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Codeine Drug Interactions

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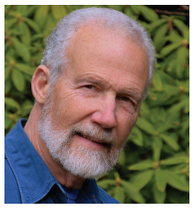

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In the late 1940s and early 1950s, Giuseppe Sanfilippo published several articles suggesting that codeine was converted to morphine, which in turn was responsible for the analgesic effect of codeine.[1-3] Little was made of this until the 1980s and 1990s, when it became clear that codeine was converted to morphine by CYP2D6, and that in people without CYP2D6 activity, giving codeine was like giving a placebo. Since then, the codeine "story" has been one of indifference, tragedy, and increasing complexity. But out of all of this, some rational guidelines have finally emerged.

Reduced CYP2D6 Activity

After it became clear that codeine is converted to morphine by CYP2D6, several studies showed that people who lacked the genes for producing CYP2D6, or who were receiving potent CYP2D6 inhibitors, did not achieve pain relief when given codeine.[4-7] It made no sense to give codeine to such people, but this information was not widely disseminated among health professionals. Of course, it was not practical to determine CYP2D6 genetic status prior to giving codeine, but it was possible to screen people for potent CYP2D6 inhibitors prior to giving codeine.

Increased CYP2D6 Activity

Around the same time that CYP2D6 deficiency was shown to inhibit codeine effect, it was discovered that some people have much higher than normal CYP2D6 activity, dubbed "ultrarapid" CYP2D6 metabolism (UM).[8,9] This phenomenon is due to a genetic variant in which multiple genes for CYP2D6 are present, leading to markedly increased CYP2D6 activity. After this discovery, it was not long before cases were reported of morphine toxicity in patients with UM who received normal doses of codeine.[10-13] In one tragic case, a mother with UM who was given codeine postpartum inadvertently induced fatal morphine toxicity in her infant through her breast milk.[12] In another case, fatal morphine toxicity occurred in a 2-year-old boy with UM who received codeine after a tonsillectomy.[13] Severe morphine toxicity was also described in UM adults.[11]

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Altered CYP3A4 Activity

Metabolism of codeine to norcodeine via CYP3A4 is normally a minor pathway, but under certain circumstances, CYP3A4 can play a role. In a person with normal CYP2D6 activity, giving CYP3A4 inhibitors has little effect because of the small percentage of codeine that is metabolized in this manner. In a UM patient who is converting much codeine into morphine, however, inhibiting CYP3A4 might increase the morphine toxicity somewhat by reducing the amount of codeine going down a non-CYP2D6 pathway. A complicating factor is that many CYP3A4 inhibitors also inhibit P-glycoprotein or other ABC transporters, and these transporters may affect morphine disposition (see below).

The effect of CYP3A4 *inducers* on codeine is a different story. Unlike the usually small effect of CYP3A4 inhibitors, CYP3A4 inducers such as rifampin can substantially increase the proportion of codeine that is converted to the inactive norcodeine at the expense of conversion to morphine. In one study, rifampin markedly reduced morphine plasma concentrations in healthy subjects given codeine.[14]

ABC Transporters

There are some intriguing recent findings on the effect of ABC transporters on the ability of morphine to gain access to sites of action (brain) and metabolism (liver). The potential ability of the efflux transporter, P-glycoprotein, to reduce the access of morphine to the brain and thereby reduce the effect of morphine is an area of intense study. Some data suggest that inhibition of P-glycoprotein with drugs can increase morphine brain access, but the clinical importance of this effect is still being worked out.[15] If it turns out that brain P-glycoprotein is important, it may reveal the possibility of codeine (and morphine) drug interactions with drugs that inhibit or induce P-glycoprotein (of which there are many).

There is also evidence that an organic cation transporter (OCT1) may facilitate uptake of morphine by the liver. Accordingly, people with a genetic lack of OCT1 function have substantially higher morphine plasma concentrations after receiving codeine.[16] This raises the question of whether people taking OCT1 inhibitors such as irinotecan, verapamil, or ondansetron would also have higher than expected morphine concentrations following codeine or morphine administration. Stay tuned.

Recommendations[17]

- Genetics: Do not use codeine in people with no CYP2D6 (lack of codeine response) or in ultrapid metabolizers of CYP2D6 (morphine toxicity).
- Drug interactions: Do not use codeine in patients receiving strong CYP2D6 inhibitors or strong CYP3A4 inducers (in both cases, there is a lack of codeine response).
- Pediatrics: Do not use codeine after tonsillectomies or in breast-feeding mothers, due to the risk of morphine toxicity. ■

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references, if any, visit www.hanstenandhorn.com.