

## 정상인의 전혈(Whole blood)에서 Triflusal(Disgren®)에 의한 혈소판 응집 억제 효과

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### The Inhibitory Effect of Triflusal(Disgren) on the Platelet Aggregation in Healthy Volunteers ; Impedance Method with the Whole Blood

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#### ABSTRACT

**Background :** Antiplatelet drugs play an important role in the prevention and treatment of coronary artery diseases. Triflusal, an antiplatelet drug structurally related to acetylsalicylic acid, selectively inhibits the cyclooxygenase of platelet and thromboxane A<sub>2</sub> formation. However there is a controversy about the clinical dosage and the quantitative evaluation of the platelet antiaggregatory effect of triflusal. In this study we have evaluated the platelet antiaggregatory effect and cost-effective dosage of triflusal in the whole blood of healthy volunteers. **Methods :** Using the whole blood of 50 healthy people, we performed a baseline platelet aggregation function test induced by adenosine diphosphate (ADP) and collagen. The subjects were subdivided into 3 treated groups (300 mg, 600 mg, 900 mg). We compared the platelet aggregation effect between the baseline results and 2 weeks after triflusal administration. **Results :** Triflusal inhibited the platelet aggregation induced by ADP and collagen in the 600 mg administration group most effectively. The platelet aggregation induced by collagen was inhibited dose-dependently. The definite inhibitory responders (% inhibition > 25) for platelet aggregation induced by collagen were more common than those induced by ADP (33% vs 27% in 300 mg, 71% vs 53% in 600 mg, 78% vs 39% in 900 mg). There were no serious clinical side-effects except gastrointestinal trouble. One volunteer in the 900 mg treated group discontinued the treatment due to epigastric pain. **Conclusion :** We conclude that triflusal has a dose-dependent inhibitory effect on platelet aggregation induced by collagen and that the most effective dosage for platelet antiaggregation effect is 600 mg per day. (**Korean Circulation J 1998;28(4):707-714**)

**KEY WORDS :** Triflusal · Platelet antiaggregatory effect · Impedance method

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## 서 론

(antiplatelet drug)

Aspirin Ticlopidine

angina) Aspirin

stacyclin(PG I<sub>2</sub>)

<sup>1)</sup>

<sup>3)4)</sup> Ticlopidine 0.9%

(total cholesterol) <sup>5)</sup>

가 Aspirin

Triflusal(Disgren®)(Fig. 1) cyclo -  
oxygenase thromboxane A<sub>2</sub>

<sup>6)7)</sup> in vitro As -  
pirin 10 가  
<sup>8)9)</sup>

Triflusal

가

가

<sup>7)10-12)</sup> (whole bl -  
ood) Triflusal

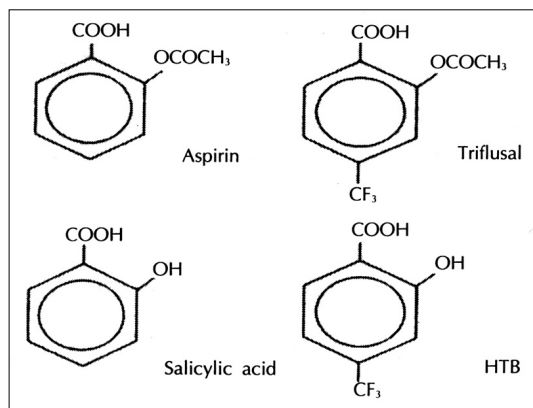


Fig. 1. Aspirin과 triflusal의 화학적 구조 및 그들의 주 대사 산물 ; HTB (2-hydrox-4-trifluoromethyl benzoic acid).

## 대 상

50 ( 23 , 27 )

1 1 (300 mg), 2 (600 mg), 3

2

25 75

49.7 ± 10.6

Triflusal

15

600 mg

8 thromboxane B<sub>2</sub>(T × B<sub>2</sub>)

6 - keto - prostaglandin F<sub>1</sub> alpha

## 방 법

채혈방법 및 투여용량

(antecubital vein) 20 22

gauge needle syringe 4.5 cc

, 3.8% sodium citrate vacutainer

sodium citrate 1 : 9 vol -  
ume . Triflusal

(whole blood) (pla -  
telet aggregation function test)

