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Norio Ogata
Nobuyuki Matsushima
Takashi Shibata

Research Institute,
Taiko Pharmaceutical Co., Ltd.,
Osaka, Japan

Pharmacokinetics of Wood Creosote: Glucuronic Acid and Sulfate Conjugation of Phenolic Compounds

Key Words
Wood creosote
Phenol
Guaiacol
p-Cresol
Creosol
Glucuronidation

Abstract

Wood creosote, principally a mixture of non-, alkyl- and/or alkoxy-substituted phenolic compounds, was orally administered to adult male volunteers to determine its metabolites and pharmacokinetic parameters. After a 133-mg single dose, its major constituents (i.e. phenol 15 mg, guaiacol 32 mg, *p*-cresol 18 mg and creosol 24 mg) were found in peripheral venous blood and urine, mostly as glucuronic acid and, except for creosol, as sulfate conjugates. Low concentrations of unconjugated phenols were also detected. The metabolites in the serum started to increase 15 min after the dose, and they reached their maximum concentrations 30 min after administration. The maximum concentrations of glucuronides were 0.18 ± 0.07, 0.91 ± 0.38, 0.33 ± 0.18 and 0.47 ± 0.23 mg/l; those of sulfates were 0.16 ± 0.06, 0.22 ± 0.09, 0.17 ± 0.07 and <0.04 mg/l for phenol, guaiacol, *p*-cresol and creosol, respectively. The 24-hour urinary recoveries of the sum of each compound and its metabolites were 75 ± 35, 45 ± 36, 103 ± 51 and 74 ± 36%, in the above order. The presence of guaiacol glucuronide in blood and urine was directly verified by its isolation and structure analyses.

Introduction

Wood creosote has long been used as an expectorant, a gastric sedative, a gastrointestinal antiseptic and an antidiarrheal agent [1–8]. It is primarily a mixture of simple phenolic compounds, mostly of alkyl- and/or alkoxy-substituted phenols, obtained as an acidic fraction of wood tar distillate [9–11]. It is liquid at room temperature and behaves as if it

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Norio Ogata, MD, PhD
Department of Internal Medicine
Nagayoshi General Hospital
Nagayoshi-nagahara 1–2–34
Hiranoku, Osaka 547 (Japan)

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consisted of a single chemical compound because of the closely similar structures of its constituent compounds [10]. Although the names cause some confusion, the wood creosote used for medicinal purposes is completely distinct from 'coal tar creosote' [9].

There is already a certain amount of literature concerning chemical analyses [10, 11] and some pharmacologic studies [12–14] of wood creosote, but no pharmacokinetic study has yet been reported. We designed the present experiment to identify the metabolites of wood creosote's four major constituents, i.e. phenol, guaiacol (2-methoxyphenol), *p*-cresol (4-methylphenol) and creosol (2-methoxy-4-methylphenol) – collectively called 'phenols' hereafter – and their relevant pharmacokinetic parameters following a single oral dose administered to healthy men. Because the substituents in these phenols differ only slightly from each other, this study gives us a chance to compare the metabolism and pharmacokinetics of very closely related phenolic compounds.

There have been some reports of pharmacokinetics and metabolism about phenol and cresol isomers administered to various animal species [15–19], but none of these reports concern guaiacol and creosol. To the best of our knowledge, our study is the first pharmacokinetic investigation of these two compounds. Verification of guaiacol glucuronidation was accomplished by isolating the glucuronide and determining its structure.

Materials and Methods

Subjects

Eight healthy male volunteers (aged 26 ± 3 years, body weight 70 ± 7 kg, height 176 ± 7 cm) participated in the study after signing written statements of informed consent. Results of physical examinations, including blood, urine, renal and liver function tests and electrocardiograms, were all within normal limits.

Materials

The lot of wood creosote (No. 9303; Perstorp Chemical, Perstorp, Sweden) used in this study contained 11.3, 24.3, 13.7 and 18.2% (w/w) of phenol, guaiacol, *p*-cresol and creosol, respectively, as determined by gas chromatography [10]. Just prior to the study, 133 mg of wood creosote and 66 mg of the carrier magnesium aluminometa-silicate (Fuji Chemical, Toyama, Japan) were put into a hard gelatine capsule (6.4 i.d. × 21 mm).

