Effect of rifampin and tobacco smoking on the pharmacokinetics of ropivacaine

Objective: Our objective was to assess the effect of rifampin (INN, rifampicin) and tobacco smoking on the pharmacokinetics of ropivacaine.

Methods: A randomized, 2-phase, crossover study was performed in both a group of 10 healthy nonsmokers and a group of 8 healthy smokers. In both groups each subject ingested daily for 5 days either placebo or 600 mg rifampin. On day 6 each subject received intravenously over 30 minutes a single dose of 0.6 mg/kg ropivacaine. Ropivacaine, 3-hydroxyropivacaine (3-OH-ropivacaine), and *(S)*-2′,6′-pipecoloxylidide (PPX) in venous plasma and urine were measured for up to 12 hours and 24 hours, respectively. Pharmacokinetic parameters were calculated with noncompartmental methods, and *t* tests were used for comparisons between the phases and between the smokers and nonsmokers. The electrocardiogram was monitored for 3 hours.

Results: There were no statistically significant differences in the area under the plasma concentration-time curve (AUC), plasma clearance (CL), or half-life ($t_{1/2}$) of ropivacaine between the smokers and nonsmokers. However, smokers excreted in urine 31% more 3-OH-ropivacaine and 62% less PPX than nonsmokers did. Rifampin decreased the AUC of ropivacaine in nonsmokers by 52% and in smokers by 38%. In nonsmokers rifampin increased the CL of ropivacaine by 93% and shortened its $t_{1/2}$ by 25%. In smokers rifampin increased the CL of ropivacaine by 47% and shortened its $t_{1/2}$ by 20%. Rifampin decreased the urinary excretion of 3-OH-ropivacaine in nonsmokers by 74% and in smokers by 68%, and it increased the excretion of PPX by 97% and 158%, respectively. No clinically significant differences in the QTc times were found between the groups or treatments.

Conclusions: Tobacco smoking increases the excretion of 3-OH-ropivacaine in urine, probably because of the increased cytochrome P450 (CYP) 1A2–mediated metabolism of ropivacaine, and decreases the excretion of CYP3A4-formed PPX in urine. Rifampin considerably increases the metabolism of ropivacaine to PPX and decreases the metabolism to 3-OH-ropivacaine in both nonsmokers and smokers. (Clin Pharmacol Ther 2001;70:344-50.)

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Ropivacaine [*S*(–)-1-propyl-2′,6′-pipecoloxylidide] is an amide-type local anesthetic with a structure similar to that of bupivacaine. Ropivacaine, commercially available in many countries since 1996, is used for surgical anesthesia and postoperative pain management by epidural administration, peripheral nerve blocks, and local infiltration. The molecular weight of ropivacaine is 274 (base), and it has a negative logarithm of the acid ionization constant (pKa) of 8.1.[1] The major part (94%) of ropivacaine in whole blood is associated with plasma proteins. The mean terminal half-life ($t_{1/2}$) of ropivacaine is 111 minutes; the plasma clearance (CL), 0.50 L/min; and the volume of distribution at steady state (V_{SS}), 42 L.[2] Ropivacaine undergoes mainly oxidative hepatic metabolism, with about 1% of an intravenous dose excreted unchanged in the urine. Studies with human liver microsomes have shown that ropivacaine is metabolized to 3-hydroxyropivacaine (3-OH-ropivacaine) mainly by cytochrome P450 (CYP) 1A2 and to 2′,6′-pipecoloxylidide (PPX) mainly by CYP3A4. These two major metabolites, identified in the urine, account for about 37% and 3%, respectively, of the

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Table I. Characteristics of subjects