Triflusal 1 300 mg, 600 mg, 900  
mg , 30

2

Triflusal

가 3

혈소판 응집능 검사

Whole blood aggregometer  
(model no. 590 2D, Chronolog corp., Havertown,  
PA, U.S.A.) (impedance met -  
hod) (Figs. 2 and 3),

ADP(adenosine diphosphate, 10 µM/ml)  
collagen(2 µg/ml)

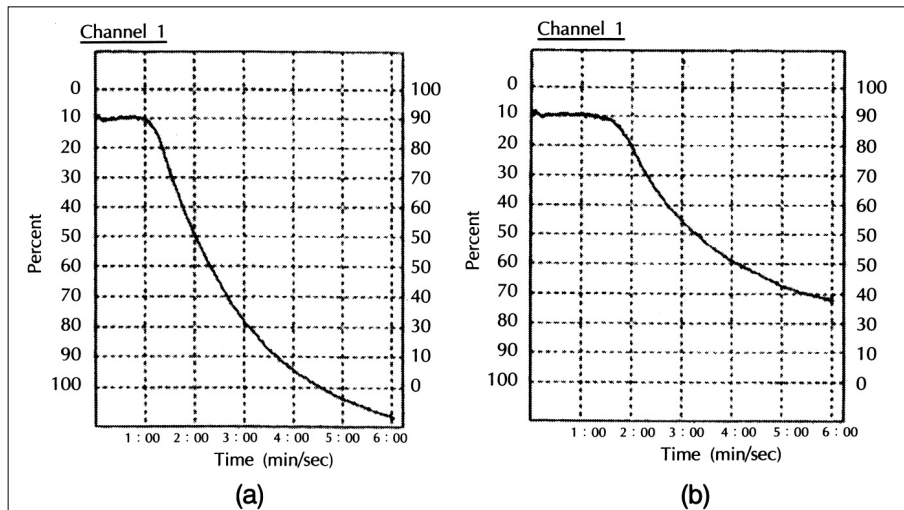


Fig.2. 혈소판 응집 곡선. (a) : ADP에 의해 유도된 혈소판 응집의 정상반응 (b) : Triflusal (600mg) 투여후 감소된 혈소판 응집반응

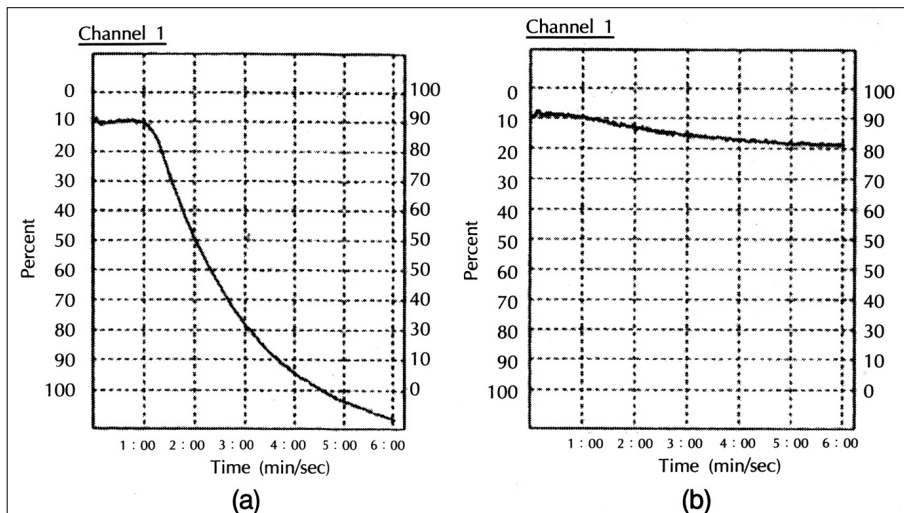


Fig.3. 혈소판 응집 곡선. (a) : Collagen에 의해 유도된 혈소판 응집의 정상반응 (b) : Triflusal (600mg) 투여후 감소된 혈소판 응집반응

450  $\mu$ l                      450  $\mu$ l    cuvette  
37    10    incubation well  
가    .    가    cuvette    sample well  
aggregometer                      가

Thromboxane B<sub>2</sub>와 6-keto-prostaglandin F<sub>1</sub> alpha의  
정량적 측정

10 cc    0.04 M indomethacin(0.05  
ml)    EDTA                      3000 g  
15  
- 20                      . Thromboxane B<sub>2</sub>    6 -  
keto - prostaglandin F<sub>1</sub> alpha                      EIA  
(enzyme immunoassay) kit(Amersham, U.K.)

