

Proposal for a New Tool to Evaluate Drug Interaction Cases

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The clinical observation of an adverse drug event often provides the initial alert associated with potential undesired drug effects. Similarly, case reports of adverse drug interactions have served to forewarn practitioners that certain combinations of drugs may produce unintended outcomes. When our knowledge of the mechanistic basis of drug interactions was limited, it was difficult to predict which combinations might interact. The clinical observation of an interaction would provide the motivation to do further studies to identify the magnitude and mechanism of the interaction. With our understanding of the major role of the cytochrome P450 system and active transmembrane transporters as the foundation of a majority of drug interactions, it has become quite easy to predict which drugs might interact and determine which alternative agents may be used to avoid potential drug interactions. Having the ability to predict drug interactions based on the metabolic pathways or pharmacokinetic properties can help us better prevent adverse events associated with drug interactions. Nevertheless, case reports are still very important to our understanding of the time course, magnitude, dose dependency, and other factors that alter the magnitude of the interaction.

One of the most challenging aspects of presenting or evaluating a case report of an adverse drug reaction is assessing causation for the observed events. In 1981, Naranjo et al.¹ presented a scale to estimate the probability that an adverse reaction was caused by the drug in question. In

The assessment of causation for a potential drug interaction requires thoughtful consideration of the properties of both the object and precipitant drugs, patient-specific factors, and the possible contribution of other drugs that the patient may be taking. The Naranjo nomogram was designed to evaluate single-drug adverse events, not drug–drug interactions. Several of the questions on the Naranjo nomogram do not apply to potential drug–drug interactions, while others do not specify object or precipitant drug. Nevertheless, it has been inappropriately used to evaluate drug–drug interactions. The Drug Interaction Probability Scale (DIPS) was developed to provide a guide to evaluating drug interaction causation in a specific patient. It is intended to be used to assist practitioners in the assessment of drug interaction–induced adverse outcomes. The DIPS uses a series of questions relating to the potential drug interaction to estimate a probability score. An accurate assessment using the DIPS requires knowledge of the pharmacologic properties of both the object and precipitant drugs. Inadequate knowledge of either the drugs involved or the basic mechanisms of interaction will be a limitation for some users. The DIPS can also serve as a guide in the preparation of articles describing case reports of drug interactions, as well as in the evaluation of published case reports.

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addition, a number of other methods to evaluate adverse drug reaction causality have been proposed.²⁻⁶ When compared with other algorithms, the Naranjo scale is usually as “good” as any other.⁶⁻⁸ The Naranjo scale has proved to be useful for assessing the causality of adverse reactions and has become widely used for this purpose. While some have questioned the validity of the Naranjo scale for evaluating single-drug adverse drug reactions, the criteria were never intended to be used to evaluate adverse events resulting from the interaction of 2 drugs.⁹ The scale is intended to assess the likelihood of an adverse drug event associated with only one drug. Drug interactions involve 2 drugs—the drug that is affected (object drug) and the drug that causes the change to the object drug (precipitant drug). Despite the lack of intent for this use and the absence of any validation as a tool to evaluate potential drug interactions, the Naranjo scale has

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been used by many authors when reporting drug interactions and is recommended by several journals to reviewers of drug interaction manuscripts. The Naranjo scale does not address several key issues that are necessary to evaluate causation of a potential drug interaction.

One only needs to examine some of the questions in the Naranjo scale to understand its lack of applicability for the evaluation of drug interactions. For example, question 3 asks, "Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?" As applied to an interaction, this has no meaning and is not interpretable. The "drug" could refer to the object drug, the precipitant drug, or both, depending on how the user interprets it. If the "drug" is interpreted to mean the object drug and the interaction involves inhibition of the object drug's clearance, of course the reaction will improve when you stop the object drug. If one chooses the "drug" to indicate the precipitant drug, the question is meaningless unless the object drug was continued without a change in dosage, which almost never happens in clinical practice. That is why we included this limitation in our Drug Interaction Probability Scale (DIPS) (Appendix I, question 5). Naranjo scale question 4, "Did the adverse reaction reappear when the drug was readministered?" has the same limitations as noted above for question 3.

Naranjo scale question 6, "Did the reaction reappear when a placebo was given?" simply does not apply to drug interactions. This question has been deleted and does not appear in the DIPS.

