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Author: H. F. Jelinek and P. Warner

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Author Address: hjelinek@csu.edu.au

pwarner@csu.edu.au

CRO Number: 30299
Digoxin therapy in the elderly: Pharmacokinetic considerations in nursing

Abstract
Digoxin is effective in controlling ventricular rhythm in atrial fibrillation and is used in heart failure when angiotensin converting enzyme inhibitors and diuretics are not effective. Due to the use of more than one drug often required with these conditions, pharmacokinetic considerations are important including complementary medicine. An increased awareness of drug action in the elderly is important as there is often an increase in body fat and leaner muscle mass as well as changes in organ function such as the kidney, which changes the drug activity. Nurses have an important role to play in the safe administration of digoxin.

Introduction
Congestive heart failure is characterised by a complex pathology that combines mechanical failure, myocardial abnormalities, and rhythm disturbance such as atrial fibrillation (AF). Several clinical trials have indicated digoxin for treatment of heart failure patients that remain symptomatic following first-line use of angiotensin converting enzyme (ACE) inhibitors, beta-blockers, diuretics and/or aldosterone antagonists [1]. Digoxin is also used for permanent/persistent AF with rapid ventricular rhythm and as first-line treatment in heart failure with co-existing AF [2]. The benefit of digoxin is that it is effective in treating congestive heart failure (CHF) and atrial fibrillation. However digoxin is an example of drugs whose pharmacokinetic profile is affected by interactions with other medication used to treat CHF and AF as well as aging [3, 4]. A good understanding of the pharmacokinetics of digoxin especially in the elderly by nurses will assure adverse consequences of drug
administration are minimised. The problem is that there is no ready algorithm to work out the correct dose as the aging process differs between individuals and occurrence of disease increases, confounded by a narrowing therapeutic window \cite{5}.

**Pharmacokinetics**

Pharmacokinetics consists of drug absorption, distribution, metabolism and elimination, and factors affecting this \cite{6}. It provides information that enables drug doses and dosing interval to be administered at an appropriate level and ensure optimum plasma concentration and effectiveness. Pharmacokinetic processes differ depending on the route of administration with oral dosing the most common. Three important pharmacokinetic parameters are volume of distribution, half-life and clearance \cite{6, 7}.

**Volume of distribution**

The volume of distribution (VD) is determined by the ratio of the amount of drug divided by the plasma concentration. The main determinant of the volume of distribution is the strength of drug binding to tissues \cite{8}. Plasma concentration in turn is determined by many factors such as drug absorption and binding to plasma proteins. Digoxin is absorbed through the intestinal wall via a P-glycoprotein transport molecule and binds to albumin or α1-acid glycoprotein (AAG) in the blood. AAG increases in numerous diseases such as HIV AIDS, inflammation, thyroid disease, renal and hepatic insufficiency, and AF, which changes the VD of digoxin \cite{9, 10}. AAGs also become more prominent in the aged and therefore may change the unbound digoxin drug fraction \cite{11}.

**Drug Half Life**
The half-life of a drug is the time taken for the plasma concentration of a drug to be half of its original concentration and depends on the volume of distribution and clearance. Half-life increases with an increase in volume of distribution or a decrease in clearance \[8, 12\].

**Clearance**

Clearance describes the irreversible removal of a drug from the circulation either through renal secretion or by metabolic processes \[8\]. The rate of elimination of the drug determines the dosing required to retain a steady-state drug plasma concentration. For digoxin clearance occurs mainly by the liver and kidney. Apart from renal disease and hepatic insufficiency, a decrease in P-glycoprotein, due to antibiotics such as erythromycin, increase serum drug concentration due to a decrease in renal clearance \[13\].

**Aging**

Differences between chronological and biological ageing and the relationship to pharmacokinetics is still under discussion in terms of whether age per se, has an influence or whether it is the concomitant structural and physiological changes that influence pharmacokinetics \[14\]. However, advanced age is always accompanied by a general decline in organ function and is more pronounced in the frail elderly \[15\]. Muscle atrophy contributing to a leaner body mass and a decrease in total body water with an increase in adipose tissue is also seen in the elderly \[14, 16\].

The distribution of the drug depends on several factors. As such in addition to the three pharmacokinetic considerations, albumin decreases primarily due to disease and is further decreased by inadequate dietary intake in the elderly. AAG may increase in
concentration in the presence of disease and therefore more of the drug is bound to plasma proteins \cite{17}. In addition tissue-binding may also change with aging \cite{18, 19}.

