Alfentanil Pharmacokinetics and Metabolism in Humans

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The metabolism of alfentanil was studied in three healthy subjects after a 1-h infusion of 2.5 mg alfentanil-³H. One of the subjects was a poor hydroxylator of debrisoquine. Pharmacokinetic parameters were similar in the three subjects and were in the same range as those reported for volunteers. The majority of the administered radioactivity was excreted in the urine (90% of the dose), but unchanged alfentanil represented only 0.16–0.47% of the dose. Alfentanil and metabolites were characterized by HPLC co-chromatography with reference compounds and/or by mass spectrometry and quantified by GLC and radio-HPLC. The main metabolic pathway was N-de-alkylation at the piperidine nitrogen, with formation of noralfentanil (30% of the dose). Other Phase I pathways were aromatic hydroxylation, N-dealkylation of the piperidine ring from the phenylpropanamide nitrogen, O-demethylation, and amide hydrolysis followed by N-acetylation. Glucuronic acid conjugation of aromatic or aliphatic hydroxyl functions was the main Phase II pathway. The second major metabolite was the glucuronide of N-(4-hydroxyphenyl) propanamide (14% of the dose). The metabolite pattern in these subjects was qualitatively very similar to that described previously in rats and dogs. Differences in the mass balance of urinary metabolites between the three subjects were very small, and there was no qualitative or quantitative evidence for a deficiency in the metabolism of alfentanil in the subject who was a poor metabolizer of debrisoquine. (Key words: Analgesics, opiate: alfentanil. Anesthetics, intravenous: alfentanil. Biotransformation, humans: alfentanil. Pharmacokinetics: alfentanil.)

ALFENTANIL is an analog of the synthetic opiate fentanyl but characterized by a shorter duration of action. Numerous papers have already dealt with the clinical pharmacokinetics of alfentanil.[1–11] However, only very few data have been published on its excretion and biotransformation in humans. The excretion of unchanged alfentanil in urine during the first 24 h after administration amounted to 0.4% of the dose.[7] Recently, some indirect evidence has been presented for a debrisoquine phenotype of polymorphic oxidation of alfentanil in humans.[12],‡‡ Impaired drug oxidation may influence the therapeutic efficacy and toxicity of drugs, for example, by reduction of first-pass metabolism with increased plasma levels and bioavailability or by alternative metabolic pathways, prompting formation of toxic metabolites.[13,14]

In rats and dogs alfentanil was metabolized very rapidly into a large number of metabolites that were excreted mainly in urine.[15] The oxidative N-dealkylation at the piperidine nitrogen, O-demethylation, and aromatic hydroxylation were the main metabolic pathways in these two animal species.[15]

The present paper describes a study on the metabolic fate of alfentanil after administration of the tritium-labeled alfentanil to three nonsurgical subjects, one of whom was a poor metabolizer and the other two extensive metabolizers of debrisoquine. An in vitro study with human liver microsomes, designed to investigate whether the metabolism of alfentanil is subject to the debrisoquine polymorphism, is described separately.[16]

Materials and Methods

Three healthy male volunteers (table 1) participated in the study after giving informed consent. No medication was allowed for at least 1 wk before and during the study. The protocol was approved by the Hospital Ethics Committee. Debrisoquine phenotyping was performed by determination of the debrisoquine/4-OH-debrisoquine metabolic ratio in the 0–8 h urine, using a reversed-phase high-performance liquid chromatography (HPLC) assay with UV-detection at 254 nm.[17] Subjects 1 and 3 were extensive metabolizers of debrisoquine, whereas subject 2 was a poor metabolizer (table 1).

The subjects had been fasted overnight before the administration of alfentanil (Janssen, Beerse, Belgium). Before dosing a catheter for serial blood sampling was inserted into an arm vein contralateral to the alfentanil infusion site. The subjects received 2.5 mg alfentanil as a 60-min infusion of 50 ml of a 50 μg/ml solution of alfentanil-³H in saline (0.56 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) and were sitting

‡‡ McDonnell TE, Bartkowski RR, Kahn C: Evidence for polymorphic oxidation of alfentanil in man (abstract). ANESTHESIOLOGY 61:A284, 1984.