No.	*Sex*	*Age (y)*	*Weight (kg)*	*Oral contraceptives*	*Cigarettes (No./d)*
Nonsmokers					
1	Female	28	57	—	—
2	Male	28	68	—	—
3	Male	20	75	—	—
4	Female	19	59	Gestodene 75 μg plus ethinyl estradiol (INN, ethinylestradiol) 30 μg	—
5	Female	21	50	Levonorgestrel 150 μg plus ethinyl estradiol 30 μg	—
6	Male	22	90	—	—
7	Male	25	65	—	—
8	Female	20	57	Desogestrel 150 μg plus ethinyl estradiol 20 μg	—
9	Male	22	70	—	—
10	Female	23	53	Gestodene 75 μg plus ethinyl estradiol 30 μg	—
Mean ± SD	—	23 ± 3	64 ± 12	—	—
Smokers					
1	Female	24	68	—	10
2	Female	24	61	—	10-12
3	Male	21	70	—	20
4	Male	27	66	—	10-15
5	Male	27	65	—	10-15
6	Female	32	74	—	15
7	Male	23	69	—	15-20
8	Female	20	58	Gestodene 75 μg plus ethinyl estradiol 20 μg	10
Mean ± SD	—	25 ± 4	66 ± 5	—	14 ± 4

original single intravenous dose.[3-5] Interaction studies in humans with "diagnostic" inhibitors have supported the role of CYP1A2 and CYP3A4 in the metabolism of ropivacaine.[6,7]

Rifampin (INN, rifampicin), which has a wide spectrum of antimicrobial activity, is a potent inducer of CYP3A4 and some other CYP enzymes and can cause numerous drug interactions.[8,9] For example, the area under the plasma concentration-time curve (AUC) of oral triazolam has been reduced by 95% by a 5-day rifampin pretreatment.[10] On the other hand, cigarette smoking induces biotransformation of drugs metabolized by CYP1A2, such as caffeine, clozapine, tacrine, theophylline, and fluvoxamine.[11,12]

We wanted to study whether there are differences in the pharmacokinetics of ropivacaine between tobacco smokers and nonsmokers and to compare the effect of rifampin on the ropivacaine pharmacokinetics in these two groups.

MATERIAL AND METHODS

Study design. The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, Helsinki, and by the Finnish National Agency for Medicines and was conducted according to the revised Declaration of Helsinki. Written informed consent was obtained from 18 healthy volunteers, 10 nonsmokers and 8 smokers (Table I). Before entering the study, the volunteers were ascertained to be healthy by medical history, clinical examination, and a 12-lead electrocardiogram. None was receiving any continuous medication, except for 5 women on a regimen of oral contraceptive steroids. The smokers had smoked 10 to 20 cigarettes per day for 2 to 17 years (mean and median, 10 years) before entering this study.

This study was randomized and crossover in design, with an interval of 6 weeks between the two phases. The volunteers ingested daily at 7 AM for 5 days either 600 mg rifampin (Rimapen; Orion, Espoo, Finland) or placebo. On day 6, at both study periods an intravenous infusion of 0.6 mg/kg ropivacaine hydrochloride (Naropin; Astra, Masala, Finland) was given over 30 minutes starting at 9 AM to 9:30 AM (ie, about 26 hours after the previous pretreatment dose). The volunteers ate a light breakfast at 7 AM and standard meals 3 and 7 hours after the start of the infusion. They were not allowed to drink grapefruit juice, alcohol, coffee, tea, or cola on the test days.

Blood and urine sampling and drug analysis. A forearm (contralateral to the ropivacaine infusion) vein of each subject was cannulated with a plastic cannula, and blood samples (10 mL) were drawn before and at ¼, ½, ¾, 1, 1¼, 1½, 2, 3, 4, 5, 6, 8, 10, and 12 hours after the start of ropivacaine adminis-

Table II. Pharmacokinetic parameters (mean ± SD) of ropivacaine, 3-OH-ropivacaine, and PPX after a 30-minute intravenous infusion of 0.6 mg/kg ropivacaine after ingestion of either placebo or rifampin 600 mg daily for 5 days

