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Pharmacological effects of (±)-11-deoxy, 16-phenoxy-prostaglandin E_1 derivatives in the cardiovascular system

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1 M&B 28,767 [(±)-11-deoxy-16-phenoxy-17,18,19,20-tetranor prostaglandin E_1] and a series of close analogues have been compared with U-46619 [(15S)-hydroxy-11α, 9α-(epoxymethano)-prosta-(5Z,13E)-dienoic acid] for prostaglandin endoperoxide-like pharmacological actions *in vitro* and *in vivo*.

2 M&B 28,767 caused powerful dose-related contraction of rabbit aorta (EC_{50}: 2.0 μM) and mesenteric artery (EC_{50}: 0.2 μM) strips *in vitro*, but was less active than U-46619 and/or noradrenaline.

3 M&B 28,767 induced rapid and irreversible aggregation of rat (0.9 times potency of U-46619) and human (0.25 times potency of U-46619) platelets in platelet-rich plasma (PRP) *in vitro*.

4 Intravenous administration of M&B 28,767 to urethane-allobarbitone anaesthetized rats produced immediate and dose-related thrombocytopoenia (equipotent with U-46619), accompanied in some animals by transient small pressor effects at low doses ($1-2\,\mu g\,kg^{-1}$) which were not statistically significant and invariably by sharp depressor effects at higher doses ($3-10\,\mu g\,kg^{-1}$). U-46619 caused moderate, but not dose-related, pressor effects at all doses tested.

5 Considerable variation in potency occurred amongst the thirteen structural analogues of M&B 28,767.

6 Platelet aggregatory activity for those members of the 11-deoxy 16-phenoxy-PGE_1 series tested in rat PRP *in vitro* demonstrated a positive and significant correlation with pro-aggregatory activity *in vivo* and agonist potency on rabbit aortic strip *in vitro*.

Introduction

The potent anti-secretory and anti-ulcer activity of a series of novel (±)-11-deoxy, 16-phenoxy-prostaglandin E_1 derivatives synthesized in these laboratories has previously been described (Banerjee *et al.*, 1981a).

Certain closely related 16-aryloxy analogues of $PGF_{2\alpha}$ possessing luteolytic properties have also demonstrated powerful broad spectrum agonist properties on a number of different tissues (Dukes *et al.*, 1974; Crossley, 1975; Broughton *et al.*, 1980). Indeed, when later examined for effect on bronchial and vascular smooth muscle from guinea-pig and rabbit *in vitro*, agonist activity comparable to that of the natural prostaglandin endoperoxides and synthetic prostaglandin H_2 (PGH_2) analogues was observed in some cases (Jones & Marr, 1977; Jones & Wilson, 1978). These published data, together with some preliminary pharmacological evaluation of the 11-deoxy 16-phenoxy-PGE_1 series (Tuffin *et al.*, 1980), prompted a thorough investigation of the prostaglandin endoperoxide-like properties of these compounds.

The parent structure M&B 28,767 previously referred to as Compound No. 1 (Banerjee *et al.*, 1981a) [(±)-11 deoxy-16 phenoxy-17,18,19,20 - tetranor PGE_1] and thirteen selected analogues have been examined for agonist activity on rat platelet-rich plasma and rabbit aorta smooth muscle *in vitro*, and for effects on rat circulating platelet count and systolic blood pressure *in vivo*. In addition, the pro-aggregatory effect of M&B 28,767 on human platelet-rich plasma was also investigated in parallel with known pro-aggregatory agents (ADP, collagen,

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and arachidonic acid). (15S)-hydroxy-11α, 9α-(epoxymethano)-prosta-(5Z, 13E)-dienoic acid (U-46619), a stable prostaglandin endoperoxide analogue (Bundy, 1975) possessing potent pro-aggregatory and smooth muscle agonist properties (Fitzpatrick *et al.*, 1978; MacIntyre *et al.*, 1978; Coleman *et al.*, 1981) was also included for direct comparison in all studies.

