

BRIEF REPORT

Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

Yvan Gasche, M.D., Youssef Daali, Pharm.D., Ph.D., Marc Fathi, Ph.D., Alberto Chiappe, Silvia Cottini, M.D., Pierre Dayer, M.D., and Jules Desmeules, M.D.

SUMMARY

Life-threatening opioid intoxication developed in a patient after he was given small doses of codeine for the treatment of a cough associated with bilateral pneumonia. Codeine is bioactivated by CYP2D6 into morphine, which then undergoes further glucuronidation. CYP2D6 genotyping showed that the patient had three or more functional alleles, a finding consistent with ultrarapid metabolism of codeine. We attribute the toxicity to this genotype, in combination with inhibition of CYP3A4 activity by other medications and a transient reduction in renal function.

ADVERSE DRUG REACTIONS ARE A MAJOR CAUSE OF DEATH IN HOSPITALIZED patients.¹ Differences among persons in the level of cytochrome P-450–dependent monooxygenase activity may lead to differences in the efficacy and toxicity of drugs metabolized by this enzyme system.²⁻⁴

Cytochrome P-450 is the product of a multigene family, and its activity may reflect drug–drug interaction. Genetic variants of the cytochrome P-450 enzyme CYP3A4 are relatively common, but to our knowledge none of them have been shown to cause a phenotypic change in drug metabolism. In contrast, various genotypes of the CYP2D6 subfamily of cytochrome P-450 enzymes correlate with phenotypic subgroups with differing rates of drug metabolism.^{5,6} A person with two nonfunctional alleles at *CYP2D6* is considered to have poor drug metabolism, whereas a person with one or two functional alleles is considered to have extensive metabolism, and one who has duplicated or amplified active *CYP2D6* genes is considered to have ultrarapid metabolism.⁷ About 7 to 10 percent of whites have poor CYP2D6 metabolism, whereas 1 to 7 percent of whites and more than 25 percent of Ethiopians have gene duplications and are classified as having ultrarapid metabolism. CYP2D6 catalyzes hydroxylation or demethylation of more than 20 percent of drugs, including codeine.

O-demethylation of codeine into morphine by CYP2D6 represents a minor pathway of codeine metabolism (accounting for less than 10 percent of codeine clearance)⁸ but is essential for its opioid activity (Fig. 1). N-demethylation of codeine into norcodeine by CYP3A4 and the glucuronidation of codeine are the main pathways (accounting for more than 80 percent of codeine clearance) for converting the molecule into inactive compounds.

We describe a patient who presented with life-threatening codeine intoxication despite having received only modest doses of the medication. Analysis of the patient's cytochrome P-450–dependent monooxygenase genotype (CYP2D6) and phenotype (CYP2D6 and CYP3A4) indicated that his unusual response to codeine might be ex-

From the Divisions of Surgical (Y.G., S.C.) and Medical Intensive Care (Y.G.), Clinical Pharmacology and Toxicology (Y.D., P.D., J.D.), and Clinical Chemistry (M.F., A.C.), Geneva University Hospital, Geneva. Address reprint requests to Dr. Gasche at the Division of Surgical Intensive Care, Department of Anesthesiology, Pharmacology, and Surgical Intensive Care, Geneva University Hospital, 24 rue Micheli-du-Crest, CH-1211 Geneva, Switzerland, or at yvan.gasche@medecine.unige.ch.

N Engl J Med 2004;351:2827-31.

Copyright © 2004 Massachusetts Medical Society.

plained by ultrarapid CYP2D6 metabolism, combined with the inhibition of CYP3A4 by other medications and the accumulation of active metabolites because of renal failure.

