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Toxicity of Aceporol 330 in Mice as Novel Solubilizer of Paclitaxel

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Abstract – The objective of this study was to investigate the single dose and 2-week repeated dose toxicity of Aceporol 330 in ICR mice following single intravenous administration and to compare its toxicity with a commercially available solubilizer of paclitaxel, Cremophor EL. In single dose toxicity test, LD_{50} of Aceporol 330 in mice was estimated to be greater than maximum applicable dose, 4 ml/kg. However, LD_{50} of Cremophor EL in male mice was determined to be 4 ml/kg. Maximum tolerated dose (MTD) of males and females in Aceporol 330-treated group and MTD of females in Cremophor EL-treated group were 3 ml/kg. MTD of males in Cremophor EL-treated group was less than 3 ml/kg. Characteristic toxic symptoms, and hematological and blood chemical changes were not observed after single dose and repeated dose of Aceporol 330 or Cremophor EL. No histopathological abnormalities were found in organs of all animal groups. Based on the linear pharmacokinetic property of paclitaxel and the higher LD_{50} in mice, Aceporol 330 has a potential for use as a safer solubilizer for paclitaxel than Cremophor EL.

Keywords □ Aceporol 330, Cremophor EL, toxicity, mice

INTRODUCTION

Paclitaxel is an anticancer agent isolated from the bark of the Pacific yew tree *Taxus brevifolia* (Nuijen *et al.*, 2001). It promotes the polymerization of tubulin, thereby interferes with mitosis and induces apoptosis by disrupting the cell division at the G2/M-phase junction (Singla *et al.*, 2002). Paclitaxel is clinically effective against advanced breast, ovarian and non-small cell lung cancer (Crown and O'Leary, 2000). However, clinical application of paclitaxel is accompanied by several problems, such as a low extraction yield from natural source and a poor solubility in aqueous medium (Singla *et al.*, 2002).

Currently, paclitaxel is commercially available as vials containing 30 mg of drug dissolved in mixture of 50% Cremophore EL (polyethoxylated castor oil; Fig. 1) and 50% dehydrated ethanol USP. Cremophor EL is also being used as a vehicle for the solubilization of a wide range of other hydrophobic drugs, including anesthetics, photosensitizers, vitamins, sedatives and anticancer drugs. Only small amount of Cremophor EL is co-administered with these drugs, although paclitaxel is an exception as the Cremophor EL content of the formulated preparation is much higher per dose, about 12 mL/m^2 (van Zuylen *et al.*,

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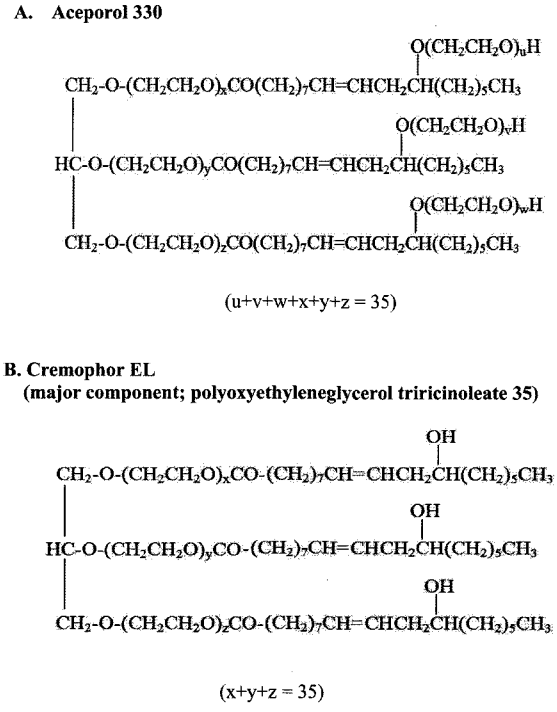

Fig. 1. Chemical structure of solubilizer

2001a).

Unfortunately, Cremophor EL is not well tolerated and leads to severe toxicity such as peripheral neurotoxicity and anaphylactic hypersensitivity reactions (Kim *et al.*, 2001; Mielke *et al.*, 2006). In order to overcome the pharmaceutical disadvantages of Cremophor EL, a large variety of new formulation vehicles for paclitaxel are in (pre) clinical development, including co-solvent systems, water-soluble polymers, emulsions, liposomes, cyclodextrines, nanocapsules and microspheres (Gelderblom *et al.*, 2001; Cai *et al.*, 2007; Kang *et al.*, 2004; Le Garrec *et al.*, 2004; Konno *et al.*, 2003). Novel paclitaxel delivery vehicles ideally should not influence the blood distribution of paclitaxel, while at least equal solubility is required and no life-threatening toxicity should occur (Loos *et al.*, 2002)

Recently, we have developed several candidate paclitaxel solubilizers, in order to improve the pharmacokinetic characteristics and to reduce the toxicity of a future paclitaxel solubilizer, as compared to Cremophor EL (Loos *et al.*, 2002; Lee, 2002). One of these candidate micelle-forming vehicles, Aceporol 330 (Figure 1) was proved to have an improved loading capacity of paclitaxel as compared to Cremophor EL, and to provide the linear pharmacokinetic characteristics of paclitaxel in whole blood and plasma of rats (Lee, 2002).

