

# Paclitaxel(Taxol)

\_\_\_\_\_ : Paclitaxel(Taxol)

paclitaxel

\_\_\_\_\_ :  
paclitaxel(10mg/kg)

paclitaxel  
8Gy  
24  
apoptosis

가 .  
paclitaxel 10mg/kg  
1  
(6 5 )

\_\_\_\_\_ : Paclitaxel

24  
6  
apoptosis  
가  
(P<0.05),

apoptosis 6  
24  
3  
Paclitaxel

가 apoptosis 24  
paclitaxel 6 3  
24  
3  
Paclitaxel  
6 24  
가 가 .

\_\_\_\_\_ :  
paclitaxel  
apoptosis,  
가 paclitaxel

가 Paclitaxel  
가 가 .

\_\_\_\_\_ : Paclitaxel,

( microtubular inhibitor ) ,4)  
가

가  
가  
가 (additive effect)

G2/M  
가 .5 8) Paclitaxel  
,9 11) paclitaxel  
paclitaxel .12)

Paclitaxel(Taxol)

가 .1 3) Paclitaxel Western yew( )  
Taxus brevifolia texane  
가 diterpene

Paclitaxel  
가 ,  
.13 16) Paclitaxel  
,  
.17,18)  
가 paclitaxel  
.19,20)  
가  
가 (therapeutic ratio)가

1998 10 8 1998 12 31  
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가 , paclitaxel 가

가 가

(reproductive death) (loss of cell integrity) 가

apoptosis가 .21) Apoptosis (progr : Paclitaxel 1999;17(1):57 64 1972 Kerr 22) 1982 apoptosis .23) apoptosis가 .24) apoptosis Paclitaxel apoptosis .25) Paclitaxel G2/M 가 , paclitaxel paclitaxel .26,27) paclitaxel 24 apoptosis , paclitaxel

1. 4 5 , 200 300gm , (Sprague-Dawley) 52 , paclitaxel , paclitaxel (Table 1). , paclitaxel

paclitaxel(Taxol, Mead Johnson, USA) 10mg/kg 1 8Gy . Paclitaxel paclitaxel (10mg/kg) 24

2. Ketamin( , , 50mg/ml), 60mg/kg 6 MV 가 (Linear accelerator NEC 1006X, Japan) 8Gy 80cm 2Gy

3. 6 , 24 , 3 , 5 10% hematoxylin-eosin apoptosis (400 ) 500 apoptosis apoptosis 가 0, 1, 2, 3

4. , apoptosis group t-test 0.05

1. 1.07% (Table 2). Paclitaxel 가 6 6.5% 가 paclitaxel 가 24 5 paclitaxel

**Table 1. Grouping of Experimental Animals**

Group	Observation time				No. of animals
	6 hours	24 hours	3 days	5 days	
Normal control	4				4
Paclitaxel	4	4	4	4	16
Radiation	4	4	4	4	16
Paclitaxel & Radiation	4	4	4	4	16
Total No. of animals					52

**Table 2. Effects of Paclitaxel and Radiation on Mitosis of Large Bowel Mucosa**

Time/Group	Normal control	Paclitaxel	Radiation	Paclitaxel + Radiation
	(Peak %, Mean ± SEM*)			
6 hours	1.07 ± 0.2	6.50 ± 2.7	0	0
24 hours	9	3	0	0
3 days	1.07 ± 0.2	0.75 ± 0.4	1.00 ± 0.	3.05 ± 1.14
5 days	9	3	50	2.85 ± 0.88
	1.07 ± 0.2	1.45 ± 0.9	1.65 ± 0.	
	9	5	31	
	1.07 ± 0.2	0.50 ± 0.0		
	9	6		

\*Mean ± SEM (Standard error of the mean)

**Table 3. Effects of Paclitaxel and Radiation on Apoptosis of Large Bowel Mucosa**

	Normal control	Paclitaxel	Radiation	Paclitaxel + Radiation
	(Peak %, Mean ± SEM*)			
6 hours	0.30 ±	3.55 ± 1.9	6.35 ± 0.3	5.10 ± 1.81
24 hours	0.06	9	9 †	0.55 ± 0.17
3 days	0.30 ±	1.65 ± 0.3	2.30 ± 0.2	1.80 ± 0.12*
5 days	0.06	1 †	5 †	0.30 ± 0.06
	0.30 ±	1.05 ± 0.3	2.30 ± 0.6	
	0.06	8	9	
	0.30 ±	1.00 ± 0.2	0.90 ± 0.3	
	0.06	6	7	