## 결 과

경 과

51

가 1

50

혈소판 응집능 검사

Triflusal 600 mg 900 mg

ADP

36.34 ± 29.

87%, 29.12 ± 27.37% 300 mg

5.14 ± 25.55%

(Table 1)(p<0.05).

collagen

collagen

18.66 ± 26.96%, 39.01

± 31.28%, 47.92 ± 25.88%

가 (Fig. 4).

ADP

(% inhibition) 25%

가 collagen

(300 mg

; 33% vs 27%, 600 mg

; 71% vs

53%, 900 mg

; 78% vs 39%),

가 600 mg

가 (Table 2)(p<0.05).

**Table 1.** 전혈에 대한 triflusal의 혈소판 응집 억제 효과

	ADP (10uM/ml)	Collagen (2ug/ml)
300 mg PRE ( )	13.33 ± 3.79	22.46 ± 2.82
(n = 15) POST ( )	12.13 ± 3.90	18.00 ± 5.76
% Inhibition	5.14 ± 25.55	18.66 ± 26.96
600 mg PRE ( )	12.17 ± 4.00	19.41 ± 4.01
(n = 17) POST ( )	7.70 ± 4.52	12.17 ± 7.51
% Inhibition	36.34 ± 29.87*	39.01 ± 31.28*
900 mg PRE ( )	13.55 ± 4.61	20.38 ± 3.38
(n = 18) POST ( )	10.33 ± 5.84	10.66 ± 5.96
% Inhibition	29.12 ± 27.37*	47.92 ± 25.88*

\* : p<0.05 vs 300 mg 투여군

Thromboxane B<sub>2</sub>(T×B<sub>2</sub>)와 6-keto-prostaglandin F<sub>1</sub> alpha의 농도변화

Triflusal 600 mg

T × B<sub>2</sub>

174.30 ± 15.70 pg/ml, 66.30 ± 24.44 pg/ml Trifl -

usal T × B<sub>2</sub> 가

6 - keto - prostaglandin F<sub>1</sub> alpha

38.84 ± 9.72 pg/ml, 36.41 ± 7.42 pg/ml

(Table 3).

임상적 부작용

6 ,

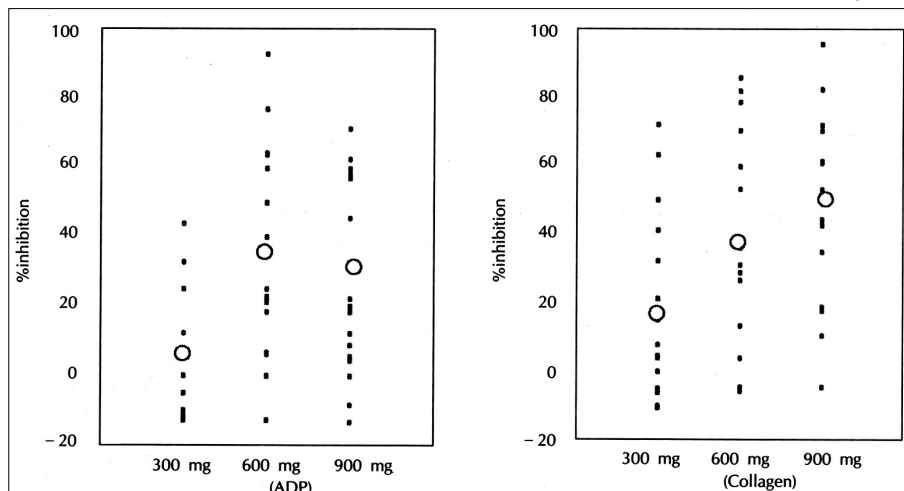
가 2 ,

1

가

(Table 4). 900 mg

1



**Fig. 4.** Triflusal의 용량에 따른 혈소판 응집 (ADP & collagen ) 억제 효과 ( : 평균값).

**Table 2.** Definite responders에 대한 triflusal의 혈소판 응집 억제 효과

	300 mg	600 mg	900 mg
	DR (%)	DR (%)	DR (%)
ADP	4 (27)	9 (53*)	7 (39 <sup>†</sup> )
% inhibition	36.5 ± 9.26	59.21 ± 19.78	58.85 ± 7.73
Collagen	5 (33)	12 (71*)	14 (78 <sup>†</sup> )
% inhibition	51.6 ± 16.16	55.05 ± 21.14	58.24 ± 17.67

