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Biopharmaceutical Studies on Guaiacol Glyceryl Ether and Related Compounds V

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Abstract □ Filtration using a crosslinked dextran gel was performed to determine the mechanism by which guaiacol glyceryl ether mononicotinate causes an increase in the solubility of cholesterol. The effects of guaiacol glyceryl ether mononicotinate and its related compounds on the incorporation of radioactive acetate into cholesterol also were investigated to obtain information concerning their hypocholesteremic behavior. Blood levels and urinary metabolites of guaiacol glyceryl ether mononicotinate in man were determined. Although the main purpose of the present study was not to investigate pharmacological effects of guaiacol glyceryl ether mononicotinate, it was noted that this compound displayed some analgesic but no antihistamine or anti-inflammatory activity.

Keyphrases □ Guaiacol glyceryl ether mononicotinate—effect on solubility of cholesterol and incorporation of radioactive acetate, blood levels and urinary metabolites in man □ Hypocholesteremic activity—guaiacol glyceryl ether mononicotinate □ Blood levels—guaiacol glyceryl ether mononicotinate, man □ Urinary metabolites—guaiacol glyceryl ether mononicotinate, man □ Cholesterol, solubility and incorporation of radioactive acetate—effect of guaiacol glyceryl ether mononicotinate

Blood levels of guaiacol glyceryl ether mononicotinate in animals, the effects of it and related compounds on bile in animals, and the hypocholesteremic effect were previously reported[1] (1).

The present study was concerned with guaiacol glyceryl ether mononicotinate; a few of the pharmacological effects, together with the hypocholesteremic mechanism of action of guaiacol glyceryl ether mononicotinate, were investigated. Moreover, blood levels and urinary metabolites of guaiacol glyceryl ether mononicotinate in human test subjects were determined as a preliminary for evaluation of clinical activities of guaiacol glyceryl ether mononicotinate.

EXPERIMENTAL

Effect of Guaiacol Glyceryl Ether Mononicotinate on Squirming and Capillary Permeability—The procedure was performed by the method of Whittle (2) and Naito *et al.* (3). Each group consisted of 10 mice (dd strain, average weight 15 g.).

Tail Withdrawal Reflex in Mice—The method for analgesimetry described in the paper of Ben-Bassat *et al.* (4) was used. Each group consisted of 12 male mice (dd strain, average weight 15 g.).

Anti-Inflammatory Activity—The method for anti-inflammatory testing (involving the use of carrageenin) reported previously (3) was used in this part of the study. Each group consisted of five male rats (Wistar strain, average weight 180 g.).

Antihistamine Activity—Guinea pigs (Hartley strain, average weight 300 g.) were used in the experiment carried out by the procedure of Labelle and Tislow (5). Each group consisted of five male guinea pigs.

Effect of Guaiacol Glyceryl Ether Mononicotinate on Duration of Sleep Induced by Hexobarbital and on Blood Level of Hexobarbital—Each test group consisted of 10 male rats (Wistar strain, average weight 150 g.). Each animal received 100 mg./kg. of hexobarbital intraperitoneally, and guaiacol glyceryl ether mononicotinate was given intraperitoneally 30 min. prior to the hexobarbital injection. The experimental design was the same as that reported by Brodie *et al.* (6).

Column Filtration—The gel[2] washed with distilled water was filled up to a 20-cm. height in a glass tube 15 mm. in diameter. One milliliter of human serum (cholesterol, 530 mg.%) from high cholesterol patients was used as a serum sample. After the addition of a serum sample to the column, 150 ml. of distilled water containing 500 mcg./ml. of either guaiacol glyceryl ether, β-(4-hydroxy-2-methoxyphenoxy)lactic acid, or β-(2-methoxyphenoxy)lactic acid was passed through the column as an eluting solvent and collected in 3-ml. fractions. It was previously ascertained that this volume of the eluant was sufficient to elute the cholesterol. Cholesterol in the eluant was determined by the method of Zurkowski (7).

Incorporation of Acetate into Cholesterol by Rat Liver Slices—Guaiacol glyceryl ether mononicotinate or *meso*-inositol hexanicotinate (inositol niacinate), which is insoluble in water, was passed through a 200-mesh screen to make an homogeneous suspension with water. The other compounds tested were all water soluble.