In this study, the single dose toxicity test and 2-week repeated dose toxicity test of a new paclitaxel solubilizer, Aceporol 330 were performed in mice after intravenous administration and we compared its toxicity data with that of Cremophor EL.

MATERIALS AND METHODS

Materials

Aceporol 330 was from Bolak Co. Ltd (Seoul, Korea). Cremophor EL was obtained from BASF Company Ltd. (Seoul, Korea). Ethyl alcohol was purchased from Sigma Chemical Co. (St. Louis, MO, USA). 5% Dextrose solution in glass bottle was from Choongwae Pharma Corporation (Seoul, Korea).

For toxicity test, Aceporol 330 or Cremophor EL was mixed with dehydrated ethyl alcohol (1:1 v/v), and diluted in 5% dextrose in water solution to a final concentration of 5% Aceporol 330/5% dehydrated alcohol or 5% Cremophor EL/5% dehydrated alcohol. Cremophor EL was administered through an in-line filter with a microporous membrane not greater than 0.22 μm.

Animals

Institute of Cancer Research (ICR) mice were obtained from Dae Han Biolink Co. Ltd (Eumseong-gun, Chungcheongbuk-do, Korea). All animals were maintained in a pathogen-free environment air-conditioned at 23±1°C under a 12 h-light/12 h-dark cycle, and allowed free access to food and water until 16-18 h prior to their use in experiments, when they were allowed only water. All procedures were approved by the institutional animal care and use committee, and the animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council).

Single dose toxicity study in mice

ICR mice (100 males and 100 females) were divided into 5 groups with 20 males (30-35 g) and 20 females (25-30 g) in each group. Cremophor EL or Aceporol 330 was administered intravenously via tail vein at dosages of 3 ml/kg or 4 ml/kg. Untreated mice group was served as control. The general behavior of the mice was observed for 14 days after treatment and any signs of toxicity and lethality were recorded every day. The animals were weighed at day 3, day 7, and day 14. At the end of the observation period, blood samples were collected from tail vein of each mouse, and then the animals were sacrificed, dissected, and examined for macroscopically visible changes. Hematological examinations were performed on 10 mice per group and biochemical investigations were performed on other 10 mice in each group.

2-Week repeated dose toxicity study in mice

In the 2-week repeated dose toxicity study in mice, ICR mice (60 males and 60 females) were divided into untreated group, Aceporol 330-treated group and Cremophor EL-treated group. Each group contains 20 males (30-35 g) and 20 females (25-30 g). Aceporol 330 or Cremophor EL was injected intravenously in the tail vein of mice every day for 14 days, at dose levels of 1.6 ml/kg/day. Untreated mice group was served as control. The general behavior of the mice was observed during treatment period and any signs of toxicity and lethality were recorded every day. The animals were weighed at day 4, day 7, day 11 and day 14. Water and food consumption of mice determined once a week. Urinalysis for glucose, bilirubin, ketone, specific gravity, blood, protein, pH, urobilinogen, nitrite and leukocytes was performed for 6 male and 6 female mice in each group using Multistix®10SG (Bayer

Co., IN, USA). The macroscopic and ophthalmoscopic examinations were performed for anterior segment of eyes (such as cornea, iris and lens), vitrous body and retina after treatment of 1% atropine sulfate eye drop. At the end of the observation period, blood samples were collected from tail vein of each mouse and the animals were sacrificed, dissected, and examined for macroscopically visible changes as described in "Autopsy study". Hematological examinations were performed on 10 mice per group and biochemical investigations were performed on other 10 mice in each group as described below. All tissues were weighed and preserved in 10% buffered formaldehyde for histopathological study as described below.

Hematological investigation and blood chemistry analysis

Hematological examinations were performed using HEMAVET 850 (CDC Technologies, Oxford, CT, USA). Hematology parameters evaluated were white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and platelet count (PLT).

