Digoxin Toxicity and Its Avoidance in Elderly Persons

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Princess Margaret Hospital
Digoxin Toxicity and Its Avoidance in Elderly Persons

Outline

Digoxin Toxicity
  • Why a concern?
  • Why are elderly people so prone to digoxin toxicity?
  • The many faces of digoxin toxicity in old age

Its Avoidance
  • When indicated and when inappropriate?
  • What digoxin dose and what digoxin level?
  • How to monitor digoxin therapy in elderly patients?
Digoxin Toxicity in Elderly Persons
Why a Concern?

- Older people are the most frequent users of digoxin because the 2 primary indications for its use, CHF & AF are highly prevalent in old age.
Older people are the most frequent users of digoxin because the 2 primary indications for its use, CHF & AF are highly prevalent in old age.

In both in-patients and out-patients increased age is associated with enhanced susceptibility to digoxin toxicity.
Age-stratified Prevalence of Definite Digoxin Toxicity in Elderly Patients (n = 297)

Overall prevalence = 7.4%

Yip WM. Digoxin toxicity among elderly patients in hospital practice. HKCP exit dissertation, 2010
Digoxin Toxicity in Elderly Persons
Why a Concern?

- Older people are the most frequent users of digoxin because the 2 primary indications for its use, CHF & AF are highly prevalent in old age.
- In both in-patients and out-patients increased age is associated with enhanced susceptibility to digoxin toxicity.
- Adverse drug reactions (ADR) with digoxin are responsible for many older people attending emergency departments (EDs) and being admitted to hospital.
- Older adults who have been hospitalised are at significantly increased risk of further hospitalisation (4.5 x) due to digoxin toxicity for up to 2 months after discharge.


# Digoxin Toxicity in Elderly Persons

**Why are elderly people so prone to digoxin toxicity?**

<table>
<thead>
<tr>
<th>Ageing</th>
<th>Diseases/Conditions</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| • Age-related reduction in volume of distribution of hydrophilic drugs | • Heart failure  
• Early phase post-myocardial infarction  
• Renal failure  
• Low lean body mass  
• Hypothyroidism  
• Hypokalaemia  
• Hypomagnesaemia  
• Acid-base imbalance  
• Hypoxia  
• Acute and chronic lung disease  
• Dementia  
• Dehydration  
• Malnutrition | • Furosemide (hypokalaemia, dehydration)  
• Amiodarone, Verapamil, Diltiazem (increase intestinal absorption & reduced clearance, inhibit p-glycoprotein)  
• Oral macrolide antibacterials (eliminate digoxin-inactivating gut bacteria)  
• Spironolactone, steroids (falsely low digoxin level)  
• Non-steroidal anti-inflammatory drugs |

Table. Factors that increase the risk of digoxin toxicity in old age.
Digoxin Toxicity in Elderly Persons
Why are elderly people so prone to digoxin toxicity?

- The narrow therapeutic window of digoxin becomes more relevant in older individuals with multiple comorbidities and polypharmacy, which greatly increase the risk of drug-drug and drug-disease interactions.

HAHO Pharmacy Data on Polypharmacy in Elders (9/2008-8/2009)
Average daily discharge episodes for 65+ elders = 1176
## Digoxin-Herb Interactions: Pharmacokinetic

<table>
<thead>
<tr>
<th>Herb</th>
<th>Clinical significance</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s wort (金絲桃)</td>
<td>increase digoxin clearance; reduced AUC and Cmax of digoxin; reduce therapeutic effect of digoxin</td>
<td>controlled clinical trial in healthy subjects; no case reports so far</td>
</tr>
<tr>
<td>(Hypericum perforatum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>貫葉連翹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgo biloba (銀杏)</td>
<td>increase AUC of digoxin; no significant difference in Cmax, half-life, plasma clearance; therapeutic drug monitoring required</td>
<td>open-label randomised crossover study in healthy volunteers</td>
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# Digoxin-Herb Interactions: Inactive digoxin analogues