The principle unit of the kidneys, the nephron, and its associated glomerulus decline in function by 30\% between the age of thirty to sixty-five \cite{16}. The reduction in renal clearance is the most important change associated with aging \cite{20}. A reduction in clearance, body mass and body water leads to a decrease in the volume of distribution, requiring adjustment of dose, to avoid toxicity \cite{21}.

Age-related changes in the rate of drug absorption \cite{15, 22}, distribution (higher fat: muscle ratio) \cite{20}, and protein binding \cite{23} are not usually clinically significant \cite{24}. However, others have argued that P-glycoprotein mediated transport does have a major role in digoxin pharmacokinetics, especially in association with polypharmacy where certain drugs such as amiodarone alter kidney elimination \cite{22, 25}. The new drug dronedarone, inhibits P-glycoprotein transport in the kidneys, leading to a doubling of digoxin plasma concentration and potential overdose \cite{26}.

**Therapeutic use of Digoxin**

Digoxin decreases heart rate by decreasing AV nodal function leading to an increase in cardiac output (systolic blood pressure) in patients in rapid atrial fibrillation, heart failure and supraventricular tachyarrhythmias \cite{27}. Findings from the Digitalis Investigation Group recommended a lower plasma concentration to previous guidelines \cite{28} and suggests that digoxin if given at appropriate levels decreases
hospitalisations and mortality in elderly individuals with a dose less than 0.125mg/d

However higher doses of digoxin are still required for treatment of persistent AF.

In patients with normal renal function, an oral daily maintenance dose without a loading dose results in a steady-state blood concentration in approximately seven days. However in about 10% of patients, oral digoxin is partially inactivated by colonic bacteria through the formation of digoxin reduction products such as dihydrodigoxin and dihydrodigoxigenin formed by the metabolism of digoxin by gastrointestinal bacteria. Antibiotics such as erythromycin may increase digoxin absorption. Once in the body, only 16% of the absorbed digoxin is metabolised, with the rest mainly excreted via glomerular filtration unchanged in the urine and a small proportion via intestinal excretion. The half-life of digoxin is 26 to 48 hours in patients with normal renal function but may double in patients with renal impairment, including the elderly, regardless whether creatinine levels change. Creatinine levels often stay normal in the aged despite reduction in renal function due to the parallel decline in muscle mass. Digoxin is not removed by exchange transfusions or peritoneal dialysis or hemodialysis, or during cardiopulmonary bypass. Plasma concentration of digoxin can be further altered by body weight and the co-administration of other medication, which are discussed below.

**Pharmacokinetics of Digoxin**

Pharmacokinetics involves absorption, distribution, metabolism and elimination of drugs. These biochemical processes influence the utility of the drug in the body, which in turn change during the lifespan and with disease. Sixty to eighty percent of digoxin is absorbed from tablets and over 90% from capsules in one to three hours, followed by a six- to eight hour tissue distribution phase.
Absorption

Digoxin shows a small reduction in the rate of absorption with aging but overall absorption is not decreased [21]. P-glycoprotein activity may also be affected by interaction with diverse medications, which includes St John’s Wart commonly used for mild depression [39].

Distribution

With aging the body weight changes as there is a decrease in muscle mass and an increase in adipose tissue. Dosing of digoxin, which is hydrophilic is dependent on lean body weight as this is associated with age-related increase in bioavailability [40, 41]. Polar drugs such as digoxin have a smaller volume of distribution in the aged resulting in a higher plasma concentration, which in turn may be balanced by a reduction in renal clearance. Therefore the half-life of digoxin may not change in the aged, but most often the half-life increases, as does the risk of toxicity [15]. Protein binding makes up about 30% [18] with AAG being one of the plasma binding proteins that increase [34]. Reduction in tissue binding of digoxin may also occur and increase toxicity [18].

Metabolism

Metabolism occurs partially in the stomach, but also may occur in the liver. Digoxin forms several metabolites some of which are bioactive and have an effect on heart function [42]. A reduction in liver mass and hepatic blood flow, as well as changes in the sinusoidal epithelium reduce liver function and metabolism of digoxin [41]. Stomach pH changes with age and therefore the portion of digoxin metabolised in the stomach also changes. However most drugs do not or have very minor pH related absorption. However, several studies have demonstrated an increase in the absorption
of digoxin when administered with protein pump inhibitors often part of polypharmacy in the aged \[43\]. With advancing age, opportunistic pathogenic bacteria increase, causing conversion of active digoxin to an inactive metabolite \[30, 44, 45\]. Antibiotics such as erythromycin reverse this, increasing the bioavailability of digoxin \[46, 47\].

