Systematic Evaluation of Drug–Drug Interaction Labeling Language and Clinical Recommendations: Digoxin as an Example of a Narrow Therapeutic Index P-Glycoprotein Substrate

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Abstract

The FDA requires sponsors to conduct comprehensive drug-drug interaction (DDI) analyses during drug development. The results of these assessments are incorporated into product labeling to communicate clinical DDI risk. Therefore, variability in labeling language may impact DDI management by clinicians.

This study's objective was to evaluate the consistency in DDI labeling language of recently marketed drugs (2012-2020) when found to alter the exposure of co-administered digoxin, a clinical P-glycoprotein (P-gp) substrate and narrow therapeutic index (NTI) medication. DDI studies were compiled from new drug application reviews using the University of Washington Drug Interaction Database (UW DIDB). A clinical study was included if the precipitant exhibited inhibition of P-gp, defined as ≥20% increase in digoxin AUC and/or C_{max}. Labeling language was systematically evaluated for the presence of mechanistic DDI information and qualitative (e.g., monitor serum concentration) and/or quantitative (e.g., percent dose decrease) clinical management recommendations with digoxin, and other P-gp substrates, then compared to broadly used clinical resources.

Twenty-nine precipitants were found to affect digoxin exposure, with 58.6% of labels including qualitative recommendations for digoxin therapy, and only 17.2% providing quantitative management strategies. Only 69.0% of labels explicitly noted that the precipitant was a P-gp inhibitor, in vitro or in vivo, and just 9 provided recommendations for concomitant use with other P-gp substrates.

Tertiary resources also significantly varied in their recommendations for DDI management with digoxin and other P-gp substrates, highlighting the challenge of interpreting FDA-approved labeling language to provide consistent DDI management strategies to clinicians.

Methods

Step 1:
- Collected positive and negative studies using the UW DIDB "Percent Change in AUC or CL" query with digoxin selected as the object and "AUC or CL" selected
- "Inhibitors" and "non inhibitors" were selected to find positive (↑20% AUC and/or C_{max}) and negative (no change/80-120% of AUC and C_{max}) studies, respectively
- Clinical DDI studies within NDA submissions approved between 2012 – 2020 were included in the analysis

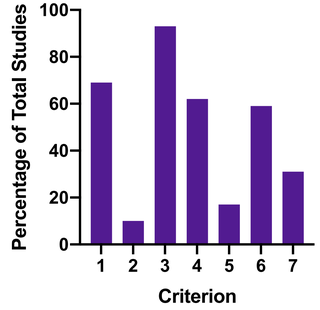
Step 2:
- Selected the most recent FDA-approved label from the Drugs@FDA website for each precipitant identified in Step 1
- Systematically evaluated labeling language surrounding DDI risk and management strategy
- Assessed how DDI study information was translated into FDA-approved labeling language

Step 3:
- Compiled information on DDIs between digoxin and precipitants identified in Step 1 using three tertiary resources, Micromedex, Facts & Comparisons, and UpToDate
- Compared clinical DDI management strategies recommended by tertiary resources to recommendations in the precipitant drug label

Step 4:
- Assessed how variability in labeling language may impact clinical DDI management
- Developed practical recommendations to decrease variation in labeling practices in order to provide consistent DDI management strategies to clinicians

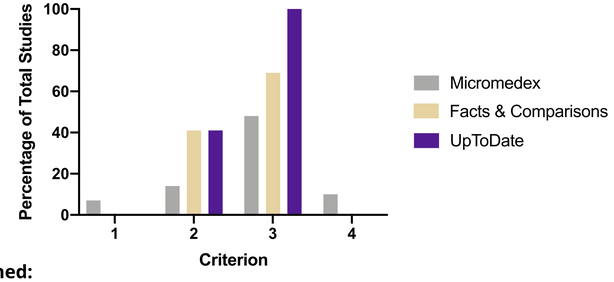
Positive DDI Study Results

Figure 1. Evaluation of FDA labeling language for digoxin inhibitors (n=29)



Criteria Examined:
1. Precipitant explicitly noted as a P-gp inhibitor
2. Other substrates of P-gp provided
3. Precipitant noted to change disposition of digoxin
4. Precipitant noted to change disposition of P-gp substrates
5. Included quantitative management specific to digoxin
6. Included qualitative management specific to digoxin
7. Included clinical management with other P-gp substrates

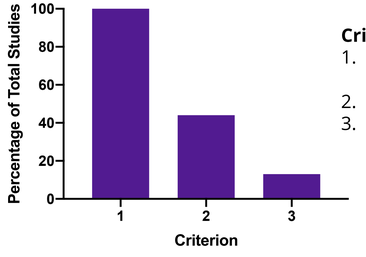
Figure 2. Comparison of recommendations from clinical resources for digoxin inhibitors (n=29)



Criteria Examined:
1. Other P-gp substrates provided
2. Included quantitative management (e.g. % dose decrease) specific to digoxin
3. Included qualitative management (e.g. monitor, refer to digoxin label) specific to digoxin
4. Included clinical management with other P-gp substrates

Negative DDI Study Results

Figure 3. Evaluation of FDA labels for non-inhibitors of digoxin (n=16)



Criteria Examined:
1. Inclusion of negative DDI study data with digoxin in labeling
2. Precipitant explicitly noted as a non-inhibitor of P-gp
3. Language extrapolates to low risk of PK-based DDI with other P-gp substrates

Different Recommendations for Precipitants with Similar *In Vivo* Effects on Digoxin Exposure

Clinical DDI Study: Glecaprevir/pibrentasvir + digoxin ↑ AUC 48% ↑ C_{max} 72%	***Similar Degree of Inhibition Observed in Clinical DDI Study***	**Clinical DDI Study:** Capmatinib + digoxin ↑ AUC 47% ↑ C_{max} 74%
FDA Labeling • Measure digoxin concentration before initiating therapy • ↓ digoxin dose by approximately 50% or modify dosing frequency and continue monitoring	***Different FDA-Approved Labeling Language Regarding DDI Management***	**FDA Labeling** • ↓ dose of NTI P-gp substrates in accordance with the approved prescribing information
Micromedex • Measure digoxin concentration before initiating treatment with P-gp inhibitor • ↓ digoxin dose by 50% or reduce dosing frequency **UpToDate/Facts & Comparisons** • Measure digoxin concentration before initiating treatment with P-gp inhibitor • ↓ digoxin dose by 15-30% or reduce dosing frequency	***Different DDI Management Recommendations from Clinical Resources***	**Micromedex** • ↓ dose of NTI P-gp substrates, as recommended **UpToDate/Facts & Comparisons** • Measure digoxin concentration before initiating treatment with P-gp inhibitor • ↓ digoxin dose by 15-30% or reduce dosing frequency

Conclusions and Practical Recommendations

- Variability in FDA labeling language translates to further inconsistencies in recommendations from tertiary clinical resources, potentially impacting interpretation of DDI risk by clinicians
- A more standardized approach to translating DDI risk into clinical management strategies in drug labels is needed, especially for NTI drugs
- FDA-approved labeling should explicitly state that the drug is an inhibitor when inhibition is observed, so that a mechanistic approach to the clinical recommendations can be implemented
- Examples of other potentially affected substrates should be provided, particularly when these involve NTIs or relevant concomitant medications
- A negative DDI study with digoxin (a marker substrate of P-gp) should, when possible, be extrapolated to suggest a low risk of pharmacokinetic DDI between the new molecular entity and other P-gp substrates

References

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