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The Pharmacokinetics and Pharmacodynamics of a New Thromboxane Synthetase Inhibitor, 6-(1-Imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (DP-1904), in Man after Single Oral Administration

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Abstract—The pharmacokinetics of DP-1904, a new potent and selective thromboxane synthetase inhibitor and its effects on ex-vivo prostanoid formation were studied in Japanese normal male volunteers, who received orally a single 10, 20, 50, 100, 200, 400 or 800 mg dose. The drug was well tolerated by all subjects without evidence of any adverse reactions. The absorption of DP-1904 from gastro-intestinal tract was rapid. After oral doses of 10-800 mg of the drug given to volunteers in the fasted state, the mean maximum drug concentrations in plasma (C_{max}) (mean ± s.e., n = 5) of 0·215 (±0·041), 0·399 (±0·037), 1·47 (±0·22), 2·86 (±0·22), 4·66 (±0·58), 7·28(±0·72) and 16·9 (±2·6) $\mu g mL^{-1}$ were reached within 1 h. DP-1904 concentrations declined monophasically after C_{max} with half lives of 30-40 min. These half lives were independent of the administered doses. The mean area under the concentration-time curves (AUCs) increased from 0·398 (±0·038) to 30·0 (±2·7) $\mu gh\ mL^{-1}$ as the dose increased from 10 to 800 mg. Linear relations between the doses and C_{max} and AUCs were observed. The correlation coefficients for C_{max} and AUC were 0·930 and 0·960, respectively. The apparent oral clearance (CL/F) and renal clearance (CL_R) did not change significantly as dose increased from 10 to 800 mg. The kinetics of DP-1904 proved to be linear in the dose range studied. The urinary excretion of DP-1904 was also independent of the administered dose, and about half of the dose was recovered in urine as unchanged form within 48 h after administration. The elimination of the drug was fast and almost complete within 6 h after dosing. On the other hand, only 0·5% of the dose was excreted into faeces as intact DP-1904 up to 48 h after 400 mg oral dose. Food intake delayed the absorption of DP-1904 but did not significantly modify its pharmacokinetics. Serum thromboxane B_2 levels (the stable metabolite of thromboxane A_2) were reduced more than 90% within 0·5 h after all doses studied. DP-1904 had a long duration of inhibitory activity and there was still more than 80, 90 and 95% suppression at 12 h after 200, 400, and 800 mg doses, respectively.

Thromboxane A_2 (TXA_2) and prostaglandin (PG) I_2 exert opposite effects on platelet aggregation and vascular resistance, and the balance between these compounds has been proposed to be one of the factors that determine platelet reactivity, endothelial thromboresistance, and vascular tone (Moncada & Vane 1978). TXA_2 may contribute to the pathogenesis of many thrombotic disorders such as coronary heart disease (Dusting 1983) and cerebral ischaemia (Furlow & Hallenbeck 1978). Selective inhibition of thromboxane synthesis and the redirection of endoperoxide metabolism toward PGI_2 will possibly offer a new therapeutic approach to those disease states in which increased thromboxane formation is critically involved.

DP-1904 [6-(1-imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid hydrochloride hemihydrate] is a new potent and long-acting thromboxane synthetase inhibitor in laboratory animals (Kanao et al 1989). The present study was undertaken to examine the pharmacokinetic characteristics of DP-1904 and its inhibitory effect on serum TXB_2 levels in normal human volunteers after single oral administration.

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Materials and Methods

Subjects

Forty eight Japanese healthy male volunteers (23–49 years old, weighing 53·5–78·0 kg) participated. The subjects were judged to be in good health based on thorough prestudy physical examination and the results from haematology, urinalysis, and biochemical tests. All subjects gave written informed consent following protocol approved by the Institutional Review Board at East Hospital of Kitasato University. On the evening before the study day the subjects reported to the hospital. Vital signs were monitored at the time of check-in, and the subjects were provided with a standard dinner. The subjects fasted overnight and did not take breakfast. The drug was administered with 300 mL of tap water around 0900 h on the next day. In the study where the influence of a meal on the pharmacokinetics of DP-1904 was investigated, the subjects took the drug around 0900 h, 30 min after a standard breakfast. A standard lunch was provided about 4 h post dosing. The subjects were allowed to drink water freely during the study.