The blood chemistry parameters such as blood urea nitrogen (BUN), glutamyl oxaloacetic transaminase (GOT), glutamyl pyrubic transaminase (GPT), albumin (ALB), glucose (GLU), alkaline phosphatase (ALP), inorganic phosphorus (IP), total bilirubin (TBIL), total cholesterol (TCHO), creatinine (CRE), triglycerides (TG), total protein (TP), calcium, sodium, potassium, chloride ion were determined using FUJI-DRY CHEM slide (Fuji Photo Film Co., Tokyo, Japan) .

Autopsy study

At the end of 2-week repeated dose toxicity study, the animals were sacrificed and dissected. During the process of dissecting, the parenchymatous organs' color, texture, lump and so on were carefully observed. The color and integrity of the cavities' mucosa were also observed. In mice, the weight of heart, liver, lung, kidney, brain and spleen were measured and recorded.

Histopathological study

Organ pieces (3-5 mm thick) were fixed in 10% buffered formaldehyde for 24 hr and washed in running water for another 24 hr. Samples were dehydrated by passing through 50, 70, 90 and 100% alcohol over a 2 day period, and then embedded in paraffin wax. Paraffin embedded organs were sliced by microtom at the thickness of 4 μm. Routine staining with haematoxylin-eosin and thorough examination using a light microscope were performed.

Statistical analysis

Results were expressed as mean±standard deviation (SD). Statistical significance was determined by a one way analysis of variance (ANOVA) followed by Turkey post hoc comparison for the comparison of the results from the various experimental groups and controls. The differences were considered significant when $P<0.05$.

RESULTS

Single dose toxicity study in mice

The objective of this study was to investigate the acute toxic potential of Aceporol 330 in ICR mice following single intravenous administration and to compare its toxicity with a commercially available solubilizer of paclitaxel, Cremophor EL. High viscosity of Cremophor EL and Aceporol 330 limited their maximum intravenously applicable dose of 4 ml/kg. In the Aceporol 330-treated group, 3 males and 2 females were dead at the dose of 4 ml/kg, and no mice was dead at the dose of 3 ml/kg (Table I). In the Cremophor EL-treated group, 9 males and 2 females were dead at the dose of 4 ml/kg, and 2 males were dead at the dose of 3 ml/kg (Table I). LD_{50} of males and females in Aceporol 330-treated group and LD_{50} of females in Cremophor EL-treated group were considered over the maximum applica-

Table I. Mortality of solubilizer in mouse single dose toxicity test

Group	Dose	Tested (No.)	Alive (No.)	Dead (No.)
Male				
No treatment	-	20	20	0
Aceporol 330	3 ml/kg	20	20	0
	4 ml/kg[a]	20	17	3
Cremophor EL	3 ml/kg	20	18	2
	4 ml/kg[b]	20	11	9
Female				
No treatment	-	20	20	0
Aceporol 330	3 ml/kg	20	20	0
	4 ml/kg[a]	20	18	2
Cremophor EL	3 ml/kg	20	20	0
	4 ml/kg[b]	20	18	2

[a,b]Dose of 4ml/kg was maximum intravenously applicable dose of Aceporol 330 and Cremophor EL due to their viscosity.

ble dose, 4 ml/kg. LD_{50} of males in Cremophor EL-treated group was 4 ml/kg. Maximum tolerated dose (MTD) of males and females in Aceporol 330-treated group and MTD of females in Cremophor EL-treated group were 3 ml/kg. MTD of males in Cremophor EL-treated group was less than 3 ml/kg.

During recovery period, the body weight of females and males in both chemical-treated groups did not show significant changes compared to control group (data not shown). Characteristic toxic symptoms, and hematological and blood chemical changes were not observed after single intravenous administration of Aceporol 330 or Cremophor EL. No pathological changes of the inner organs were discernible with the naked eye during autopsy in all animals tested (data not shown). Therefore, based on LD_{50} and MTD of two chemicals, Aceporol 330 was less toxic than Cremophor EL.

2-Week repeated dose toxicity study in mice

The animals in all groups survived to the scheduled end of the study. Three males and three females showed salivation at day 2 and day 3. Salivation was also observed 4 males and 2 females in Cremophor EL-treated group at day 2 and day 3. 2 males in Aceporol 330-treated group and 2 males in Cremophor EL-treated group showed reduction of spontaneous movement at day 2 and day 3. Local intolerances such as swollen tails (all animals in Aceporol 330 or Cremophor EL-treated groups) as well as necrotic tails (nine males and eight females in Aceporol 330-treated groups and ten males and ten females in Cremophor EL-treated groups) were observed. Other overt toxic effects were not observed.

