Pharmacogenetic Determinants of Codeine Induction by Rifampin: The Impact on Codeine’s Respiratory, Psychomotor and Miotic Effects

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Accepted for publication December 13, 1996

ABSTRACT

Our objective was to examine the effect of rifampin on codeine’s pharmacodynamics and pharmacokinetics in extensive (EMs) and poor (PMs) metabolizers of debrisoquin. Fifteen healthy, nonsmoking males, 9 EMs and 6 PMs of debrisoquin, received codeine (120 mg) before and after rifampin (600 mg/d) for 3 weeks. The effects of codeine on respiration, pupil diameter and psychomotor performance were measured before codeine administration and during each study day. The pharmacokinetics of codeine were determined from the respective plasma and urine concentrations. Before the administration of rifampin, the pharmacodynamic effect of codeine was more prominent in the EMs and poor metabolizers of debrisoquin, whereas its O-demethylation was induced only in EMs. Relative to base-line values, codeine N-demethylation was induced to a greater extent, resulting in a marked reduction in the plasma concentrations of codeine and codeine metabolites and elevated plasma concentrations of norcodeine, norcodeine-glucuronide, and normorphine. The reduction in morphine plasma concentration was associated in the EMs with a significant attenuation of codeine’s respiratory and psychomotor effects, whereas its miotic effect was unaltered. In PMs, codeine’s respiratory and psychomotor effects were unaltered by rifampin, but its pupillary effect was reduced. Codeine O-demethylation to produce morphine can be significantly induced by rifampin, but this induction is phenotypically determined. However, because (relative to base-line values) rifampin enhanced codeine N-demethylation more than codeine O-demethylation, morphine plasma concentrations were reduced—and hence codeine’s pharmacodynamic effects were attenuated—in EMs of debrisoquin.

Codeine is a commonly used opioid that exerts its therapeuetic effects through the formation of MOR (Snafillippo, 1948). The O-demethylation of codeine to MOR, which accounts for less than 10% of codeine biotransformation, has been shown to cosegregate with CYP2D6 activity (Yue et al., 1989; Mortimer et al., 1990; Yue et al., 1991). Among Caucasian populations, CYP2D6 is polymorphically distributed, about 5% to 10% of individuals being of the PM phenotype (Alvan et al., 1990; Wedlund et al., 1984). Those PMs who lack functional CYP2D6 generate negligible amounts of MOR from codeine, so codeine’s analgesic effect is markedly diminished (Yue et al., 1989; Sindrup et al., 1991; Desmeules et al., 1991). Furthermore, we have recently shown that after codeine administration, the inability of PMs to produce MOR is associated with significantly reduced respiratory, pupillary and psychomotor effects of codeine (Caraco et al., 1996a).

The importance of CYP2D6 in mediating the biotransformation of many drugs, including antiarrhythmics (propafenone, encainide and flecainide), antihypertensives (propranolol, metoprol, timolol and debrisoquin), tricyclic antidepressants (desipramine, amitryptyline, nortryptiline and imipramine) and opioids [codeine, ethylmorphine (O-deethylation), dextromethorphan and hydrocodone], is well established (Wrighton and Stevens, 1992; Guengerich, 1994). In PMs of debrisoquin, the metabolism of CYP2D6 substrates is substantially slower than in EMs of debrisoquin, and for those drugs with a narrow therapeutic window, this slow metabolism results in an exaggerated and potentially toxic pharmacological response (Eichbaum and Gross, 1990; Tucker, 1994).
CYP2D6 activity is largely genetically determined (Bock et al., 1994; Steiner et al., 1985). The influence of various factors such as liver disease, age, gender and diet on the in vivo indexes of CYP2D6 is generally of minor magnitude compared with the major genetic effect (Bock et al., 1994; Steiner et al., 1985; Larrey et al., 1989). On the other hand, subtherapeutic doses of quinidine, a non-CYP2D6 substrate, produce complete inhibition of the enzyme in EMs, resulting in a process termed phenocopying (Nielsen et al., 1990). Conversely, enzyme induction by cigarette smoking, the consumption of oral contraceptives or the administration of a potent cytochrome P450 inducer such as phenobarbital do not affect the in vivo indexes of CYP2D6 (Bock et al., 1994; Eichelbaum et al., 1986; Schellens et al., 1989). The effect of rifampin on reactions mediated by CYP2D6 is less clear. In EMs of debrisoquin, rifampin administration was associated with a 30% increase in the metabolic clearance of sparteine, but the debrisoquin metabolic ratio was not affected (Eichelbaum et al., 1986; Leclercq et al., 1989). In PMs of debrisoquin, a 6-fold increase in the metabolic clearance of sparteine and a significant decrease in the debrisoquin metabolic ratio were noted after the administration of rifampin, but the phenotypic assignment changed from PM to EM in only 2 out of the 6 genotypic PMs (Eichelbaum et al., 1986; Leclercq et al., 1989).