TABLE 1. Individual Details of Male Volunteers and Pharmacokinetic Parameters of Alfentanil after a 1-h Infusion of 2.5 mg of Alfentanil-^{3}H

Parameters	Subject 1	Subject 2	Subject 3	Mean ± SD
Age (yr)	43	39	28	37 ± 8
Body weight (kg)	72	75	76	74 ± 2
Height (cm)	175	176	183	178 ± 4
Metabolic ratio DB/4-OH-DB	0.30	35.1	0.36	—
V_c (ml·kg^{-1})	173	122	208	168 ± 43
α (min^{-1})	0.0254	0.0331	0.0249	0.0278 ± 0.0046
β (min^{-1})	0.00700	0.00939	0.00879	0.00839 ± 0.00124
k_{21} (min^{-1})	0.0149	0.0173	0.0124	0.0149 ± 0.0025
k_{12} (min^{-1})	0.0055	0.0073	0.0036	0.0055 ± 0.0019
k_{10} (min^{-1})	0.0120	0.0179	0.0177	0.0159 ± 0.0034
$t_{1/2\alpha}$ (min)	27	21	28	25 ± 4
$t_{1/2\beta}$ (min)	99	74	79	84 ± 13
Cl (ml·min^{-1}·kg^{-1})	2.07	2.19	3.68	2.65 ± 0.90
V_{dss} (ml·kg^{-1})	237	174	268	226 ± 48
V_{darea} (ml·kg^{-1})	297	233	419	316 ± 94

R° (rate of infusion) = 2.5 mg·h^{-1} = 0.56 (±0.02) μg·kg^{-1}·min^{-1} for the three subjects. Metabolic ratio DB/4-OH-DB = ratio of unchanged debrisoquine/4-OH-debrisoquine in the 0–8 h urine. V_c = apparent volume of central compartment; α and β = disposition rate constants; k_{21} and k_{12} = transfer rate constants between compartments;

k_{10} = elimination rate constant; $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$ = elimination half-life; Cl = total body clearance; V_{dss} = apparent volume of distribution at steady state; V_{darea} = area-based apparent volume of distribution calculated as Cl/β.

in a chair during the infusion. Alfentanil-^{3}H was specifically labeled with tritium in the 3-position of the phenyl ring,[15] and showed a radiochemical purity >99% (radio-HPLC). The radioactive dose amounted to 4.36 mBq (118 μCi) per 2.5 mg alfentanil-^{3}H base. The subjects were allowed to drink mineral water *ad libitum*. After the infusion all subjects were ambulatory and had a light lunch 3 h later.

Plasma samples obtained by centrifugation of the heparinized blood were analyzed for total radioactivity (TR), nonvolatile radioactivity (NVR),[15] and for unchanged alfentanil (GLC-assay).[18] Individual plasma concentration time curves of unchanged alfentanil were fitted to a two-compartment open model described by the following equation[19]:

$$C = \frac{k_0 \cdot (k_{21} - \alpha)}{V_c \cdot \alpha \cdot (\alpha - \beta)} \cdot (e^{-\alpha t_{end}} - 1) \cdot e^{-\alpha(t - t_{end})}$$

$$+ \frac{k_0 \cdot (\beta - k_{21})}{V_c \cdot \beta \cdot (\alpha - \beta)} \cdot (e^{-\beta t_{end}} - 1) \cdot e^{-\beta(t - t_{end})}$$

where k_0 is the infusion rate constant, t is the time after the start of the infusion, and t_{end} is the end time of the infusion. The two-compartment model was selected by evaluation of the standard errors of the parameter estimates, scatter plots of the residuals between experimental and predicted plasma concentration, and the maximum likelihood function. Pharmacokinetic parameters V_c, k_{21}, α, and β were estimated by extended least squares nonlinear regression.[20] All other kinetic parameters were calculated by standard methods.[19]

Total urinary output was collected over various time intervals up to 48 h after the infusion. Urine levels of

TR, NVR, and unchanged alfentanil were determined as for plasma. The mass balance for alfentanil and its metabolites in urine was made up by radio-HPLC. Therefore, aliquots up to 2.0 ml of various urine samples, before or after hydrolysis with β-glucuronidase and/or arylsulfatase,[15] were automatically injected by a WISP 710B (Waters, Milford, MA) onto a Hypersil C18 column (5 μm; Shandon, Run Corn, UK). Gradient elution and on-line radioactivity detection were performed as described previously.[15] Areas of the radioactivity peaks were converted into disintegrations per minute values by a SP 4270 computing integrator (Spectra-Physics, San Jose, CA), using a calibration curve made up by injection of known amounts of alfentanil-^{3}H (n = 11, ranging from 870 to 40,361 dpm) and linear regression analysis of the corresponding areas of the radioactivity peaks (r = 0.9992). Known amounts of alfentanil-^{3}H were injected regularly for the control of the validity of the calibration curve over the entire series of analysis.