Male rats (SD strain, average weight 250 g., 7 weeks old) were used for this experiment. After the rats were killed by decapitation, their livers were quickly removed and sliced with a microtome and approximately 500 mg. of slices was placed in 5 ml. of Krebs–Ringer buffer (pH 7.4, a mixture of 41.8 ml. of 0.9% NaCl, 63.8 ml. of 1.15% KCl, 3.0 ml. of 1.22% $CaCl_2$, 1.0 ml. of 2.11% KH_2PO_4, 1.0 ml. of 3.82% $MgSO_4 \cdot 7H_2O$, and 21.0 ml. of 1.30% $NaHCO_3$). The buffer containing sodium acetate-1-^{14}C (2.3 μc./5 μmoles/flask)

[1] Guaiacol glyceryl ether is officially known as glyceryl guaiacolate.

[2] Sephadex G-25 Medium, Pharmacia, Uppsala, Sweden.

Table I—Effect of Test Compounds on Incorporation of Acetate-1-^{14}C into Cholesterol by Rat Liver Slices

Compound	Concentration, mcg./5 ml. Krebs–Ringer Buffer	d.p.m.[a]/mg. Tissue, *MV* ± *SE*[b]	d.p.m./mg. Cholesterol, *MV* ± *SE*
Control	—	6.40 ± 0.64	2964 ± 437
Nicotinic acid	1550	6.46 ± 0.65	3005 ± 486
Guaiacol glyceryl ether	2500	5.61 ± 0.16	2347 ± 49
Control		5.03 ± 0.68	1644 ± 141
Mixture of: guaiacol glyceryl ether and nicotinic acid	2500 + 1550	3.06 ± 0.42	1247 ± 138
Control	—	11.34 ± 0.75	3565 ± 103
(2-Methoxyphenoxy)-acetic acid	2500	4.53 ± 0.98	1396 ± 281
β-(2-Methoxyphenoxy)-lactic acid	2500	2.21 ± 0.22	698 ± 32
β-(4-Hydroxy-2-methoxy)lactic acid	2500	2.37 ± 0.03	766 ± 44
Control	—	6.62 ± 0.33	1657 ± 87
Guaiacol glyceryl ether mononicotinate	2500	4.24 ± 0.14	1090 ± 25
meso-Inositol hexanicotinate	2500	3.00 ± 0.30	759 ± 84

[a] Disintegrations per minute. [b] Mean value with standard error was obtained from five experiments.

and a test compound having the concentration shown in Table I was oxygenated for 30 min. prior to use. This mixture was incubated under oxygen, with shaking, at 37 ±1° for 2 hr. A control flask was set up at the same time, identical in all respects to the test sample except that no compounds other than those of the buffer were added.

Excess moisture was removed from the liver slices with filter paper, and then these slices were homogenized with 20 ml. of a mixed solvent of chloroform and methanol (2:1 v/v) and centrifuged. The residue was reextracted with 10.5 ml. of the mixed solvent already mentioned. The combined extract was evaporated to dryness and redissolved in 15 ml. of petroleum ether. The petroleum ether solution was washed with 10 ml. of water and evaporated to dryness, and the residue was dissolved in 3 ml. of ethanol. One milliliter of this ethanol solution was mixed with 1 ml. of 0.5 *N* KOH, and the mixture was hydrolyzed at 50° for 30 min.

This mixture was neutralized with 30% acetic acid (phenolphthalein being used as an indicator) and concentrated to about 0.1 ml. over a steam bath. The concentrate was mixed with 1 ml. of 1% digitonin solution (a mixed solvent of ethanol and water, 3:1, being used), and the mixture was allowed to stand overnight at room temperature. After centrifugation, the supernate was removed and the precipitate was washed successively with 2 ml. each of acetone and ether and redissolved in 1 ml. of acetic acid. This acetic acid solution was then used for the determination of radioactivity and cholesterol using the following procedures:

1. A mixture of 0.5 ml. of the acetic acid solution, 3 ml. of methanol, and 10 ml. of toluene scintillator (5 g. of 2,5-diphenyloxazole and 0.3 g. of dimethyl 1,4-bis-2-(4-methyl-5-phenyloxazolyl)benzene to make 1000 ml. with toluene) was used for determination of radioactivity, using a liquid scintillation counter[3]. Corrections for quenching were made by the channel ratio method.