Pharmacokinetic Analysis

One wood creosote capsule and 200 ml of water were orally administered to each subject soon after a light breakfast, and peripheral venous blood and urine were collected at various time intervals. The urine and the serum separated from the collected blood were stored at −20°C until high-performance liquid chromatography (HPLC) analyses were performed. The pharmacokinetic parameters of the serum were calculated as follows. A terminal half-life ($t_{½}$) was determined from the terminal slope of the log concentration versus time plot (minimum of 3 points). An area under the serum concentration versus time curve, from time zero to infinity (AUC_∞), was calculated by a log-linear method, with extrapolation to infinity. Oral plasma clearance (Cl_p/F) was calculated as the dose, figured for each compound from its respective concentration in wood creosote, divided by AUC_∞; an apparent volume of distribution was obtained by dividing the Cl_p/F by the terminal slope. As undosed human serum and urine are known to contain phenol, *p*-cresol [20, 21] and guaiacol [unpubl. data] together with their metabolites, the concentrations of these 'endogenous' phenols are subtracted for calculations of $t_{½}$ and AUC_∞ as 'background levels'. Likewise, for urinary phenol recoveries, the levels in the undosed subjects were subtracted from the original values.

Chemical Analysis of Serum and Urine

Two milliliters of the serum were subjected to ultrafiltration through a membrane of molecular weight cutoff range 5,000 (Molcut; Millipore Corp., Bedford, Mass., USA) to remove proteins. The filtrate (400 µl) was next mixed with an internal standard (i.e. 4 µl of 101 mg/l 2-fluorophenol), and a 20-µl aliquot was injected into the HPLC column before or after treatment with either bovine liver β-glucuronidase (EC 3.2.1.31, type B-10, 100 Fishman units/µl; Sigma Chemical, St. Louis, Mo., USA) or *Aerobacter aerogenes* sulfatase (EC 3.1.6.1, 19 units/ml, Sigma). For the β-glucuronidase digestion, a 150-µl aliquot of the filtrate was mixed with 3 µl of 4 mol/l sodium acetate-

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buffer (pH 5.0) and 3 µl of the enzyme, and the mixture was incubated at 37°C for 2 h. For the sulfatase digestion, another 150-µl aliquot was mixed with 3 µl of 2.5 mol/l Tris-HCl buffer (pH 7.5) and 3 µl of the enzyme, and then incubated at 37°C for 1 h. The enzyme-treated samples were again ultrafiltrated, and 20 µl of the filtrate was injected into the HPLC column. The phenols were quantified by comparing their peak heights with that of 2-fluorophenol. The phenol conjugates were quantified by subtracting the unconjugated ones and corrected for the dilution caused by the addition of the reagents.

To quantify the phenols in urine, 1 ml of urine was mixed with 40 µl of 2.6 g/l 2-fluorophenol, 200 µl of a solution consisting of 0.49 mol/l $MgCl_2$ and 3.7 mol/l NH_4Cl, and 50 µl of 14 mol/l NH_4OH, then left at 25°C for 5 min. The insoluble phosphate salt that formed was removed by centrifugation for 5 min at 8,000 *g*. The supernatant was ultrafiltrated as above and a 20-µl aliquot was subjected to HPLC. Another 550-µl aliquot was mixed with 100 µl of 4 mol/l sodium acetate buffer (pH 4.8) and 5 µl of Glufatase (Funakoshi, Tokyo, Japan), a β-glucuronidase (42,000 Fishman units/ml), and sulfatase (21,000 Roy units/ml) mixture from the apple snail *(Pomacea canaliculata)*. It was incubated at 60°C for 2 h. After the incubation the mixture was ultrafiltrated, and a 20-µl aliquot was injected into the HPLC column. The concentrations were corrected for the dilution caused by the addition of the reagents.

