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Silly Cytochromes

Pharmacists often have difficulty taking drug interactions seriously. Many are theoretical, occur infrequently or have spotty evidence of support. As such, we have learned to often look the other way and ignore them. A few interactions do get us excited, however. Many of these are caused by the utterly confusing cytochrome P450 (CYP) enzyme system in the liver.

I first started paying attention to cytochromes back in the 80s, when initial reports of grapefruit juice interactions began to surface. I chuckled at the suggestion that a couple of glasses of grapefruit juice could cause muscle breakdown and kidney failure in patients taking statins or hypotension and cardiac collapse in combination with calcium channel blockers. A component of grapefruit juice was soon found to inhibit the 3A4 enzyme of the complex and before long jus de pamplemousse was a feared beverage, never again to be seen in nursing facilities. Another 3A4 villain is Biaxin®. It can do the same sort of damage in a more conventional drug-drug interaction.

CYP 2C19 has been a recent newsmaker. Proton pump inhibitors, Losec® being the worst of the bunch, are potent inhibitors of this enzyme. 2C19 is required to activate Plavix® and metabolize Celexa®. Notably, there have been reports of heart attacks and strokes when Losec® is added to Plavix®, and cardiac arrhythmias when it is used in conjunction with Celexa®.

In spite of the importance of these interactions, I did not intend to write about cytochromes this month, until I attended a recent lecture. The presenter spoke about CYP 2D6 (essential for activating tamoxifen and turning codeine to morphine). It is already widely known that common SSRI antidepressants, such as Paxil® and Prozac® impair 2D6 and such drugs are not used with tamoxifen or codeine products. What I was not aware of, is that duloxetine (Cymbalta®) also inhibits 2D6. This has extraordinary significance, as Cymbalta® is often combined with codeine in an effort to treat stubborn, resistant pain symptoms. Codeine is a flawed analgesic, having no activity in some patients and producing toxicity in others. This interaction gives us another reason to avoid it in favour of more predictable narcotics, such as morphine or hydromorphone.

Antidepressant Advance

Major changes are coming in antidepressant therapy. Ketamine, an intravenous drug used as an anesthetic for many years, has shown itself to have remarkable antidepressant properties in some recent small trials.

The drug has been given to individuals with resistant depression who have failed multiple courses using conventional antidepressants. In some cases, patients have responded in less than 24 hours. Some have improved to the point that they are no longer considered depressed.

The main barrier to the use of this medication is that it must be injected intravenously. A new trial compared 50mg of nasally administered ketamine to a saline solution in patients with major depressive disorder. A significant improvement in depressive indicators, such as sleep disturbance, appetite, initiative and diminished sadness could be shown after just 24 hours.

Safety data must still be collected and ideal dosing and administration frequency remain to be determined. If all goes well, this NMDA receptor blocker may be on the market soon.

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