CASE REPORT

A 62-year-old man with a history of chronic lymphocytic leukemia presented with a three-day history of fatigue, dyspnea, fever, and a cough. He had last received chemotherapy three months earlier. His only medication was valproic acid (1500 mg daily), which he had been taking for several years after he had had a post-traumatic generalized seizure. On arrival at the hospital, the patient was alert and oriented and was hypoxemic (partial pressure of arterial oxygen, 56 mm Hg; fraction of inspired oxygen, 0.21) but normocapnic (partial pressure of arterial carbon dioxide, 37 mm Hg). Clinical and radiologic findings were compatible with bilateral pneumonia limited to the inferior lobes. Because of his immunocompromised state, bronchoalveolar lavage was performed. Preliminary results showed no *Pneumocystis carinii* but revealed yeast. Therapy with ceftriaxone, clarithromycin, and voriconazole was initiated, and oral codeine (25 mg three times a day) was administered to relieve the cough.

On hospital day 4, the patient's level of consciousness rapidly deteriorated, and he became unresponsive. His last dose of codeine had been administered 12 hours earlier. Arterial blood gas measurements revealed a partial pressure of oxygen of 56 mm Hg, with a fraction of inspired oxygen of 0.5 and a partial pressure of carbon dioxide of 80 mm Hg. The patient was treated with noninvasive ventilation and was transferred to the intensive care unit. Initial neurologic examination showed a score of 6 on the Glasgow Coma Scale (no eye opening, no verbal response, and limb withdrawal after pain stimulation). The patient's pupils were miotic, and no focal deficits were detected.

Ninety minutes after the initiation of noninvasive ventilation, repeated measurements of arterial blood gases showed that the partial pressure of oxygen was 68 mm Hg and the partial pressure of carbon dioxide was 56 mm Hg, but no neurologic improvement was observed. The serum urea nitrogen and creatinine levels were elevated, at 45.4 mg per deciliter (16.2 mmol per liter) and 2.06 mg per deciliter (182 μ mol per liter), respectively; the levels subsequently normalized with hydration. The se-

rum level of valproic acid was 62.4 mg per liter (433 μ mol per liter; normal range, 50.4 to 101 mg per liter [350 to 700 μ mol per liter]) on the patient's usual dosage. The blood level of ammonia was normal. Intravenous administration of naloxone (0.4 mg) that was repeated two times resulted in a dramatic improvement in the patient's level of consciousness; with titration of naloxone (a continuous perfusion of 0.4 mg per hour for six hours), a normal level of consciousness was maintained and respiratory failure resolved. Two days after the acute event, the patient had recovered completely.

METHODS

The blood levels of codeine, morphine, and their metabolites were determined by liquid chromatography–mass spectrometry.⁹ Duplication or multiduplication of the *CYP2D6* gene was detected by restriction-fragment–length polymorphism analysis of genomic DNA isolated from leukocytes, after digestion with restriction enzymes *Xba*I and *Eco*RI, as described elsewhere.^{6,10} The *CYP2D6* and *CYP3A4* phenotype was also determined. The widely used dextromethorphan substrate was used as a probe drug to evaluate CYP phenotypic activity. In humans, dextromethorphan is metabolized into dextrorphan by *CYP2D6* and into 3-methoxymorphinan, mainly by *CYP3A4*. Moreover, 3-hydroxymorphinan is obtained through *N*- and *O*-didemethylation by *CYP3A4* and *CYP2D6*, respectively. Hence, the partial metabolic clearance of dextromethorphan to the *O*-demethylated metabolites can be used as an index of *CYP2D6* activity, whereas the partial metabolic clearance of dextromethorphan to the *N*-demethylated metabolites can be used as an index of *CYP3A4* activity, as described by Di Marco et al.¹¹

To assess the relative activities of *CYP2D6* and *CYP3A4*, we used both a traditional method based on a metabolic-ratio calculation obtained by dividing the amount of dextromethorphan by the amount of deconjugated dextrorphan excreted in urine (for *CYP2D6*) and a partial metabolic-clearance approach as described above. According to a standardized protocol, a single 25-mg oral dose of dextromethorphan was administered to our patient seven days after his discharge from the intensive care unit, after complete recovery of renal function but while he was still receiving clarithromycin and voriconazole. We used high-performance liquid chromatography to assay deconjugated dextromethorphan and

Figure 1. Metabolic Pathways of Codeine Biotransformation.