<table>
<thead>
<tr>
<th>Herb</th>
<th>Clinical significance</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siberian ginseng (西伯利亞人參)</td>
<td>modest interference with polyclonal-based digoxin immunoassays; elevate synthetic digoxin drug levels without clinical toxicity</td>
<td>animal studies;</td>
</tr>
<tr>
<td><em>Eleutherococcus Senticosis</em></td>
<td></td>
<td>case report</td>
</tr>
<tr>
<td>Asian ginseng (亞洲人參)</td>
<td>modest interference with polyclonal-based digoxin immunoassays</td>
<td>animal studies</td>
</tr>
<tr>
<td><em>Panax ginseng</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dan Shen (丹參)</td>
<td>modest interference with polyclonal-based digoxin immunoassays</td>
<td>animal studies</td>
</tr>
<tr>
<td><em>Salvia miltiorrhiza</em></td>
<td></td>
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</tr>
</tbody>
</table>


Digoxin-Herb Interactions: Active digoxin analogues
Plant origin: Apocynaceae (夾竹桃科)

Digoxin

\[(C_{18}H_{31}O_9)O\]

Oleandrin

\[(C_{7}H_{13}O_3)O\]
Digoxin-Herb Interactions: Active digoxin analogues
Plant origin: Apocynaceae (夾竹桃科)

Nerium oleander
Common oleander 夾竹桃

Thevetia peruviana
Yellow oleander 黃花夾竹桃

Strophanthus divaricatus
Goat Horns 羊角拗

Cerbera manghas
Sea mango 海芒果

Digoxin-Herb Interactions: Active digoxin analogues
Animal origin: Bufonidae (蟾蜍科) → Toad Venom (蟾酥)
**Digoxin-Herb Interactions: Active digoxin analogues**  
Animal origin: *Bufonidae* (蟾蜍科) → Toad Venom (蟾酥)

<table>
<thead>
<tr>
<th>Chinese Medicine</th>
<th>English Translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>蟾酥藥粉/丸, 乾蟾皮炭</td>
<td>癌, 止痛, 瘡毒, 心弱</td>
</tr>
<tr>
<td>牛黃消炎片</td>
<td>咽喉腫痛</td>
</tr>
<tr>
<td>六神丸 (Lu-Shen-Wan), 六應丸</td>
<td>咽喉腫痛, 口苦咽幹</td>
</tr>
<tr>
<td>救心 (Kyushin)</td>
<td>胸痹</td>
</tr>
<tr>
<td>靈寶護心丹, 靈香保心丸</td>
<td>胸痹</td>
</tr>
<tr>
<td>血栓心脈寧膠囊</td>
<td>中風, 胸痹</td>
</tr>
<tr>
<td>金蒲膠囊</td>
<td>清熱解毒, 消腫止痛</td>
</tr>
<tr>
<td>梅花點舌丸</td>
<td>清熱解毒, 消腫止痛</td>
</tr>
<tr>
<td>牙痛一粒丸</td>
<td>牙齦腫痛</td>
</tr>
<tr>
<td>薏藥</td>
<td>暑濕</td>
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中華人民共和國藥典2005年版第一部


Digoxin Toxicity in Elderly Persons
Recognizing the many faces of digoxin toxicity in old age
AN ACCOUNT OF THE FOXGLOVE, AND
Some of its Medical Uses:
WITH PRACTICAL REMARKS ON DROPSY,
AND OTHER DISEASES.

BY WILLIAM WITHERING, M. D.
Physician to the General Hospital at Birmingham.

BIRMINGHAM: PRINTED BY M. SWINNEY;
FOR C. C. J. AND J. ROBINSON, PENTHRUWE-ROW, LONDON.