\*Mean ± SEM (Standard error of the mean)

† P < 0.05 compared to normal control

**Table 4. Histopathologic Findings of Large Bowel Mucosa**

Group	Vesiculation	Atypia	Reduction of Goblet cell
Normal control	0,0,0,0	0,0,0,0	0,0,0,0
Paclitaxel			
6 hours	1,1,2,2	1,1,2,2	1,2,1,3
24 hours	1,1,1,3	1,1,2,3	3,3,3,3
3 days	2,2,3,3	2,2,3,3	2,2,3,3
5 days	0,0,0,0	0,0,0,0	0,0,0,0
Radiation			
6 hours	0,0,0,0	1,1,1,1	2,2,2,2
24 hours	0,1,1,1	0,0,1,1	1,1,2,2
3 days	3,3,3,3	3,3,3,3	3,3,3,3
5 days	1,1,2,2	1,1,2,2	2,2,2,2
Paclitaxel + Radiation			
6 hours	4,4,4,4	4,4,4,4	3,3,3,3
24 hours	2,2,3,3	2,2,3,3	2,2,3,3
3 days	3,3,3,4	3,3,3,4	2,2,3,3
5 days	1,1,1,1	1,1,1,1	2,2,2,2

0: no change, 1: mild change, 2: moderate change,

3: severe change

**2. Apoptosis**

paclitaxel apoptosis 0.3%  
 paclitaxel 24 1.65% † (P < 0.05) 3 (Fig. 1).

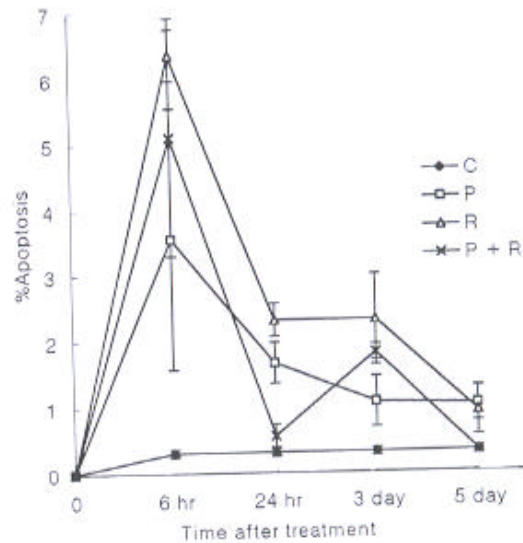
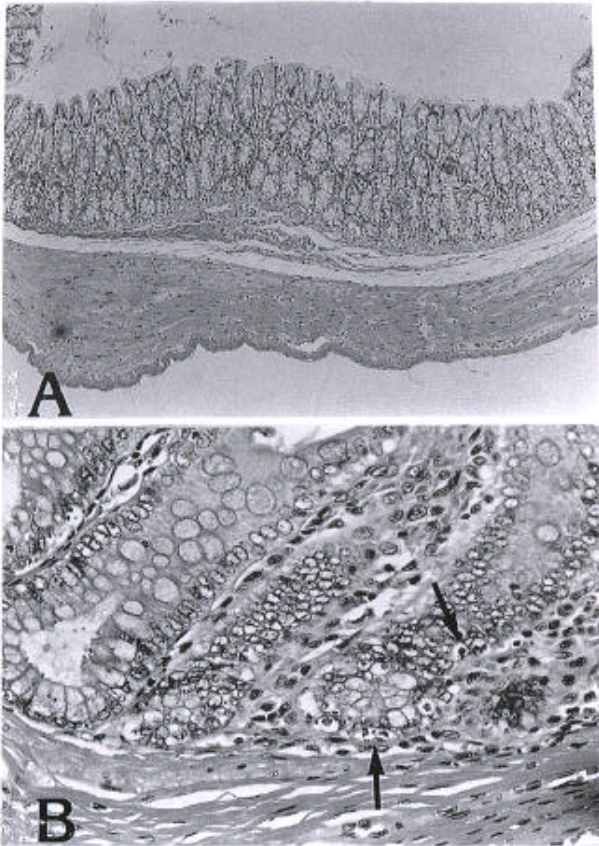


Fig. 1. Percentage of apoptosis in large bowel mucosa of rat treated with paclitaxel (P), Radiation R), paclitaxel plus radiation (P+R) and normal control group (C).