2. Cholesterol in 0.2 ml. of the acetic acid solution was determined by the method of Zak (8).

The weight of the slices used was calculated by comparison with the cholesterol content in accurately weighed slices prepared separately (9).

Detection of Metabolites in Incubation Mixtures of Rat Liver Slices with Test Compounds—Guaiacol glyceryl ether, nicotinic acid, or a mixture of guaiacol glyceryl ether and nicotinic acid was used as a test sample. An incubation mixture of rat liver slices with a test sample was prepared under the same experimental conditions as described in the experiment of *Incorporation of Acetate into Cholesterol by Rat Liver Slices*. After centrifugation of an incubation mixture, 1 ml. of the supernate was mixed with 2 ml. of ethanol and this mixture was stirred thoroughly. After standing for 15 min. in an ice bath, the material was centrifuged and the supernate was evaporated to dryness *in vacuo* below 50°. The residue obtained was mixed with 50 μl. of ethanol, and the mixture was subjected to TLC (12). In TLC used for this experiment, a mixture of benzene, methanol, and chloroform (4:3:4) was used as a solvent, and Dragendorff's reagent was used as a color developer.

[3] Packard Tri-Carb, model 3380.

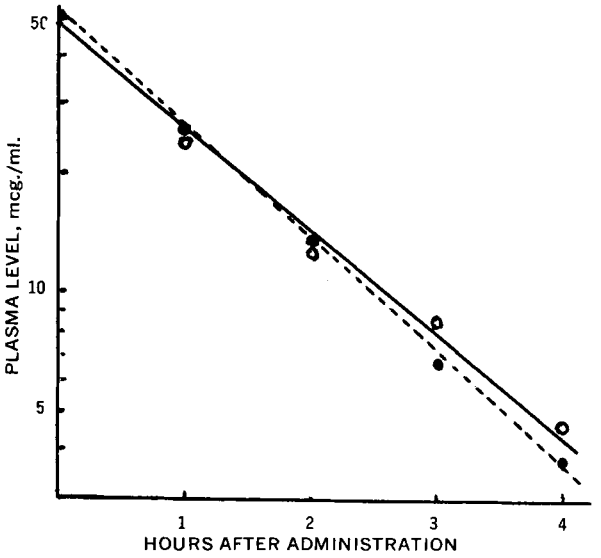

Figure 1—*Mean plasma level of hexobarbital after the intraperitoneal administration of 100 mg./kg. of hexobarbital to rats. Key: ●, hexobarbital injection; and ○, guaiacol glyceryl ether mononicotinate (100 mg./kg.) given prior to hexobarbital injection.*

Blood Level of Guaiacol Glyceryl Ether Mononicotinate in Human Subjects—To each male human subject fasted overnight, 400 mg. of guaiacol glyceryl ether mononicotinate, screened through a 100-mesh sieve, was administered orally in capsule form. Blank urine and blood samples were collected prior to the oral administration of the test sample. Venous blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 7.0 hr. after the oral administration; about 100 ml. of water was given orally every sampling time. Unchanged guaiacol glyceryl ether mononicotinate and free nicotinic acid as the hydrolysis product of guaiacol glyceryl ether mononicotinate in human blood were assayed by a method previously described (10) using barbital and ammonia buffers, respectively.

Detection of Metabolites of Guaiacol Glyceryl Ether Mononicotinate in Human Urine—In the 7-hr. period following the administration of the 400-mg. dose of guaiacol glyceryl ether mononicotinate, approximately 1340 ml. of urine was collected. The urine samples were freeze dried and a 50-g. residue was obtained. Appropriate controls were obtained by freeze drying the blank urine samples obtained prior to administration of the test dose.

A mixture of 200 mg. of the freeze-dried residue and 1 ml. of 5 *N* HCl was incubated at 37 ± 2° for 1 hr. This mixture was then extracted three times with 10 ml. of ether, and the combined ethereal solution was evaporated *in vacuo*. An ethanol solution of this residue was analyzed qualitatively using TLC as shown in Table II.

