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Why Can't We Just Get Relevant Alerts?

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Everyone who is exposed to drug–drug interaction (DDI) clinical decision support (CDS) asks this question. It seems obvious that too many irrelevant alerts are seen, as evidenced by override rates that are typically greater than 80%, so why not fix the CDS to only display alerts for DDIs that are clinically important?

The major reason that it is difficult to create a DDI CDS that limits alerts to those that may cause patient harm is that it is nearly impossible to identify these DDIs a priori. Many variables need to be examined to arrive at a reasonable risk assessment.

Variables Affecting DDI Magnitude

One of the problems with trying to define the risk of a DDI is that the interpatient variability of DDIs is often quite large. For example, a study of the effect of voriconazole on tacrolimus reported that the mean increase in tacrolimus concentration was approximately 140% but ranged from -32% to 685%.[1] Similarly, diltiazem increased the area under the concentration-time curve of lovastatin in 10 subjects from 51% to 906%.[2] It is not uncommon to see a 5- to 6-fold range in the magnitude of a DDI among patients.

This interpatient variability is the result of numerous factors, including the doses (plasma concentration) of the precipitant and object drugs, routes of administration, drug formulations, the order of administration of the object and precipitant drugs, and the duration of administration, as well as the patient's genetic makeup (especially their genotype for elimination of the object and precipitant drugs), age, gender, and comorbid conditions. Each of these variables can result in a large difference in the magnitude, and therefore the potential clinical significance, of a DDI.

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It is not surprising that it is very difficult to predict the magnitude of an interaction in any specific patient. However, the risk of some interactions can be defined by patient characteristics. For example, the risk of hyperkalemia with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers plus potassium-sparing diuretics is almost entirely associated with renal dysfunction.

Responding to a Potential DDI

No currently available DDI CDS is able to factor each of these variables into an estimate of the risk of an adverse reaction. It is left up to the practitioner to judge the risk in any particular patient and take appropriate steps to avoid adverse outcomes.

There are only a few options available to respond to a potential DDI: change the object drug, change the precipitant drug, change the dose or formulation, or monitor for evidence of the DDI. Choosing an alternative for either the object drug or precipitant drug is often dependent on identifying an alternative drug with similar pharmacologic properties without the tendency to interact.

When a DDI alert is encountered, the usual response is to find an alternative to the second drug of the interaction pair that is prescribed. Because physicians will rarely change the drug ordered by another physician, they will try to identify an alternative agent for the one they have selected that has triggered the interaction alert.

Pharmacists are in a unique position to recommend changing either of the interacting drugs based on their assessment of the most appropriate option. Instead of recommending an alternative drug, it may be possible to suggest a change in dose, formulation, or order or time of administration to avoid the interaction.

When changing drugs is not required to avoid DDI-induced toxicity, suitable monitoring is often an appropriate alternative. Monitoring recommendations should be based on the pharmacokinetic and pharmacodynamic properties of the drugs and the availability of symptomatic or laboratory tests.

Recognizing the multiple variables that influence the magnitude of a DDI, and therefore the risk to a patient, it is easy to understand how difficult it is to develop absolute guidelines for the risk of a potential DDI to cause patient harm. It is imperative that each patient be evaluated for their specific risks prior to determining the best response to a potential DDI. ■

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