Urinary metabolites were identified by HPLC co-chromatography with reference compounds, which corresponded to alfentanil metabolites in rats and/or dogs.[15] The two main metabolites (AM5 and AM11) were identified by mass spectrometry after isolation and purification. Urine was extracted twice with dichloromethane at pH 11, twice with dichloromethane/2-propanol (4:1) at pH 9 and twice with the same solvent system at pH 7, and further with ethyl acetate at pH 2. Thereafter, the remaining aqueous phase was hydrolyzed with β-glucuronidase/arylsulfatase and subsequently extracted once again following the same extraction scheme. Isolation of the metabolites from the extracts was performed by HPLC on a C18 column and final purification occurred on a
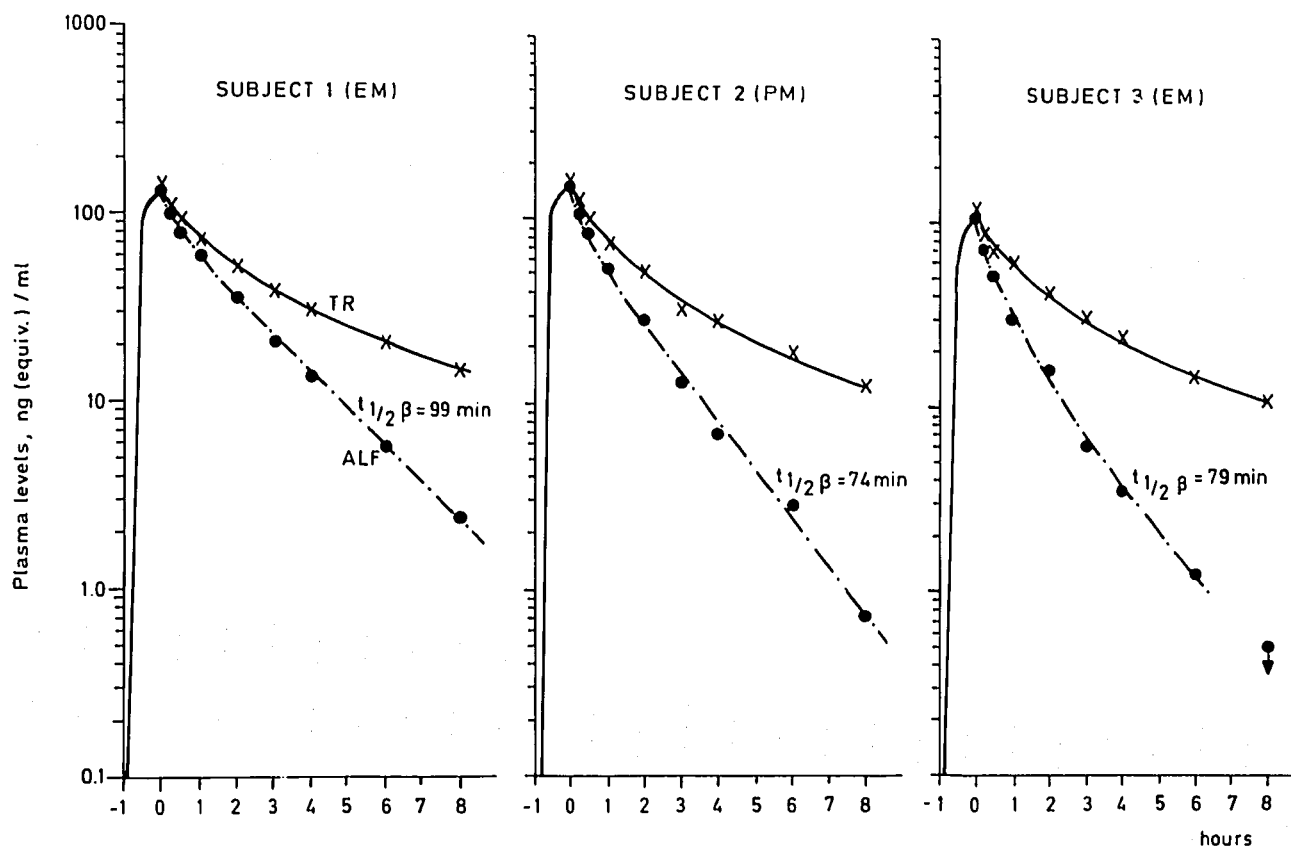
FIG. 1. Individual plasma levels of the total radioactivity (TR, X——X) and of the parent drug (ALF, ●–·–●) in three male volunteers after a 1-h infusion of 2.5 mg of alfentanil-^{3}H. EM = extensive metabolizer; PM = poor metabolizer (debrisoquine oxidation phenotyping). Time point 0 h corresponds to the end of the infusion. The dot with the downward arrow denotes a concentration lower than the limit of detection by the GLC-assay ($\leq$0.5 ng/ml).

