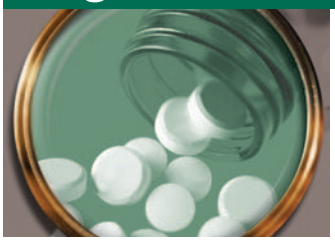

Narcotic Analgesics Metabolized by CYP2D6

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The use of both nonnarcotic and narcotic analgesics in the treatment of acute and chronic pain has been the focus of renewed interest during the past few years. Although some of these medications have been utilized for many years, the appropriate use of analgesics requires knowledge of their risks, benefits, and potential drug interactions. Several common analgesics are substrates of the enzyme CYP2D6—including codeine, dihydrocodeine, and tramadol. A recent study found that ~20% of patients receiving these drugs also were administered a drug known to inhibit the activity of CYP2D6.[1]

Codeine

Codeine is a prodrug with no analgesic activity. About 10% of a dose of codeine is converted in the body by CYP2D6 to morphine, an active metabolite. The morphine is glucuronidated to both active and inactive metabolites that are eliminated by the kidneys. The rest of the codeine is metabolized by glucuronidation and CYP3A4 to inactive metabolites. Thus, CYP2D6 is necessary for much of the analgesic action of codeine.

Most Caucasians rapidly convert codeine to morphine via CYP2D6. Approximately 7% to 10% of Caucasians, however, have a genetic variant that produces limited CYP2D6 activity and slow metabolism of CYP2D6 substrates. In these patients, conversion of codeine to morphine is reduced, as is the analgesic efficacy. Administration of codeine to these patients will not provide the expected degree of analgesia.

Side effects of codeine also are reduced when intrinsic CYP2D6 activity is reduced. Similarly, drugs that reduce CYP2D6 activity will inhibit the analgesic activity of codeine.[2,3] The Table lists some common inhibitors of CYP2D6. Whereas not all CYP2D6 inhibitors have been studied with codeine, all would be expected to interact to some extent.

Table

Some Inhibitors of CYP2D6
Amiodarone
Chloroquine
Cimetidine
Clomipramine
Diphenhydramine
Duloxetine
Fluoxetine
Hydroxychloroquin
Paroxetine
Propafenone
Propoxyphene
Quinidine
Terbinafine

As noted above, a large portion of a dose of codeine is metabolized by CYP3A4 and glucuronidation. A patient receiving codeine and a potent inhibitor of CYP3A4 would be expected to have more codeine going through the CYP2D6 and glucuronidation pathways. This process could result in an increased production of active metabolites. Although data are limited, patients taking a CYP3A4 inhibitor may be more susceptible to codeine toxicity, particularly if they are very rapid converters of codeine to morphine.[4]

Dihydrocodeine

Dihydrocodeine is metabolized to the active metabolite dihydromorphone. In a study of 11 normal subjects, quinidine pretreatment reduced dihydromorphone concentrations between 3- and 4-fold, compared with dihydrocodeine administered alone. Quinidine, however, did not reduce the analgesic response to experimentally induced pain following dihydrocodeine. It would appear that dihydrocodeine or another metabolite that is not dependent on CYP2D6 has analgesic activity, but further studies in patients with pain are needed.[5] Little information on the effect of CYP2D6 inhibitors on other codeine derivatives is available.

Tramadol

Tramadol is an analgesic that is converted by CYP2D6 to an active metabolite. Tramadol itself does have some analgesic activity, but the majority of its activity depends on the formation of the active metabolite. As with codeine and its derivatives, tramadol analgesic activity will be reduced in patients with low CYP2D6 activity caused by drugs or genetic variation. Note that tramadol also increases serotonin activity, and the coadministration of selective serotonin reuptake inhibitors with tramadol could increase the risk of serotonin syndrome.

Summary

The clinical outcome of CYP2D6 inhibition in patients taking codeine or tramadol is a reduction in the analgesic activity. This reduction can lead to unnecessary patient discomfort and to increasing doses of analgesic. If the CYP2D6 inhibitor is discontinued in these patients, an excess narcotic effect may occur if the patient is not closely monitored and the dose of the analgesic adjusted. The use of CYP2D6 inhibitors in patients taking codeine or tramadol should be avoided. If a CYP2D6 inhibitor must be used, consider an analgesic that is not metabolized by CYP2D6, such as morphine, methadone, or fentanyl. PT

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