Naranjo question 7, "Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?" will be misleading and result in an incorrect probability score if the drug interaction results in reduced concentrations of the object drug. If a patient develops a subtherapeutic concentration of the object drug (as measured by assay) after receiving the precipitant drug (eg, an enzyme inducer), one would answer the question NO. But if, in fact, the measured concentration of the object drug did exactly what would be expected with enzyme induction, then the answer should be YES.

Naranjo question 8, "Was the reaction more severe when the dose was increased or less severe when the dose was decreased?" applies only to the precipitant drug. As the question is stated, it could be interpreted to mean either or both of the object and precipitant drugs.

These serious limitations of the Naranjo scale for the evaluation of drug interactions should not be considered as criticism of its only intended use: the evaluation of single-drug adverse reactions. It is unclear just how the Naranjo scale came to be accepted as a tool to assist in the evaluation of drug interaction causation, but it is certainly time to abandon this inappropriate use.

The DIPS was designed to assess the probability of a causal relationship between a potential drug interaction

and an observed event.¹⁰ The Naranjo scale provided the basis of DIPS but was modified to reflect the important differences between a single-drug event and one caused by a drug–drug interaction. The DIPS adds or subtracts points based on the answers to a series of questions specific to the assessment of a potential drug interaction. The application of the DIPS to a potential drug interaction requires knowledge of the pharmacologic, pharmacokinetic, and pharmacodynamic properties of both the object drug and the precipitant drug involved in the interaction. Proper estimation of causation may require consideration of many drug variables and properties including factors affecting absorption, routes of elimination, pathways of metabolism, active transporters, metabolism and transporter inhibition or induction potential, activity of metabolites, standard pharmacokinetic parameters, concentration–response relationships, therapeutic response and adverse event indicators, and the contribution of disease or genetics to altered drug parameters. Thus, proper use of the DIPS often requires careful and comprehensive investigation into the properties of the object and precipitant drugs.

Affirmative responses to questions generally add to the probability that the observed event was caused by an interaction. Negative responses generally reduce the probability, while questions that cannot be answered due to lack of information or applicability are not considered in the evaluation. The presence of the column labeled with unknown (Unk) or not applicable (NA) is to account for situations in which one is unable to obtain sufficient information about the drugs or patient to answer the question. Use of the DIPS assumes that the case has been assessed for factors that would eliminate the interaction as the cause of the event (eg, the event occurred before the patient received the interacting combination or the event has an obvious cause that is more likely than the interaction).

The following describes the questions contained in the DIPS and brief descriptions of what to consider in answering each question.

Question 1. Are there previous *credible* reports of this interaction in humans?

The key in this question is the word *credible*. A credible report is considered to be either a case report or prospective trial that clearly provides evidence supporting the interaction. If the DIPS is used to evaluate the other case(s), at least one case should have achieved a "possible" DIPS rating. Since faulty case reports should not propagate additional faulty case reports, it is important to disregard previous reports that do not meet minimal standards for case reports. If no other case reports exist, answer the question with NA (not applicable). If a study appropriately designed to test for the interaction shows no evidence of an interaction, answer NO.

Question 2. Is the observed interaction consistent with the known interactive properties of precipitant drug?

The precipitant drug is the one that appears to be causing the interaction. This question asks you to assess the mechanism of the interaction. For example, if the case involves apparent metabolic inhibition, are there any data that support the idea that the precipitant drug is an inhibitor of a metabolic pathway responsible for the metabolism of the object drug? Although lists of enzyme inhibitors are now common, caution is necessary when evaluating in vitro evidence of enzyme inhibition due to the potential differences in precipitant drug concentrations compared with in vivo values. If the interaction is inconsistent with known properties of the precipitant drug, answer the question NO. If you are unsure of the precipitant drug properties or data are insufficient to evaluate whether the interaction is consistent with the precipitant properties, answer Unk. The case evaluator must know the properties of the precipitant drug to properly answer this question.

Question 3. Is the observed interaction consistent with the known interactive properties of object drug?