THE Foxglove when given in very large and quick-
ly-repeated doses, occasions sickness, vomiting,
purging, giddiness, confused vision, objects appear-
ing green or yellow; increased secretion of urine,
with frequent motions to part with it, and sometimes
inability to retain it; slow pulse, even as slow as 35
in a minute, cold sweats, convulsions, syncope, death.*

http://manybooks.net/support/w/witheringw/witheringw2488624886-8.exp.html
Digitalis lanata (Woolly Foxglove) 毛花洋地黃 → digoxin

Digitalis purpurea (Common Foxglove) 洋地黃 → digitoxin
Presentations of Digitalis Intoxication

Withering W. Account of the Foxglove, 1785.

- Sickness
- Vomiting
- Purging
- Giddiness
- Confused vision - objects appearing green or yellow
- Increased secretion of urine
- Frequent motions
- Slow pulse
- Cold sweats
- Convulsions
- Syncope
- Death

n (treated) = 163

n (poisoned) = 179

- Fatigue 95%
- Visual symptoms 95%
- Muscular weakness 82%
- Nausea 81%
- Anorexia 80%
- Psychic symptoms 65%
- Abdominal pain 65%
- Dizziness 59%
- Dreams 54%
- Headache 45%
- Diarrhoea 41%
- Vomiting 40%

The Starry Night (Van Gogh, June 1889)
a typical example of digitalis toxicity with haloes and yellow vision

Portrait of Dr Gachet (1890) by Vincent van Gogh

Note the foxglove (digitalis) which was used to treat Van Gogh’s epilepsy.


Non-cardiac Manifestations of Digoxin Intoxication: Visual Dysfunction

• Mechanism
  – Reversible rod and cone dysfunction occur during exposure to toxic levels of digoxin (blockade of Na+, K+-ATPase pumps)

• Clinical message
  – Important to consider the possibility of digitalis intoxication in patients (especially elderly patients) who have new visual symptoms while receiving digoxin, even if serum digoxin levels are within the normal therapeutic range
  – Such patients often report new visual symptoms to a physician (usually an ophthalmologist) other than the one who prescribed digoxin, and the association may be overlooked.


Called to see a 90-year-old man c/o anorexia, failing memory (noted by his family), dizziness since discharge

• Just discharged 3 days ago with discharge Dx: CHF, AF, Community acquired pneumonia

CLOX1 = 5/15
Called to see a 90-year-old man c/o anorexia, failing memory (noted by his family), dizziness since discharge

- Just discharged 3 days ago with discharge Dx: CHF, AF, Community acquired pneumonia
Electrocardiogram lead aVf. Atrioventricular junctional escapes with aberrancy in the presence of atrial fibrillation. Frequent impulses from the fibrillating atria (A) enter the atrioventricular junction (A-V) but are prevented from penetrating to the ventricles (V) by the high degree of entrance block produced by digitalis. (The fibrillating impulses are present throughout the tracing but are diagrammed in one area only.) The junctional pacemaker then escapes at an interval of 1.32 to 1.36 Sec (rate of 44 beats/ min) and is conducted in an aberrant fashion (jagged lines) to the ventricles (marked X in the tracing). The entrance block, however, is not sufficient to block all atrial impulses. A few are transmitted (marked QRS) with normal intraventricular conduction. Note that the escape intervals are the longest on the record. Retrograde conduction to the atria (dotted lines on the ladder diagram) does not occur.

Called to see a 90-year-old man c/o anorexia, failing memory (noted by his family), dizziness since discharge

BW = 46 kg, serum creatinine = 85 umol/L, Na 128 mmol/L, K 4.3 mmol/L, eCrCl=33/min

---

**Digoxin**

1.6 nmol/L

1.3 - 2.6

**Footnotes:**

Digoxin-Collection time: 6 hr post dose or more: otherwise, the level maybe erroneously high.  
The recommended level for the treatment of heart failure is < 1.3 nmol/L.  
Conversion factor: 1 nmol/L = 0.78 ng/ml
Called to see a 90-year-old man c/o anorexia, failing memory (noted by his family), dizziness since discharge.