If enzyme induction alters codeine O-demethylation to MOR, this would be expected to produce profound changes in codeine’s pharmacodynamic effects. The present study was therefore undertaken to determine the effect of rifampin on the pharmacokinetics and pharmacodynamics of codeine in EMs and PMs of debrisoquin.

Methods

Subjects. Sixteen healthy, nonsmoking Caucasian males, 10 EMs and 6 PMs of debrisoquin, participated in the study. None of the subjects was consuming any medication regularly, and the subjects were requested not to use any medications, including alcohol and over-the-counter medications, for the week before the initiation of the study and throughout the entire study period. Mean (± S.E.M.) weight of the EM subjects was 78.7 ± 2.1 kg, and their mean age was 32.1 ± 1.1 years. Mean weight (87.3 ± 5.5 kg) and age (34.2 ± 1.3 years) values in the PM group were similar (P > 2), and each subject’s weight in both groups was within 20% of his ideal body weight. All subjects had a normal physical examination and underwent routine laboratory tests, including tests of liver and renal function. The study protocol was approved by the Vanderbilt University Hospital Committee for the Protection of Human Studies, and all the subjects gave written informed consent to participate in the study.

The subjects were recruited from a list of potential volunteers who had previously been phenotyped for both debrisoquin and mephénytoin hydroxylation capacity (Brosen, 1990; Wilkinson et al., 1989). They also participated in another study of codeine’s effects (Curaco et al., 1996a). Phenotypic assignment was reconfirmed, within 2 weeks before the first study day, by the administration at bedtime of 10 mg of debrisoquin (Declinax, Roche Laboratories, Nutley, NJ) together with 200 ml of water. CYP2D6 activity was determined from the DMR (i.e., the urinary ratio of debrisoquin and 4'-hydroxydebrisoquin); a value above 12.6 in an 8-h urine collection was taken to denote a PM phenotype (Brosen, 1990). Mean DMR value was 1.04 ± 0.26 (range: 0.46–2.05) in the EMs and 93.6 ± 21.5 (range: 21.4–151.2) in the PMs.

Study design. The subjects received 600 mg of rifampin daily as a single morning dose for 3 weeks. Codeine pharmacokinetics and pharmacodynamics were evaluated within a week before the first rifampin dose and again 1 h after the last rifampin dose. On the morning of each study day and after an overnight fast and 24 h of abstinence from caffeine-containing food and beverages, the subjects received a single 120-mg p.o. dose of codeine phosphate. Food was not permitted for the initial 6 h, and then standardized, caffeine-free meals were provided 6 and 10 h after drug intake. The subjects remained in the study room for the entire 12 h of each study day. In between study sessions the subjects could either sit or lie down, but physical activity of any kind was not permitted. Blood (5 ml) was sampled just before drug administration, every 10 min during the first hour and 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h after codeine intake. Blood samples were obtained through an indwelling i.v. catheter, except for the last (24-h) blood sample, which was drawn through a separate venipuncture. Plasma was immediately separated and kept frozen at 20°C until analyzed. Urine was collected after drug intake over three time intervals: 0 to 12 h, 12 to 24 h, and 24 to 48 h. The subjects were closely monitored as inpatients for the appearance of adverse effects for the initial 24 h after each codeine dose and on a daily basis throughout the entire study period. The consumption of rifampin was confirmed by frequent direct inquiries and pill counting done at random on several occasions.