The object drug is the agent affected by the precipitant drug. To adequately answer this question, the evaluator must understand the pharmacokinetic and pharmacologic properties of the object drug. How is the object drug cleared from the body? What percentage of its total metabolism is via each pathway? Are any transporting proteins involved? What is the first-pass metabolism of the object drug? Does the primary metabolic enzyme/transporter exhibit genetic polymorphism that affects the disposition and pharmacodynamic response of the object drug independent of a drug–drug interaction? Do other physiological events (eg, inflammatory responses) affect the activities of the primary enzyme/transport protein? Knowledge of the object drug's pharmacologic properties (eg, receptor polymorphism, potential effects of concurrent diseases) is important for evaluation of potential pharmacodynamic interactions. Answering this question based on an incomplete understanding of the object drug can lead to incorrect assessment of causation. Adverse reactions occurring with drugs whose pharmacodynamic responses are affected by many factors (eg, warfarin) are more likely to be mislabeled as interactions. If the potential interaction is not consistent with known properties of the object drug, answer the question NO. If unsure of the object drug properties or data are insufficient to evaluate whether the interaction is consistent with the object drug properties and known possible effects of the precipitant drug, answer Unk or NA. The case evaluator must know the properties of the object drug to properly answer this question.

Question 4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?

The time course of drug interactions is usually quite predictable. The half-life of the precipitant drug will provide an estimate of the length of time for maximum inhibition to occur, and the inhibited half-life of the object drug will indicate when the maximum change in object drug concentration can be expected. If the time to the onset of the interaction does not fit with the properties of the drugs, one should look for an alternative reason for the interaction. If the interaction time course is inconsistent with what would be expected, answer NO. If unable to estimate expected time course or insufficient data are available to assess the time course, answer Unk or NA.

Question 5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?

Stopping the precipitant drug should bring about resolution of the interaction, even if the object drug is continued without change. Often, the response to a potential interaction is the discontinuation of both the object and precipitant drugs. While the clinical situation may demand such action, changing the dosage of the object drug limits the ability to assess the potential role of the precipitant drug. However, a positive dechallenge of the precipitant drug is an important indication that the interaction was related to the administration of the precipitant drug. If precipitant drug dechallenge without change in object drug produces no change in the interaction, alternative causes for the alteration in the object drug are likely. The evaluator should also consider changes in other factors including disease activity, diet, or other drugs that may occur simultaneously with dechallenge of the precipitant drug and affect the object drug. If the doses of both medications are changed, dechallenge cannot be assessed. If dechallenge of the precipitant drug without a change in object drug did not result in remission of the interaction, answer NO. If no dechallenge occurred, the doses of both drugs were altered, or no information on dechallenge is provided, answer NA.

Question 6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?

A positive rechallenge with the precipitant drug is a strong indicator of causation. Concerns for patient safety often preclude rechallenge, but occasional reports of deliberate or inadvertent rechallenge have appeared. Rechallenges done with appropriate patient monitoring will be unlikely to result in adverse outcomes. If the precipitant

drug was readministered in the presence of the object drug and no interaction occurred, answer NO. If no rechallenge with the precipitant drug was attempted or no data were provided, answer Unk or NA.

Question 7. Are there reasonable alternative causes for the event?

This is perhaps the most difficult question in the DIPS to answer. Assessing alternative causes requires knowledge of the object and precipitant drugs, other agents the patient may be taking, the potential influence of disease states, adherence to drug regimens, and the presence of other risk factors that might alter drug pharmacokinetics or pharmacodynamics. Failure to assess alternative causes for observed effects is one of the most common shortcomings of drug interaction evaluations. It occurs frequently in the clinical setting and can often be detected in published case reports. Limited drug knowledge, combined with a preconceived notion of the cause of a potential interaction, merge to prevent adequate assessment of alternative explanations for the observed outcome. Answer this question NO only if you are confident that no other reasonable causes exist. If unsure, answer Unk or NA.

Question 8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?

This question assesses the relationship between the expected outcome of the interaction and measured outcomes. For example, if one suspects an inhibition of object drug metabolism, measured concentrations should reflect decreased clearance. If object drug concentrations are not consistent with the interaction, answer NO. If object drug concentrations are not measured, answer NA. Pharmacodynamic drug interactions generally do not involve a change in object drug concentrations, so the response to this question would be NA for such interactions.

Question 9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?

Objective evidence of the interaction could be clinical evidence such as changed physiological parameters or an adverse reaction that is consistent with the known pharmacology of the object drug. The answer to this question may reflect the magnitude of the interaction, since drugs with broad therapeutic windows may not demonstrate easily measured changes in patient response in the presence of altered plasma concentrations. Assessment of pharmacodynamic interactions will occur here. If response to the object

drug was assessed but no change was observed, answer NO. If no assessment was made or reported, answer NA.