On digoxin:
- CLOX1 = 5/15

Digoxin stopped:
- (6 days later) CLOX1 = 12/15
- (14 days later) CLOX1 = 12/15
Non-cardiac Manifestations of Digoxin Intoxication: Neuropsychiatric Dysfunction

“Women the poorer class in Derbyshire drink large draughts of Foxglove tea, as a cheap means of obtaining the pleasures, or the forgetfulness, of intoxication.”

Withering’s son

• Mechanism
  – Drug-induced delirium & cognitive decline from cumulative anti-cholinergic burden


Non-cardiac Manifestations of Digoxin Intoxication:
Neuropsychiatric Dysfunction

• Clinical message
  – Neuropsychiatric symptoms and delirium may be the first and only manifestation of digoxin toxicity without accompanying electrocardiographic abnormalities in elderly patients, and can occur at serum concentrations within or above the therapeutic range.
  – When delirium complicates an already complex syndrome, the drug is often not suspected
  – It may form part of the picture of Wernicke's encephalopathy from thiamin deficiency secondary to prolonged anorexia from digitalis intoxication.


An 89-year-old Woman With “Poor Feeding”

- Stroke R hemiparesis
- Lasix
- Digoxin
- Fluid restriction
- CHF, AF
- Poor feeding due to depression
- R/T feeding Restraint
- Forehead haematoma
- Confusion (yelling)

Hosp 1
Hosp 2

- Albumin/2
- Na/10
- CrCl
- Hb
- 100 x U/C
- K
- Creat/100

01/11/98 11/11/98 21/11/98 01/12/98 11
An 89-year-old Woman With “Poor Feeding”

- Stroke R hemiparesis
- Lasix, Digoxin, Fluid restriction
- Poor feeding due to depression
- R/T feeding Restraint
- Forehead haematoma
- Confusion (yelling)
- Depression
- Hyperkalaemia, Digoxin overdose (3.4)
- Acute myocardial infarction

Results:
- Albumin/2:
- Na/10:
- CrCl:
- Hb:
- 100 x U/C:
- K:
- Creat/100:

Timeline:
01/11/98 11/11/98 21/11/98 01/12/98 11/12/98 21/12/98 31/12/98
Non-cardiac Manifestations of Digoxin Intoxication: Gastrointestinal (nausea, anorexia, vomiting)

- **Mechanism**
  - due to stimulation of a chemoreceptor zone in the medulla (area postrema)
  - (local emetic action: gastric irritation)

- **Clinical message**
  - Nausea, anorexia and vomiting are the earliest & commonest manifestations of digoxin toxicity
  - May lead to dehydration, reduced renal clearance, hypokalaemia; completing the vicious cycle of digoxin intoxication
  - Forced (tube) feeding without diagnosing “poor feeding” will add further distress


A 89-yr-old woman cared by her younger sister (aged 86, with multiple myeloma)

2006
- hypertension
- recurrent falls with # hips, vertebral collapse
- osteoporosis
- rehab to walk with frame

2009 (then aged 92)
- on wheelchair, accompanied by 2 daughters and a relative
- just discharged 2 wk ago after a 2-wk hospitalization with Dx:
  - recurrent stroke (ischaemic),
  - complicated by UTI;
  - also AF detected and started on digoxin 125mcg daily
- now bed- and chair-bound
- poor feeding.
- can tolerate enacal feeding
- doubly incontinent, on napkins
- BP 133/63 mmHg, P 91/min AF
- heel sores+ superficial perineal sore
- poor sitting posture, lean to her left
- refer CNS for pressure sore care;
- check digoxin level (watch out for digoxin overdose),
- reduce digoxin
Admitted to another hospital the same night, died 8 hours later, referred coroner for unknown cause of death and sudden arrest

Discharge diagnoses:
- Atrial fibrillation
- CVA
- Decreased general condition
- Hypertension

↓GC with passage of loose stool
vomited out sputum
no fever recorded
SOB+-
no cough/ sputum