HPLC Analysis

For 'standard' HPLC analysis of the phenols in serum and urine, a Cosmosil 5C18 reverse-phase column (4.6 i.d. ×250 mm; Nacalai Tesque, Kyoto, Japan) mounted on a HPLC system (Jusco, Tokyo, Japan) equipped with a 275-nm ultraviolet detector was used at 25°C at a flow rate of 1 ml/min. Mobile phase A (acetonitrile:acetic acid:methanol:water, 250:45:250:1,455) or mobile phase B (acetonitrile:acetic acid:methanol:water, 21:23:21:935) was used for elution.

Purification of Peak X Compound from Urine

Urine was collected for 8 h (400 ml) after an oral administration of 133 mg of wood creosote as above. A 50-ml portion of the urine was applied at 25°C to a column (2 i.d. ×4 cm) of anion-exchange resin (AG 1-X8, 200–400 mesh, formate form; Bio-Rad, Richmond, Calif., USA). The column was washed with 80 ml of water and then eluted with 50 ml of 4 mol/l formic acid. The eluate was lyophilized and then reconstituted in 0.5 ml of water; a portion was next injected eight times into the HPLC column in 20-µl aliquots using mobile phase B. Peak X was collected, pooled, lyophilized, reconstituted in 20 µl of water and loaded again on the HPLC system using mobile phase A. The peak was collected, lyophilized and reconstituted in 0.6 ml of D_2O.

Analysis of Peak X Compound

Peak X in D_2O was subjected to proton-nuclear magnetic resonance spectroscopy (^{1}H-NMR) using a JSX-400 NMR spectrometer (399.65 MHz; Jeol, Tokyo, Japan). The spectral conditions were as follows: spectral width 14,700.0 Hz, acquisition time 3.277 s, pulse width 4.7 µs and delay time 27 µs. The spectrum was measured between 0 and 10 ppm in proton chemical shift at 30°C using a standard of 3-(trimethylsilyl)propionic acid sodium. The spectral conditions of ^{13}C-NMR (100.40 MHz) were as follows: spectral width 16,650.0 Hz, acquisition time 1.311 s, pulse width 4.3 µs and delay time 46 µs. It was measured between 0 and 190 ppm of chemical shift at 30°C.

A 2-µl aliquot of peak X in D_2O was next subjected to liquid chromatography-mass spectrometry using an Inertsil ODS-2 column (1.5 i.d. ×150 mm) mounted on a model LC6A micro-HPLC system (Shimadzu, Kyoto, Japan). The HPLC was run with a linear gradient of acetic acid:water (1:99) to acetonitrile at a flow rate of 40 µl/min at 25°C. The effluent was fed to an Xe-FAB-mass spectrometer (model JMS-SX102A; Jeol) operating in the negative ion mode with an acceleration voltage of 5 kV on a glycerine matrix. Measurements were obtained for mass/charge values of 10–1,500.

Results

The calibration curves for quantifications of phenols on HPLC showed good linearity (fig. 1). The detection limits of phenol and guaiacol were 0.02, and those of *p*-cresol and creosol were 0.04 mg/l. The coefficients of variation were 15, 10, 18 and 8% at 0.25 mg/l, and 4, 2, 3 and 9% at 1.0 mg/l for phenol, guaiacol, *p*-cresol and creosol, respectively. The HPLC retention times were, in the above order, 13.3 ± 0.2, 15.7 ± 0.2, 27.5 ± 0.3 and 32.1 ± 0.5 min.

When 30-min postdose serum was subjected to HPLC, only small peaks of phenol,

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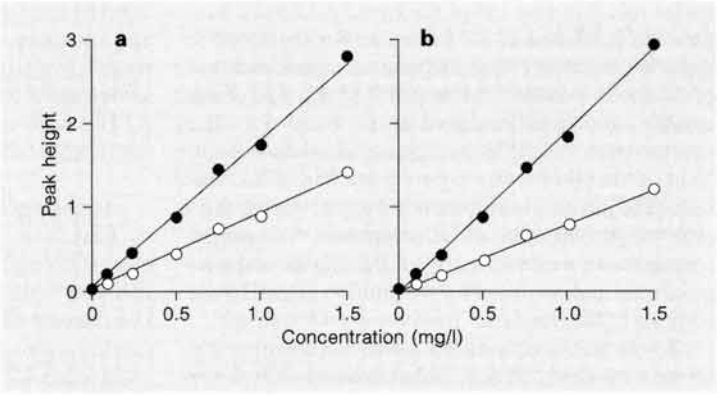

Fig. 1. Calibration curves for quantification of phenols, showing linear relations between phenol (**a**, ●), guaiacol (**b**, ●), *p*-cresol (**a**, ○) and creosol (**b**, ○) versus an internal standard, 2-fluorophenol. Each point is the mean of 4 independent experiments.