The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation usually represents 80 percent of codeine clearance, and conversion of codeine into morphine by CYP2D6 represents only 10 percent of codeine clearance (blue arrows). Morphine is further metabolized into morphine-6-glucuronide and into morphine-3-glucuronide. Morphine and morphine-6-glucuronide have opioid activity (green arrows). Glucuronides are eliminated by the kidney and are thus susceptible to accumulation in cases of acute renal failure. The patient (red arrows) had ultrarapid CYP2D6 metabolism, inhibition of CYP3A4 as a result of treatment with clarithromycin and voriconazole, and glucuronide accumulation due to acute renal failure. Red arrows with dotted lines indicate low levels of drug conversion or elimination, green arrows with dotted lines indicate low levels of brain penetration, and thick arrows indicate high levels.

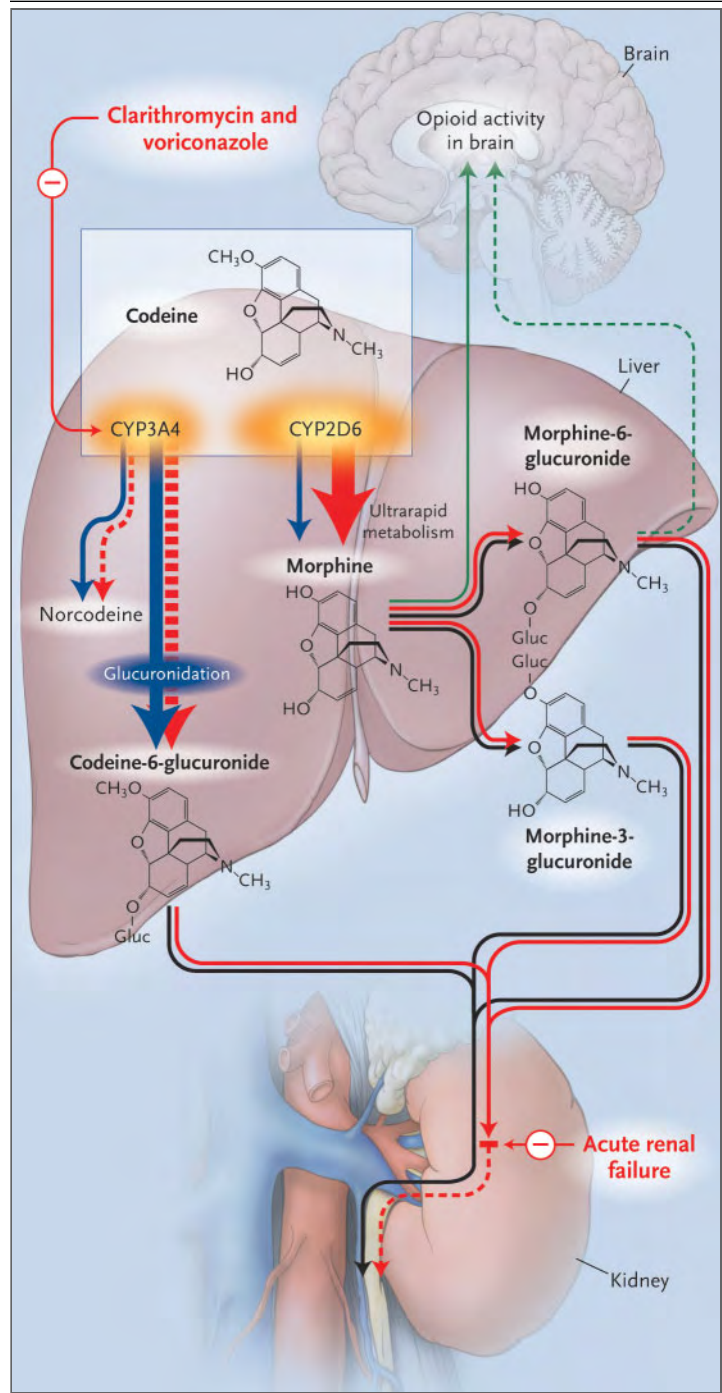
its metabolites in a hydrolyzed urine specimen obtained in the eight hours after the dose of dextromethorphan had been administered.