	Nonsmokers (n = 10)			*Smokers (n = 8)*		
	Placebo	*Rifampin*	*P value**	*Placebo*	*Rifampin*	*P value†*
Ropivacaine						
AUC(0-∞) (μg · L^{-1} · h)	1624 ± 488	776 ± 168	*P* = .000	1433 ± 586	894 ± 224	*P* = .015
C_{max} (μg/L)	759 ± 141	548 ± 129	*P* = .003	830 ± 206	755 ± 247	NS
$t_{½}$ (h)	2.1 ± 0.6	1.6 ± 0.4	*P* = .004	1.8 ± 0.4	1.4 ± 0.3	*P* = .013
CL (mL/min)	391 ± 157	753 ± 151	*P* = .000	466 ± 185	685 ± 151	*P* = .005
CL_R (mL/min)	1.7 ± 1.2	4.7 ± 6.4	NS	3.9 ± 5.9	3.0 ± 6.0	NS
MRT (h)	2.5 ± 0.8	1.6 ± 0.3	*P* = .002	2.1 ± 0.6	1.4 ± 0.2	*P* = .006
V_{ss} (L)	54 ± 11	72 ± 17	*P* = .015	54 ± 10	57 ± 13	NS‡
V (L)	65 ± 16	101 ± 33	*P* = .015	68 ± 18	83 ± 22	NS
E_H	0.42 ± 0.17	0.81 ± 0.16	*P* = .000	0.50 ± 0.20	0.73 ± 0.16	*P* = .005
$f_{e\ (excreted\ in\ urine)}$	0.01 ± 0.01	0.01 ± 0.01	NS	0.01 ± 0.01	0.00 ± 0.01	NS
3-OH-ropivacaine						
AUC(0-12) (μg · L^{-1} · h)	54 ± 34	7 ± 6	*P* = .001	59 ± 34	19 ± 14	*P* = .001‡
AUC ratio	0.03 ± 0.02	0.01 ± 0.01	*P* = .000	0.04 ± 0.01	0.02 ± 0.01	*P* = .000‡
C_{max} (μg/L)	18.6 ± 9.5	5.5 ± 2.2	*P* = .001	20.1 ± 7.8	11.6 ± 7.4	*P* = .001
t_{max} (h)	0.9 ± 0.2	0.7 ± 0.1	*P* = .045	0.8 ± 0.2	0.7 ± 0.2	*P* = .020
$t_{½}$ (h)	2.0 ± 0.4	1.2 ± 0.5	*P* = .003	2.4 ± 1.0	1.3 ± 0.3	*P* = .010
$f_{m,\ 3OH\ (excreted\ in\ urine)}$	0.30 ± 0.10	0.08 ± 0.03	*P* = .000	0.39 ± 0.04§	0.12 ± 0.05	*P* = .000‡
PPX						
AUC(0-12) (μ · L^{-1} · h)	203 ± 138	469 ± 130	*P* = .000	107 ± 35	369 ± 132	*P* = .000
AUC ratio	0.15 ± 0.08	0.74 ± 0.20	*P* = .000	0.09 ± 0.03	0.51 ± 0.22	*P* = .001‡
C_{max} (μg/L)	21.8 ± 14.3	57.9 ± 13.7	*P* = .000	12.9 ± 3.0	49.3 ± 11.9	*P* = .000
t_{max} (h)	5.3 ± 2.6	2.5 ± 1.0	*P* = .009	3.6 ± 1.9	1.7 ± 0.9	*P* = .006
$t_{½}$ (h)	11.3 ± 5.1	6.7 ± 2.9	*P* = .008	8.1 ± 3.1	5.0 ± 1.7	*P* = .009
$f_{m,\ PPX\ (excreted\ in\ urine)}$	0.05 ± 0.05	0.10 ± 0.07	*P* = .002	0.02 ± 0.01§	0.05 ± 0.03	*P* = .014‡

AUC(0-∞), Area under the drug plasma concentration-time curve from zero hours to infinity after the start of ropivacaine infusion; C_{max}, peak plasma concentration; $t_{½}$, elimination half-time; CL, plasma clearance; CL_R, renal clearance; MRT, mean residence time; V_{ss}, steady-state volume of distribution; V, volume of distribution during elimination phase; E_H, hepatic extraction ratio; f_e, fraction of unchanged ropivacaine excreted in urine; AUC(0-12), area under the drug plasma concentration-time curve from time zero to 12 hours after the start of ropivacaine infusion; AUC ratio, ratio of AUC(0-12) of 3-OH-ropivacaine or PPX to that of ropivacaine; t_{max}, time to peak plasma concentration; $f_{m,\ 3OH}$, fraction metabolized to 3-OH-ropivacaine; $f_{m,\ PPX}$, fraction metabolized to PPX; NS, not significant.