−N(CH$_3$)$_2$ HPLC column.[15] Electron impact (EI) and positive chemical ionization (PCI) mass spectra of the metabolites were obtained on a Finnigan 4500 mass spectrometer (Finnigan Mat, Bremen, FRG), coupled to an Incos data system. EI or PCI mass spectrometric conditions after direct introduction (AM11) or after GLC-separation on a capillary column inserted into the ion source (trimethylsilylated AM5) were similar to those described previously.[15]

Results

Figure 1 shows the individual plasma level–time curves of TR and unchanged alfentanil. Alfentanil levels were below the limit of detection (0.5 ng/ml) at 12 h after the end of the infusion, whereas TR as well as NVR levels could still be determined until 24 h. NVR plasma levels were almost identical to TR levels during the first 6 h after the end of infusion; after 24 h NVR and TR levels were 2.2 ± 0.7 and 3.3 ± 0.6 ng eq/ml, respectively, indicating that tritiated water in body water accounted for only about 2% of the dose. The elimination half-life of NVR was approximately 7 h. The contribution of al-

fentanil to NVR plasma levels decreased gradually from 94% at the end of the infusion to 50–80% at 1 h and to 10–25% at 6 h after the infusion. A two-compartment model best fitted the alfentanil data. The derived pharmacokinetic parameters of the unchanged alfentanil are listed in table 1.

The excretion of the radioactivity in the urine exceeded half of the dose after 8 h and averaged 87.9 ± 1.5% of the dose 48 h after the infusion (fig. 2). The maximum urinary excretion rate of TR (10% of the dose/h) was reached between 1 and 2 h after the end of infusion (fig. 3). The half-life of the urinary excretion rate of TR was 7.7 ± 0.4 h for the three subjects. Urine levels of NVR were almost identical to TR levels until 48 h, confirming the minimal formation of tritiated water. Urine levels of alfentanil, as measured by the GLC-assay, were 1–3% of the TR levels in the urine voided up to 1 h after the infusion, and decreased very rapidly to less than 0.1% of the sample radioactivity at 6 h. The total amount of parent drug excreted in the urine amounted to 0.16% of the dose in subject 1, 0.18% in subject 2, and 0.47% in subject 3. Table 2 presents the mass balance of alfentanil (AM15)
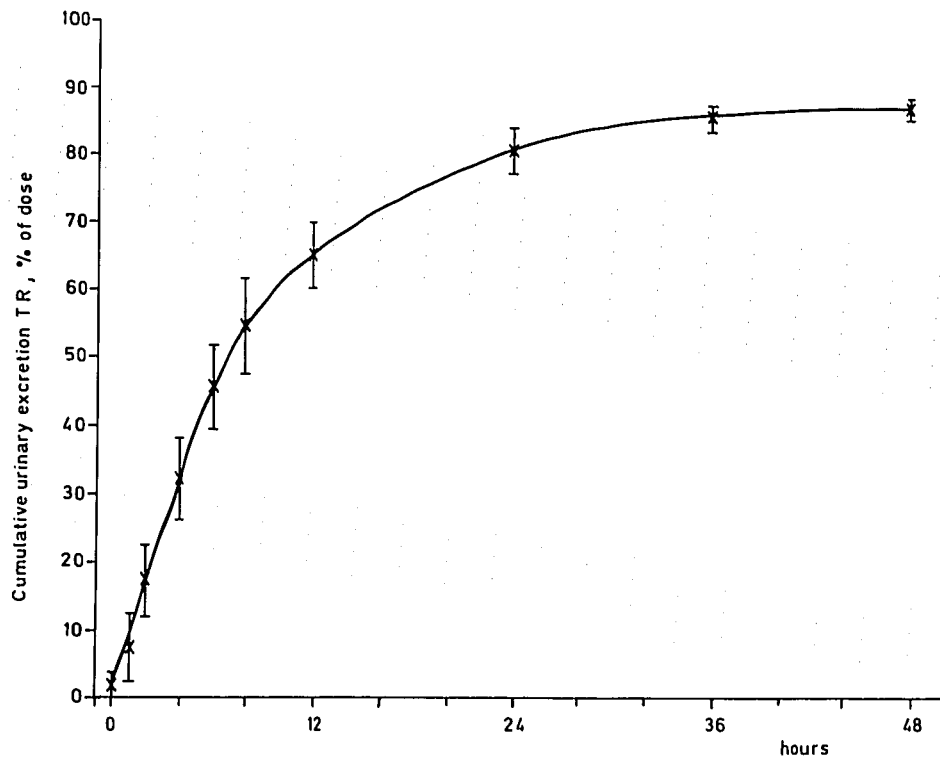
FIG. 2. Cumulative excretion of the total radioactivity (TR) in the urine of three male volunteers after a 1-h infusion of 2.5 mg alfentanil-³H (mean ± SD). Time point 0 h corresponds to the end of the infusion.