**Elimination**

Elimination of digoxin occurs primarily in the kidneys. A reduction in glomerular filtration rate parallels the aging process and affects water-soluble drugs such as digoxin. The reduction in renal clearance has a greater effect on digoxin due to the small therapeutic window, with an increased chance of adverse side effects. Drug interactions may also affect P-glycoprotein and lead to digoxin toxicity \[3\].

**Digoxin Toxicity**

Susceptibility of older people to adverse drug reactions is a function of prescribing and medication management as well as compliance, and pharmacokinetics and pharmacodynamics associated with changes in body function and an increased occurrence of disease in the elderly \[48, 49\]. Adverse effects are concentration-dependent, and are rare when plasma digoxin concentration is <0.8 μg/L \[50\]. Common adverse effects include anorexia, nausea, vomiting, diarrhoea, blurred vision, muscle weakness, confusion, drowsiness, rash and gynaecomastia \[51\]. More severe adverse effects are acute psychosis, delirium, amnesia, shortened QRS complex, atrial or ventricular extrasystoles, paroxysmal atrial tachycardia with AV block, ventricular tachycardia or fibrillation and heart block \[50, 51\].
Age-related changes in pharmacokinetics that lead to drug toxicity are often due to changes in drug clearance. Transport mechanisms are also important in terms of drug interaction. For drugs with narrow therapeutic windows, changes in the concentration of the plasma binding protein AAG may alter drug distribution such as that of digoxin and can also predispose to toxicity. Importantly, diuretics reduce the extracellular space and increase the likelihood of digoxin toxicity [20].

Nursing Issues of Administration

**IV Digoxin**
- takes 5-10 minutes for effect to be noticed
- maximal effect within 2 hours
- Rapid IV infusion may cause vasoconstriction and hypertension leading to a worsening of symptoms

**Oral Digoxin**
- takes 1 hour for effect to be noticed
- maximal effect 4-6 hours

**Maintenance dose**
- 62.5-250 micrograms orally once or twice daily. In an emergency a loading dose may be required

Nursing Care

The most important nursing consideration with IV administration is that a loading dose should never be administered in a single bolus dose (if over 0.5mg). The reason for this is to avoid possible toxicity. Rapid infusion or a large bolus dose can cause systemic and coronary arteriolar constriction. It is also advisable to obtain an ECG 6 hours after each dose and check for signs of AV block, sinus bradycardia, atrial or
nodal ectopic beats and ventricular arrhythmias\textsuperscript{[52, 53]}. Further a decreased heart rate is often found in patients, but this does not always return to normal. Due to the inherent arrhythmogenicity and action of digoxin the heart rate needs to be measured over a full minute. Chest pain may resolve with decrease in heart rate. Watch for decreased dyspnea and increased urinary output as glomerular filtration rate improves with improving cardiac output. Digoxin is contraindicated for patients with ventricular tachyarrhythmias and ventricular fibrillation, patients with 2nd and 3rd degree heart block, accessory A-V pathways such as Wolff-Parkinson-White Syndrome and hypertrophic cardiomyopathy.

An important adjunct to nursing care of the patient on digoxin is not only to teach the patient about digoxin therapy but also family members, including taking of the pulse prior to taking the drug, withhold dose if pulse rate is lower than 60 beats per minute and contact general practitioner. Signs and symptoms of digoxin toxicity need to be discussed with the patient and family that include nausea, vomiting, diarrhoea, fatigue, vision changes and abnormal slow pulse rate. If taking potassium supplements or diuretics, the patient needs to be informed about hypokalemia and hyperkalemia symptoms such as weakness, fatigue, nausea and abdominal cramps, and muscle tenderness, fatigue and constipation respectively.