Codeine and codeine metabolites HPLC assay. The plasma and urine concentrations of codeine and its metabolites were determined by an ion-paired reverse-phase HPLC method as published previously with some modifications (Yue et al., 1991; Curaco et al., 1996a). This method involved solid-phase extraction (Sep-pak C18, Waters, Milford, MA) and the combined use of an UV detector (Spectroflow 773 UV detector, Kratos Analytical Instruments, Foster City, CA) for the determination of M3G, NCG, C6G, NC and codeine and a coulometric electrochemical detector (Coulochem 5100A with 5021 conditioning cell and 5011 analytical cell, ESA, Inc., Bradford, MA) for the determination of M6G, NM and MOR. Preliminary testing done in our laboratory indicated that neither rifampin nor rifampin metabolites interfered significantly with the determination of codeine and codeine metabolites in plasma or urine. The chromatographic apparatus consisted of a 6000-A pump, two 730 data modules, a Wisp 710A autoinjector, and a Bondapak C18, 10-μm, 300×3, 9-mm column (Waters Associates). The mobile phase consisted of 21% acetonitrile and 79% buffer containing 5 mM sodium phosphate monobasic and 0.25 mM dodecyl sodium sulfate (pH 3.14).

Pharmacodynamic Evaluation

The effect on respiration, pupillary diameter and psychomotor performance was assessed on each study day 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after the intake of codeine. Three pharmacodynamic measurements were performed before the administration of codeine, and the average was taken as the base-line value for that particular day.

Measuring the effect on respiration. The effect on respiration was evaluated by measuring resting minute ventilation, the end-tidal carbon dioxide content, and the ventilatory response to increasing concentrations of CO2 by using the rebreathing method of Read (1967). In brief, the subjects were requested to breathe through a mouthpiece while wearing a nose clip until the minute ventilation and the end-tidal CO2 were stable. Then they were connected through a three-way valve to a balloon containing 1.5 times their respective vital capacity volume of a gas mixture of 7% carbon dioxide and 93% oxygen. The increasing concentration of carbon dioxide stimulated a progressive hyperventilation that was continued for approximately 2 min, by which time the end-tidal CO2 had reached a value of approximately 60 mm Hg. Tidal volume, ventilatory rate and end-tidal CO2 were continuously measured by a computerized exercise module (Cybermedics, Boulder, CO), using a pneumotach and infrared CO2 analyzer. The instrument was calibrated before the determination of each CO2-response curve. To familiarize the subjects with the procedure, the participants underwent a single rebreathing session a week before the study began and...
as part of the screening process to simulate the test conditions during future study days.

The data obtained in each study session were analyzed by plotting the minute ventilation measured at 10-s intervals against the respective end-tidal CO₂ tension. The slope of the line relating minute ventilation to CO₂ tension (the slope of the CO₂-response curve) and the VE55 were calculated by least-squares linear regression analysis.

**Measuring the effect on pupillary diameter.** A 35-mm camera (Nikon FG) equipped with a 53-mm micro-Nikon lens and a ring-flash (Nikon 5B-21B) and attached to a chin-head rest was used to photograph periodically the subject's left eye from a fixed distance. Light conditions were monitored by a light meter (Minolta autometer 2) and were kept constant throughout the entire study period. The pupil and iris diameters in their longest axis were measured from a 5-by-7-inch color print with the aid of a ruler and a caliper. To avoid measurement errors that might have occurred by slight change in the location of the eye relative to the camera lens, the ratio of pupil diameter to iris diameter was used for pharmacodynamic evaluation. The coefficient of variation for repeated calculations of the ratio of pupil diameter to iris diameter from duplicates of the same print was 2.5%.

**Measuring the effect on psychomotor performance.** Psychomotor performance was evaluated through the subjects' periodic performance of a revised DSST (Wechsler, 1981). The subjects were given 90 s to fill in, with the appropriate letters, as many empty boxes as they could according to a figure-letter code provided on the top of each form. The number of boxes that were correctly filled in within the time limit of 90 s was taken as the score. In order to minimize the effect of learning on the DSST results, the subjects did the test twice a week before the first study day, and several different test versions were used at different times throughout the study days.

