How to Assess Drug Interaction Case Reports

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Case reports represent a substantial portion of the literature on drug interactions. Unfortunately, many of these reports are difficult to evaluate due to incomplete and sometimes confusing information. We will present some of the important factors to consider when assessing a drug interaction case report. As usual, we will use "object drug" to signify the drug affected by the interaction and "precipitant drug" for the drug that causes the interaction.

Look at Previous Literature

One of the essential questions to ask yourself is whether the interaction case report makes sense, given the known interactive properties of the drugs involved. For example, an increased warfarin response after a patient is started on a potent CYP2C9 inhibitor such as sulfamethoxazole is completely consistent with what one would expect from combining a CYP2C9 substrate (warfarin) with a CYP2C9 inhibitor (sulfamethoxazole).

Alternatively, case reports where the outcome is the opposite of what would be expected, given the interactive properties (of either the object drug, precipitant drug, or both drugs), is evidence against a causal relationship. It does not completely eliminate the possibility of a drug interaction, however, because sometimes drugs have differing interactive properties, depending on how they are used (eg, short-term vs long-term use, large vs small doses, etc).

Sometimes there is insufficient published information about the interactive properties of one or both drugs involved in a case report. It would be wrong to assume, however, that just because information in the literature is lacking, the drugs do not have particular interactive properties that simply have not yet been detected. Diphenhydramine (Benadryl), for example, had been used for decades before it was discovered that it is a relatively potent CYP2D6 inhibitor.

Look at Details of the Case

Time Course

As discussed in this column in the March 2006 issue *(Disaster: Failing to Consider the Time Course)*, drug interactions tend to have a characteristic time course, depending largely on the mechanism of the interaction and the pharmacokinetics of the object drug. If the interaction takes place much more rapidly or much more slowly than the expected time course, a causal relationship is less likely. Sometimes careful examination of the time course of drug interaction case reports can effectively rule out the drug interaction as a cause; for example, when the interaction occurs before the object drug is given. (This sounds preposterous, but such errors happen more often than one might think.)

Stopping One or Both Drugs

If a drug interaction is suspected of causing drug toxicity in a patient, often both interacting drugs are stopped simultaneously in order to reduce the toxicity as rapidly as possible. This is sensible and is usually in the best interests of the patient, but does not provide much information for assessing a causal relationship. In those cases where it is safe to stop only the precipitant drug without changing the dose of the object drug, one can watch for the expected change in the response to the object drug. This is called a positive dechallenge and is one of the key elements in establishing a causal relationship. Then, if the precipitant drug is restarted and the expected effect on the object drug recurs, that is additional evidence of causality. This is called a positive rechallenge. Case reports of drug interactions rarely include a dechallenge and even more rarely include a rechallenge. This is one of the primary reasons why case reports are difficult to evaluate.

Alternative Explanations

It is important to look for other causes of the adverse outcome. Sometimes they are obvious, such as an increase in the dose of the object drug at the same time that the precipitant drug is started. In some cases, however, it may be difficult to assess other causes, particularly in a patient with multiple fluctuating diseases who is having frequent changes in his or her drug regimen. Depending on the drug interaction under consideration, many alternative explanations need to be considered, such as chronic diseases, changes in disease states, infections, other interacting drugs, dietary factors, lack of adherence to drug regimens, pharmacogenetics, and many more.

Summary

Although assessing causality in drug interaction case reports is difficult, attention to the guidelines discussed above can facilitate this process. Such guidelines can be useful in assessing published case reports, as well as cases that one personally observes in practice. PT

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