**P* value for rifampin versus placebo phase (nonsmokers).

†*P* value for rifampin versus placebo phase (smokers).

‡Smokers significantly different from nonsmokers in the rifampin phase (*P* < .05).

§Smokers significantly different from nonsmokers in the placebo phase (*P* < .05).

tration. Plasma was separated within 2 hours and stored at –20°C until analysis. Urine was collected at intervals of 0 to 12 and 12 to 24 hours after the start of the infusion.

Concentrations of ropivacaine and PPX were determined by gas chromatography with etidocaine as an internal standard.[13] For plasma the quantitation limit was 1 μg/L for ropivacaine and 2 μg/L for PPX. The interday coefficients of variation (CV) for ropivacaine were 5.6%, 3.4%, and 1.6% at 2.13 μg/L, 40.3 μg/L, and 1.50 mg/L, respectively (n = 8 at each concentration). The CVs for PPX were 10.1%, 8.0%, and 2.3% at 1.99 μg/L, 40.7 μg/L, and 370 μg/L, respectively (n = 8 at each concentration).

For urine, the quantitation limit was 5 μg/L for both ropivacaine and PPX. The CVs for ropivacaine were 5.0% at 40.9 μg/L (n = 6) and 5.5% at 1.49 mg/L (n = 6). The CVs for PPX were 5.0% at 40.9 μg/L (n = 6) and 5.5% at 1.49 mg/L (n = 6).

Concentrations of 3-OH-ropivacaine were determined by liquid chromatography with lidocaine as an internal standard.[14] The quantitation limit was 2 μg/L. The CVs for plasma were 3.9%, 3.1%, and 1.6% at 4.90 μg/L, 20.6 μg/L, and 41.5 μg/L, respectively (n = 13 at each concentration). The CVs for urine were 7.9% at 0.40 mg/L (n = 6) and 7.5% at 1.46 mg/L (n = 6).

Pharmacokinetic analysis. The peak ropivacaine, PPX, and 3-OH-ropivacaine concentrations (C_{max}) and corresponding peak concentration times (t_{max}) were observed directly from each profile. The area under the ropivacaine plasma concentration-time curve was estimated by means of the logarithmic trapezoidal rule with extrapolation to infinity [AUC(0-∞)]. With the metabolites, no extrapolation

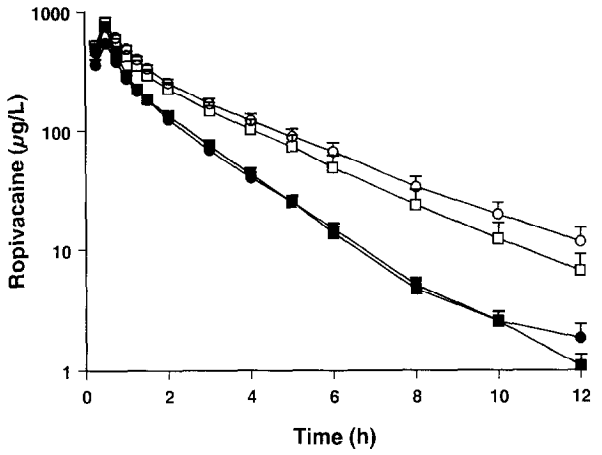

Fig 1. Mean (and SEM) plasma concentrations of ropivacaine after a 30-minute intravenous infusion of 0.6 mg/kg ropivacaine after ingestion of either placebo or rifampin 600 mg daily for 5 days. *Open circles,* Nonsmokers; *solid circles,* nonsmokers, rifampin; *open squares,* smokers; *solid squares,* smokers, rifampin.