**Data analysis.** Plasma concentrations of codeine and its metabolites were plotted semilogarithmically against time, and the respective (b) were derived by least-squares linear regression analysis of the terminal portions of the curves. Codeine and codeine metabolite AUCs until the last measured concentration (AUC0→) were calculated by the log-trapezoidal rule and extrapolated to infinity (AUC0→). The T½ of codeine and its metabolites was calculated from T½ = 0.693/b. Codeine was assumed to be completely absorbed from the GI tract (Bechtel and Sinterhauf, 1978), so 120 mg of codeine phosphate corresponded to 103 mg of codeine base. Codeine CL0 was derived from the ratio between the codeine dose and codeine AUC0→. Codeine partial metabolic clearances by glucuronidation (CL Glucuronidation), N-demethylation (CL N-demethylation) and O-demethylation (CL O-demethylation) were calculated as follows:

\[
\begin{align*}
\text{CL}_{\text{Glucuronidation}} &= \frac{\text{CL}_{0}}{U_{\text{CGG}} / \text{dose}} \\
\text{CL}_{\text{N-demethylation}} &= \frac{\text{CL}_{0} \cdot (U_{\text{NC}} + U_{\text{SCG}} + U_{\text{NM}})}{\text{dose}} \\
\text{CL}_{\text{O-demethylation}} &= \frac{\text{CL}_{0} \cdot (U_{\text{M}} + U_{\text{EMG}} + U_{\text{MGG}} + U_{\text{NM}})}{\text{dose}}
\end{align*}
\]

U represents the urinary molar amount of the respective codeine metabolite. Renal clearance (renal cl) was determined by dividing the urinary molar amount of codeine or one of its metabolites by the respective AUC0→.

Pharmacodynamic measurements were converted to percent of base line, and the AUE over the initial 6 h after drug administration (AUE0→) was calculated by the trapezoidal rule.

Inter- and intrapoplogenic comparisons were carried out by two-way ANOVA with repeated measurements, followed if appropriate by paired or unpaired Student's t test or nonparametric test (Wilcoxon signed rank test), as indicated. Linear and Spearman correlation tests were used to evaluate the relationship between pharmacokinetic and pharmacodynamic variables. P values of less than .05 were considered statistically significant.

**Results**

The data obtained on the study day before the administration of rifampin have been published previously (Caraco et al., 1996a). One of the EM subjects, who experienced marked drowsiness and nausea after the first codeine dose, decided not to participate in the second study day, so data for only 9 EMs were available for analysis.

**Pharmacokinetics before rifampin.** Morphine and morphine metabolites were present only in the plasma samples obtained from EM subjects. Overall, codeine CL0 and its partial metabolic clearances through glucuronidation and N-demethylation did not differ between EMs and PMs, but the partial metabolic clearance by O-demethylation was about 200-fold greater in the EM than the PM subjects (162.7 ± 36.6 vs. 0.86 ± 0.65 ml/min respectively, P < .002) (fig. 1).
b) Pharmacokinetics: after rifampin. The change in codeine pharmacokinetics caused by rifampin is described as mean (± S.E.M.) percent change derived from the individual difference between the rifampin and the codeine-alone study days. After the administration of rifampin, codeine and C6G plasma concentrations were significantly reduced in both phenotypes, and the respective AUCs decreased by a mean of 79.4 ± 2.3% and 28.1 ± 3.4% in the EMs (P < .001) (table 1) and by a mean of 83.5 ± 3.0% (P < .001) and 36.6 ± 4.5% (P < .003) in the PMs, respectively (table 1). In both phenotypes the plasma concentrations of codeine’s N-demethylated metabolites were greater after rifampin, and accordingly the AUCs of NC and NCG increased by 139 ± 37% (P < .004) and 80 ± 24% (P < .02) in the EMs and by 77 ± 40% (P > .1) and 98 ± 23% (P < .03) in the PMs, respectively (tables 1 and 2).

MOR and MOR metabolites were detected only in the plasma samples obtained from EMs of debrisoquin. After the administration of rifampin, the plasma concentrations of M3G, M6G and MOR were lower, resulting in a mean decrease in the AUCs of 32 ± 16% (P < .008), 53 ± 9% (P < .03) and 56 ± 10% (P < .02), respectively. In contrast, after rifampin, NM plasma concentrations were higher and its AUC was increased by a mean of 173 ± 33% (P < .001) (table 2).

After the administration of rifampin, codeine CLo and its partial metabolic clearances through glucuronidation and N-demethylation were markedly enhanced by a mean of 489 ± 130% (P < .001), 533 ± 214% (P < .02) and 1937 ± 845% (P < .002) in the EMs (fig. 1) and by a mean of 626 ± 178% (P < .03), 297 ± 88% (P < .02) and 1685 ± 843% (P < .02) in the PMs, respectively (fig. 1). The partial metabolic clearance through O-demethylation was increased in the EMs only, by a mean of 826 ± 311% (P < .002). In both EMs and PMs, the absolute increase in codeine’s clearance through glucuronidation was significantly greater than the increase in its clearances through N- and O-demethylation (P < .01). However, in the EMs, the percent increase in codeine N-demethylation clearance was significantly greater than the percent increase in codeine CLo (P < .004) and the percent increase in codeine’s partial metabolic clearances through glucuronidation (P < .004) and O-demethylation (P < .01). In PMs, the percent induction of the N-demethylation pathway was significantly greater than the percent induction of the glucuronidation (P < .05) and the O-demethylation (P < .001) pathways. The renal clearance of codeine and codeine metabolites was not affected by the treatment with rifampin in either phenotype.