Dosing and sample collection for drug analysis

The 48 subjects were randomly assigned to one of eight groups of equal size. Thus, seven groups received a 10, 20, 50,

100, 200, 400, or 800 mg dose of DP-1904 in the fasted state, respectively. One group in the non-fasted state received a 400 mg dose. One subject in each group received placebo. The study was conducted under a double blind design. Venous blood samples were collected in heparinized tubes at 0 (predose), 0·25, 0·5, 1, 2, 4, 6, 8, 12, 24 h. After centrifuging at 3000 rev min^{-1} for 15 min, plasma was separated and frozen at −20°C as soon as possible. Quantitative urine collections were obtained for the 0-0·5, 0·5-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-24, and 24 to 48 h intervals. The faecal samples were collected at 24 h intervals for 2 days in a single 400 mg dose study. All samples were stored frozen at −20°C until analysed.

Drug analysis

DP-1904 in plasma and urine samples was analysed by a sensitive and selective high-performance liquid chromatographic method (Tanaka et al 1988). The method involved a solid-phase extraction procedure with Sep-pak C_{18} cartridge. The separation was achieved by using TSK-GEL ODS-80TM column (Tosoh, Tokyo, Japan) and a mobile phase of 0·5% KH_2PO_4 (pH 3·0)-tetrahydrofuran (16:1, v/v). Both DP-1904 and internal standard [DQ-2481, 6-(1-imidozolylmethyl)-5,6,7,8-tetrahydronaphthalene-3-carboxylic acid] were detected at a wavelength of 240 nm. The lower limits of detection were 50 ng mL^{-1} with 3·80% of coefficient of variation (CV) for plasma samples and 1·0 μg mL^{-1} with 4·49% of CV for urine samples.

Faecal specimens were homogenized with 0·01 M HCl (300 or 800 mL) depending on their weights. A 1g sample of the homogenate was diluted tenfold with distilled water, and the resulting mixture centrifuged at 1800 *g* for 15 min. The supernatant was then processed through the same analytical procedure as the plasma samples. The sensitivity and selectivity of the analyical method for faecal homogenate were almost identical to those for plasma samples.

Assay of serum thromboxane B_2

Thromboxane B_2 (TXB_2) levels were measured by radioimmunoassay in samples of serum derived from 5mL of whole blood drawn into a glass tube. The blood was allowed to stand at 37°C for 1 h in a water bath for maximum production of TXB_2. The serum was removed after centrifugation at 1800 *g* for 15 min and stored at −20°C until analysed. RIA assay was done using extracted serum and a ^{125}I-RIA Kit (New England Nuclear, Mass., USA) (Kawano et al 1987).

Pharmacokinetic analysis

The plasma concentration of DP-1904 was plotted versus time, and pharmacokinetic parameters for the resulting curves were calculated using a curve-fitting program for personal computer (PC-9801, Nippon Electric Co., Ltd, Tokyo, Japan) (Yamaoka et al 1981). A one compartment open model with first-order absorption after lag time was used to describe the plasma concentration of DP-1904 after oral administration. The plasma concentration (C) of DP-1904 for any time, t after oral dose is given by the relationship:

$$C = A\{e^{-Ke(t-t_0)} - e^{-Ka(t-t_0)}\}$$

Where A is a hybrid intercept term having units of concentration and Ke and Ka are elimination rate constant and absorption rate constant, respectively; t_0 is the lag time elapsing before the start of first order absorption. Half life ($t_{\frac{1}{2}}$) values were calculated by the following equation: $t_{\frac{1}{2}} = 0{\cdot}693/Ke$. The time of maximum concentration (t_{max}) and the maximum concentration in plasma (C_{max}) were observed values and not model dependent values. The area under the plasma concentration curve (AUC) from the time of administration to 24 h post dosing was calculated by linear trapezoidal method. The apparent oral clearance (CL/F) and the apparent distribution volume (V/F) were calculated using the following equations: CL/F = dose/AUC, and V/F = Ka(dose)/A(Ka-Ke), in which F is the fraction of the dose absorbed into systemic circulation. The renal clearance (CL_R) was calculated as [X]/AUC, where [X] is cumulative urinary excretion of DP-1904 from 0 to 48 h after administration.