DR : Definite responders (rate of inhibition ≥ 25%)  
\* : p<0.05, † : p<0.05

**Table 3.** Triflusal (600 mg)에 의한 혈중 Thromboxane B<sub>2</sub> 및 6-keto-prostaglandin F<sub>1</sub> alpha 농도 변화 (n = 8)

	Thromboxane B <sub>2</sub> (pg/ml)	6-keto-prostaglandin F <sub>1</sub> alpha (pg/ml)
PRE	174.30 ± 15.70	38.84 ± 9.72
POST	66.30 ± 24.44	36.41 ± 7.42

**Table 4.** 임상적 부작용

	N (%)			
	300 mg	600 mg	900 mg	Total
	1	2	3 (1*)	6 (12)
/	0	0	2	2 ( 4)
	0	0	1	1 ( 2)
	0	0	0	0 ( 0)
	1	2	6	9 (18)

\* : 투여 중단자

1  
.

## 고 안

(atheroma)

(thrombus)

가

Aspirin

Ticlopidine

pirin cyclooxygenase

thrombox -

ane A<sub>2</sub>

,

ostacyclin(PG I<sub>2</sub>)  
(Prinzmetal angina)

<sup>1)</sup>

( 200

300 mg) Aspirin  
(proaggregatory effect)

가 <sup>2)</sup>

<sup>3)4)</sup> Ticlopidine cyclooxygenase ADP

0.9%

(total cholesterol)  
<sup>5)</sup> Triflusal(Disg -

ren<sup>®</sup>) 1981 Uriach  
2 - acetoxy - 4 - trifluoromethyl be -  
nzoic acid Aspirin 4  
CF<sub>3</sub>(trifluoromethyl)

. Aspirin ,  
. 1 30  
가 2 - hydroxy -  
4 - trifluoromethylbenzoic acid(HTB)  
4 Aspirin

cyclooxygenase ,  
cyclooxygenase thrombo -  
xane A<sub>2</sub> <sup>6)7)</sup>

c - AMP 가

PRP

. adenosine receptor  
adenosine uptake

adenosine 가

. Triflusal in vitro  
ADP epinephrine

Aspirin 10 가

<sup>8)9)</sup>

(bleeding time), Triflusal

platelet adhesiveness test, recalcification time, prothrombin consumption test, ADP secretion test

Triflusal 900 mg 600 mg

가

. Definite responder(% inhibition >25)

(optical) , (luminescence) , (impedance) , 1962 Born 가 ADP

(platelet rich plasma, PRP) 600 mg 가 , collagen

900 mg 가 600 mg

900 mg 가 Triflusal 1

600 mg 가

가

100% PRP , Triflusal

600 mg 8 Thrombox -

ane B<sub>2</sub> 가 Triflusal

, 6 - keto - prostaglandin F<sub>1</sub> alpha

stress Triflusal prostacyclin

pH

가

(hypercholesterolemia) (turbid) , Putz ,<sup>16)</sup> Esmatjes Trifl -

usall<sup>17)</sup> Masotti<sup>18)</sup>

PRP (whole blood) 가 가

(sensitivity)가 ,<sup>10)11)19)</sup>

Triflusal , Garay

<sup>19)</sup> 1,318 2 600 mg

900 mg 8%

가

<sup>14)15)</sup> (proaggregatory effect)가<sup>20)</sup>

<sup>10)</sup> 1 900 mg, 8

16.7%

PRP ,<sup>11)</sup> 1

가 900 mg, 2 14%

Triflusal PRP 16%

epinephrine, collagen, ADP arachidonic acid<sup>7)8)</sup>

ADP collagen

Triflusal

가 Triflusal

가

요 약

연구배경 :

가 Aspirin  
Triflusal(Disgren )  
cyclooxygenase  
thromboxane A<sub>2</sub>  
Triflusal  
가 (whole  
blood)  
Triflusal

방 법 :

50 Triflusal 300  
mg, 600 mg, 900 mg 2

Whole blood aggregometer  
ADP  
collagen  
결 과 :  
Triflusal 600 mg  
..Collagen  
가  
Collagen  
(% inhibition) 25%  
가 ADP  
가 600 mg  
가 , 900 mg  
900 mg 1

결 론 :  
Triflusal collagen

1 600 mg

중심 단어 : Triflusal

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