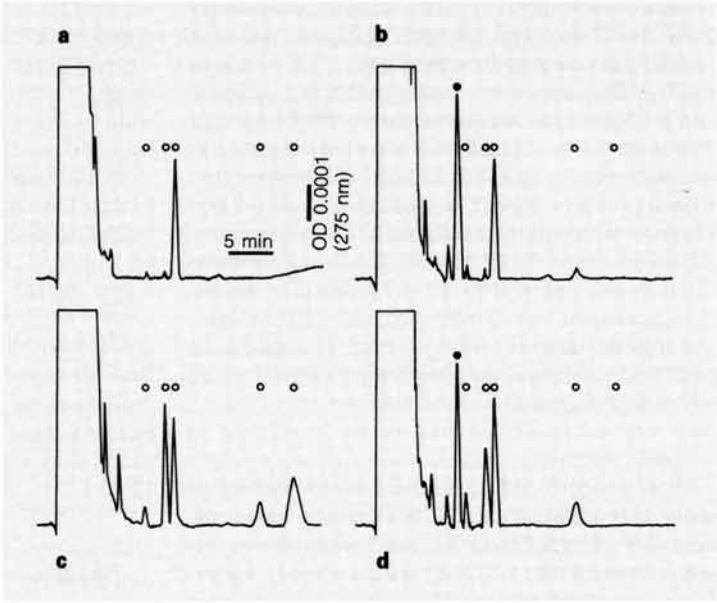

Fig. 2. HPLC of human serum before (**a**) or after (**b, c, d**) oral administration of wood creosote. The ultrafiltrated serum was used for chromatography directly (**a, b**) or after treatment with either β-glucuronidase (**c**) or sulfatase (**d**). Open circles indicate retention times of (from left to right) phenol, guaiacol, 2-fluorophenol, *p*-cresol and creosol; filled circles indicate retention times of peak X.

guaiacol and *p*-cresol were detected (fig. 2b). The treatment of the same serum with β-glucuronidase gave large peaks of four phenols (fig. 2c), indicating that they are glucuronidated. Sulfatase treatment of the serum yielded large peaks of phenol, guaiacol, and *p*-cresol (fig. 2d), thus indicating that there are also sulfate forms of the phenols.

The serum concentrations of these conjugated and unconjugated phenols started to rise 15 min after the oral dose, and they reached the maximum 30 min after dosing (fig. 3). This rapid increase in serum concentrations would suggest that phenols, such as wood creosote in the present capsule, are absorbed mainly from the stomach mucosa. The maximum serum concentrations (C_{max}) of glucuronides were 0.18 ± 0.07, 0.91 ± 0.38, 0.33 ± 0.18 and 0.47 ± 0.23 mg/l, and of sulfates were 0.16 ± 0.06, 0.22 ± 0.09, 0.17 ± 0.07 and <0.04 mg/l for phenol, guaiacol, *p*-cresol and creosol, respectively. The C_{max} for unconjugated phenols

