Chem. Pharm. Bull. 26(4)1257—1260(1978)

UDC 615.214.24.015.2.033.076.9 : 615.453.014.2

Effects of Vegetable Oils on the Biological Disposition of Ethchlorvynol. I. The Effects on the Distribution of Ethchlorvynol in Rat[1]

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(Received October 6, 1977)

Distribution of ethchlorvynol (EC) to the blood, liver, jejunum, lung, kidney, adipose tissue and brain of rat were studied after oral administration of 150 mg/kg of EC in two dosage forms. The peaks of blood and tissue levels appeared more rapidly after dosing EC suspended in 5% polyethylene glycol 400 aqueous solution (PEG-sol.) than with vegetable oils, while the peak values were almost similar. The most remarkable effect of the oils used was shown in the brain levels of EC. The peak values of brain EC levels were 3.0, 5.9, and 5.9 μg/g wet tissue after dosing with corn oil, peanut oil and soybean oil, respectively, while 19.5 μg/g wet tissue with PEG-sol. The ED_{50} and LD_{50} of EC in mice were calculated as 138 mg and 357 mg/kg, respectively, when dosed as PEG-sol., while as 185 mg and 424 mg/kg when dosed together with corn oil. Thus, the vegetable oils were shown to inhibit the transport of EC into rat brain.

Keywords——ethchlorvynol; distribution; brain level; vegetable oils; corn oil; peanut oil; soybean oil

Ethchlorvynol(EC) is a nonbarbiturate hypnotic with ethynyl-carbinol in its chemical structure, and has a low solubility in water.

Pharmacological studies on the drug have studied by P'an and co-workers.[3] The tissue distribution of the drug, however, was not fully known yet because of lacking the suitable assay method for EC in biological materials.

An available method for determining EC in biological materials has reported by the authors,[4] and the distribution of EC to the blood and tissues of rats after oral administration of the drug was studied using the method described therein. In the studies, the vegetable oils used as vehicles of EC were shown to affect on the distribution of EC into the rat brain.

This paper concerns with the effect of the vegetable oils on the distribution of EC to the blood and tissues of rats after receiving the drug orally.

Experimental

Materials and Administration of EC——Female rats of Wistar strain weighing 220—250 g were used for the distribution studies. Female mice of ddY strain weighing 18—22 g were employed for the determination of LD_{50} and ED_{50} of EC. All animals were fasted for 20—24 hr prior to receiving EC. As a standard dosage form, EC was suspended in 5% polyethylene glycol 400 aqueous solution (PEG-sol.). Otherwise, EC was dissolved in corn oil, peanut oil or soybean oil (J.P. IX). All solutions were prepared to contain 30 mg/ml of EC. EC (150 mg/kg) was administered orally by intubation or intraduodenally after ligating pylorus to rats.

Determination of EC in Blood and Tissues——At the definite times after dosing EC, rats were sacrificed by bleeding from carotid, and were immediately dissected to remove brain, lung, liver, jejunum, kidney and adipose tissue. The blood samples were hemolyzed with 10 volumes of water to assay for EC. The tissues

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3) S.Y. P'an, M.J. Kodet, J.F. Gardoki, W.M. MacLamore, and A. Bavly, *J. Pharmacol. Exp. Ther.*, **114**, 326 (1955).
4) Y. Nitta, T. Murata, and K. Ito, *Yakuzaigaku*, **36**, 200 (1976).

were homogenized with 10 volumes of water, and the homogenates were used for determination of EC. All the estimations of EC were carried out according to the GLC method as reported by the authors.[4]

Determination of ED_{50} and LD_{50}——Groups of six mice of female were used for the determination of ED_{50} and LD_{50}. Hypnotic activity was determined by the loss of righting reflex within 3 hr after oral dosing. Both LD_{50} and ED_{50} were calculated according to the method of Litchfield and Wilcoxon.[5]