and its major metabolites in individual urine samples, as made up by radio-HPLC. Figure 4 shows one of the radiochromatograms. Individual differences for the mass balance of the metabolites were very small. Radio-HPLC analysis of urine samples hydrolyzed with β-glucuronidase/arylsulfatase in the absence or presence of the β-glucuronidase inhibitor saccharo-1,4-lactone, showed glucuronic acid conjugates of the metabolites AM3, AM5,

and AM6. The main alfentanil metabolite, AM11, could be identified as noralfentanil by mass spectrometry and HPLC co-chromatography (table 3). Noralfentanil excreted in the 0–24 h urine accounted for approximately one-third of the dose (table 2), and its urinary excretion rate was similar to that of TR (fig. 3). Glucuronic acid or sulfate conjugates of noralfentanil were not detected. The second major alfentanil metabolite was the glucuronide
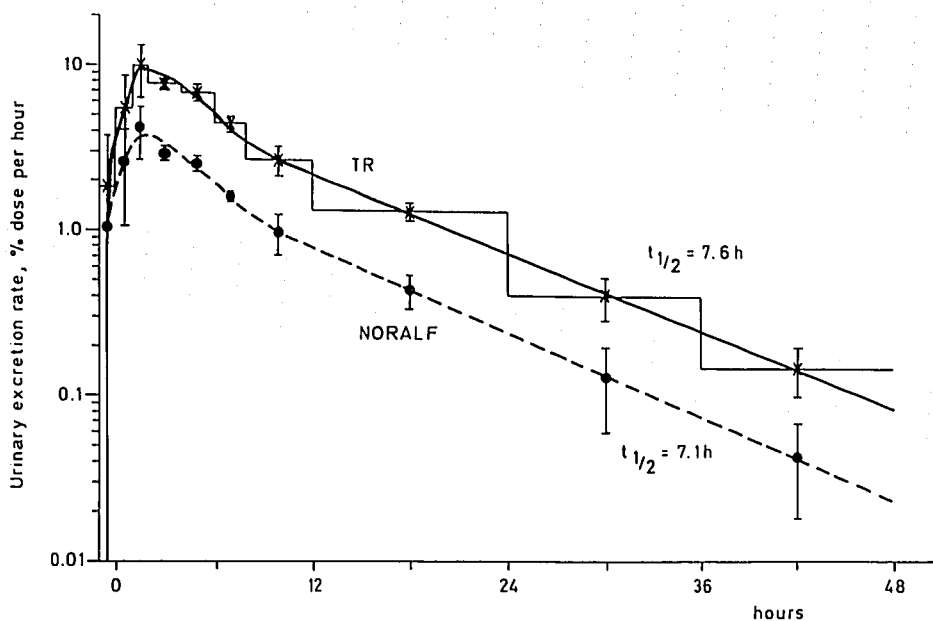
FIG. 3. Urinary excretion rate of total radioactivity (TR, ✕——✕) and of the main metabolite noralfentanil (NORALF, ●----●) in three male volunteers after a 1-h infusion of 2.5 mg alfentanil-³H (mean ± SD). Time point 0 h corresponds to the end of the infusion. One of the subjects was not able to produce a −1 to 0 h urine sample.

TABLE 2. Mass Balance of Alfentanil (ALF) and Its Major Metabolites in Urine after 1-h Infusion of 2.5 mg Alfentanil-³H

Metabolite (Total Radioactivity)	% of Sample Radioactivity (% of Dose Radioactivity)								
	Subject 1 (EM)			Subject 2 (PM)			Subject 3 (EM)		
	−1 to 4 h (27.48%)	4–8 h (19.90%)	8–24 h (30.50%)	−1 to 4 h (30.31%)	4–8 h (24.72%)	8–24 h (25.70%)	−1 to 4 h (39.11%)	4–8 h (22.39%)	8–24 h (23.20%)
AM3-conjugate	1.0 (0.3)	3.1 (0.6)	4.5 (1.4)	1.3 (0.4)	4.2 (1.0)	5.2 (1.3)	<1.0	3.6 (0.8)	5.1 (1.2)
AM5-conjugate	16.7 (4.6)	17.3 (3.4)	17.9 (5.5)	16.9 (5.1)	18.6 (4.6)	17.3 (4.4)	15.1 (5.9)	21.6 (4.8)	22.1 (5.1)
AM3	2.8 (0.8)	4.8 (1.0)	4.8 (1.5)	4.9 (1.5)	4.6 (1.1)	3.7 (1.0)	5.0 (2.0)	5.0 (1.1)	4.2 (1.0)
AM6-conjugate	4.3 (1.2)	3.0 (0.6)	1.1 (0.3)	<1.0	2.3 (0.6)	3.0 (0.8)	<1.0	3.0 (0.7)	3.1 (0.7)
AM5	1.1 (0.3)	1.9 (0.4)	2.0 (0.6)	1.6 (0.5)	3.8 (0.9)	2.8 (0.7)	4.1 (1.6)	3.4 (0.8)	2.9 (0.7)
AM6	5.6 (1.5)	5.6 (1.1)	7.3 (2.2)	6.0 (1.8)	4.7 (1.2)	5.9 (1.5)	6.3 (2.5)	5.6 (1.3)	5.5 (1.3)
AM10	5.6 (1.5)	4.8 (1.0)	3.2 (1.0)	3.8 (1.2)	4.5 (1.1)	5.6 (1.4)	4.8 (1.9)	5.2 (1.2)	3.2 (0.7)
AM11	45.9 (12.6)	41.6 (8.3)	39.8 (12.1)	40.7 (12.3)	31.6 (7.8)	32.9 (8.5)	40.1 (15.7)	32.9 (7.4)	34.2 (7.9)
AM15 (ALF)	1.1 (0.3)	<1.0	<1.0	1.0 (0.3)	<1.0	<1.0	1.4 (0.5)	<1.0	<1.0
Total	84.1 (23.1)	82.1 (16.4)	80.6 (24.6)	76.2 (23.1)	74.3 (18.3)	76.4 (19.6)	76.8 (30.1)	80.3 (18.1)	80.3 (18.6)

