

Drug Labels & Interactions on the Front Lines



FDA Pharmaceutical Science & Clinical Pharmacology Advisory Committee

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Overview

- Perception of DDIs at the coal face
- Labels
 - How they're used
 - What's wrong with them
- Suggestions for improvement



How Clinicians Perceive DDIs

- Word association
 - N ~ 25
- Responses
 - “Ignore”
 - “Warfarin”
 - “Complicated”
 - “Hassle”
 - “Lawsuit”
 - “Oy”
 - “Death”





How Clinicians Perceive DDIs

- Some are intuitive / universally appreciated
 - Opioids + benzodiazepines, alcohol, etc.
 - ASA + oral anticoagulants
- A few are ingrained
 - MAO inhibitors + SSRIs
- Clinicians otherwise overwhelmed
 - Sheer number of DDIs
 - Complexity of mechanisms, terminologies



How Clinicians Perceive DDIs

- “Our language”
 - Not intuitive
 - pharmacokinetic, pharmacodynamic
 - AUC, C_{\max} etc.
- Most have only heard of CYP450
 - Know nothing about transporters
- Limited inclination to catch up / keep up
 - No appreciation for the quality of evidence



How Clinicians Use Labels

- MDs generally don't
 - They rely on pharmacists
- Pharmacists' tools
 - Brain
 - Essential but inadequate
 - DDI-specific resources
 - Reference texts
 - Electronic / web
 - Google / PubMed / Review articles



What's In a Label?

Example: Warfarin

It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including herbal products, are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

STATES THE OBVIOUS

Drugs may interact with COUMADIN through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with COUMADIN are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with COUMADIN are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

INUNDATES & SEDATES

The following factors, alone or in combination, may be responsible for INCREASED

EXOGENOUS FACTORS:

Potential drug interactions with COUMADIN are listed below by drug class and by specific drugs.

Classes of Drugs		
5-lipoxygenase Inhibitor	Antiplatelet Drugs/Effects	Leukotriene Receptor Antagonist
Adrenergic Stimulants, Central	Antithyroid Drugs†	Monoamine Oxidase Inhibitors
Alcohol Abuse Reduction Preparations	Beta-Adrenergic Blockers	Narcotics, prolonged
Analgesics	Cholelitholytic Agents	Nonsteroidal Anti-Inflammatory Agents
Anesthetics, Inhalation	Diabetes Agents, Oral	Proton Pump Inhibitors
Antiandrogen	Diuretics†	Psychostimulants
Antiarrhythmics†	Fungal Medications, Intravaginal, Systemic†	Pyrazolones
Antibiotics†	Gastric Acidity and Peptic Ulcer Agents†	Salicylates
Aminoglycosides (oral)	Gastrointestinal Prokinetic Agents	Selective Serotonin Reuptake Inhibitors
Cephalosporins, parenteral	Ulcerative Colitis Agents	Steroids, Adrenocortical†
Macrolides	Gout Treatment Agents	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Miscellaneous	Hemorrhologic Agents	Thrombolytics
Penicillins, intravenous, high dose	Hepatotoxic Drugs	Thyroid Drugs
Quinolones (fluoroquinolones)	Hyperglycemic Agents	Tuberculosis Agents†
Sulfonamides, long acting	Hypertensive Emergency Agents	Uricosuric Agents
Tetracyclines	Hypnotics†	Vaccines
Anticoagulants	Hypolipidemics†	Vitamins†
Anticonvulsants†	Bile Acid-Binding Resins†	
Antidepressants†	Fibric Acid Derivatives	
Antimalarial Agents	HMG-CoA Reductase Inhibitors†	
Antineoplastics†		
Antiparasitic/Antimicrobials		