Statistical analysis was carried out by Student's *t*-test.

To evaluate the dose proportionality of DP-1904 in doses ranging from 10 to 800 mg, linear regression analysis of pharmacokinetic parameters (C_{max} and AUC) and dose were performed.

All of the data were expressed as mean ± standard error (n = 5).

Results

Safety assessment

None of the subjects in the present studies developed symptoms or adverse experiences attributable to the drug, and there was no significant change in standard laboratory testing or platelet counts that could be drug-related. The electrocardiogram recordings did not show any changes that could be related to the compound.

Pharmacokinetics of DP-1904

Mean plasma concentration-time curves following a single oral 10-800 mg dose of DP-1904 are shown in Fig. 1. The kinetic profiles can be fitted to a one compartment open model with first order absorption after lag time. The

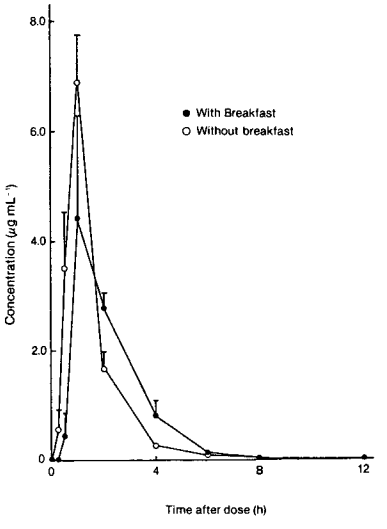

FIG. 1. Mean plasma concentration-time profiles of DP-1904 in five normal Japanese volunteers after single oral doses.

Table 1. Pharmacokinetic parameters for DP-1904 in five normal volunteers following single oral administration.

Dose mg	t_0 min	$t_{\frac{1}{2}}$ min	Ka h^{-1}	Vd L	t_{max} min	C_{max} $\mu g\,mL^{-1}$	AUC(0~12 h) $\mu g\,h^{-1}\,mL^{-1}$	CL/F $mL\,min^{-1}$	CL_R $mL\,min^{-1}$
10	16·9	32·0	10·7	31·9	36·0	0·215	0·398	434	232
	±2·90	±2·37	±3·31	±3·57	±6·00	±0·041	±0·038	±39·8	±24·5
20	25·3	37·3	13·2	31·1	54·0	0·399	0·796	454	248
	±2·74	±3·86	±2·41	±1·23	±6·00	±0·037	±0·125	±57·6	±30·3
50	17·1	33·3	21·2	24·1	42·0	1·47	2·02	419	247
	±2·45	±4·21	±8·52	±4·08	±7·32	±0·22	±0·12	±26·2	±15·5
100	14·8	32·2	15·2	22·6	42·0	2·86	3·68	458	243
	±0·49	±3·47	±6·87	±2·42	±7·32	±0·22	±0·19	±27·3	±11·8
200	16·9	27·9	5·40	22·8	48·0	4·66	6·53	532	289
	±3·44	±4·16	±2·88	±3·10	±7·32	±0·58	±0·66	±52·8	±22·6
400	15·6	32·3	6·08	36·2	54·0	7·28	10·1	687	291
	±0·63	±3·48	±4·33	±4·29	±6·00	±0·72	±1·1	±71·2	±20·5
800	10·5	40·5	12·9	28·1	51·0	16·9	30·0	456	212
	±2·94	±4·15	±10·9	±3·06	±9·00	±2·6	±2·7	±34·7	±22·1

t_0: lag time, $t_{\frac{1}{2}}$: half life.
(Mean ± s.e.).

pharmacokinetic data are summarized in Table 1. The lag times ranged from 10 to 25 min after all doses studied. The absorption of DP-1904 from the gastro-intestinal tract was very rapid. DP-1904 was detectable in the plasma at 15 min after administration of tablets. The mean C_{max} of DP-1904 were reached within 1 h post dosing. After C_{max} was reached, the plasma level of DP-1904 decreased rapidly with the half lives of 30–40 min. The half lives proved to be independent of the dose. DP-1904 in the plasma was not detectable at 24 h even after the highest dose of 800 mg. The mean AUCs after single oral doses of DP-1904 were also shown in Table 1 and they increased dose-dependently.