Pharmacodynamics: before rifampin. The pharmacodynamic effects of codeine in these EMs and PMs of debrisoquin have been published previously (Caraco et al., 1996a). Briefly, before rifampin treatment, the extent of codeine’s respiratory, psychomotor and pupillary effects was significantly greater in the EMs than in the PMs, resulting in a greater effect on resting minute ventilation (P < .01), resting end-tidal CO2 (P < .01), VE55 (P < .01), slope of the CO2 response curve (P < .003), psychomotor performance as evaluated by DSST (P < .008) and pupillary constriction (P < .007) (figs. 2 A and B).

Pharmacodynamics: after rifampin. In the EMs, the treatment with rifampin significantly attenuated codeine’s respiratory and psychomotor effects, resulting in a significantly lower effect on resting minute ventilation (P < .003), resting end-tidal CO2 (P < .01), VE55 (P < .01), slope of the CO2 response curve (P < .01) and psychomotor function as evaluated by DSST (P < .001) (fig. 2A). In contrast, codeine’s miotic effect was not significantly changed in EMs by the treatment with rifampin (P > .2) (fig. 2A). In the PMs, the only significant effect of rifampin treatment was to reduce codeine’s pupillary effect (P < .001); its respiratory and psychomotor effects were unaltered (P > .3) (fig. 2B).

The attenuation of codeine’s respiratory and psychomotor effect by rifampin was significantly greater in the EMs than in the PMs, resulting in a greater decrease in codeine’s effect on resting minute ventilation (P < .01), VE55 (P < .01), slope of the CO2 response curve (P < .03) and psychomotor performance evaluated by DSST (P < .03) (fig. 3). Thus after the administration of rifampin, no significant differences were noted between EMs and PMs in codeine’s respiratory and psychomotor effects (P < .3), but its miotic effect was still greater in the EMs than in the PMs (P < .01).

When the subjects of both phenotypes were analyzed together, the decreases in codeine’s effects on resting minute

### Table 1
Mean (± S.E.M.) codeine and codeine metabolites pharmacokinetics before and after the administration of rifampin in EMs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Before (h)</th>
<th>After (h)</th>
<th>Before (nM-h)</th>
<th>After (nM-h)</th>
<th>Renal Clearance (ml/min)</th>
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<td>M3G</td>
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<td>(117)</td>
<td>(52.5)</td>
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<td></td>
<td>(0.27)</td>
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<td>(93)</td>
<td>(41)</td>
<td>(20.9)</td>
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<tr>
<td>M6G</td>
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<td>2.04</td>
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<td>(93)</td>
<td>(41)</td>
<td>(20.9)</td>
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<td>NM</td>
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<td>(0.14)</td>
<td>(93)</td>
<td>(41)</td>
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<td>(0.16)</td>
<td>(286)</td>
<td>(98)</td>
<td>(17.7)</td>
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* a P < .05
* b P < .01
* c P < .001

### Table 2
Mean (± S.E.M.) codeine and codeine metabolites pharmacokinetics before and after the administration of rifampin in PMs

<table>
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<th>Compound</th>
<th>Before (h)</th>
<th>After (h)</th>
<th>Before (nM-h)</th>
<th>After (nM-h)</th>
<th>Renal Clearance (ml/min)</th>
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<td>(0.23)</td>
<td>(0.31)</td>
<td>(489)</td>
<td>(155)</td>
<td>(10.0)</td>
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</table>

* a P < .05
* b P < .01
* c P < .001
ventilation, \( V_{E_{55}} \), the slope of the \( CO_2 \)-response curve and DSST were significantly correlated with codeine’s effects before rifampin (\( r = -0.786, r = -0.693, r = -0.777 \) and \( r = -0.775 \), respectively; \( P < .001 \)). In addition, the debrisoquin metabolic ratio was inversely and significantly correlated with the decrease in codeine effect caused by rifampin (\( r = -0.686 \ P < .001, r = -0.839 \ P < .001, r = -0.429 \ P < .05 \) and \( r = -0.762 \ P < .001 \), respectively). In the EM subjects only, codeine’s miotic effect after rifampin administration was significantly correlated with MOR (\( r = -0.706, P < .03 \)) and NM (\( r = -0.747, P < .02 \)) AUC values.