Body weight development was not affected by the administration of Aceporol 330 and Cremophor EL. Food consumption and water consumption in Aceporol 330-treated groups and Cremophor EL-treated groups didn't show the significant difference from controls. The macroscopic and ophthalmoscopic examination was performed for anterior segment of eyes (such as cornea, iris and lens), vitrous body and retina. The anterior segments of eyes were normal for all of animals and no abnormality of blood vessels and optic nerve disc and no bleeding in retina were found. Urinalysis revealed no findings of statistical and toxicological significance in Aceporol 330-treated groups and in Cremophor EL-treated groups (data not shown). Organ weight changes and hematology and blood chemistry analysis of all animals in Aceporol 330-treated group and Cremophor EL-treated group showed no statistically significant difference from control group at the end of the recovery period (Table II-IV). No histopathological abnormalities were found in organs of all animal groups.

DISCUSSION

The current paclitaxel formulation vehicle Cremophor EL presents a number of serious problems, such as a wide variety of toxicity that limits the dosage of drug that

Table II. Organ weight of mouse after 2-week repeated dose toxicity test

	Body weight	Heart	Liver	Lung
Male				
No treatment	31.33±3.36	0.22±0.06	1.64±0.36	0.33±0.11
Aceporol 330	30.36±3.16	0.17±0.04	1.59±0.25	0.30±0.04
Cremophor EL	29.83±3.06	0.18±0.03	1.45±0.19	0.27±0.04
Female				
No treatment	25.07±2.51	0.17±0.04	1.28±0.12	0.29±0.05
Aceporol 330	25.23±1.06	0.13±0.03	1.32±0.14	0.23±0.04
Cremophor EL	25.68±1.69	0.11±0.02	1.18±0.15	0.20±0.03
	Spleen	Kidney (left)	Kidney (right)	Brain
Male				
No treatment	0.13±0.03	0.26±0.04	0.25±0.04	0.46±0.06
Aceporol 330	0.19±0.04	0.23±0.03	0.23±0.04	0.46±0.04
Cremophor EL	0.17±0.03	0.23±0.04	0.24±0.04	0.48±0.04
Female				
No treatment	0.11±0.02	0.19±0.03	0.19±0.04	0.48±0.04
Aceporol 330	0.14±0.04	0.19±0.04	0.19±0.03	0.45±0.05
Cremophor EL	0.09±0.02	0.16±0.02	0.15±0.02	0.43±0.02

Data represent the mean ± SD (n=10; unit, g).

Table III. Hematological test for mouse after 2-week repeated dose toxicity test

	WBC	RBC	HB	HCT	MCV	MCH	PLT
unit	10^3/ul	10^6/ul	g/dl	%	fL(=10^{-15}liter)	pg(=10^{-12}g)	10^3/ul
Male							
No treatment	5.90±3.60	10.07±1.43	16.21±1.47	59.30±9.27	58.83±2.47	16.24±1.40	874.33±346.91
Aceporol 330	4.09±2.89	7.84±2.07	13.18±3.51	41.14±11.43	59.15±2.91	16.81±1.78	1100.25±397.70
Cremophor EL	3.76±1.52	9.90±0.95	15.94±1.59	59.52±7.83	60.07±4.45	16.14±1.06	1163.78±369.18
Female							
No treatment	6.74±2.21	9.88±1.16	16.56±0.76	59.22±7.19	59.99±3.07	16.91±1.56	934.00±351.86
Aceporol 330	4.55±1.84	9.81±1.94	15.45±1.30	56.97±12.57	57.95±3.08	16.10±2.25	826.73±379.48
Cremophor EL	4.16±1.92	8.72±1.34	15.12±2.03	50.87±7.37	58.61±3.71	17.45±1.24	952.91±361.48

Abbreviation: Ace330, Aceporol 330; CreEL, Cremophor EL; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelet count.
Data represent the mean ± SD (n=10).

can be safely administered (van Zuylen *et al.*, 2001a).

Many researches also reported that modulation of the paclitaxel disposition profiles by alteration of the blood distribution resulted from entrapment of this compound in circulating micelles, and that Cremophor EL seems to play a crucial role in non-linear pharmacokinetics of paclitaxel (van Zuylen *et al.*, 2001b; Nuijen et al., 2001; Gliederblom *et al.*, 2001). In contrast to Cremophor EL, Aceporol 330 was proved to provide the dose-dependent linearity of paclitaxel concentration in whole blood and plasma of rat (Lee, 2002).