RESULTS AND DISCUSSION

Concurrent changes in the peritoneal capillary permeability during squirming were measured according to the method of Whittle (2). The ED_{50} of guaiacol glyceryl ether mononicotinate for inhibition of squirming is 178 (98.9–320.4) mg./kg. Since reduction of the permeability response was less than 50% over the entire range of doses that inhibited squirming, there are no corresponding ED_{50} values for the permeability effect. Therefore, it was shown that guaiacol glyceryl ether mononicotinate inhibits squirming at a dose level which does not reduce peritoneal capillary permeability.

Computation of the ED_{50} and its confidence limits for the tail withdrawal reflex in mice (4) was made by probit analysis. The

Table II—TLC[a]

	TLC System	Color Developer	Material	R_f	Color of Spot[b]
A	Benzene–methanol–xylene–acetic acid (45:5:5:2)	$K_2Cr_2O_7$[c]	β-(4-Hydroxy-2-methoxyphenoxy)-lactic acid	0.06	Y
			(4-Hydroxy-2-methoxyphenoxy)-acetic acid	0.13	Y
			β-(2-Methoxyphenoxy)lactic acid	0.21	G
			Guaiacol glyceryl ether	0.37	G
			Urine	0.01	B
				0.06	Y
				0.21	G
				0.34	L-B
				0.37	G
				0.47	P
				0.52	G
B	Toluene–methanol–acetic acid (45:5:2)	$K_2Cr_2O_7$	β-(4-Hydroxy-2-methoxyphenoxy)-lactic acid	0.10	Y-Gn
			(4-Hydroxy-2-methoxyphenoxy)-acetic acid	0.14	Y-Gn
			β-(2-Methoxyphenoxy)lactic acid	0.22	G-V
			Guaiacol glyceryl ether	0.33	V
			Urine	0.10	Y-Gn
				0.22	G-V
				0.33	V
				0.49	L-B
C	Benzene–methanol–xylene–acetic acid (45:5:5:2)	DABA[d]	Guaiacol glyceryl ether	0.27	R-V
			Guaiacol glyceryl ether mononicotinate	0.36	R-V
			β-(2-Methoxyphenoxy)lactic acid	0.10	R-V
			Urine	0.02	B
				0.05	B
				0.10	R-V
				0.27	R-V
				0.30	B
				0.43	B
				0.51	R-B

[a] Adsorbent: Diatomite (Kieselgel G), 0.25 mm. in thickness; distance developed 15 cm. No spots were found in the control urine in TLC Systems A, B, and C. [b] Y, yellow; G, gray; B, brown; L-B, light brown; P, pink; Y-Gn, yellowish-green; G-V, gray-violet; V, violet; R-V, reddish-violet; R-B, reddish-brown. [c] $K_2Cr_2O_7$–3% $K_2Cr_2O_7$ in concentrated sulfuric acid. [d] DABA–1% *p*-dimethylaminobenzaldehyde in equivoluminal mixture of ethanol and 50% sulfuric acid.

method involved dividing the animals reacting after 30 min. into two groups: "refractory" (pain reaction time of 1.7 sec. or more) and "nonrefractory" to aminopyrine and guaiacol glyceryl ether mononicotinate. The ED_{50} and 95% confidence limits were 37 (22–59) and 107 (76–150) mg./kg. for aminopyrine and guaiacol glyceryl ether mononicotinate, respectively.

No anti-inflammatory effect of guaiacol glyceryl ether mononicotinate on edema induced by carrageenin was observed at 100-, 200-, and 300-mg./kg. doses, and no antihistaminic activity of guaiacol glyceryl ether mononicotinate was observed at 200-, 300-, 350-, and 400-mg./kg. doses.

The hexobarbital concentration obtained in plasma with and without guaiacol glyceryl ether mononicotinate is shown in Fig. 1. The concentration of hexobarbital in brain homogenate was not affected by guaiacol glyceryl ether mononicotinate administration. The plasma concentration of hexobarbital, at the time of the return of the righting reflex, was estimated graphically from the plasma level curve. Duration of action[4], plasma level on awaking[5], and

[4] Time interval between loss and return of righting reflex.
[5] Return of righting reflex.