**Adverse effects.** After the administration of the first codeine dose, all EM subjects experienced dizziness, drowsiness and sleepiness. The peak effect was noted within 2 h, and it usually subsided gradually within the initial 4 h after codeine intake. Variable degrees of nausea were also reported by five of the EM subjects. After the administration of rifampin, mild drowsiness and dizziness were experienced by only five out of nine EMs, and this effect usually disappeared within 2 h of the administration of codeine. Only 2 of the 6 PM subjects reported mild nausea and drowsiness soon after the administration of codeine, both before and after rifampin.

**Discussion**

It is well established that enzyme induction by drugs such as rifampin and phenobarbital alters drug metabolism. For drugs whose effect is produced primarily by the parent compound, such induction would be expected to increase the drug’s clearance, lower drug concentrations and decrease the drug’s pharmacological effect (Piazzi, 1991; Heimark et al., 1987; Modry et al., 1985). However, for drugs such as codeine, whose pharmacological effect is produced largely by its metabolism to the active metabolite, MOR, the effect of enzyme induction on the drug’s pharmacodynamic effects depends on the relative change in the plasma concentration of MOR. Codeine is metabolized by a number of pathways, including glucuronidation, O-demethylation to MOR and N-demethylation to NC (Yue et al., 1991). Because the plasma concentrations of morphine produced after enzyme induction depend on the relative extent of the induction of the various pathways, including the further metabolism of MOR itself, it was not possible to predict intuitively the net effect of rifampin induction on codeine pharmacodynamics before this study. A further complicating factor is that the O-demethylation of codeine is mediated by CYP2D6, the cytochrome P450 responsible for the metabolism of debrisoquin and many other substrates (Yue et al., 1989; Wrighton and Stevens, 1992; Guengerich, 1994). This cytochrome is polymorphically distributed so that PMs of debrisoquin who lack active CYP2D6 might be expected to respond differently to enzyme induction.

Previous studies have shown that exposure to enzyme inducers produces a selective induction of codeine metabolism by different pathways. Cigarette smoking increased codeine CL, by 17% but produced only a slight increase in codeine glucuronidation. This resulted in no change in the formation of MOR or in the codeine O-demethylation metabolic ratio (Rogers et al., 1982; Hull et al., 1982). Subchronic treatment with carbamazepine (400–600 mg/day for 3 weeks) resulted in accelerated codeine N-demethylation, but as with smoking, the codeine O-demethylation ratio was unaltered (Yue et al., 1994).

We have demonstrated in the present study that administration of rifampin to EMs of debrisoquin was associated with a significant 2- to 12-fold increase in the partial metabolic clearance of codeine through O-demethylation. The importance of considering the role played by other pathways of codeine metabolism in defining the overall effect of enzyme induction is shown by the fact that in spite of the enhanced rate of codeine O-demethylation in EMs, MOR and MOR glucuronides plasma concentrations were reduced overall without any change in the codeine O-demethylation ratio. The decrease in MOR plasma concentrations reflected the relatively greater induction of the N-demethylation pathway of codeine so that not only was the metabolism of codeine itself shunted down that route to NC, but in addition, the metabolism of MOR to NM was increased, further reducing plasma morphine concentrations. The extent of enzyme induction by inducers such as rifampin is dose-dependent, 1200 mg/day having greater effect than 600 mg/day (Ohnhaus et al., 1987; Price et al., 1986). In theory, it is possible that
exposure to higher and to lower rifampin doses may have different effects.