<table>
<thead>
<tr>
<th></th>
<th>Urgency</th>
<th>Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>2.9</td>
<td>1.3 - 2.6</td>
<td>nmol/L</td>
</tr>
</tbody>
</table>
Lesson to Learn: 
Geriatric Presentations of Digoxin Intoxication


92-year old woman

- **Physical functional decline:**
  - on wheelchair, require 3 to escort to OPD, bed sores
  - decreased general condition
- **Poor feeding**
- **Loose stool**
- **Vomiting out sputum**
- **At risk:**
  - Extreme old age
  - Recent hospital discharge
  - Digoxin newly added
  - Poor feeding leading to dehydration
- **No warning ECG signs**

### Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>95%</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>95%</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>82%</td>
</tr>
<tr>
<td>Nausea</td>
<td>81%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>80%</td>
</tr>
<tr>
<td>Psychic symptoms</td>
<td>65%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>65%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>59%</td>
</tr>
<tr>
<td>Dreams</td>
<td>54%</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>41%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Graph showing symptom frequencies among poisoned individuals.*
In a meta-analysis of 29 observational studies on medication use and falls risk, use of digoxin was found to be significantly associated with falls (OR = 1.2)

Clinical implication: increases operative risk of injurious falls

Clinical implications of not recognizing the manifestations of Digoxin Intoxication:

Increases the investigations/ procedure burden (can be risky)

Digoxin toxicity

- nausea, anorexia, vomiting → OGD
- poor feeding → tube feeding, aspiration risk
- confusion, delirium → CT brain, LP, EEG, restraint
- falls, syncope → Holter, carotid sinus massage
- death → post-mortem
Clinical implications of not recognizing the manifestations of Digoxin Intoxication:

may be ascribed to the underlying condition of heart failure

Prescribing Cascade Completing the Vicious Cycle

Digoxin overdose → Pre-renal failure from dehydration

Fatigue

Nausea

Tachycardia

Fluid intake

↑ Fluid output

Symptoms attributed as due to heart failure (esp. with “normal” digoxin level)

↑ Digoxin

↑ Diuretics
Avoiding Digoxin Toxicity in Elderly Persons
When indicated?

CHF, SR, LVSD

- digoxin should be considered as an add-on therapy for CHF with abnormal LV EF (< 45%) & SR patients who are still symptomatic after optimum therapy (ACEI, β-blocker, diuretics)
- benefit weighed vs toxicity
- for a patient with CHF who is taking digoxin but not an ACEI or a β-blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted
How applicable is DIG Trial to CHF in Elders?

<table>
<thead>
<tr>
<th>Patients recruited in DIG trail</th>
<th>Majority of elderly patients with CHF in the community/long-term care facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>less often female (22.4 % female)</td>
<td>primarily women</td>
</tr>
<tr>
<td>younger (mean age 64 years)</td>
<td>much older, with multiple comorbidities, on multiple medications, functionally impaired</td>
</tr>
<tr>
<td>more likely to have reduced ejection fraction</td>
<td>often with systolic function preserved</td>
</tr>
</tbody>
</table>


Is Digoxin Useful in HFPEF (“diastolic heart failure”)?

- has been considered contraindicated in HFPEF, being thought to aggravate HF by increasing LV stiffness and thus filling pressure through increasing contractility
- However, recent evidence has suggested that digoxin, at low concentration, can improve early myocardial relaxation through neurohormonal modulation in HFPEF
- In a parallel sub-study of the DIG trial that enrolled 988 patients (mean age 67 years, 64% aged >=65 years) with HFPEF in sinus rhythm (ejection fraction > 45%, mean 55%), the addition of digoxin to ACEI and diuretics resulted in an insignificant 18% reduction (p = 0.136) in the combined outcome of heart failure mortality or heart failure hospitalization
- The American College of Cardiology 2009 updated guideline and the Canadian Cardiovascular Society guideline state that the use of digitalis to minimize symptoms of heart failure in patients with HFPEF might be considered (recommendation class: IIb; level of evidence: C).
Use of digoxin in AF