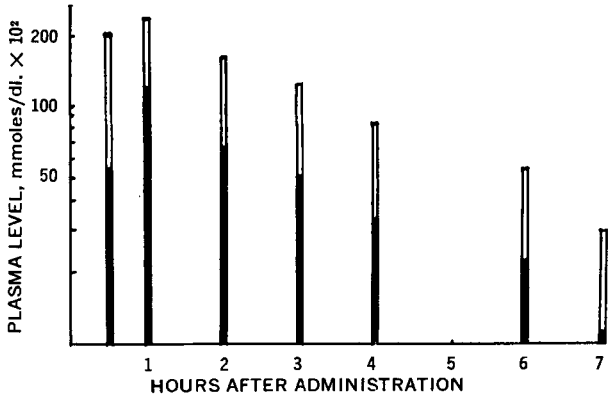

Figure 2—*Mean blood level of unchanged guaiacol glyceryl ether mononicotinate and nicotinic acid liberated from guaiacol glyceryl ether mononicotinate by hydrolysis in human blood after oral administration of 400 mg. of guaiacol glyceryl ether mononicotinate. Key: ■, unchanged guaiacol glyceryl ether mononicotinate; and □, nicotinic acid liberated by hydrolysis. Three human subjects were tested. They were, respectively, 35, 44, and 53 years old; 53, 68, and 74 kg. in body weight; and 164, 160, and 164 cm. in height.*

biological half-life of hexobarbital were found to be 28.9 ± 7.4 min., 38 mcg./ml., and 66 min., respectively, after intraperitoneal administration of hexobarbital, and 28.7 ± 4.4 min., 36 mcg./ml., and 69 min., respectively, after the administration of hexobarbital and guaiacol glyceryl ether mononicotinate. Thus, no effect of guaiacol glyceryl ether mononicotinate on hexobarbital concentration in plasma or on duration of sleep induced by hexobarbital was observed.

To determine how guaiacol glyceryl ether, in an incubation mixture of guaiacol glyceryl ether and human high cholesterol serum, increases solubility of cholesterol through the dextran gel filtration (11), column filtration over the gel was carried out with distilled water containing guaiacol glyceryl ether or its metabolites such as β-(4-hydroxy-2-methoxyphenoxy)lactic acid and β-(2-methoxyphenoxy)lactic acid. In this determination, these compounds did not increase the water solubility of cholesterol, within the experimental error. This finding indicates that guaiacol glyceryl ether is not responsible for the increase in the water solubility of cholesterol in an incubated mixture of guaiacol glycerol ether and high cholesterol human serum (11). On the other hand, it was ascertained that no metabolites of guaiacol glyceryl ether were present in an incubated mixture of guaiacol glyceryl ether and human serum containing high cholesterol levels (12).

Perry (13) reported that the incorporation of radioactive acetate into cholesterol was diminished in liver slices treated with nicotinic acid. The failure of this work to support this finding may be attributable to the employment of a concentration of nicotinic acid lower than that used in the Perry study. The concentrations of guaiacol glyceryl ether and nicotinic acid used were selected considering the molar ratio of both compounds in the guaiacol glyceryl ether mononicotinate molecule.

Among the compounds tested, β-(2-methoxyphenoxy)lactic acid and β-(4-hydroxy-2-methoxyphenoxy)lactic acid markedly depressed the incorporation of radioactive acetate into cholesterol. Analogous results were also observed with (4-hydroxy-2-methoxyphenoxy)acetic acid, guaiacol glyceryl ether mononicotinate, and *meso*-inositol hexanicotinate. The results obtained with these compounds seem to be somewhat inexact inasmuch as a suspension rather than a solution of guaiacol glyceryl ether mononicotinate in Krebs–Ringer buffer was used.

As shown in Table I, the mixture of nicotinic acid and guaiacol glyceryl ether proved inhibitory to the incorporation of radioactive acetate into cholesterol. Conversely, no such inhibitory influence was exerted when each compound was employed separately. In an attempt to determine the reason for this difference, an investigation was made of the metabolites resulting from the 2-hr. incubation of liver slices with nicotinic acid alone and with nicotinic acid in combination with guaiacol glyceryl ether. No metabolites of nicotinic acid other than those in the control nicotinic acid mixture were

found in the incubated mixture with guaiacol glyceryl ether mononicotinate.