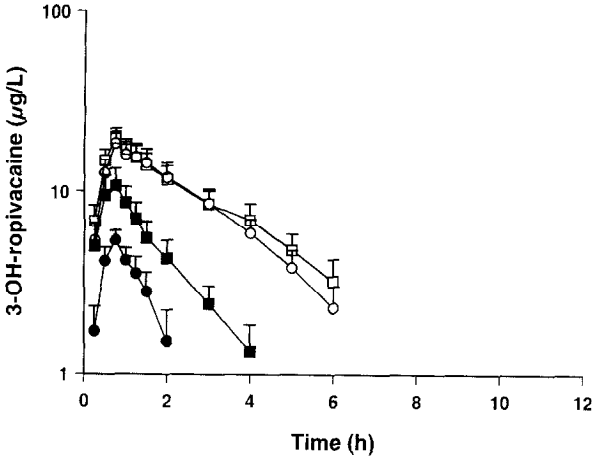

Fig 2. Mean (and SEM) plasma concentrations of 3-OH-ropivacaine after a 30-minute intravenous infusion of 0.6 mg/kg ropivacaine after ingestion of either placebo or rifampin 600 mg daily for 5 days. *Open circles,* Nonsmokers; *solid circles,* nonsmokers, rifampin; *open squares,* smokers; *solid squares,* smokers, rifampin.

was done, and the AUC was calculated up to 12 hours [AUC(0-12)]. The AUC ratio was computed as the ratio of AUC(0-12) of 3-OH-ropivacaine or PPX to the AUC(0-12) of ropivacaine (in micromoles). Terminal log-linear phases of the drug plasma concentration-time curves were identified visually, and the elimination rate constants (k_e) for ropivacaine, 3-OH-ropivacaine, and PPX were determined for each subject by regression analysis. Elimination half-lives ($t_{1/2}$) were calculated from the following equation: $t_{1/2} = \ln 2/k_e$. The plasma clearance (CL) of ropivacaine was computed as CL = Dose/AUC, and renal clearance (CL_R) was $CL_R = f_e \times CL$. The steady-state volume of distribution (V_{ss}) was calculated as $V_{ss} = MRT \times CL$, and the volume of distribution during the elimination phase (V) was $V = CL/k_e$. MRT is mean residence time, which was calculated as MRT = AUMC/AUC − t/2, where t is the infusion time (0.5 hour) and AUMC is the area under the first moment of the ropivacaine plasma concentration-time curve, calculated by the logarithmic trapezoidal rule with extrapolation to infinity. The hepatic extraction ratio (E_H) was estimated for ropivacaine from the following formula: $E_H = CL/(C_p/C_b) \times 1/\text{Hepatic blood flow}$, where the plasma/blood concentration ratio (C_p/C_b) was 0.69[2] and hepatic blood flow was assumed to be 1.35 L/min.[15]

The cumulative 24-hour excretions of ropivacaine, 3-OH-ropivacaine, and PPX in urine were measured. Fractions of the infused dose excreted in urine as ropivacaine (f_e), 3-OH-ropivacaine ($f_{m,\ 3\text{-OH}}$), and PPX ($f_{m,\ PPX}$) were calculated by A_e/Dose (in micromoles), where A_e was the total amount excreted in the urine.