- Digoxin monotherapy may only be adequate for control of ventricular rate in the older, sedentary patient with permanent AF.
- Combining digoxin with either a β-blocker or non-dihydropyridine calcium channel blocker may be done to achieve optimal heart rate during activity.
- **not recommended** for acute treatment of rapid ventricular response to AF in settings associated with high sympathetic tone or a haemodynamically compromised state due to its slow onset of action, possible adrenergic activity and lack of efficacy in these conditions:
  - exercise, fever, thyrotoxicosis, acute volume loss, postoperative state, paroxymal AF.
Use of digoxin in CHF + AF

• Though digoxin is prescribed routinely in patients with HF and chronic AF, $\beta$-blockers are usually more effective when added to digoxin in controlling the ventricular rate, especially during exercise
• digoxin may be used initially while the $\beta$-blocker is being introduced
• alternatively, digoxin may be used as adjunct therapy to $\beta$-blockers in patients with AF and HF because of its synergistic effect with $\beta$-blockers on the AV node in rate control
• enhanced survival with the digoxin-carvedilol combination has been demonstrated in a retrospective analysis of the US Carvedilol Heart Failure Trials program
• Though non-dihydropyridine calcium channel blockers (including verapamil and diltiazem) also are effective rate-controlling agents, they may not be tolerated at doses required for optimal ventricular rate control because of their negative inotropic effect, especially in patients with low EF.
Rising Mortality Rates with Increasing Serum Digoxin (SDC) Concentrations (Post hoc analysis of DIG trial)

- SDC of 0.8 – 1.3 nmol/L (0.6 – 1.0 ng/mL) is the likely optimal therapeutic range for digoxin therapy
- may represent the most clinically efficacious balance of digoxin’s competing neurohormonal & inotropic effects

Irrespective of LVEF, low SDC reduced mortality & hospitalizations

Kaplan-Meier plots for cumulative risk of death due to all causes by serum digoxin concentration (SDC) in the Digoxin Investigation Group (DIG) trial

Avoiding Digoxin Toxicity in Elderly Persons
What digoxin dose and what digoxin level?

• Evidence of clinical efficacy of digoxin at the lower SDC and higher risk of toxicity and mortality at higher SDC, resulted in a revised lower therapeutic range for SDC in heart failure (0.6 - 1.2 nmol/L)
• Although there is some overlap in ‘therapeutic’ and toxic levels in the original study by Smith (1970’s), none have digoxin toxicity with the newly adopted therapeutic SDC of less than 1.3 nmol/L
• Quoting the lower therapeutic digoxin range on computerized and printed laboratory report forms is therefore important to guide clinicians to avoid unnecessarily high SDC without compromising the benefit for heart failure


Harrison’s Principles of Internal Medicine, 17th edition, 2008. Vol 2, Ch. 227, p 1451
Avoiding Digoxin Toxicity in Elderly Persons
What digoxin dose and what digoxin level?

• No geriatric dose
• For most older patients with preserved renal function (est. creatinine clearance > 50 ml/minute), digoxin 125 mcg daily provides a therapeutic effect.
• Lower dosages (< 125 mcg daily) should be used in patients with renal insufficiency (titrate according to CrCl for CrCl < 50 ml/min).
• “It is much better to give a smaller dose every day than to rely on the failing memory of the elderly to take the tablets just on certain days of the week (5 days a week).”


Avoiding Digoxin Toxicity in Elderly Persons
What digoxin dose and what digoxin level?
How to titrate with eGFR?

• Most dosing guidelines use the Cockcroft-Gault formula
• *Cockcroft-Gault eGFR (ml/min) in SI units*  
  \[(140—age (years)) \times bodyweight (kg)1.23]/(serum creatinine (umol/L)) 0.85 (if the subject is female)
• The modification of diet in renal disease (MDRD) equation does not use body weight to estimate the GFR.
• The MDRD derived eGFR has not been validated for extremes of age or dose adjustment. Unadjusted for body surface area, in the presence of the reduced height and weight observed in normal aging, the MDRD is likely to overestimate renal clearance in older adults.
Avoiding Digoxin Toxicity in Elderly Persons
What digoxin dose and what digoxin level?
How to titrate with eGFR?