Specific Drugs Reported

acetaminophen	fenofibrate	oxymetholone
alcohol†	fenopropfen	pantoprazole
allopurinol	fluconazole	paroxetine
aminosalicylic acid	fluorouracil	penicillin G, intravenous
amiodarone HCl	fluoxetine	pentoxifylline
argatroban	flutamide	phenylbutazone
aspirin	fluvastatin	phenytoin†
atenolol	fluvoxamine	piperacillin
atorvastatin†	gefitinib	piroxicam
azithromycin	gemfibrozil	pravastatin†
bivalirudin	glucagon	prednisone†
capecitabine	halothane	propafenone
cefamandole	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ifosfamide	propylthiouracil†
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	rabeprazole
celecoxib	ketoprofen	ranitidine†
cerivastatin	ketorolac	rofecoxib
chenodiol	lansoprazole	sertraline
chloramphenicol	lepirudin	simvastatin
chloral hydrate†	levamisole	stanozolol
chlorpropamide	levofloxacin	streptokinase
cholestyramine†	levothyroxine	sulfamethizole
cimetidine	liothyronine	sulfamethoxazole
ciprofloxacin	lovastatin	sulfapyrazole
cisapride	mefenamic acid	sulfisoxazole
clarithromycin	methimazole†	sulindac
clofibrate	methyl dopa	tamoxifen
COUMADIN overdose	methylphenidate	tetracycline
cyclophosphamide†	methylsalicylate ointment (topical)	thyroid
danazol	metronidazole	ticarcillin
dextran	miconazole (intravaginal, oral, systemic)	ticlopidine
dextrothyroxine	morizine hydrochloride†	tissue plasminogen activator (t-PA)
diazoxide	nalidixic acid	tolbutamide
diclofenac	naproxen	tramadol
dicumarol	neomycin	trimethoprim/sulfamethoxazole
diflunisal	norfloxacin	urokinase
disulfiram	ofloxacin	valdecoxib
doxycycline	olsalazine	valproate
erythromycin	omeprazole	vitamin E
esomeprazole	oxandrolone	zafirlukast
ethacrynic acid	oxaprozin	zileuton
ezetimibe		



What's wrong with this?

- It's exactly what clinicians do not want
- Problems:
 - No structure
 - Far too much information
 - Wrong information
 - Little-used / archaic drugs
 - No conveyance of risk
 - No real guidance



Making DDI Labels Better



Suggestions

1. Simplify
2. Declutter
3. Structure
4. Update periodically
5. Provide links to more information



1. Simplify

- Minimize subspecialty lingo
 - Pharmacokinetic
 - Pharmacodynamic
 - AUC, C_{\max}
 - Detailed mechanistic information
- Eliminate meaningless phrases
 - “Altered physiologic control loop...”



2. Declutter

- Warfarin example:
 - Archaic drugs
 - chenodiol, moricizine, oxymetholone, tolbutamide...
 - Other coumarins
 - Warfarin overdose
- Maybe “reported” shouldn’t be the bar
 - especially when no DDI mechanism apparent

3. Structure

Warfarin as an example

DRUGS THAT MAY INCREASE RISK OF HEMORRHAGE

Drugs that impair platelet function

- ASA, clopidogrel, prasugrel, ticagrelor...
- Selective serotonin reuptake inhibitors (SSRIs)
- etc...

Drugs that reduce warfarin's metabolism

- Antibiotics (SMX/TMP & other examples...)
- Antifungals (fluconazole...)
- Amiodarone
- etc...

Drugs that directly enhance warfarin's effect

- Acetaminophen

3. Structure

Warfarin as an example



DRUGS THAT MAY REDUCE WARFARIN EFFECTIVENESS

Drugs that may enhance warfarin metabolism

- Carbamazepine
- Rifampin
- Barbiturates
- Bosentan...

Drugs that directly oppose warfarin's effect

- Vitamin K



4. Update Periodically

Are Drug Labels Static or Dynamic?