Question 10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?

This question simply assesses the effect of the precipitant drug dose on the magnitude of the interaction. While data are not often available to answer this question, when the dose–response relationship can be assessed, it provides important insight to causation. This is particularly important for inhibitors that exhibit variable inhibitory properties at different doses/serum concentration. Answer NO if precipitant drug doses are changed without a change in object drug response. If the effect of precipitant drug dose changes on the object drug was not assessed, answer NA.

Discussion

A case report of a drug interaction will serve as an example of how to employ the DIPS to evaluate a potential interaction. The case is a well-written, detailed report of a complex patient who is taking cyclosporine and experienced an elevated cyclosporine concentration during the administration of azithromycin.¹¹ The authors noted that, using the Naranjo scale, the case scored 5 points, a probable rating for causation. They appropriately suggested monitoring cyclosporine concentrations, particularly in patients who are critically ill. In Table 1, we have used the DIPS to evaluate this published case. The “Comments” section in the table describes the rationale used to arrive at each answer.

The total DIPS score achieved, as shown in Table 1, is 1 point, suggesting a doubtful score for causation. The fact that the Naranjo scale and DIPS produce different estimates of causation is not as important as the fact that the DIPS represents a more complete tool for evaluating the case. Does azithromycin cause cyclosporine concentrations to increase? In this case, the evidence does not strongly support azithromycin as the cause of the altered cyclosporine concentrations. The higher score from the Naranjo scale suggests that an event related to cyclosporine is likely to have occurred. However, the role of azithromycin in this event is doubtful. This outcome should not be generalized to all cases of azithromycin–cyclosporine coadministration. One cannot rule out the possibility that the interaction may occur in certain predisposed patients or that other case reports could present a more compelling case for azithromycin-induced changes in cyclosporine concentrations. However, a number of studies summarized by Strachan et al.,¹⁴ in which azithromycin was coadministered with cyclosporine, failed to detect an interaction. Bachmann et al.¹⁵ noted a 7% increase in the mean cyclosporine area under the concentration–time curve in 8 patients coadminis-

tered azithromycin for 3 days. These studies were published 2 years after the case example noted above.

Several limitations apply to the use of the DIPS to evaluate potential drug interactions. First, it has been used by only a few evaluators and would benefit from wider exposure with user feedback and modification. Also, potential drug interaction case reports that provide only limited data could result in a low causation score. This may lead to a false negative evaluation of causation. The use of the DIPS requires a fairly complete knowledge of the 2 drugs involved in the potential interaction. For example, failure to recognize alternative causes of altered object drug response can result in false positive causation assessments. Often, warfarin–antibiotic interaction cases are reported in which the authors do not consider the effect of the patient’s infection on warfarin metabolism and vitamin K intake.

It is important to understand that the DIPS is simply a tool to evaluate a potential drug interaction in a specific patient. It serves as a reminder to consider drug properties and other causes that may alter a patient’s response when evaluating a potential drug interaction. The probability score is not absolute. It will likely be different for the same interaction occurring in different patients because the patients will respond differently and will have different con-

founders. The probability score is relevant only to the case used to estimate it. It does not apply to all patients receiving the interacting drugs or even to all patients who experience an adverse outcome as a result of receiving the drugs. The DIPS will help to identify potential interactions in patients and guide further study of potential drug interactions.

Summary

The current understanding of drug metabolism and transport has greatly increased our ability to more accurately predict drug interactions occurring in patients. The DIPS offers a methodology developed specifically to evaluate potential drug–drug interactions in the clinical setting, based on our current understanding of the drugs’ important features. We have used the DIPS for many years in the evaluation of drug interaction case reports considered for inclusion in tertiary drug interaction references. It represents a simplified version of the evaluation process that we believe is necessary to assess causation. While it is important to correctly identify a potential drug interaction as the cause of a patient’s adverse clinical event, it is equally important to rule out a potential interaction and focus on other reasons that might be causing a patient’s problem.