• Digoxin dosing based on eGFR must be supplemented by clinical acumen as these formulae tend to underestimate at higher ranges of creatinine clearance and overestimate in the lower ranges, and are unreliable in sick hospitalized patients.

• Serum digoxin concentrations rapidly rise as creatinine clearance/eGFR falls.

• A reasonable rule of thumb is: use lower doses in small, old, females and even lower doses when the person is sick!


Avoiding Digoxin Toxicity in Elderly Persons
What digoxin dose and what digoxin level?
Lack of an optimal “therapeutic” serum digoxin concentration for the use of digoxin in atrial fibrillation

- Relatively few studies have systematically evaluated the efficacy and safety profile of digoxin in AF.
- Further systematic study is required.
- In 30 patients with acute AF and 30 patients with chronic AF, digoxin was found to be relatively ineffective in controlling the ventricular rate at the traditional “therapeutic” SDC concentrations; and in some instances adequate rate control was only achieved at “toxic” SDC.
- The poor correlation between SDC and resting heart rate in patients with AF may result in digoxin overdose if ventricular response is used as a yardstick for adjusting digoxin dose requirements.
- The American College of Cardiology guidelines caution that “Although digoxin continues to play a role in some patients with heart failure and AF, the traditional practice of arbitrarily increasing the dose and SDC of digoxin until ventricular response is controlled should be abandoned, because the risk of digoxin toxicity increases as well.”
Avoiding Digoxin Toxicity in Elderly Persons
How to monitor digoxin therapy in elderly patients?

• Therapeutic Drug Monitoring
  – to ensure that it is within the therapeutic range, serum digoxin concentration (SDC) should be measured 2 - 4 weeks after starting digoxin:
    • in patients with deranged renal function
    • when used with agents that alter the disposition of digoxin
    • or whenever digoxin toxicity is suspected
  – Digoxin dosage should be adjusted and the SDC monitored in patients with an acute illness which might cause a decline in renal function and also when medication changes.
  – Ensuring that laboratory reports include the latest, lower and narrower therapeutic range of SDC (0.6 - 1.2 nmol/L) in heart failure, will help reduce the chance of the clinician overdosing the patient.
  – limitation of therapeutic drug monitoring (TDM): wile digoxin TDM allows a clinician to compensate for factors that alter its pharmacokinetics (lean body mass, renal function, drug interactions), TDM cannot account for age-related changes in pharmacodynamic response to digoxin
  – A SDC within the therapeutic range may not assure absence of digoxin toxicity, and clinical monitoring is just as important as TDM

Avoiding Digoxin Toxicity in Elderly Persons
How to monitor digoxin therapy in elderly patients?

• Clinical monitor
  – Associated comorbidities, acute illnesses and medications that impact on hydration and renal function, and potential drug interactions should also be taken into consideration in adjusting digoxin dosage
  – The transition of care from the inpatient to the outpatient setting is an especially vulnerable period
  – Close monitoring to ensure the correct dosage is prescribed and is being taken. The reasons given for nonadherence may indicate intolerance due to toxicity
  – A heightened vigilance must be maintained not only for the cardiovascular (arrhythmia), but also for the gastrointestinal (commonly nausea, vomiting, anorexia), and neuropsychiatric symptoms and signs of digoxin overdose.

• Functional monitor (listen to patient/carers)
  – Any decline in functional level, such as recent confusion, instability and falls, may also indicate digoxin toxicity.

• ? ADR
  – A useful rule of thumb in identifying any ADR is simply to ask oneself “could this patient’s condition be due to one or more of the drugs they have taken?”
  – Disappearance of presumed toxic symptoms upon stopping digoxin may support the clinical suspicion of digoxin toxicity.