MJ Seminerio¹ and MJ Ratain¹

Understanding drug metabolism is essential for identifying drug–drug interactions (DDIs). As new data concerning a drug’s pharmacokinetics arise, updates to drug labels and administration procedures should rapidly follow. However, the US Food and Drug Administration (FDA) has inconsistently updated drug labels, based on new research findings (i.e., in peer-reviewed publications). In this Commentary, we highlight recent findings on the metabolism of imatinib and argue for a more stringent protocol for updating drug labels.

CPT Sep. 2013

The changing history of imatinib

Once called by *Time* magazine the “magic bullet” to cure cancer, the tyrosine kinase

leukemia (CML), advanced gastrointestinal stromal tumors, and various hematological and oncological malignancies.¹



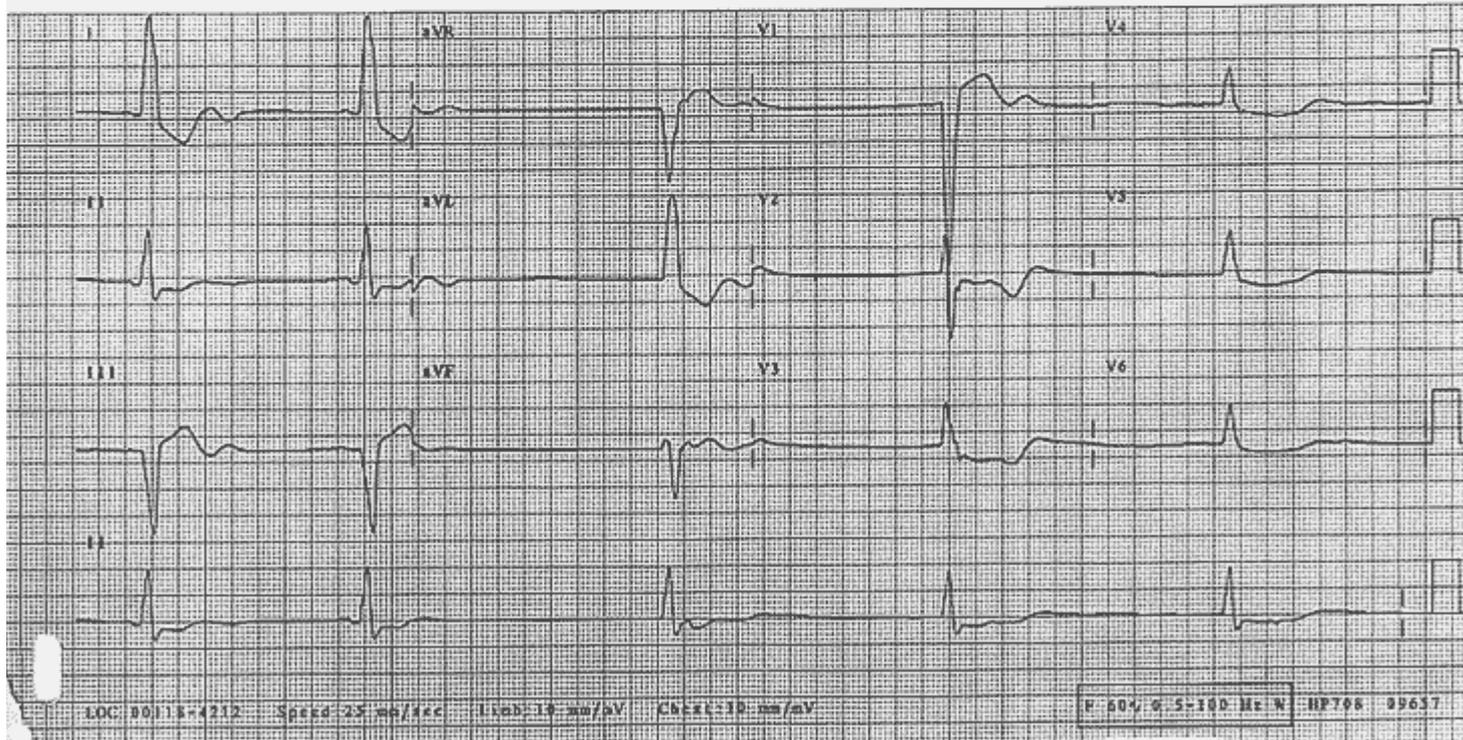
Digoxin + Clarithromycin

2009/10/25 10:25:21
92 years Female

Rate 28 . Slow junctional rhythm, rate 28
PR . Atrial premature complex
QRSD 154 . Left bundle branch block
QT 672
QTc 459