Table 1. Example of Completed DIPS Form

DIPS QUESTIONS	Answer/Score	Comments
1. Are there previous <i>credible</i> reports of this interaction in humans?	NA / 0	At the time of the report, 1 case report purporting an interaction and 1 report of 6 cases without an interaction had been published. ^{12,13} Neither report met the criteria for a credible report; both are disregarded as evidence in this case.
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	no / -1	Cyclosporine is a substrate for CYP3A4 and P-glycoprotein. Azithromycin is not known to inhibit CYP3A4 or P-glycoprotein.
3. Is the observed interaction consistent with the known interactive properties of object drug?	NA / 0	Since no known properties of azithromycin affect cyclosporine, the answer is NA.
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	yes / 1	The time course of the change in cyclosporine concentrations would be consistent with a change in its elimination.
5. Did the interaction remit upon dechallenge of the <i>precipitant</i> drug with no change in the object drug? (If no dechallenge, use “Unknown or NA” and skip Question 6).	yes / 1	Stopping azithromycin did coincide with a fall in the concentration of cyclosporine.
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	no / 0	No rechallenge was attempted.
7. Are there reasonable alternative causes for the event?	yes / -1	As noted by the authors, alternative reasons existed (eg, cytokine-induced inhibition of CYP3A4 metabolism) that could lead to reduced cyclosporine metabolism.
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	yes / 1	Cyclosporine concentrations were measured and varied appropriately with the administration and discontinuation of azithromycin.
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	NA / 0	There was no other evidence of the interaction except elevated cyclosporine concentrations.
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	NA / 0	There was no change in the precipitant drug dose.

DIPS = Drug Interaction Probability Scale; NA = not applicable.

The DIPS does not affect how one manages a drug interaction. It is intended to provide guidance when considering the contributory role of a potential drug interaction versus other potential causes of a specific patient outcome. Using the DIPS can assist authors in preparing a more reliable drug interaction case report and assist reviewers with the evaluation of reports submitted for publication; it is also very helpful when evaluating published cases, particularly those that were not subject to careful critique. The Naranjo scale should be used to evaluate potential single-drug-induced adverse reactions. Information generated with the assistance of the DIPS will support clinicians attempting to minimize adverse events associated with drug interactions and help generate more reliable literature in the study of drug interactions.

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Drs. Horn and Hansten are authors of several references on drug interactions, including: *The Top 100 Drug Interactions: A Guide to Patient Management and Drug Interactions Analysis and Management*. In addition, they author a Web site devoted to drug interactions (www.hanstenandhorn.com).

References

1. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
2. Jones JK. Adverse drug reactions in the community health setting: approaches to recognizing, counseling, and reporting. *Fam Commun Health* 1982;5:58-67.
3. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA* 1979;242:623-32.
4. Mashford ML. The Australian method of drug-event assessment. *Drug Inf J* 1984;18:271-3.
5. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther* 1977;21:247-54.

Appendix I. Drug Interaction Probability Scale

The Drug Interaction Probability Scale (DIPS) is designed to assess the probability of a causal relationship between a potential drug interaction and an event. It is patterned after the Naranjo ADR Probability Scale (*Clin Pharmacol Ther* 1981;30:239-45).

Directions:

- Circle the appropriate answer for each question, and add up the total score.
- Object drug = Drug affected by the interaction.
Precipitant drug = Drug that causes the interaction.
- Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (eg, no dechallenge; dose not changed, etc.).

Questions	Yes	No	Unk or NA
1. Are there previous <i>credible</i> reports of this interaction in humans?	+1	-1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	-1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	-1	0
5. Did the interaction remit upon dechallenge of the <i>precipitant</i> drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6)	+1	-2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	-1	0
7. Are there reasonable alternative causes for the event? ^a	-1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	-1	0

^aConsider clinical conditions, other interacting drugs, lack of adherence, risk factors (eg, age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score ____