The percent increase in codeine N-demethylation was significantly greater in the present study than the percent increase in codeine’s O-demethylation and glucuronidation. There appears to be a close link between the extent of induction and the nature of the biochemical reaction(s) involved in the biotransformation of the drug in question. Thus when the same inducer is administered concomitantly with different drugs, the extent of induction may vary greatly (Venkatesan, 1992; Price et al., 1986; Baciewicz and Self, 1984). Furthermore, for a drug like antipyrine whose metabolism probably involves several different P450s, the administration of rifampin has been shown to induce the formation of norantipyrine preferentially (Teunissen et al., 1984). The inducing effect of rifampin appears to be most prominent for drugs metabolized by CYP3A4. It is therefore of interest that by using human hepatic microsomal preparations in vitro, we have recently shown that CYP3A4 is the major enzyme involved in codeine N-demethylation (Caraco et al., 1996b). Therefore, the marked increase in NC, NG and NM and the parallel reduction in MOR, NCGs and C6G plasma concentrations can be ascribed to the preferential induction of CYP3A4 by rifampin (Ged et al., 1989). In the PMs of debrisoquin, rifampin treatment resulted in enhanced codeine N-demethylation and glucuronidation, but codeine O-demethylation was unaffected.

The activity of CYP2D6 is believed to be determined primarily by genetic factors, which accounts for as much as 79% of the interindividual variability in debrisoquin 4-hydroxylation (Bock et al., 1994; Steiner et al., 1985; Eichelbaum et al., 1986). Similarly, the inducibility of CYP2D6 by potent enzyme inducers is generally of minor magnitude. Debrisoquin hydroxylase activity was not enhanced in liver microsomes derived from rats treated with a variety of inducers, including phenobarbital, 3-methylcholanthrene, dexamethasone and β-napthoflavone (Wolff and Strecke, 1985; Birgersson et al., 1985). Similarly, in humans phenobarbital does not appear to alter sparteine metabolic clearance (Eichelbaum et al., 1986; Schellens et al., 1989). However, rifampin does alter CYP2D6 activity slightly, increasing the metabolic clearance of sparteine in EMs by 30% (Eichelbaum et al., 1986) and decreasing the debrisoquin metabolic ratio in PMs, resulting in the apparent phenotype being changed from PM to EM in two of the genotypic PMs (Leclercq et al., 1989). Rifampin treatment also increased 4-fold the metabolic clearance of propranolol by 4-hydroxylation, a CYP2D6-mediated pathway. However, the absolute increase was much greater in the EM than in the PM subjects, in whom the absolute change was very small (Shaheen et al., 1989).

After the administration of rifampin, the respiratory and psychomotor effects were greatly reduced in EMs, whereas no significant change occurred in PMs. In vitro data have shown that the affinity of codeine for μ receptors is only about 1/200 to 1/3000 that of its O-demethylated metabolite MOR (Chen et al., 1991). Thus the marked differences previously noted between EMs and PMs of debrisoquin in codeine’s analgesic respiratory, psychomotor and miotic effects has confirmed the central role played by the O-demethylated metabolite in mediating codeine’s pharmacodynamic effects (Sindrup et al., 1991; Caraco et al., 1996a). This was further supported by our previous demonstration that the coadministration of quinidine with codeine that inhibits the production of MOR and its metabolites almost completely abolished codeine’s respiratory, psychomotor and miotic effects.

The explanation for the persistence of the miotic effects of codeine in EMs of debrisoquin, despite the lower MOR and M6G plasma concentrations, is unclear. Like the respiratory and analgesic effects, the pupillary constrictive effect of opioids is mediated through μ receptor stimulation (Mather, 1989). Nor-
morphine binds to \( \mu \) receptors with approximately 1/4 the affinity of buprenorphine (Chen et al., 1991) and is thought to exert about 25% of the analgesic effect of MOR in postsurgical patients (Lasagna and DeKornfeld, 1958). Hence, it is possible that after rifampin, codeine's micturition effect was retained in EMs by the 2.7 \pm 0.3-fold mean increase in the NM AUC, which at least partially counterbalanced the drop in MOR plasma concentrations. The finding that the NM AUC value after rifampin was significantly correlated with codeine's micturition effects, but not with its respiratory or psychomotor effects, therefore provides further support for this hypothesis.

Codeine demethylation to produce MOR is enhanced by treatment with rifampin in EMs, but not in PMs, of debrisoquin. The preferential induction of codeine's biotransformation by rifampin was associated with a greater percent increase in codeine's N-demethylation than the percent increase in glucuronidation and O-demethylation. It therefore resulted in decreased plasma concentrations of the main active metabolites, MOR and M6G. The reduced concentrations of the active metabolites produced a significant attenuation of codeine's respiratory and psychomotor effects in the EMs but not in the PMs.


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