--AXIS--
P 10d.
QRS -21
T 166

[digoxin] 6.7 ng/mL





Digoxin + Clarithromycin

NDA 09330/S-025

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Drug Interactions: Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam,* and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result (see **CLINICAL PHARMACOLOGY: Absorption**). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids,*



Digoxin & Clarithromycin: What do we know?

Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin–clarithromycin interaction

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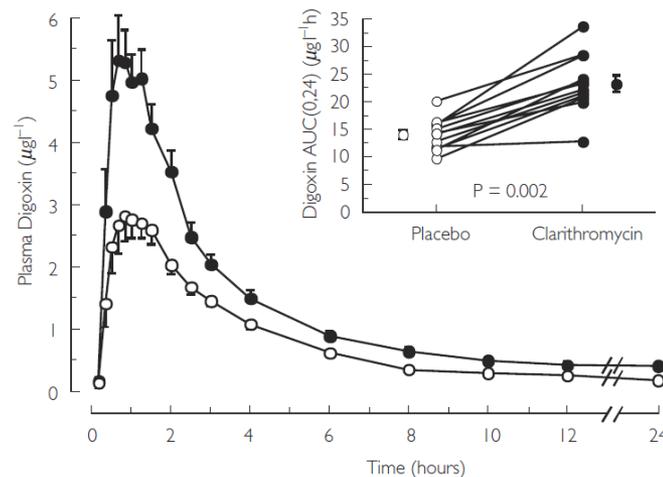
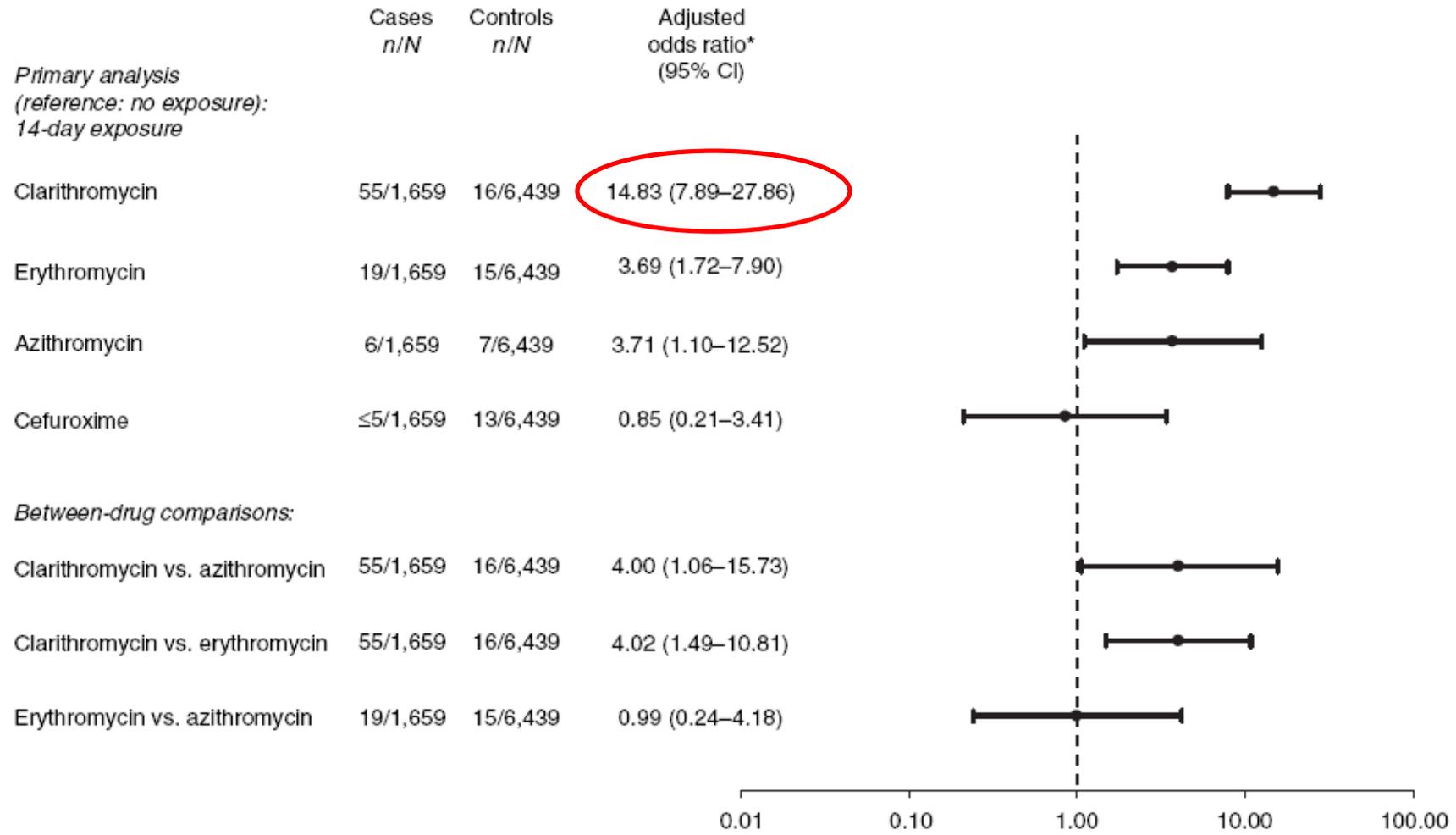