**Potential Drug Interactions**

Drug interactions are common in the elderly, with most taking two or more different medications daily\textsuperscript{[54]} such as diuretics, calcium channel blockers and (ACEI) in addition to digoxin. Diuretics, unless they are potassium sparing such as spironolactone, amiloride and triamterene will decrease potassium. Potassium and digoxin bind to the same receptor and therefore an increase or decrease in potassium levels will lead to a decrease or increase in digoxin effectiveness. Due to the retention
of calcium when using digoxin, any additional administration of calcium needs to carefully monitored especially if it is intravenous. Drugs that increase digoxin serum concentration due to a reduction in clearance or volume of distribution include the antiarrhythmics quinidine, propafenone, amiodarone and verapamil. The interaction with calcium channel blockers is with nondihydropyridine drugs including diltiazem and verapamil. Combining calcium channel blockers such as amiodarone and digoxin is useful in atrial fibrillation therapy but have additive effects on AV node conduction that can lead to complete heart block. Similarly beta-blockers, which also reduce AV conduction and heart rate, can lead to bradycardia when combined with digoxin. Carvedilol, a non-specific adrenergic blocker used for mild or moderate CHF leads to an increase of up to 15% in digoxin plasma levels. Further the use of sympathomimetics increase the likelihood of cardiac arrhythmias. Dronedarone is a new drug that cuts the risk of cardiovascular hospitalization in patients with paroxysmal AF or in patients with persistent AF. Dronedarone is safer than amiodarone as an antiarrhythmic but concomitant administration with digoxin results in up to 2.5-fold increase in digoxin concentration [55]. The increase is likely due to interaction with the P-glycoprotein transporter and requires careful consideration of all aspects of pharmacokinetics with a 50% reduction in digoxin dose in adults recommended [26,55]. Dabigatran etexilate, a new antithrombic agent used in AF has not been approved by the FDA although it is currently included in the Canadian AF guidelines, which were also updated in 2010. Current clinical research indicates that there is no interaction effect with digoxin [56], although it has shown minor interaction with the P-glycoprotein pathway. Non-steroidal anti-inflammatory medication such as indomethacin that is used to reduce fever, pain and stiffness increase digoxin levels as do the anti-fungal agent
itraconazole and benzodiazepines such as alprazolam and diazepam for anxiety.

Diphenoxylate, an opioid agonist used for the treatment of diarrhea decreases gut motility and therefore has a tendency to increase digoxin absorption\textsuperscript{[57]}. Conversely the elderly are often on antacids and may be on anticancer medication that may interfere with intestinal absorption of digoxin. In patients with renal dysfunction, rifampin may decrease serum digoxin levels by increasing the non-renal clearance of digoxin. Vasodilators such as nitroprusside and hydralazine also reduce serum concentration of digoxin. Many elderly are on thyroid hormone replacement and this can also decrease digoxin serum levels requiring an increase in dose\textsuperscript{[58]}. Therefore these drugs require close monitoring when initiating, adjusting or discontinuing digoxin drug therapy.

Complimentary medicines that contain cardiac glycosides increase the likelihood of digoxin toxicity. Both squill, which is an expectorant and used in traditional cough medicines and Strophanthus a cardiac stimulant produce cardiac glycosides. Oleander is a very toxic plant currently being promoted for use in skin cancer. It also contains cardiac glycosides, while Senna and Cascara are used as laxatives and increase potassium loss, leading to digoxin toxicity. In contrast the herbal product St John's Wort reduces serum digoxin levels by about 25\%\textsuperscript{[59]}.

**Conclusion**

Digoxin continues to be absorbed well with aging but the time to reach steady state plasma concentration is increased and the volume of distribution as well as renal clearance is decreased. Therefore the amount of drug utilised and more importantly its clinical efficacy and unwanted side effects are affected. Start low and go slow, is what clinicians advocate for digoxin dosing in the elderly. Changes in body function are associated with aging. However the extent of these changes varies from individual to
individual. The elderly on average take more medications and often suffer from several concurrent diseases. These factors influence the pharmacokinetics of digoxin by primarily changing the volume of distribution and clearance. Lesser effects are attributable to absorption and the effect of protein binding. Digoxin distributes very little into body fat and doses must be based on lean body weight, as digoxin is relatively hydrophilic. Distribution is not altered by obesity. There appears to be a gradual contraction in the volume of distribution as renal function deteriorates. A reduction in dose, especially in the frail elderly is recommended as a depressed clearance without dosage reduction is the most common reason for hospitalisation due to adverse drug effects. Drugs with a narrow therapeutic window such as digoxin are more difficult to titrate to an appropriate dosing level with intra- and inter-patient variability adding to the difficulty. These age related changes combined with covariates such as kidney disease, and polypharmacy have important practical implications for the clinical management of elderly patients with respect to cardiovascular medication.

References