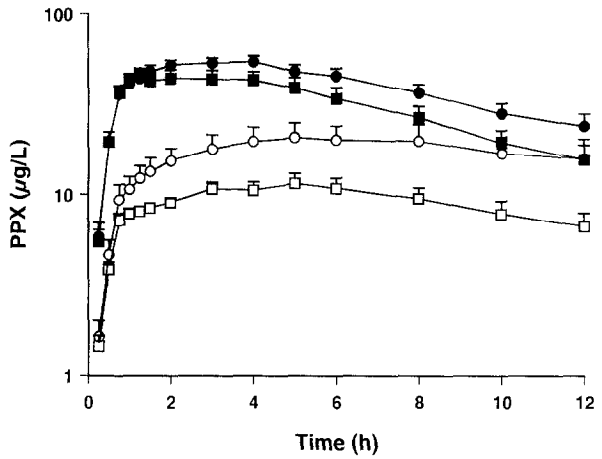

Fig 3. Mean (and SEM) plasma concentrations of PPX after a 30-minute intravenous infusion of 0.6 mg/kg ropivacaine after ingestion of either placebo or rifampin 600 mg daily for 5 days. *Open circles,* Nonsmokers; *solid circles,* nonsmokers, rifampin; *open squares,* smokers; *solid squares,* smokers, rifampin.

The pharmacokinetic variables were calculated with the use of the pharmacokinetic program MKMODEL (version 5.0; Biosoft, Cambridge, United Kingdom).

Safety assessment. A 3-lead electrocardiogram was monitored for 3 hours after the start of the ropivacaine

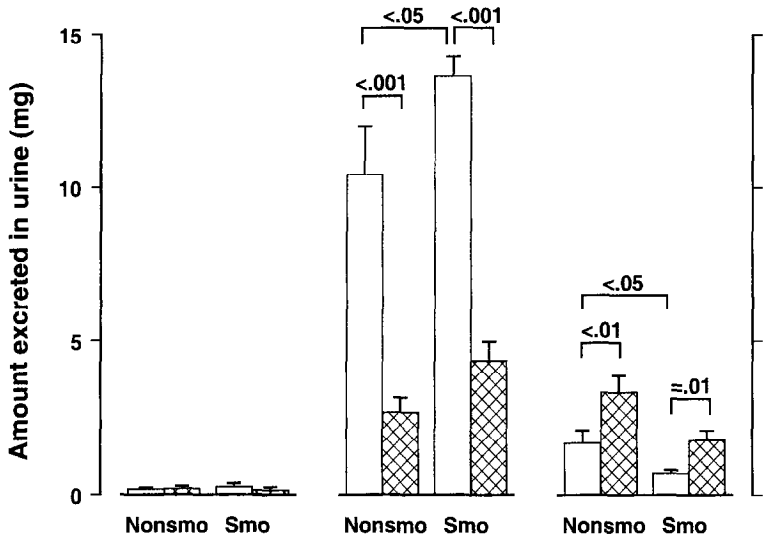

Fig 4. Mean (and SEM) amounts of ropivacaine *(left)*, 3-OH-ropivacaine *(middle)*, and PPX *(right)* excreted in urine in nonsmokers (Nonsmo) and smokers (Smo) within 24 hours after a 30-minute intravenous infusion of 0.6 mg/kg ropivacaine after ingestion of either placebo *(open bars)* or rifampin 600 mg *(hatched bars)* daily for 5 days.

infusion, and symptoms of central nervous system toxicity were assessed by direct questioning. The length of the QTc interval was measured by a 12-lead electrocardiogram device (Schiller AT-6C/SP; Schiller Ag, Baar, Switzerland) before and at ½ hour and 2 hours after the start of infusion.

Statistics. For comparisons of all pharmacokinetic parameters between the smokers and nonsmokers, the 2-sample separate variance *t* test was used. Placebo and rifampin phases were analyzed separately. The paired samples *t* test was used for the comparisons between the placebo and rifampin phases, separately for nonsmokers and smokers. No correction for multiple tests was used, and the exact *P* values are given in Table II. The results are expressed as means ± standard deviation (SD), except in the figures, in which, for clarity, we used mean values ± standard errors of the mean (SEM). Differences were regarded as significant if $P < .05$. All data were analyzed with the statistical program Systat for Windows, version 6.01 (SPSS Inc, Chicago, Ill).

RESULTS

Pharmacokinetics of ropivacaine in nonsmokers and smokers (Figs 1-4, Table II). In the placebo phase, smokers excreted in urine 31% more 3-OH-ropivacaine ($P < .05$) and 62% less PPX ($P < .05$) than nonsmokers. During the rifampin phase, smokers excreted in urine 64% more 3-OH-ropivacaine ($P < .05$) and 50% less PPX ($P < .05$) than nonsmokers. Smokers had a 126% higher AUC ratio of 3-OH-ropivacaine ($P < .05$) and a 31% lower AUC ratio of PPX ($P < .05$) during the rifampin phase than nonsmokers (Table II).