The correlation of C_{max} ($Y = 0{\cdot}0203X + 0{\cdot}231$, $R = 0{\cdot}930$) and AUC ($Y = 0{\cdot}0358X + 0{\cdot}427$, $R = 0{\cdot}960$) with the doses showed a linear increase in the values of these two pharmacokinetic parameters over the dose range studied.

The mean CL/F did not change significantly as the dose increased (Table 1).

As shown in Table 2, approximately 50% of the dose administered was recovered as intact drug in urine within 48 h after single oral doses (10-800 mg). Excretion of DP-1904 into urine was rapid and almost complete at 6 h post dosing and was not dose dependent. The renal clearance (CL_R) was more than 200 mL min^{-1} and did not change significantly as the dose increased (Table 1). These values are larger than the mean glomerular filtration rate, which indicates that active processes take place in urinary excretion of DP-1904.

The faecal excretion of DP-1904 after a single 400 mg dose was studied and proved to be low, 0·234 ± 0·118% of the administered dose being recovered up to 24 h post dosing and 0·557 ± 0·080% up to 48 h, respectively.

The same dose of DP-1904 (400 mg) was given to the subjects in fasting and non-fasting states. The pharmacokinetic characteristics are shown in Table 3 and Fig. 2. The pharmacokinetic data were found to be similar in both conditions, with the exception of C_{max}, t_0, and t_{max}. The C_{max} of DP-1904 were lower in non-fasting than in fasting subjects: (5·58 ± 1·20 and 7·28 ± 0·72 $\mu g\,mL^{-1}$). The t_0 was longer in non-fasting than in fasting subjects (29·3 ± 9·46 and 15·6 ± 0·63 min). The t_{max} was delayed in non-fasting subjects: 84·0 ± 14·7 min instead of 54·0 ± 6·00 min in fasting subjects. However, the differences in all pharmacokinetic parameters between fasting and non-fasting states were not statistically significant ($P < 0{\cdot}05$).

Table 2. Cumulative urinary excretion of DP-1904 after single oral administration to five normal male volunteers (% of dose).

Dose mg	Time after administration (h). 0·5	1	2	4	6	8	12	24	48
10	1·43	22·1	41·8	49·8	51·3		52·7	53·3	53·4
	±0·53	±1·52	±1·45	±1·82	±1·98	NT	±2·14	±2·45	±2·46
20	0·58	20·3	43·9	52·2	53·7		54·4	54·8	55·0
	±0·19	±2·20	±1·09	±0·48	±0·46	NT	±0·54	±0·58	±0·60
50	2·82	25·8	48·9	56·2	57·5		58·4	58·9	58·9
	±1·01	±5·05	±3·46	±2·34	±2·19	NT	±2·08	±2·07	±2·07
100	2·54	25·7	45·1	51·8	52·6	53·0	53·2	53·4	53·4
	±0·67	±1·88	±2·12	±2·05	±2·09	+2·09	±2·06	±2·05	±2·05
200	2·38	20·5	44·3	52·7	54·1	54·5	54·7	54·9	54·9
	±1·52	±2·87	±1·77	±2·08	±2·19	±2·25	±2·25	±2·25	±2·25
400	0·77	14·5	35·1	41·6	42·6	42·9	43·2	43·4	43·5
	±0·31	±2·17	±2·05	±3·19	±3·47	±3·46	±3·48	±3·48	±3·47
800	1·95	12·6	32·5	43·2	44·6	45·3	45·9	46·4	46·5
	±0·76	±2·34	±0·77	±1·74	±1·58	±1·50	±1·48	±1·48	±1·48

NT = not tested.
(Mean ± s.e.).

