Time Course for Enzyme Induction and Deinduction

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This column has previously discussed the factors that determine the time course for drug interactions caused by enzyme inhibitors.[1] Based on the short half-life of most inhibitors, inhibition can occur over just a few days. A less intuitive approach is needed when estimating the time course of interactions caused by enzyme induction. Rifampin is known to induce multiple enzymes responsible for drug metabolism including cytochrome P450 (CYP)1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and some glucuronidation pathways. In addition, it has been reported to induce the activity of several drug transporters, such as the organic anion transporter and P-glycoprotein.

ENZYME INDUCTION TIME COURSE

Usually, we consider the half-life of a precipitant drug to estimate the time required to maximize its effect on an enzyme. For example, if an enzyme inhibitor has a half-life of 6 hours, about 24 hours will be required for it to reach steady state and exert its maximum inhibitory effect on the enzyme.

Rifampin has a half-life of about 4 hours, but the time required to produce maximum enzyme induction is much longer due to the requirement of producing additional enzyme. The time required for rifampin-induced induction to reach steady state seems to depend primarily on the time required to upregulate the metabolizing enzymes, assuming the half-life of the drug is less than the degradation half-life of the enzyme. For example, new steady-state propranolol and prednisolone concentrations require 10 to 14 days following the initiation of rifampin.[2] Even longer periods of time to reach steady state have been noted during phenobarbital-induced enzyme induction.[3]

The delayed attainment of maximum enzyme induction and the resulting decline in object drug plasma concentration requires a different monitoring strategy than an enzyme inhibition interaction. In addition to typically monitoring for the potential loss of object drug efficacy—instead of increased toxicity, as commonly occurs with enzyme inhibitors—one has to continue monitoring the patient for several weeks to adequately assess the magnitude of the interaction. Further, drug toxicity (eg, warfarin-induced bruising or bleeding) is often quicker and easier to detect than loss of efficacy (eg, risk of thrombosis or stroke), which may take some time to become clinically evident.

A recent report noted that 2 to 4 weeks were required for rifampin-induced midazolam clearance to return to baseline values.

ENZYME DEINDUCTION TIME COURSE

When the enzyme-inducing precipitant drug is discontinued, deinduction of the enzyme occurs gradually. The time course for the enzymes to return to normal activity is delayed compared with the time required for offset of an enzyme inhibitor.

A recent report noted that 2 to 4 weeks were required for rifampin-induced midazolam clearance to return to baseline values.[2] The authors estimated that the deinduction half-life was 7.7 days. Deinduction of hepatic enzymes is likely to depend on elimination of the inducing drug and, more importantly, the natural degradation time of the enzymes.

Chronic rifampin dosing has been noted to reduce digoxin plasma concentrations. This effect is considered to be caused by the induction of P-glycoprotein that transports digoxin out of enterocytes back into the intestinal lumen, particularly during the absorption of digoxin. Following rifampin discontinuation, digoxin absorption returned to baseline after 14 days.[2]

The faster return of P-glycoprotein activity to baseline compared with hepatic enzyme activity may reflect the more rapid turnover of enterocytes compared with hepatocytes.

Just as it is important to think about the time course of an interaction caused by an inhibitor of drug elimination, the pharmacist has to consider the prolonged onset and offset of interactions based on enzyme or transporter induction. Few computerized clinical decision support programs include guidance for these circumstances.

Although knowledge of the half-lives of the 2 interacting drugs will be helpful to estimate the onset and offset of enzyme inhibition interactions, using drug half-lives will usually underestimate the time required for induction onset and offset. It is particularly important to consider the delayed offset of a recently discontinued enzyme inducer when monitoring drugs that have been newly prescribed. ***PT***

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