The patient provided oral consent for testing and for publication of the report. Our institutional review board did not require written consent because the investigation was considered to be part of clinical care.

RESULTS

At the time of the patient's coma and respiratory depression, the plasma level of codeine was 114 μg per liter, as compared with a maximal expected plasma level in the range of 13 to 75 μg per liter for the same dose in a person with extensive CYP2D6 metabolism.¹² The codeine glucuronide level was 361 μg per liter (expected range in extensive CYP2D6 metabolism, 700 to 1670 μg per liter), the blood level of morphine was 80 μg per liter (expected range, 1 to 4 μg per liter), the morphine-3-glucuronide level was 580 μg per liter (expected range, 8 to 70 μg per liter), and the morphine-6-glucuronide level was 136 μg per liter (expected range, 1 to 13 μg per liter). Among these metabolites, only morphine and morphine-6-glucuronide have clinically relevant opioid activity.

CYP2D6 genotyping showed three or more functional alleles, a finding consistent with ultrarapid metabolism. Eight hours after the administration of dextromethorphan, the level of the drug in the pa-



tient's urine was below the detection limit of the assay (10 ng per milliliter). Thus, the ratio of the amount of dextromethorphan to that of dextrorphan in urine was less than 0.0005, a finding that is compatible with an ultrarapid-metabolism phenotype. As previously described for CYP2D6 pheno-

typing,¹³ a logarithmic scale can be used to classify the various types of CYP2D6 metabolism. Ultrarapid metabolism is characterized by a ratio of dextromethorphan to dextrorphan that is below 0.003, extensive metabolism by a ratio between 0.003 and 0.03, intermediate metabolism by a ratio between 0.03 and 0.3, and poor metabolism by a ratio above 0.3.

The phenotype of ultrarapid CYP2D6 metabolism was confirmed by calculation of the partial metabolic clearance related to *O*-demethylation of dextromethorphan, with a value of 0.48 indicating a high level of production of dextromethorphan metabolites through the CYP2D6 pathway. CYP3A4 activity was evaluated by calculation of the partial metabolic clearance related to *N*-demethylation of dextromethorphan; the value was 0.04, which is below the mean (\pm SD) calculated metabolic clearance in healthy volunteers (0.14 ± 0.04).¹²

DISCUSSION

We describe a patient in whom opioid intoxication occurred after the administration of small doses of codeine, a condition that was attributable to a CYP2D6 ultrarapid-metabolism genotype and phenotype, in combination with drug-induced inhibition of CYP3A4 activity and a reduction in renal function.

Codeine is ineffective at usual doses in 7 to 10 percent of the white population because of homozygosity for nonfunctional mutant CYP2D6 alleles.² On the other hand, among persons who have ultrarapid metabolism, codeine intake may result in an increase in morphine production. An inverse correlation is expected between the ratio of dextromethorphan to dextrorphan and the amount of *O*-demethylated codeine metabolites (i.e., morphine, morphine-3-glucuronide, and morphine-6-glucuronide). The concentration of *O*-demethylated metabolites can be as much as 45 times as high in persons with ultrarapid CYP2D6 metabolism as it is in those with poor metabolism.¹⁴ In our patient, the metabolic ratio of dextromethorphan to dextrorphan was extremely low, and 12 hours after the last dose of codeine, the blood level of morphine was 20 to 80 times as high as the blood level that

would have been expected on the basis of measurements in healthy persons with extensive CYP2D6 metabolism.¹²

Along with CYP2D6 gene duplication, a drug-drug interaction may have contributed to the observed toxic effects in our patient. In addition to undergoing *O*-demethylation into morphine, codeine is *N*-demethylated into norcodeine by CYP3A4 and also undergoes glucuronidation¹⁴ (Fig. 1). Our patient was concomitantly treated with a macrolide and an azole derivative, both known inhibitors of CYP3A4. These agents thus may have further reduced the clearance of codeine and increased the risk of an opioid overdose associated with the CYP2D6 gene duplication. Phenotyping with dextromethorphan *N*-demethylation confirmed the low activity of CYP3A4, whereas the CYP2D6 phenotype was consistent with the CYP2D6 ultrarapid-metabolism genotype. Norcodeine was not detected in the blood, and the level of codeine-6-glucuronide, an inactive metabolite of codeine, was only one third of the expected blood level after repeated administration of oral codeine under normal conditions.¹²