Table 3. Pharmacokinetic parameters for DP-1904 in five normal volunteers following ingestion of two 200 mg tablets (400 mg/subject) in fasted and non-fasted states.

1) fasted state

Subject	t_0 min	$t_{\frac{1}{2}}$ min	Ka h^{-1}	Vd L	t_{max} min	C_{max} $\mu g\,mL^{-1}$	AUC(0~24h) $\mu g\,h\,mL^{-1}$	CL/F $mL\,min^{-1}$	CLR $mL\,min^{-1}$
I	16·6	30·2	1·57	32·6	60	6·19	7·62	875	350
II	17·4	33·4	1·52	45·4	60	10·02	13·49	494	244
III	14·4	45·2	23·4	46·1	30	6·89	10·05	663	246
IV	15·8	27·7	2·01	33·3	60	6·08	8·13	820	301
V	14·1	25·3	1·91	23·4	60	7·24	11·40	585	315
Mean	15·6	32·3	6·08	36·2	54·0	7·28	10·14	687	291
s.e.	0·63	3·48	4·33	4·29	6·00	0·72	1·08	71·2	20·5

2) non-fasted state

Subject	t_0 min	$t_{\frac{1}{2}}$ min	Ka h^{-1}	Vd L	t_{max} min	C_{max} $\mu g\,mL^{-1}$	AUC(0~24h) $\mu g\,h\,mL^{-1}$	CL/F $mL\,min^{-1}$	CLR $mL\,min^{-1}$
VI	30·0	25·7	14·2	22·1	60	9·09	10·22	652	322
VII	0·0	56·4	0·82	45·8	120	2·98	7·86	848	468
VIII	59·7	52·4	0·94	56·5	120	2·78	8·26	807	387
IX	26·9	40·6	4·28	37·3	60	6·68	11·09	601	277
X	29·9	40·3	2·89	35·4	60	6·35	11·20	595	323
Mean	29·3	43·1	4·63	39·4	84·0	5·58	9·73	701	355
s.e.	9·46	5·39	2·48	5·71	14·7	1·20	0·70	53·1	33·2

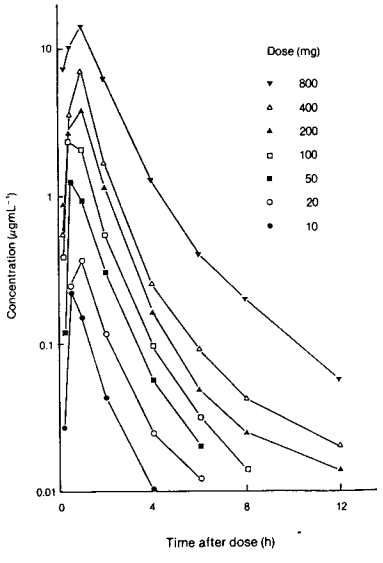

FIG. 2. Mean plasma concentration-time profiles of DP-1904 after a 400-mg oral dose to five normal volunteers with or without breakfast. Bars ± s.e.

Effect of DP-1904 on thromboxane synthetase

The serum thromboxane (TXB_2) changes after single oral doses of DP-1904 are shown in Table 4. DP-1904 caused a marked reduction in serum TXB_2 levels, with the maximum effect occurring 0·5 to 1 h after oral administration. The mean maximal reduction was more than 90% with all doses studied. Twelve hours after a single 200, 400 or 800 mg dose there was still more than 80, 90, and 95% suppression, respectively. All dose groups receiving 20 mg or higher demonstrated statistical significance when compared with the predrug control values through 24 h ($P < 0·05$).

Discussion

DP-1904 is a potent and long-acting thromboxane synthetase inhibitor. Extensive clinical trials are in progress in the management of angina pectoris in Japan.

In the present study, pharmacokinetics and pharmacodynamics of DP-1904 in Japanese normal volunteers after a single oral dose were studied. There were no adverse reactions, subjective symptoms, or cardiovascular changes in the present studies.