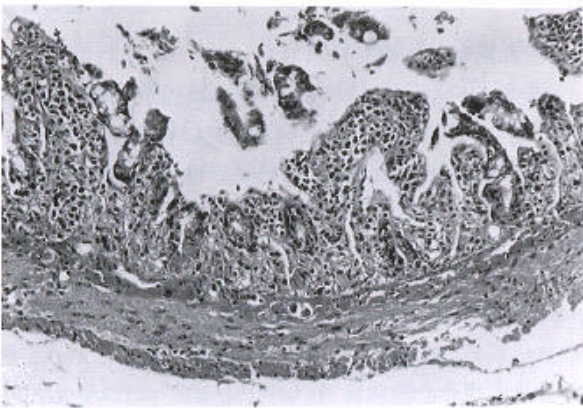
24 2.3% 가 6 6.35%, (P < 0.05) 5  
 6 . Paclitaxel  
 3 1.8%  
 가 (P < 0.05)  
 가

**3.**

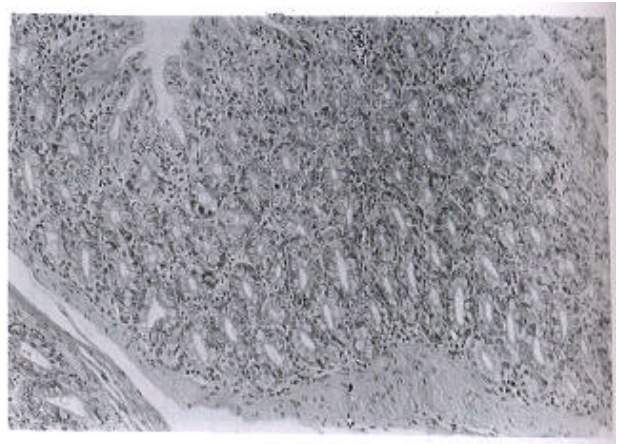
Paclitaxel 6 (vesiculation) (atypia) 6 (goblet cell) 가  
 24 3 가 5  
 (Fig. 2).  
 6  
 3 가 5 가  
 (Fig. 3). Paclitaxel  
 6  
 가 5 (Fig. 4).  
 paclitaxel 6 3.67,  
 1.00, 24 2.5, 0.92  
 가 가 (P < 0.05) 3  
 5 가 .  
 paclitaxel paclitaxel  
 가 (additive  
 effect)



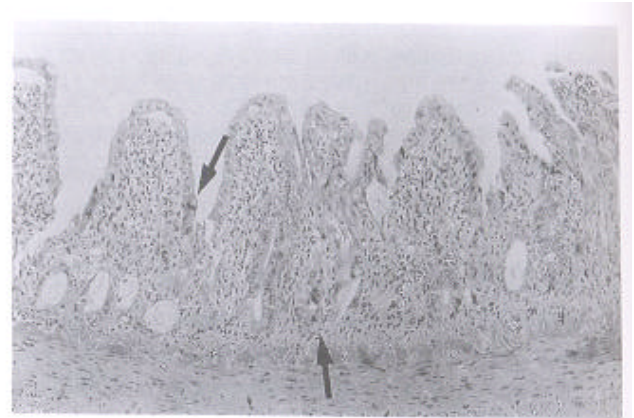
**Fig. 2.** Six hours after irradiation (B) compared to control (A) showed markedly increased numbers of apoptosis(arrows) (H-E stain . A: \*20). B: \*100)



**Fig.3.** Twenty hours after paclitaxel infusion showed marked atypia of colonic gland epithelium with nuclear vesiculation and decreased of goblet cell(H-E stain, \*50)



**Fig.4.** Three days after irradiation moderate atypia of colonic glandular with markedly decreased numbers of goblet cell(H-E stain, \*40).



**Fig.5.** Three days after combined paclitaxel infusion and irradiation showed marked atypia of colonic glandular epithelium with enlarged nuclei(arrows) and no goblet cell(H-E stain, \*33).

paclitaxel  
 (microtubule assembly)  
 (tubulin polymer)  
 ,4)  
 G2/M  
 apoptosis .13,28,29) Mason  
 26) paclitaxel(10mg/kg)  
 , apoptosis 24  
 , 가 가