Highly Probable:	>8
Probable:	5-8
Possible:	2-4
Doubtful:	<2

6. Koh Y, Li SC. A new algorithm to identify the causality of adverse drug reactions. *Drug Saf* 2005;28:1159-61.
7. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. *Am J Hosp Pharm* 1986;43:1709-14.
8. Berry LL, Segal R, Sherrin TP, Fudge KA. Sensitivity and specificity of three methods of detecting adverse drug reactions. *Am J Hosp Pharm* 1988;45:1534-9.
9. Kane-Gill SL, Kirisci L, Pathak DS. Are the Naranjo criteria reliable and valid for determination of adverse drug reactions in the intensive care unit? *Ann Pharmacother* 2005;39:1823-7. Epub 4 Oct 2005. DOI 10.1345/aph.1G177
10. Hansten PD, Horn JR. The top 100 drug interactions: a guide to patient management. 2006 ed. Freeland, WA: H&H Publications, LLP, 2006: 230-1.
11. Page RL, Ruscin JM, Fish D, LaPointe M. Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy* 2001; 21:1436-43.
12. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. *Nephron* 1995;70:130.
13. Gomez E, Sanchez JE, Aguado S, Alvarez-Grande J. Interaction between azithromycin and cyclosporin? *Nephron* 1966;73:724.
14. Strachan D, Burton I, Pearson GJ. Is oral azithromycin effective for the treatment of cyclosporine-induced gingival hyperplasia in cardiac transplant recipients? *J Clin Pharm Ther* 2003;28:329-38.
15. Bachmann K, Jauregui L, Chandra R, Thakker K. Influence of a 3-day regimen of azithromycin on the disposition kinetics of cyclosporine A in stable renal transplant patients. *Pharmacol Res* 2003;47:549-54.

EXTRACTO

La evaluación de las causas para las interacciones potenciales entre fármacos requiere una evaluación cuidadosa de las propiedades tanto del fármaco precipitante como del fármaco afectado, y la posible contribución de otros fármacos que el paciente pudiera estar utilizando. El nomograma de Naranjo fue diseñado para evaluar eventos adversos relacionados al uso de fármacos en individuos, no interacciones entre varios fármacos. Algunas de las preguntas del nomograma de Naranjo no aplican a interacciones potenciales entre fármacos mientras otras no distinguen entre el fármaco precipitante y el afectado. Sin embargo, el instrumento ha sido utilizado para evaluar interacciones entre fármacos. La Escala de Probabilidad de Interacciones entre Fármacos (EPIF, DIPS) fue desarrollada específicamente para proveer una guía para evaluar las

causas de una interacción entre fármacos en un paciente específico. La intención es que se utilice el instrumento para asistir al personal clínico en la evaluación de los efectos adversos relacionados a las interacciones entre drogas. La EPIF utiliza una serie de preguntas relacionadas al potencial de interacción para estimar una puntuación de probabilidad. Una evaluación certera utilizando el instrumento requiere conocimiento de las propiedades farmacológicas tanto del fármaco precipitante como del afectado. Un conocimiento inadecuado tanto de los fármacos en consideración como de los mecanismos básicos de interacciones entre drogas sería una limitación para algunos usuarios. La Escala de Probabilidad de Interacciones entre Fármacos también puede servir como guía en la preparación de publicaciones sobre casos de interacciones entre fármacos y en la evaluación de casos que hayan sido publicados.

Mitchell Nazario

RÉSUMÉ

L'évaluation de la causalité lors d'une interaction médicamenteuse potentielle requiert la prise en considération des propriétés des médicaments impliqués, des facteurs spécifiques au patient, et de la possible contribution des autres médicaments que le patient consomme. L'algorithme de Naranjo a été conçu pour évaluer des effets indésirables aux médicaments seulement, et non des interactions entre médicaments. Plusieurs des questions de l'algorithme de Naranjo ne s'appliquent pas aux interactions entre médicaments alors que d'autres ne spécifient pas le médicament précipitant ou le médicament affecté. Néanmoins, il a été utilisé pour évaluer des interactions entre médicaments. L'échelle de probabilité des interactions médicamenteuses (EPIM) a été développée spécifiquement pour fournir un guide à l'évaluation de causalité des interactions médicamenteuses chez un patient donné. Son utilisation a été prévue pour assister les cliniciens dans l'évaluation des effets indésirables résultant des interactions médicamenteuses potentielles. L'EPIM utilise une série de questions ayant trait à une interaction médicamenteuse potentielle pour estimer un pointage de probabilité. Une évaluation précise par le biais de l'EPIM requiert la connaissance des propriétés pharmacologiques des 2 médicaments impliqués. Une connaissance inadéquate des médicaments impliqués ou encore des mécanismes de base des interactions médicamenteuses sera une limite pour certains utilisateurs. L'EPIM peut aussi servir de guide dans la rédaction des rapports de cas signalant une interaction médicamenteuse et dans l'évaluation des rapports de cas publiés.

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