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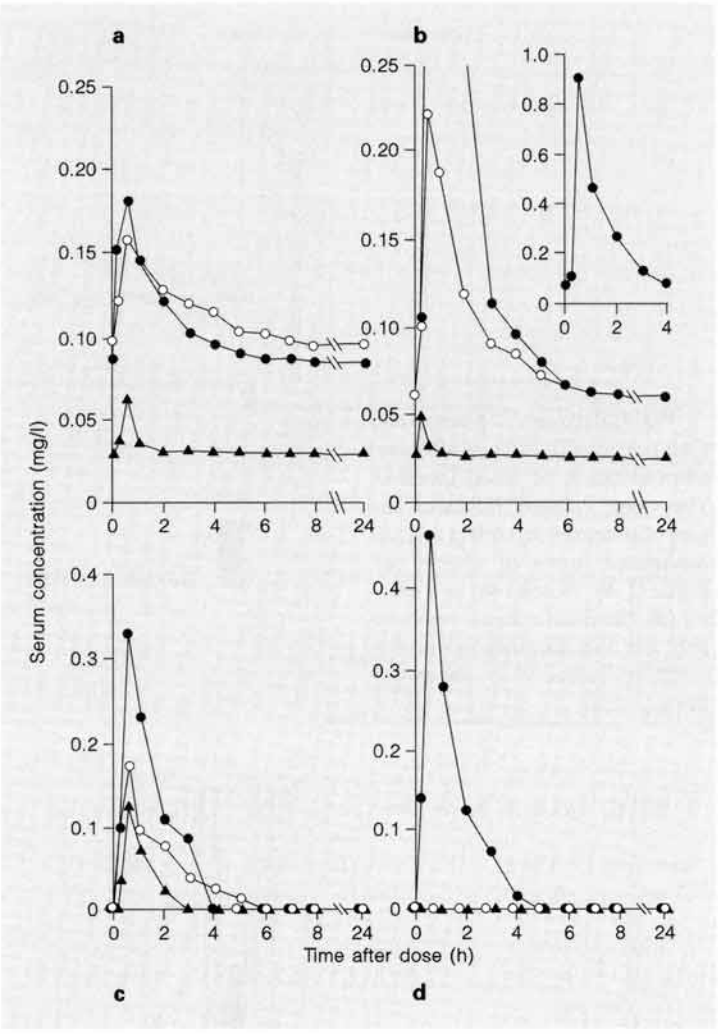

Fig. 3. Time course of serum concentrations of glucuronide (●), sulfate (○) or unconjugated (▲) forms of phenol (**a**), guaiacol (**b**), *p*-cresol (**c**) and creosol (**d**) after an oral administration of 133 mg of wood creosote. Each point is the mean of 8 individuals. **Inset:** peak of guaiacol glucoronide.

were 0.06 ± 0.01, 0.05 ± 0.01, 0.12 ± 0.05 and <0.04 mg/l in the above order. Other pharmacokinetic parameters of the conjugates in the serum are shown in table 1. The urinary recoveries of the sum of the conjugated and unconjugated forms of each phenolic compound were 75 ± 35, 45 ± 36, 103 ± 51 and 74 ± 36%, for phenol, guaiacol, *p*-cresol and creosol, respectively (fig. 4).

In the 30-min postdose serum, but never in the predose serum (fig. 2a), a prominent peak of retention time – 11.8 ± 0.1 min – was seen (fig. 2b, filled circle). This peak disappeared after β-glucuronidase digestion with a concomitant increase in phenol peaks (fig. 2c) but not after sulfatase digestion. This finding suggests that this peak (termed peak X) is a glucuronide of some of the phenols. Because peak X was also present in the postdose urine (data not shown), we purified it from the urine with an anion-exchange resin and then with two-step HPLC, first with mobile phase B (reten-

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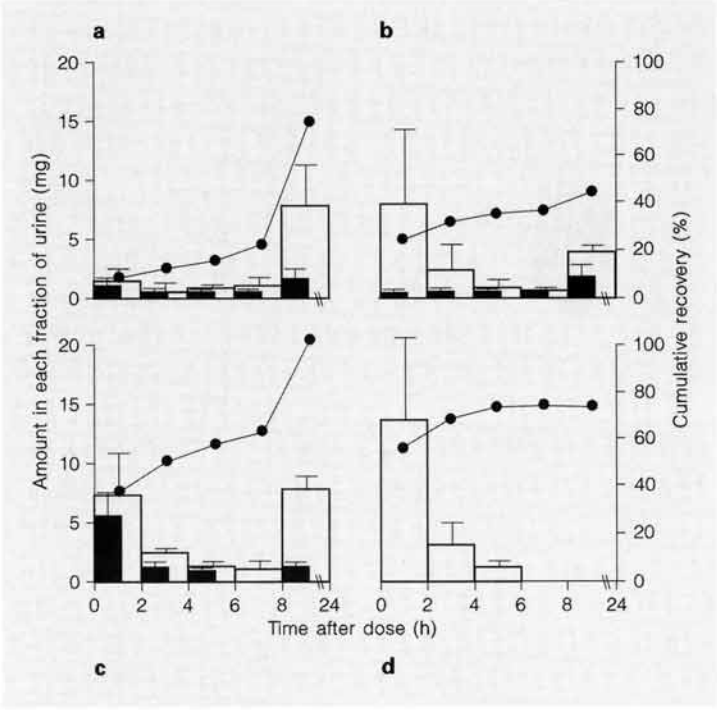