Mass balances were obtained by radio-HPLC analysis of individual pools of urine samples. Metabolites were arranged and coded by their order of elution from the C18 column. Metabolites not retaining the phenyl ring with the tritium label could not be measured. Time point −1 h corresponds to the start, time point 0 h to the end of the infusion. EM = extensive metabolism; PM = poor metabolism.

of AM5 [N-(4-hydroxyphenyl)propanamide] (table 3). Other metabolites, characterized by HPLC co-chromatography with reference compounds (fig. 4), were N-(4-hydroxyphenyl)acetamide (AM3) and N-[4-(hydroxymethyl)-4-piperidinyl]-N-phenylpropanamide (desmethylnoralfentanil, AM6) (fig. 5). AM15 corresponded to the unchanged drug. A small amount of desmethylalfentanil (AM14, fig. 5) could be detected in some hydrolyzed samples. Metabolite AM10 was identical to a metabolite detected previously in incubates of alfentanil with rat hepatocytes, but its structure has not yet been determined.[21]

Discussion

The clearance and volumes of distribution in the present study are similar to those reported for volunteers[8] and patients[10] but apparently lower than in most other studies with surgical patients undergoing general anesthesia.[1–7,9,11] Pharmacokinetics of alfentanil in the poor and extensive debrisoquine phenotype metabolizers were similar (table 1). Plasma levels of the radioactivity as well as the percent of the plasma radioactivity accounted for by unchanged alfentanil in the poor metabolizer were intermediate between those in the two extensive metabolizers. These data do not confirm the previous suggestions by McDonnell et al. on alfentanil oxidation exhibiting a debrisoquine type of genetic polymorphism.§§ In addition, their suggestions were based on one subject with impaired clearance of phenacetin§§ and alfentanil.¶¶

§§ McDonnell TE, Bartkowski RR, Kahn C: Evidence for polymorphic oxidation of alfentanil in man (abstract). ANESTHESIOLOGY 61:A284, 1984.

¶¶ McDonnell TE, Bartkowski RR, Bonilla FA, Henthorn TK, Williams JJ: Nonuniformity of alfentanil pharmacokinetics in healthy adults (abstract). ANESTHESIOLOGY 57:A236, 1982.
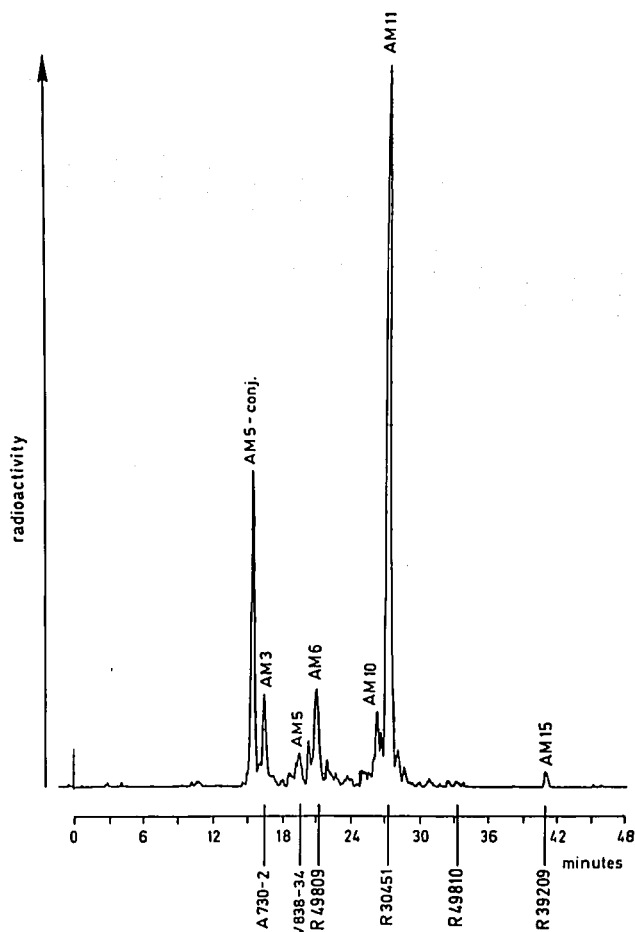

FIG. 4. Radio-HPLC chromatogram obtained for the −1 to 4 h urine sample from subject 3 after a 1-h infusion of 2.5 mg alfentanil-³H. Retention times of some reference compounds, corrected for the delay between UV and radioactivity detection, are indicated. A730-2 = N-(4-hydroxyphenyl)acetamide; V838-34 = N-(4-hydroxyphenyl)-propanamide; R 49 809 = desmethylnoralfentanil; R 30 451 = noralfentanil; R 49 810 = desmethylalfentanil; R 39 209 = alfentanil.