Effect of rifampin on ropivacaine (Fig 1, Table II). Plasma ropivacaine concentrations were considerably lower during the rifampin phase than during the placebo phase in both nonsmokers and smokers. Rifampin decreased the AUC(0-∞) of ropivacaine in nonsmokers by 52% ($P < .001$) and in smokers by 38% ($P < .05$), increased the CL of ropivacaine by 93% ($P < .001$) and 47% ($P < .01$), and shortened the $t_{½}$ of ropivacaine by 25% ($P < .01$) and 20% ($P < .05$), respectively. Rifampin also decreased the MRT by 36% ($P < .01$) and 33% ($P < .01$), decreased the C_{max} by 28% ($P < .01$) and 9% (not significant), and increased the E_H by 93% ($P < .001$) and 46% ($P < .01$), respectively.

Effect of rifampin on 3-OH-ropivacaine (Fig 2, Table II). Plasma concentrations of 3-OH-ropivacaine were considerably lower during the rifampin phase than during the placebo phase in both groups and particularly in the nonsmokers. Rifampin decreased the AUC(0-12) of 3-OH-ropivacaine by 86% ($P = .001$) and 67% ($P = .001$) in nonsmoker and smoker groups, respectively, and decreased the C_{max} by 70% ($P = .001$) and 42% ($P = .001$). Rifampin shorted the $t_{½}$ of 3-OH-ropivacaine in nonsmokers from 2.0 to 1.2 hours ($P < .01$) and in smokers from 2.4 to 1.3 hours ($P = .01$). Rifampin also reduced the amount of 3-OH-ropivacaine excreted in urine by 74% ($P < .001$) in nonsmokers and 68% ($P < .001$) in smokers (Fig 4).

The fractions of the dose metabolized to 3-OH-ropivacaine and excreted in urine ($f_{m,\ 3OH}$) were reduced from 0.30 to 0.08 and from 0.39 to 0.12, respectively.

Effect of rifampin on PPX (Fig 3, Table II). Plasma concentrations of PPX were much higher during the rifampin phase than during the placebo phase in both groups. Rifampin increased the AUC(0-12) of PPX by 131% ($P < .001$) in nonsmokers and 245% ($P < .001$) in smokers and increased the C_{max} by 166% ($P < .001$) and 282% ($P < .001$), respectively. Rifampin also shortened the $t_{½}$ from 11.3 to 6.7 hours ($P < .01$) and from 8.1 to 5.0 hours ($P < .01$) and increased the $f_{m,\ PPX}$ from 0.05 to 0.10 ($P < .01$) and from 0.02 to 0.05 ($P = .01$), respectively.

Safety assessment. There were no clinically significant differences in the recorded QTc times between the groups, treatments, or measuring times at 0, ½, and 2 hours.

DISCUSSION

This investigation was designed to study whether there are clinically significant differences in the pharmacokinetics of ropivacaine between nonsmokers and smokers (parallel groups study) and to study the effect of the potent CYP-enzyme inducer rifampin on the pharmacokinetics of ropivacaine in these two groups (crossover study).

Smokers excreted more 3-OH-ropivacaine and less PPX in urine than nonsmokers did. There were, however, only minor and statistically nonsignificant differences in the CL, $t_{½}$, and AUC of the parent ropivacaine between the two groups. In contrast to the minor effect of smoking, rifampin considerably increased the CL and decreased the AUC and $t_{½}$ of ropivacaine, decreased the AUC and excretion of 3-OH-ropivacaine, and increased the AUC and excretion of PPX in both nonsmoker and smoker groups.