Results

Blood and Tissue Distribution at Oral Administration

Blood and tissue levels of EC at the various times after oral dosing of 150 mg/kg of EC with PEG-sol., corn oil, peanut oil, and soybean oil are shown in Tables I—IV, respectively. The peaks of blood and tissue levels appeared more rapidly after dosing EC with PEG-sol. (*ca.* 0.5 hr) than with vegetable oils (1—3 hr), while the peak values were almost similar. The most remarkable effect of the vehicles used was shown in the brain levels of EC. The peak values of brain EC levels were 3.0, 5.9 and 5.9 μg/g wet tissue after dosing with corn oil, peanut oil and soybean oil, respectively, and 19.5 μg/g wet tissue with PEG-sol. Thus, the vegetable oils were seemed to inhibit the transport of EC into rat brain.

Table I. Tissue Levels of Unchanged EC in Rats after Oral Administration of 150 mg/kg of EC suspended in 5% Polyethylene Glycol 400 Aqueous Solution

Tissue	EC, μg/ml or μg/g wet tissue Time after administration, hr				
	0.5	1	3	6	24
Blood	24.2± 3.8[a]	26.2±0.7	10.2±2.9	8.8±0.8	1.8±0.3
Liver	55.3±13.3	49.0±7.8	8.2±2.5	7.3±1.1	1.3±0.3
Jejunum	82.2±11.6	30.4±6.2	11.3±0.6	5.3±0.6	1.7±0.7
Lung	32.7± 7.2	9.3±0.4	3.5±0.6	4.6±0.9	1.2±0.2
Kidney	28.2± 8.7	17.5±5.2	5.7±1.2	7.6±1.9	2.1±0.2
Adipose	633±46	211±40	170±56	152±24	47±11
Brain	19.5± 3.8	8.3±2.3	8.2±2.3	4.8±0.7	0.5±0.2

a) Values reported are mean ±SEM for 3 rats.

Table II. Tissue Levels of Unchanged EC in Rats after Oral Administration of 150 mg/kg of EC dissolved in Corn Oil

Tissue	EC, μg/ml or μg/g wet tissue Time after administration, hr				
	0.5	1	3	6	24
Blood	3.0±0.6[a]	18.8± 5.5	21.9±2.7	5.5±1.2	0.8±0.1
Liver	6.3±2.1	56.0± 3.2	65.9±6.2	7.4±2.3	1.6±0.4
Jejunum	12.8±5.8	86.4±12.1	74.6±5.0	7.4±1.2	1.3±0.3
Lung	2.4±1.1	8.8± 4.9	4.3±0.3	2.3±0.2	1.6±0.3
Kidney	4.7±2.1	14.8± 6.3	12.6±3.3	5.4±0.6	2.2±1.3
Adipose	56±40	159±29	211±39	115±28	15±7
Brain	3.0±1.1	1.4±0.4	1.2±0.4	2.4±1.6	0.1±0.0

a) Values reported are mean ±SEM for 3 rats.

Distribution at Intraduodenal Administration

EC was dissolved in corn oil, and administered intraduodenally to rats. As shown in Table V, the peak levels of EC in the blood and tissues other than brain appeared more rapidly than dosing orally. Those results suggested that the oils used as the vehicles affected on the gastric emptying rate of EC.

5) J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Table III. Tissue Levels of Unchanged EC in Rats after Oral Administration of 150 mg/kg of EC dissolved in Peanut Oil

Tissue	EC, μg/ml or μg/g wet tissue Time after administration, hr			
	0.5	1	3	6
Blood	13.3±3.4[a)]	17.9± 3.0	21.2± 2.9	6.1±1.3
Liver	31.5±2.8	59.1±24.9	55.1± 9.6	7.8±1.1
Jejunum	28.9±7.7	40.2±18.3	42.8±13.2	4.4±1.3
Lung	7.4±1.4	15.6± 6.7	10.9± 2.0	3.6±1.4
Kidney	16.8±3.3	22.4± 5.5	17.0± 0.5	5.5±1.2
Adipose	106±17	163±52	166±30	112±25
Brain	4.1±0.6	5.9± 0.8	5.9± 1.0	1.2±0.1

a) Values reported are mean±SEM for 3 rats.