On the other hand, β-(2-methoxyphenoxy)lactic acid was found in an incubated mixture of guaiacol glyceryl ether and nicotinic acid with liver slices, although only unchanged guaiacol glyceryl ether was found in an incubated mixture of guaiacol glyceryl ether alone with liver slices (12). This fact shows that nicotinic acid accelerated transformation of guaiacol glyceryl ether to β-(2-methoxyphenoxy)lactic acid. It would follow that the inhibitory influence of the incubated mixture with guaiacol glyceryl ether and nicotinic acid on the incorporation of radioactive acetate in cholesterol (occurring only with this mixture) is attributable to the action of the β-(2-methoxyphenoxy)lactic acid formed (exclusively) in this mixture.

When mean human blood levels of unchanged guaiacol glyceryl ether mononicotinate and nicotinic acid (liberated from guaiacol glyceryl ether mononicotinate by hydrolysis after oral administration of a guaiacol glyceryl ether mononicotinate at 400-mg. doses) were plotted on a semilogarithmic paper, an almost linear relationship appeared. About 60% of the guaiacol glyceryl ether mononicotinate absorbed was hydrolyzed in human blood (Fig. 2), although about 40% of guaiacol glyceryl ether mononicotinate was hydrolyzed in rabbit blood (10).

TLC systems used for detection of the metabolites of guaiacol glyceryl ether mononicotinate are shown in Table II. β-(4-Hydroxy-2-methoxyphenoxy)lactic acid, β-(2-methoxyphenoxy)lactic acid, and guaiacol glyceryl ether were ascertained qualitatively by Systems A, B, and C. Guaiacol glyceryl ether mononicotinate could not be detected by TLC in human subjects or in rabbits (12). In rabbit urine, guaiacol glyceryl ether, β-(2-methoxyphenoxy)lactic acid, and (2-methoxyphenoxy)acetic acid were detected by TLC (12). (2-Methoxyphenoxy)acetic acid could not be found in human urine, and β-(4-hydroxy-2-methoxyphenoxy)lactic acid could not be detected in rabbit urine after oral administration of guaiacol glyceryl ether mononicotinate. However, the latter compound was detected in rabbit urine after oral administration of guaiacol glyceryl ether instead of guaiacol glyceryl ether mononicotinate (12).

SUMMARY

1. Guaiacol glyceryl ether mononicotinate seems to have moderate analgesic activity according to the results of squirming and tail withdrawal reflex tests.

2. Guaiacol glyceryl ether mononicotinate has no anti-inflammatory and antihistamine activities.

3. No effect of guaiacol glyceryl ether mononicotinate on hexobarbital concentration in plasma and on duration of sleep induced by hexobarbital was observed.

4. The increased (aqueous) solubility of cholesterol in an incubated mixture of guaiacol glyceryl ether and human high cholesterol serum appears to be attributable to the incubation rather than the presence of guaiacol glyceryl ether in the mixture.

5. Guaiacol glyceryl ether mononicotinate or β-(2-methoxyphenoxy)lactic acid inhibited the incorporation of radioactive acetate into cholesterol, although guaiacol glyceryl ether did not. β-(2-Methoxyphenoxy)lactic acid, one of the metabolites of guaiacol glyceryl ether *in vivo*, was formed in an incubated mixture with guaiacol glyceryl ether in the presence of nicotinic acid but not with guaiacol glyceryl ether alone. This finding suggests that the activity of guaiacol glyceryl ether mononicotinate to inhibit incorporation of radioactive acetate in the incubated mixture may be the result of its provision of nicotinic acid through hydrolysis and the consequent transformation of guaiacol glyceryl ether to the active metabolite, β-(2-methoxyphenoxy)lactic acid.

6. Guaiacol glyceryl ether mononicotinate was absorbed from the human intestine; about 60% of the guaiacol glyceryl ether mononicotinate absorbed was hydrolyzed in human blood. β-(4-Hydroxy-2-methoxyphenoxy)lactic acid, β-(2-methoxyphenoxy)-lactic acid, and guaiacol glyceryl ether were found in human urine after oral administration of guaiacol glyceryl ether mononicotinate.

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