TABLE 3. Identification of the Two Major Metabolites of Alfentanil

Compound	HPLC Retention Time (min)*		m/z (Relative Intensity) Mass Spectral Data (EI Mode)†	
	C18 Column	−N(CH₃)ₐ Column	M⁺	Principal Fragment Ions
Metabolite AM5†	18.9	12.3	237 (32)	222(8), 182(11), 181(100), 167(5), 166(30), 150(1), 149(2), 106(5)
N-(4-hydroxyphenyl) propanamide (V838-34)†	18.9	12.3	237 (49)	222(10), 182(14), 181(100), 167(5), 166(41), 150(1), 149(1), 106(4)
Metabolite AM11	26.9	20.8	276(<1)	231(5), 219(1), 203(5), 186(1), 175(11), 164(1), 158(3), 150(2), 146(35), 132(4), 128(16), 127(6), 126(3), 118(5), 96(47), 95(17), 94(7), 93(14), 82(100)
Noralfentanil (R 30 451)	26.9	20.8	276(<1)	231(16), 219(3), 203(20), 186(2), 175(22), 164(1), 158(7), 150(3), 146(46), 132(6), 128(28), 127(13), 126(6), 118(9), 96(52), 95(24), 94(11), 93(18), 82(100)

M⁺ = molecular ion.

* A delay of 0.3 min between the on-line linked radioactivity detector (for detection of metabolites) and UV-detector (for detection of reference compounds) was taken into account.

† Trimethylsilylation of both metabolite AM5 and reference compound V838-34 resulted in the introduction of two trimethylsilyl groups [(M + H)⁺ PCI m/z 310]; evaporation of solvent and reconstitution in methanol results in monosilylated compounds [(M + H)⁺ PCI m/z 238], the EI spectral data of which were tabulated.

Approximately 90% of the dose was recovered in the urine. The excretion of 0.16–0.47% of the dose as unchanged alfentanil with the urine agrees with the earlier by Schüttler and Stoeckel reported 0.36 ± 0.18%.[7] In general, urinary excretion data in humans were similar to those observed in rats and dogs. In these two animal species the excretion of the radioactivity also occurred predominantly with the urine and unchanged alfentanil in urine accounted for less than 0.7% of the dose.[15]

In humans, just as in rats and dogs,[15] alfentanil was metabolized into a large number of metabolites. The main metabolic pathway was oxidative N-dealkylation at the piperidine nitrogen, resulting in noralfentanil (AM11, fig. 5) and some of its secondary metabolites. This metabolic pathway was also a main one for fentanyl in humans.[22] The second major metabolite of alfentanil was the glucuronide of N-(4-hydroxyphenyl)propanamide (AM5). This metabolite resulted from a combination of aromatic hydroxylation of the phenyl and oxidative N-dealkylation of the piperidine moiety from the phenylpropanamide nitrogen.[15] When alfentanil was incubated with human liver microsomes, the latter pathway yielded N-phenylpropanamide, a major *in vitro* metabolite,[16] which was, however, not detected in urine or feces. Other metabolic pathways were O-demethylation, amide hydrolysis fol-

lowed by N-acetylation, and the formation of ether glucuronides (fig. 5). The present study shows that the various metabolic pathways in humans are identical to those in rats and dogs,[15] but there are rather large quantitative species differences. In humans noralfentanil (31% of the dose) was much more abundant than in rats (4%) and dogs (7%). The relative amount of AM5 plus its conjugate in humans (17%) was intermediate between that in rats (11%) and dogs (25%). Metabolite AM3 plus its conjugate were less abundant in humans (6%) than in rats (14%), whereas these metabolites could not be detected in dogs. This latter finding can be explained by the inability of dogs to acetylate aromatic amines.[15] The relative amount of AM6 (desmethylnoralfentanil) plus its conjugate (6%) was much smaller than in rats (30%) but similar to that in dogs (4%). In the urine of humans desmethylalfentanil (AM14) could only be detected in trace amounts as its glucuronide. Due to its rather large molecular weight, desmethylalfentanil glucuronide is eliminated most probably preferentially with the bile and excreted as desmethylalfentanil in the feces, as in dogs.[15]