Table IV. Tissue Levels of Unchanged EC in Rats after Oral Administration of 150 mg/kg of EC dissolved in Soybean Oil

Tissue	EC, μg/ml or μg/g wet tissue Time after administration, hr			
	0.5	1	3	6
Blood	9.7±2.2[a)]	16.6± 4.3	19.5± 2.1	4.3±2.1
Liver	26.1±3.7	52.3± 7.7	61.9±11.3	6.4±2.3
Jejunum	22.8±8.3	69.3±29.3	42.8± 6.5	7.8±1.8
Lung	13.9±3.1	13.0± 1.6	15.0± 1.4	4.1±1.9
Kidney	17.4±3.0	17.5± 3.6	25.1± 5.0	3.6±1.3
Adipose	141±40	199±47	153±13	92±16
Brain	5.9±1.0	4.2± 1.7	4.8± 0.9	1.6±0.5

a) Values reported are mean±SEM for 3 rats.

Table V. Tissue Levels of Unchanged EC in Rats after Intraduodenal Administration of 150 mg/kg of EC dissolved in Corn Oil

Tissue	EC, μg/ml or μg/g wet tissue Time after administration, hr		
	0.5	1	3
Blood	15.0± 4.0[a)]	12.7±2.7	12.2±2.4
Liver	69.6±11.3	34.8±5.8	22.0±7.2
Jejunum	104.6±21.3	81.4±7.0	8.8±2.4
Lung	14.7± 3.3	13.1±3.2	7.2±1.5
Kidney	10.0± 2.9	15.7±2.1	7.0±1.3
Adipose	170±37	95±14	103±25
Brain	6.3± 1.6	2.9±0.8	2.8±0.9

a) Values reported are mean ±SEM for 3 rats.

Table VI. ED_{50} and LD_{50} of EC in Mice

	In PEG-sol.	In corn oil	p
ED_{50}	138 mg/kg (128—149) $s^{a)}=1.14$	185 mg/kg (168—203) $s=1.15$	<0.05
LD_{50}	357 mg/kg (326—391) $s=1.17$	424 mg/kg (389—461) $s=1.12$	<0.05

a) Slope function.
EC was orally administered in 5% polyethylene glycol 400 aqueous solution (PEG-sol.), and in corn oil.
Groups of 6 mice were used for each of a series of 5 dosage levels between 0 and 100% effect.

ED_{50} and LD_{50}

Since the main target organ of EC is thought to be brain,[3] the effect of the oils on ED_{50} and LD_{50} were estimated in mice. The ED_{50} and LD_{50} of EC in mice were calculated as 138 mg and 357 mg/kg, respectively, when dosed as PEG-sol., while as 185 mg and 424 mg/kg when dosed together with corn oil (Table VI).

Discussion

Such oils as corn, peanut and soybean oils were sometimes used as a solvent and vehicles for injections. These agents are known to decrease the rate of absorption and, hence, prolong the duration of action of the drug when injected intramuscullary.[6]

A few report has been concerned with the effect of the fatty oils of vegetable origin on the disposition of drug when administered orally. Kelleher *et al.*[7] reported that the peanut oil used as vehicle had an inhibitory effect on the distribution of α-tocopherol to liver in rats. In other study, the investigators found that the activities of testosteron, androsterone and predonisolone and their esters were greater when these drugs were orally administered with sesame oil solution than with aqueous suspension.[8]

In the present studies, such vegetable oils as corn, peanut and soybean oils were shown to have an inhibitory effect on the distribution to brain in rats, resulting in significantly lowered the hypnotic activity and toxicity.

And the results suggested that such substance as chylomicron originated from the oils ingested might prevent the transport of EC into the rat brain.

The studies on the mechanism of the inhibitory effects of oils on the transport of EC into brain is now progress in our laboratory.

Acknowledgement A part of this investigation was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

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