Fig. 4. Recovery of phenols and their metabolites in urine after oral administration of wood creosote. The open column indicates the sum of glucuronide, sulfate and unconjugated forms of phenol (**a**), guaiacol (**b**), *p*-cresol (**c**) and creosol (**d**); the filled column indicates only the unconjugated forms. Cumulative recovery is shown by filled circles.

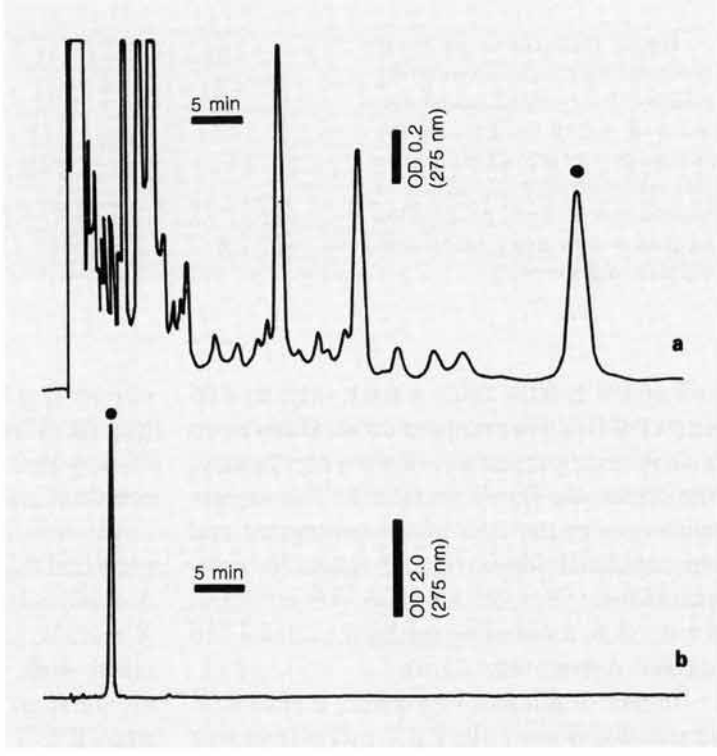

Fig. 5. Purification of peak X compound from urine collected after the oral administration of wood creosote. The peak X after the anion-exchange column was run on HPLC in the mobile phase B (**a**), and peak X (●) was collected. It was next run on the same HPLC in mobile phase A (**b**).

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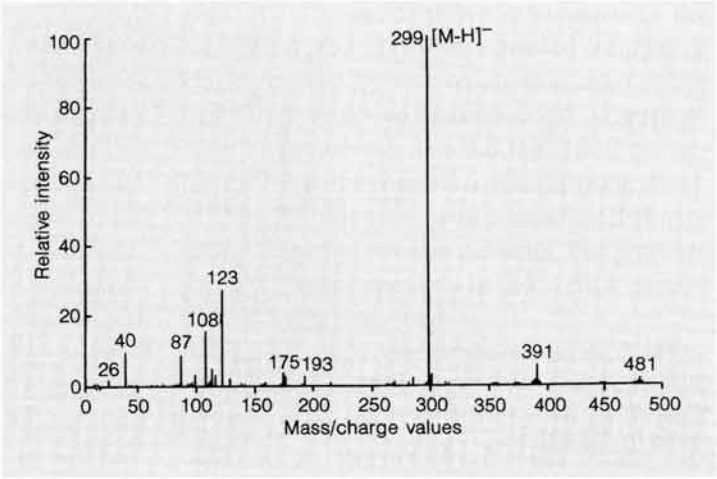

Fig. 6. A mass spectrum of peak X compound in a negative ion mode.