The present study did not produce evidence for a debrisoquine type of genetic polymorphism in the metabolism of alfentanil. The same metabolic pathways were found in the poor and extensive metabolizers, and dif-
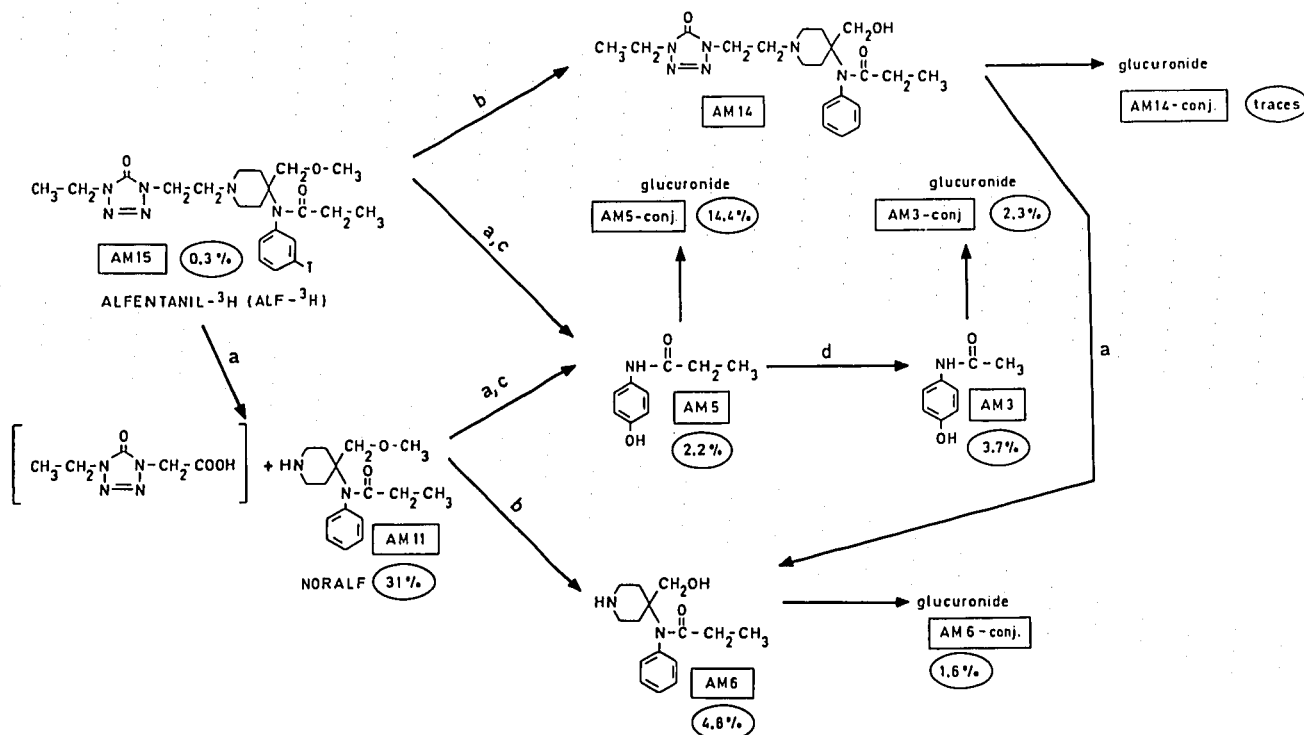
FIG. 5. Major metabolic pathways of alfentanil in humans. The position of the ^{3}H-label in alfentanil-^{3}H is denoted by the symbol T. The percents of the dose accounted for by the various metabolites in the urine voided up to 24 h after the end of infusion are presented. Metabolite AM14 could only be detected in trace amounts as its glucuronide. The structure between brackets could not be detected as it did not bear a radiolabel. NORALF = noralfentanil; a = oxidative N-dealkylation; b = oxidative O-demethylation; c = aromatic hydroxylation; d = amide hydrolysis + acetylation.

ferences for the mass balance of the metabolites were small (table 2). The large similarity of the metabolite patterns and of pharmacokinetic parameters of alfentanil in poor and extensive metabolizers of debrisoquine counters suggestions by McDonnell et al.*** and Henthorn et al.[12] of a polymorphic oxidation of alfentanil by the same cytochrome P-450 isoenzymes involved in the genetic polymorphism of debrisoquine. The absence of such a polymorphic oxidation of alfentanil was confirmed by an in vitro study with human liver microsomes. Cytochrome P-450 forms catalyzing the metabolism of debrisoquine did not contribute to the metabolism of alfentanil in a wide concentration range.[16] Nevertheless, much larger groups of both poor and extensive metabolizers need to have their pharmacokinetic profile and metabolism characterized in order to draw a definite conclusion on the effect of debrisoquine phenotype on alfentanil kinetics.

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