Ropivacaine is metabolized by CYP1A2 yielding 3-OH-ropivacaine and, to a lesser extent, by CYP3A4 yielding PPX.[3-7] Both 3-OH-ropivacaine and PPX have significantly lower local anesthetic activity, as investigated in guinea pigs, in comparison with ropivacaine.[6] Inhibition of CYP1A2 by fluvoxamine has reduced the ropivacaine CL by 68% to 77%.[6,7] On the other hand, inhibition of CYP3A4 by ketoconazole, itraconazole, clarithromycin, or erythromycin has caused only insignificant (5%-15%) reduction in the CL of ropivacaine.[6,7,16] The greatest reduction (86%) in ropivacaine CL has been reported after combined use of fluvoxamine and erythromycin.[7]

Rifampin is a potent inducer of CYP enzymes, including not only CYP3A4 but also CYP1A and CYP2C.[17] Rifampin induces also P-glycoprotein[18] and some phase II reactions (eg, glucuronidation of lorazepam[19] and propafenone[20]). Polycyclic aromatic hydrocarbons in tobacco smoke are believed to be responsible for the induction of CYP1A1, CYP1A2, and possibly CYP2E1.[11]

In this study smokers excreted more (31%) 3-OH-ropivacaine in urine than nonsmokers did. This is in accordance with the earlier studies indicating that smoking increases the activity of CYP1A2,[11] the isozyme involved in the formation of 3-OH-ropivacaine. The small effect of smoking on the AUC of the parent ropivacaine was somewhat surprising, because 3-OH-ropivacaine is considered to be the major metabolite of ropivacaine.[3-5] An explanation seems to be the diminished formation (ie, plasma concentrations) and urinary excretion of PPX in smokers compared with nonsmokers. Another possible explanation could be an increased renal clearance of 3-OH-ropivacaine in the smokers, maybe as a result of changes in the urine pH (which was not measured in this study).

Rifampin clearly accelerated the elimination of ropivacaine and increased the AUC and excretion of PPX. This is in harmony with the fact that rifampin is a potent inducer of CYP3A4,[17] the isozyme involved in the formation of PPX.[3-5] Rifampin is also an inducer of CYP1A2, but in this study rifampin decreased the AUC and excretion of 3-OH-ropivacaine, suggesting that CYP3A4 was induced more than CYP1A2 by rifampin.

The combined cumulative fraction (of the infused ropivacaine dose) excreted in urine within 24 hours as 3-OH-ropivacaine and PPX (sum of $f_{m,\ 3OH}$ and $f_{m,\ PPX}$) was considerably lower after rifampin pretreatment (0.18 for nonsmokers and 0.17 for smokers) than after placebo (0.41 and 0.35, respectively), whereas the fraction of unchanged ropivacaine remained at about 0.01. This could be explained by further rifampin-induced metabolism of 3-OH-ropivacaine and PPX, by a greatly increased rate of formation of PPX (in relation to its slow renal excretion) during the rifampin phase (so that the body still has considerable stores of PPX at 24 hours), or by increased production of 4-OH-ropivacaine and 2-OH-methyl-ropivacaine, which usually are two minor metabolites formed by CYP3A4.[3-5]

The accelerated elimination of intravenous ropivacaine by rifampin, observed in this study, is not likely to have a notable effect on the quality or duration of the local anesthesia induced by ropivacaine. In clinical use the local anesthetics are administered locally, near the nerves to be desensitized. Induction of CYP enzymes is not likely to affect local anesthetic before it enters the systemic blood circulation. Also the changes in the

plasma levels of the ropivacaine metabolites are not likely to have toxicologic consequences, because PPX and 3-OH-ropivacaine have significantly lower local anesthetic activity than ropivacaine.[6]

In conclusion, smoking increases the excretion of 3-OH-ropivacaine and decreases the excretion of PPX in urine but causes only a minor reduction, if at all, in the ropivacaine AUC. Rifampin considerably increases the elimination of ropivacaine, decreases the AUC and excretion of 3-OH-ropivacaine, and increases the AUC and excretion of PPX. The effect of smoking and rifampin should be taken into account in clinical studies on the pharmacokinetics of ropivacaine.

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