Figure 1 Mean (\pm SEM) plasma concentration–time curves for oral digoxin (0.75 mg) with coadministration of placebo (○) or clarithromycin (●) in 12 healthy men. Insert: individual and mean (\pm SEM) values AUC(0,24) of digoxin with placebo or clarithromycin.



Macrolides and Digoxin

Gomes et al CP&T 2009





In contrast to monograph:

350a

DRUG INTERACTIONS ANALYSIS AND MANAGEMENT

3

Clarithromycin (eg, *Biaxin*)

Digoxin (eg, *Lanoxin*)

MANAGEMENT OPTIONS:

➔ **Consider Alternative.** Select an antibiotic known to have no effect on digoxin concentrations in patients receiving chronic digoxin therapy. If azithromycin (*Zithromax*) or dirithromycin (*Dynabac*) are used, monitor for changes in digoxin concentrations.

➔ **Monitor.** In patients receiving digoxin, monitor for changes in digoxin concentrations when clarithromycin is added or removed from the drug regimen.

SUMMARY: Clarithromycin administration increases the plasma concentration of digoxin; digoxin toxicity including nausea, malaise, visual changes, and arrhythmias may occur.

RISK FACTORS: No specific risk factors are known.

MECHANISM: Clarithromycin may enhance the absorption of digoxin and/or reduce its renal and biliary elimination by inhibiting p-glycoprotein in the intestine, kidney, and liver.

CLINICAL EVALUATION: Clarithromycin has been reported in a number of case studies to increase the plasma concentration of digoxin.¹⁻⁵ Digoxin clearance may be reduced 60%, and plasma concentrations may increase 2-fold.

RELATED DRUGS: Digitoxin[†] would likely be affected in a similar manner by clarithromycin. Erythromycin also increases digoxin plasma concentrations. There is little data on the effect of other macrolides on digoxin.