Table 1. Pharmacokinetic parameters of phenol metabolites after a single oral administration of 133 mg wood creosote

Compound	C_{max} mg/l	$T_{½}$ h	AUC_{∞} h·mg/l	Cl_p/F l/h	V_{area}/F liters
Phenol (15 mg)					
Glucuronide	0.18±0.07	2.7±0.6	0.32±0.16	47±24	185±94
Sulfate	0.16±0.06	2.0±0.8	0.33±0.14	45±19	130±55
Guaiacol (32 mg)					
Glucuronide	0.91±0.38	2.1±0.6	0.97±0.22	33±8	100±24
Sulfate	0.22±0.09	2.5±0.6	0.30±0.13	108±46	396±170
p-Cresol (18 mg)					
Glucuronide	0.33±0.18	1.2±0.6	0.56±0.31	33±18	58±32
Sulfate	0.17±0.07	0.8±0.4	0.30±0.12	61±24	74±29
Creosol (24 mg)					
Glucuronide	0.47±0.23	1.0±0.2	0.62±0.31	39±20	56±29

V_{area}/F = Apparent volume of distribution. Each value is the mean ± SEM of 8 individuals. The amount of each phenolic compound, indicated in parentheses, was calculated from the concentration of the respective compounds in wood creosote.

tion time 53.1 ± 0.2 min, fig. 5a) and then with mobile phase A (retention time 6.9 ± 0.2 min, fig. 5b).

The purified peak X was subjected to negative-mode liquid chromatography-mass spectrometry (fig. 6). A molecular ion ($M-H^-$) of mass/charge value 299 was found as a main peak, and this is compatible with guaiacol glucuronide (1-*O*-(2-methoxyphenyl)-β-*D*-glucuronic acid) whose molecular weight is 300. Peak X was next subjected to ^1H- (fig. 7) and ^{13}C- (fig. 8) NMR spectroscopies, the re-

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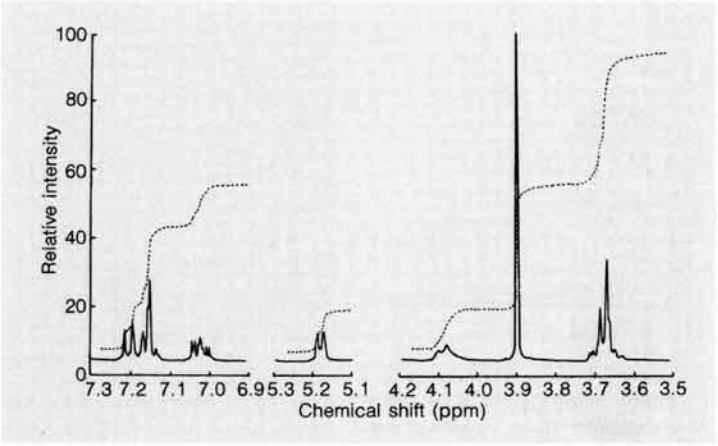

Fig. 7. A proton-NMR spectrum of peak X compound. The integrations of the peak areas are shown by dotted lines.

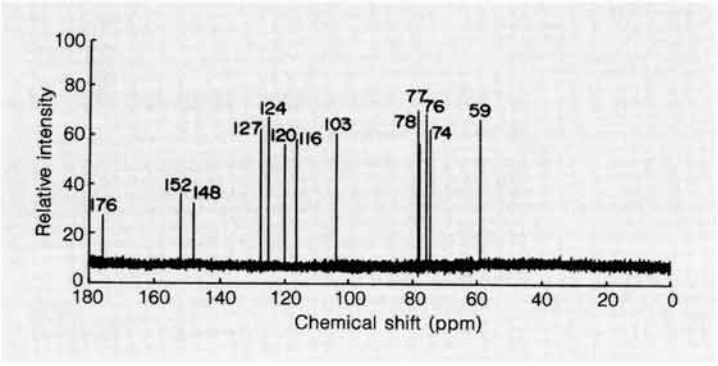

Fig. 8. A ^{13}C-NMR spectrum of peak X compound.

sults also being perfectly compatible with guaiacol glucuronide. Thus we conclude that peak X is guaiacol glucuronide. This conclusion is further supported by the fact that β-glucuronidase treatment of peak X yields guaiacol (data not shown). These results confirm that guaiacol in orally administered wood creosote is glucuronidated.