The single dose toxicity tests of Aceporol 330 and Cremophor EL were performed in mice and determined LD_{50} of intravenously administered Cremophor EL, as 4 ml/kg in male mice (Table I) which corresponds to the data that manufacturers provided. LD_{50} of Aceporol 330 was considered over 4 ml/kg, because high viscosity of Cremophor EL and Aceporol 330 limited their maximum intravenously applicable dose of 4 ml/kg. Much lower lethality of Aceporol 330 than Cremophor EL suggests that Aceporol 330 has a potential for use as a safer solubilizer for paclitaxel than Cremophor EL.

Cremophor EL is well known to cause an acute hypersensitivity reaction, the hyperlipidemia, and the alteration of the biochemical properties of lipoproteins (van Zuylen *et al.*, 2001a; Weiss *et al.*, 1990; Singla *et al.*, 2002; Shimomura *et al.*, 1998). However, in our single dose and repeated dose toxicity test, all mice which were treated Cremophor EL or Aceporol 330 showed no hypersensitivity reaction. Moreover, there was no significant change of hematological and biochemical properties in mice (Table III-IV).

It has been reported that Cremophor EL caused the neurotoxicity, and that this toxicity is induced by residual unsaturated fatty acids, possibly due to the appearance of peroxidation products (Gelderblom *et al.*, 2001). In our experiments, we couldn't find any evidence of neurotoxicity of Cremophor EL and Aceporol 330 even in the histo-

Table IV. Blood chemistry analysis of mouse after 2-week repeated dose toxicity test

	BUN	GOT	GPT	ALB	GLU	ALP	IP	TBIL
unit	mg/dl	U/l	U/l	g/dl	mg/dl	U/l	mg/dl	mg/dl
Male								
No treatment	35.99±4.58	66.75±16.08	21.13±4.39	2.19±0.16	41.13±21.19	197.13±68.36	7.85±1.85	0.45±0.14
Aceporol 330	28.70±4.52	63.86±17.93	17.14±8.57	2.31±0.17	90.86±24.15	122.71±27.63	11.60±1.41	0.56±0.31
Cremophor EL	31.24±5.17	65.56±6.04	17.56±7.02	2.29±0.21	71.00± 26.39	170.11±29.25	12.27± 2.10	0.49±0.14
Female								
No treatment	26.05±3.84	63.75±13.30	20.00±9.47	2.25±0.11	56.50± 18.04	265.50± 76.14	8.38±0.94	0.46±0.30
Aceporol 330	30.14±11.36	55.57±15.27	11.78±3.99	2.38±0.11	99.78± 28.13	148.22± 52.11	11.32±1.49	0.50±0.18
Cremophor EL	30.22±4.39	60.11±9.91	13.33±3.91	2.50±0.17	89.89± 30.15	241.89± 42.33	14.70±0.44	0.49±0.11

Abbreviation: BUN, blood urea nitrogen; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyrubic transaminase; ALB, albumin; GLU, glucose; ALP, alkaline phosphatase; IP, inorganic phosphorus; TBIL, total bilirubin.
Data represent the mean ± SD (n=10).

Table IV. Blood chemistry analysis of mouse after 2-week repeated dose toxicity test (continued)

	TCHO	CRE	TG	Ca	TP	Na	K	Cl
unit	mg/dl	mg/dl	mg/dl	mg/dl	g/dl	meq/l	meq/l	meq/l
Male								
No treatment	174.63±37.88	0.41±0.11	153.75±34.08	9.19±0.48	7.18±1.78	142.00±3.30	9.33±1.78	109.63±2.77
Aceporol 330	138.57±21.09	0.26±0.11	160.43±38.38	8.50±0.15	5.60±0.27	149.57±3.10	8.51±0.63	105.71±2.93
Cremophor EL	135.89±26.69	0.18±0.11	96.30±39.67	8.38±0.32	5.53±0.34	148.00±2.12	7.82±1.11	107.22±2.33
Female								
No treatment	115.38±19.26	0.38±0.13	137.88±25.51	9.20±0.42	5.43±0.52	143.25±2.38	10.36±1.08	109.00±0.93
Aceporol 330	106.22±24.40	0.14±0.05	88.33±7.94	8.36±0.19	5.49±0.22	148.89±2.37	8.10±1.30	106.11±1.76
Cremophor EL	88.78±14.83	0.20±0.09	97.67±16.17	8.63±0.25	5.49±0.26	147.56±2.01	8.09±0.96	108.33±3.61

Abbreviation: TCHO, total cholesterol; CRE, creatinine; TG, triglycerides; TP, total protein.
Data represent the mean ± SD (n=10).

pathological study in mice.

Based on the linear pharmacokinetic property of paclitaxel and the higher LD_{50} in mice, Aceporol 330 has a potential for use as a safer solubilizer for paclitaxel than Cremophor EL.

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