DP-1904 was rapidly absorbed on an empty stomach. The C_{max}s were reached within 1 h after administration. Linear relations between the doses and C_{max}s and AUC were observed with the correlation coefficients for C_{max}s and AUC being 0·930 and 0·960, respectively. The total body clearance and renal clearance were almost constant at ascending doses (10 to 800 mg) (Table 1). These data indicated that the pharmacokinetics of DP-1904 was linear in the dose range studied and that absorption, distribution, metabolism and excretion of DP-1904 did not become saturated even at higher doses. The TXB_2 concentrations in serum were reduced more than 90% within 1 h even after the lowest 10 mg dose. The plasma concentrations and duration of the inhibition of TXB_2 formation were dose-dependent. Compared with other thromboxane synthetase inhibitors such as OKY-1581 (Ito et al 1983), dazoxiben (Tyler et al 1981), dazmegrel (Fischer et al 1983) and CGS-13080 (MacNab et al 1984), the time course of TXB_2 inhibition was significantly prolonged and the effective doses were considerably lower with DP-1904. Although the plasma half life of DP-1904 was short (about 0·5 h) and in most of the subjects plasma concentrations of DP-1904 were barely quantifiable 12 h after the single oral doses, the simultaneously measured TXB_2 concentrations were still reduced by 70 to 96% of predrug control values for doses higher than 100 mg. A possible explanation for this finding could be the high affinity of DP-1904 for thromboxane synthetase in platelets or other tissues.

Table 4. Percent of serum thromboxane B_2 levels after single oral doses of DP-1904.

Dose mg	Predose TXB_2 serum level (ng mL^{-1})	TXB_2 level (% of control) 0·5	1·00	2·00	4·00	6·00	8·00	12·00	24·00
10	344	5·26	3·08	5·28	12·1	25·5		70·8	62·5
	±135	±0·91	±0·60	±1·37	±2·69	±4·02	NT	±25·0	±20·0
20	216	5·10	3·82	5·26	13·1	19·7		47·5	61·7
	±25	±0·47	±0·53	±0·21	±1·91	±3·33	NT	±6·30	±8·83
50	75	8·72	9·20	15·1	15·1	17·0		39·0	67·2
	±20	±3·96	±2·88	±6·94	±5·39	±4·73	NT	±6·79	±6·22
100	117	5·22	6·14	5·48	10·3	13·1	19·4	30·4	53·7
	±23	±1·11	±2·09	±1·32	±3·36	±3·12	±5·42	±8·67	±14·0
200	83	2·17	3·35	2·63	3·90	7·35	9·65	17·5	19·6
	±16	±0·31	±1·39	±0·49	±0·93	±1·91	±1·89	±6·38	±4·37
400	308	3·22	3·18	2·58	5·62	4·54	5·90	10·5	30·5
	±93	±0·90	±0·57	±0·35	±1·33	±0·45	±0·50	±1·05	±6·42
800	260	2·92	2·78	2·78	2·22	2·66	2·44	4·24	13·6
	±56	±0·59	±0·98	±1·02	±0·64	±1·19	±0·46	±0·78	±2·62

NT = not tested.
(Mean ± s.e.).

About half of the dose administered was recovered in urine as an unchanged form up to 48 h after the 400 mg dosing. Faecal excretion of DP-1904 until 48 h post dose accounted for only ca 0·5% of the administered dose. These data suggest that DP-1904 was almost completely absorbed from the gastrointestinal tract and that about half of the dose given was excreted in urine or faeces as metabolites.

The effects of the meal on the pharmacokinetics of DP-1904 was investigated by comparing the pharmacokinetic parameters obtained in the single 400 mg dose in fasted state and non-fasted state. The food intake slightly delayed the absorption of DP-1904 from the gastrointestinal tract, but the differences in all pharmacokinetic parameters between fasting and non-fasting states were not statistically significant ($P < 0·05$).

In conclusion, the data obtained in the present study show that the kinetics of DP-1904 is linear in the dose range studied and that DP-1904 is a selective and long-acting inhibitor of thromboxane synthetase. The absence of any adverse effects or signs of toxicity has encouraged us to proceed with further studies of this compound in normal volunteers and in patients.

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