Discussion

Because we found some noncovalent binding of unconjugated phenols to serum albumin [unpubl. data], we had to add 2-fluorophenol as an internal standard after, not before, separation of serum proteins by ultrafiltration. Judging from this binding to serum albumin, the possibility that there is some amount of the protein-bound unconjugated phenols in the serum that might have escaped our detection cannot be ruled out. This possibility could be clarified by using radiolabeled wood creosote.

Phenol injected into humans is reported to appear in serum and urine as glucuronide, sulfate and in unconjugated form [18]. Inhaled phenol also appears in urine as glucuronide and sulfate [19]. Capel et al. [15] reported that ^{14}C-phenol administered orally to various animals (i.e. human, rhesus monkey, dog, rabbit, rat, guinea pig and chicken) was also excreted

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in urine as sulfate (77% in 24 h, human) and glucuronide (16% in 24 h, human). Glucuronidation and sulfation of intramuscularly administered phenol occur in the rhesus monkey and some other primates [17]. These and our data indicate that phenol administered to humans and to a wide variety of animals is mostly conjugated to glucuronic acid and sulfate, no matter how it is administered. These observations are quite plausible given the facts that phenol is relatively insoluble in neutral water (1 g being dissolved in 15 ml of water [19]) and that glucuronidation or sulfation generally and markedly increases the solubility of the parent compounds [22, 23].

Some amount of toluene (methylbenzene) inhaled by humans is metabolically oxidized to *o*-, *m*- and *p*-cresol, and these cresol isomers are known to be excreted in conjugated forms, possibly glucuronide and sulfate, in urine [16].

Human phenol UDP-glucuronosyltransferase (EC 2.4.1.17) and phenol sulfotransferase (EC 2.8.2.1) can conjugate simple phenols, e.g. 4-nitrophenol or 4-methylphenol, in vitro [22–28]. Based upon these substrate specificities of the enzymes, it is curious that creosol was not conjugated with sulfate (fig. 1). The apparent absence of sulfate conjugation of creosol could be explained if the catalytic rate of UDP-glucuronosyltransferase were much higher than that of sulfotransferase. If this were the case, the sulfation of creosol would compete with glucuronidation, and only a trace amount of sulfate conjugate will be formed.

Wengle and Hellström [20] reported that undosed healthy human serum contains conjugated (possibly sulfate) *p*-cresol (2.3. ± 1.7 mg/l) and phenol (0.2 ± 0.3 mg/l). Their *p*-cresol result differs from ours (fig. 3); we found unconjugated and conjugated (glucuronide and sulfate) *p*-cresol only in the postdose serum at the detection limit of 0.04 mg/l. Despite this controversy, the presence of the 'endogenous' *p*-cresol in undosed humans is yet supported by our result that the control urine from undosed humans does contain it in both conjugated (5.3 ± 3.6 mg/l) and unconjugated (0.6 ± 0.9 mg/l) forms [unpubl. data]. Müting [29] found *m*- and *p*-cresol and phenol in the serum of uremic patients, but whether this is a special case only in the uremic patient is not clearly described.

The presence of endogenous phenol, as unconjugated (0.03 ± 0.01 mg/l), glucuronide (0.08 ± 0.04 mg/l) and sulfate (0.10 ± 0.04 mg/l) forms, in healthy human serum was confirmed by our results (fig. 3a, time 0). The concentration of the sulfate was half that of the reported value, 0.2 ± 0.3 mg/l [20]. We also found guaiacol in undosed human serum, as unconjugated, glucuronide and sulfate forms (fig. 3b, time 0). Endogenous guaiacol has not been reported in the literature. The origin of these endogenous phenolic compounds in human blood has not been elucidated, but some investigators speculate that endogenous phenol might be formed in the gut by bacterial degradation of aromatic amino acids derived from ingested proteins [21, 30]. This view of *p*-cresol is supported by the fact that a decrease in dietary protein content decreases the serum *p*-cresol concentration [20].

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