.9 ng/ml.[17,18] Ventricular rate control in atrial fibrillation patients will usually require higher digoxin steady state serum concentrations. The toxicity increases as the serum drug levels increase above 2.0 ng/ml. The narrow therapeutic range of digoxin makes it a difficult drug to administer. In patients with comorbidities or other factors affecting digoxin metabolism (including other drugs) and/or the elderly, the maintenance dose may also be difficult to estimate theoretically, and in this situation, it should be established empirically, based on the measurements of digoxin concentration in peripheral blood.[15] When measuring a digoxin serum level, it is essential to draw blood at least 6–8 h after the last dose. Considering the narrow therapeutic range and limited availability of serum digoxin measurements, a digoxin 'holiday' is given where the patient is given the dose 5–6 days a week to minimise digoxin

toxicity due to the lack of therapeutic drug monitoring.[19] It is not clear whether this 'holiday' is justified in all cases since digoxin plasma levels might decrease to below therapeutic levels.[20,21] Despite this fact, 'digoxin holiday' is frequently used in many countries.[22-24] The practice of prescribing digoxin with 'breaks' on weekends or even a weekday is based on traditional treatments or ancient preparations and does not have a proven scientific basis.[25] There is still no consensus statement recommending interrupted digoxin therapy. It is excreted exponentially, with an elimination half-life of 36–48 h in patients with normal renal function, resulting in the loss of about one-third of body stores daily.[4] After 2 days of rest, the levels of digoxin, from a pharmacokinetic point of view, can decrease by half. It is not clear if these interrupted digoxin regimens really offer a safer alternative over the continuous dosing regimens without compromising the effectiveness and patient QoL. It is anticipated that plasma digoxin levels may fall below the therapeutic range during the holiday which may affect patient clinical status.

DIGOXIN HOLIDAY AND THE EFFECTIVENESS OF THERAPY

Works done in Spain such as that of Gnocchi *et al.*[23] or that of Pedre *et al.*[22] demonstrated that in patients who tend to 'rest,' blood levels of digoxin were subtherapeutic, compared to patients who 'do not rest.' Although the number of patients in these studies was small, the results were statistically significant.[25] In the single-blind randomised prospective study done in 36 patients with CHF and systolic dysfunction with AF or normal sinus rhythm by Gnocchi *et al.*,[23] the results obtained also suggested that digitalis toxicity could be prevented by adjusting the dose according to the renal function rather than interrupting the treatment as is usual practice in their country. In the crossover prospective study conducted by Pedre *et al.*,[22] the uninterrupted regimen proved better than the discontinuous one in controlling the heart rate. Similar results were obtained by Nematipour *et al.*,[24] in their prospective crossover clinical trial done in Iranian patients. In their study, the two regimens used in patients with chronic atrial fibrillation showed that an interrupted regimen for digoxin prescriptions led to an insufficient serum concentration. Changing the holiday regimen to the continuous form led to better control of resting heart rate. In India, George and Thomas[26] studied serum concentrations of digoxin on days 5th, 6th, and 7th in patients taking digoxin on a 5/7 schedule. There was a significant fall in serum digoxin concentration when therapy was interrupted for 2 days. Although the sample size was small, the fall in digoxin concentration from day 5 to 7 was found to be uniform across their study population. A prospective cohort study was done by Sadray *et al.*,[21] in 123 patients of CHF or AF, to evaluate the continuous and interrupted digoxin regimens. Based on the results, they concluded that a 1 tablet/day regimen is to be preferred.

Contrary to the above observations, a study conducted by Reinbach *et al.*,[27] using four digoxin drug schedules – 0.25 mg/day, from Monday to Friday; 0.25 mg/day from Monday to Saturday; 0.25 mg/day, and 0.125 mg/day showed that the most patients using these different therapeutic schedules had plasma drug levels within the therapeutic range.

DIGOXIN HOLIDAY AND QoL

The first study to assess the QoL for atrial fibrillation patients taking different digoxin treatment regimens was done by Alshabasy *et al.*[28] in the Egyptian population. It was a prospective randomised parallel study and the four digoxin regimens used were – 0.25 mg daily except Friday; 0.25 mg daily except Thursday and Friday; 0.125 mg/day or a tailored daily dose based on the patient's renal function and ejection fraction. They concluded that calculating the proper dose based on kidney function was superior to all other regimens in maintaining the steady state of digoxin in the therapeutic range. The 2-day holiday led to a great fluctuation in the serum digoxin concentration with most patients falling below the therapeutic range post-holiday. Once daily tablet (0.25 mg) was suitable in maintaining digoxin serum concentration in the recommended therapeutic range. However, the fluctuation in digoxin serum concentration did not affect QoL for atrial fibrillation patients.

CONCLUSION

Serum concentration monitoring is a suitable guideline for the selection of a digoxin regimen.

Proper management of patients receiving digoxin also requires attention to renal function, electrolytes, and the associated drugs which the patient is receiving.

Although digoxin toxicity is a real concern, prescribing the drug in an uninterrupted regimen, without a 'holiday' is justified in patients with atrial fibrillation for achieving the therapeutic range and for better control of the heart rate.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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