The opioid effects of codeine are related to plasma morphine concentrations produced after codeine intake. In our patient, blood concentrations of morphine metabolites, morphine-3-glucuronide, and morphine-6-glucuronide were substantially elevated, a finding likely to be attributable to renal failure; morphine-6-glucuronide has recognized opioid activity.^{15,16} The total amount of morphine and metabolites in our patient corresponded to 75 percent of the total amount of codeine present in his body, whereas the usual amount of morphine that is produced after the administration of multiple doses of codeine rarely reaches 10 percent of the total amount of codeine in a person with extensive CYP2D6 metabolism.¹²

This report of central nervous system depression after the administration of small doses of codeine in a patient with a CYP2D6 ultrarapid-metabolism phenotype supports the potential usefulness of the determination of genotype and phenotype in elucidating serious adverse drug reactions and in preventing subsequent inappropriate selection or doses of drugs.

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
2. Desmeules J, Gascon MP, Dayer P, Magistris M. Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991;41:23-6.
3. Sindrup SH, Brosen K. The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* 1995;5:335-46.
4. Caraco Y, Sheller J, Wood AJ. Impact of

- ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects. *J Pharmacol Exp Ther* 1999;290:413-22.
5. Meyer UA. Pharmacogenetics and adverse drug reactions. *Lancet* 2000;356:1667-71.
 6. Johansson I, Lundqvist E, Bertilsson L, Dahl ML, Sjoqvist F, Ingelman-Sundberg M. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. *Proc Natl Acad Sci U S A* 1993;90:11825-9.
 7. Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population: analysis of the molecular genetic basis. *J Pharmacol Exp Ther* 1995;274:516-20.
 8. Dayer P, Desmeules J, Leemann T, Stri-berni R. Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome P-450 db1/buff). *Biochem Biophys Res Commun* 1988;152:411-6.
 9. Schänzle G, Li S, Mikus G, Hofmann U. Rapid, highly sensitive method for the determination of morphine and its metabolites in body fluids by liquid chromatography-mass spectrometry. *J Chromatogr B Biomed Sci Appl* 1999;721:55-65.
 10. Muller B, Zopf K, Bachofer J, Steimer W. Optimized strategy for rapid cytochrome P450 2D6 genotyping by real-time long PCR. *Clin Chem* 2003;49:1624-31.
 11. Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP. The effect of grapefruit juice and Seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein. *Life Sci* 2002;71:1149-60.
 12. Yue QY, Hasselstrom J, Svensson JO, Sawe J. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1991;31:635-42.
 13. Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br J Clin Pharmacol* 2002;53:111-22.
 14. Yue QY, Alm C, Svensson JO, Sawe J. Quantification of the O- and N-demethylated and the glucuronidated metabolites of codeine relative to the debrisoquine metabolic ratio in urine in ultrarapid, rapid, and poor debrisoquine hydroxylators. *Ther Drug Monit* 1997;19:539-42.
 15. Sawe J, Odar-Cederlof I. Kinetics of morphine in patients with renal failure. *Eur J Clin Pharmacol* 1987;32:377-82.
 16. Osborne R, Joel S, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br Med J (Clin Res Ed)* 1986;292:1548-9.

Copyright © 2004 Massachusetts Medical Society.

JOURNAL INDEX

The index to volume 351 of the *Journal* will be available on February 17, 2005. At that time, it can be downloaded free in PDF format from www.nejm.org or can be ordered in a printed and bound format. To order a bound copy, please call 1-800-217-7874 from the United States and Canada (call 651-582-3800 from other countries) or e-mail info@valeoip.com.

CORRECTION

Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism . On page 2829, in Figure 1, the double arrows leading to codeine-6-glucuronide should have originated in the box representing codeine, rather than in the oval representing cytochrome P-450 enzyme CYP3A4, as printed. We regret the error.