1 3 가  
 2 4 가  
 (lag period)가  
 6 ,  
 paclitaxelx 8  
 24 가  
 . paclitaxel 가  
 가  
 Hruban 19) paclitaxel .13 16)  
 , , ,  
 .30,31)  
 paclitaxel  
 , paclitaxel  
 Apoptosis  
 paclitaxel 24 1.65% 0.3%  
 가 3  
 paclitaxel apoptosis  
 .  
 (reproductive death)  
 가  
 apoptosis가 .21)  
 ,  
 apoptosis 32)  
 apoptosis  
 (postmitotic cell) 33)  
 34)  
 apoptosis 35,36) apoptosis  
 . Meyn 37)  
 apoptosis  
 apoptosis가  
 가  
 Milas 38) apoptosis  
 4 6 12  
 , Hendry 23)  
 3 6  
 apoptosis가  
 apoptosis가 6.35%  
 6  
 가 24  
 5  
 24  
 3 가  
 5  
 apoptosis

Paclitaxel 가 G2/M  
 .5 8) Paclitaxel  
 paclitaxel 가 . Milas 38)  
 paclitaxel 60mg/kg 1 가  
 가 , apoptosis가  
 apoptosis . Milas  
 39) 가  
 ,  
 paclitaxel 4%, 9 30%, 24 12% 1  
 9  
 1.47, 1.70,  
 2.49 가  
 .  
 24 paclitaxel  
 paclitaxel  
 apoptosis  
 . Steren 12)  
 paclitaxel 48 가  
 24  
 paclitaxel  
 24 가 ,  
 cell) 가 (stem  
 .39)  
 paclitaxel 24  
 .  
 Mason 26) paclitaxel 40mg/kg 1  
 가 2 4 가  
 1.07 가 ,  
 paclitaxel  
 .  
 paclitaxel 24  
 0.89 0.92  
 paclitaxel  
 가  
 paclitaxel 24  
 .  
 , apoptosis 3  
 1.8% 가 ( $P<0.05$ )  
 2.3% 가

paclitaxel , apoptosis가 가 paclitaxel  
 paclitaxel . Stromberg 10) paclitaxel  
 12 24  
 , paclitaxel  
 가 Apoptosis ,  
 paclitaxel  
 6 , 24 paclitaxel  
 paclitaxel 가 가 가  
 , Mason 26) .  
 paclitaxel 24  
 apoptosis ,  
 가 . ,  
 가 , paclitaxel  
 paclitaxel 가 .  
 paclitaxel paclitaxel  
 , paclitaxel  
 가 .

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## Effect of the Paclitaxel and Radiation on the Large Bowel Mucosa of the Rat

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**Purpose:** Paclitaxel is a chemotherapeutic agent with a potent microtubule stabilizing activity that arrests mitosis at G2-M phase of cell cycle which is the most radiosensitive period. Therefore paclitaxel is considered as a cell cycle-specific radiosensitizer. This study investigates the effect of paclitaxel on the radiation response of the normal large bowel mucosa of the rat.

**Materials and Methods:** The rats were divided into the three groups i.e., single intraperitoneal infusion of paclitaxel (10 mg/kg), a single fraction of irradiation (8 Gy, x-ray) to the whole abdomen, and a combination of irradiation (8 Gy, x-ray) given 24 hours after paclitaxel infusion. The histological changes as well as kinetics of mitotic arrest and apoptosis were evaluated on the large bowel mucosa at 6 hours, 1 day, 3 days and 5 days after treatment with paclitaxel alone, radiation alone and combination of paclitaxel and radiation.

**Results:** The incidence of the mitotic arrest was not increased by paclitaxel infusion. The apoptosis appeared in 24 hours after paclitaxel infusion, and the histopathologic changes such as vesiculation, atypia and reduction of the goblet cell of the mucosa of the large bowel were demonstrated during the period from 6 hours to 3 days after, and returned to normal in 5 days after paclitaxel infusion. In irradiated group, the apoptosis was increased in 6 and 24 hours after irradiation, and the histopathologic changes of the mucosa were appeared in 24 hours and markedly increased in 3 days and returned to normal in 5 days. In combined group of irradiation and paclitaxel infusion, the apoptosis was appeared in 3 days and the histopathologic changes appeared during the period from 6 hours to 3 days after infusion. On the basis of the incidence of apoptosis and the degree of the histopathologic changes of the large bowel mucosa, there seemed to be additive effect by paclitaxel on radiation rather than sensitizing effect.

**Conclusion:** The histopathological changes of large bowel mucosa in combined group compared to radiation alone group suggested an additive effect of paclitaxel on radiation response in the large bowel of rat.

Key Words: Paclitaxel, Radiation, Large bowel, Mitotic arrest, Apoptosis