REFERENCES:

1. Xu H, et al. Clarithromycin-induced digoxin toxicity: a case report and review of the literature. *Conn Med.* 2001;65:527-529.



5. Link to More Info

UpToDate®

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Patient Info

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▼ All Topics



▶ Drug Interactions



Lexicomp[®] Lexi-Interact[™]

Lookup

Enter item name to lookup.

Analyze

New List

[Clarithromycin](#)

[Digoxin](#)

Lexi-Comp Online™ Interaction Monograph

Title Cardiac Glycosides / Macrolide Antibiotics

Risk Rating C: Monitor therapy

Summary Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. **Severity** Moderate **Reliability Rating** Excellent

Patient Management Monitor for increased serum concentrations and toxic effects (e.g., gastrointestinal distress, weakness, dizziness, arrhythmia) of cardiac glycosides if a macrolide antibiotic is initiated/dose increased, or decreased serum concentrations and therapeutic effects if a macrolide antibiotic is discontinued/dose decreased.

Cardiac Glycosides Interacting Members Digitoxin*; Digoxin*

Macrolide Antibiotics Interacting Members Azithromycin (Systemic)*; Clarithromycin*; Erythromycin (Systemic)*; Spiramycin; Telithromycin* **Exceptions** Fidaxomicin

* Denotes agent(s) specifically implicated in clinical data. Unmarked agents are listed because they have properties similar to marked agents, and may respond so within the context of the stated interaction.

Discussion Numerous case reports describe patients receiving digoxin who experienced increased digoxin serum concentrations (up to 4 fold) and/or signs/symptoms of digoxin toxicity (commonly gastrointestinal distress, weakness, dizziness, but in some cases arrhythmia as well) during or shortly after courses of treatment with erythromycin or clarithromycin.^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17} Most patients in these cases were over 70 years old, and several likely had an elevated risk of digoxin toxicity due to additional factors such as renal impairment or hypokalemia. Case reports have also described similar effects in patients receiving digoxin with telithromycin or azithromycin,^{18,19} and digitoxin with azithromycin.²⁰

Almost all clinical investigations into the interaction between macrolides and cardiac glycosides have involved clarithromycin administration with digoxin. In an observational study of 7 patients 69-90 years old receiving oral digoxin, concomitant treatment with clarithromycin was consistently associated with increased digoxin serum concentrations after 4-7 days.²¹ In a prospective study of 8 patients, digoxin pre-dose (trough) serum concentrations were approximately 60% higher on average after 7 days of concomitant clarithromycin.²² Similarly, the oral digoxin (0.75 mg single dose) maximum concentration and AUC increased by 83% and 64%, respectively, and the non-glomerular digoxin clearance decreased by 40%, in 12 healthy volunteers during clarithromycin coadministration (250 mg orally twice daily, starting the day before digoxin).²³ In contrast to the findings with oral digoxin, in a clinical study of healthy volunteers, coadministration of erythromycin (200 mg orally 4 times daily) or clarithromycin (200 mg orally twice daily) had no impact on intravenous digoxin maximum concentration or AUC, and both were actually associated with 35-40% increases in renal digoxin clearance.²⁴

In a clinical study summarized in the telithromycin prescribing information, coadministration of telithromycin with digoxin increased the maximum and trough digoxin concentrations by 73% and 21%, respectively.²⁵



Summary – The Ideal DDI Label

- Easy to access and navigate
- Minimal pharmacology jargon
- Structured in a clinically intuitive way
- Imparts sense of severity or risk
 - Including uncertainty, as appropriate
- Does not include
 - Archaic drugs
 - Non-interacting drugs
 - ‘Reported’ drugs lacking a plausible mechanism



Summary – The Ideal DDI Label

- Links to more detailed info
 - Case reports
 - Reviews
 - PK / PD studies
 - Magnitude of risk (if available)
- Management suggestions
 - Dose adjustment
 - Monitoring
 - Therapeutic alternatives



Thanks