Methods

Arterial smooth muscle in vitro

Rabbits (NZW males, 3.0–3.5 kg) were stunned by a blow on the head, exsanguinated, and the thoracic aorta and mesenteric artery removed. Arterial strips were cut spirally, set up in cascade fashion, and superfused with warmed (37°C) and gassed (95% O_2, 5% CO_2) Krebs balanced salt solution containing indomethacin (1.0 μg ml^{-1}) and a mixture of antagonists (Vane, 1964) at a flow rate of 10 ml min^{-1}. Dimensions of the arterial strips were approximately 3 mm width × 30 mm length (aorta) and 1.5 mm width × 20 mm length (mesenteric artery). Test compounds and noradrenaline were added to the Krebs medium as required, and superfused over the assay tissues for a contact time of 2 min. Contractions (mm displacement) were measured by means of Harvard smooth muscle isotonic transducers under initial tension of 1.5 g (aorta) or 1.0 g (mesenteric artery) connected to a Devices multichannel pen recorder. Each test compound and noradrenaline were superfused at a range of concentrations sufficient to obtain log dose-response data for comparison with M&B 28,767 by parallel line assay, maximal responses not being achieved in all cases.

Platelet aggregation in vitro

Blood was collected in a heparinized syringe (5 uml^{-1}) from the abdominal aorta of rats anaesthetized with pentobarbitone (Sprague-Dawley 400 g males), pooled, and centrifuged at 300 *g* for 15 min. Platelet-rich plasma (PRP) was taken off, and platelet-poor plasma (PPP) obtained by recentrifugation of the remaining blood at 1500 *g* for 10 min. PRP cell counts were adjusted with PPP to 1.0×10^9 ml^{-1}.

Human PRP and PPP were prepared from a 20–30 ml sample of ante-cubital venous blood collected from healthy male volunteers aged 18–35 years who had not taken any medication for at least 7 days. The blood was mixed with 3.15% trisodium citrate solution (10% v/v), and centrifuged at 150 *g* for 20 min to obtain PRP. PPP was again prepared by further centrifugation at 1500 *g* for 10 min. If necessary, the volume of PRP was adjusted with PPP to give a final platelet count of approximately 2.5×10^8 cells ml^{-1}.

Aggregation of both rat and human PRP was measured turbidometrically by means of a two channel platelet aggregometer (Malin Electronics) and pen recorder, with the plasma at 37°C, a stirrer speed of 1000 r.p.m., and the recording wavelength set at 660 nm. The parameters determined for each agonist were:

(1) EC_{min}: The threshold concentration (μM) of drug causing first detectable aggregation.

(2) ΔT_{50}: the concentration (μM) of drug causing a 50% increase in light transmission at 4 min after addition to PRP (from which relative activity values are derived).

Platelet aggregation in vivo

Rats (Sprague-Dawley 450–600 g males) were anaesthetized with urethane-dial (12 g:1 g) by intraperitoneal injection 0.1 ml 100 g^{-1} body weight. No systemic anticoagulant was administered. The trachea was cannulated to ensure a free airway, and to allow artificial ventilation if required. The left femoral vein was cannulated to allow administration of test compounds. A specially designed double cannula (Smith & Freuler, 1973) was inserted into the right carotid artery such that trisodium citrate (3.15%) was continuously pumped through the outer part of the cannula to the tip at a flow rate of 0.015 ml min^{-1} and mixed with arterial blood at the tip. Citrated blood was simultaneously pumped out of the carotid artery through the inner part of the double cannula at a flow rate of 0.1 ml min^{-1} into the manifold of a Technicon Platelet Autocounter. The rats had baseline circulating platelet counts in the range $7.0–11.0 \times 10^8$ ml^{-1}. Arterial blood pressure was monitored from a femoral artery throughout each experiment. The pro-aggregatory activity of prostaglandins administered i.v. was determined by comparison of ED_{20} values (the bolus dose causing a 20% fall in circulating platelet count). The effect of vehicle was determined using comparable dose volumes (0.05–0.2 ml).

Chemicals

All the compounds studied were synthesized in our laboratories and have been described by Banerjee *et al.* (1978), and Broughton *et al.* (1980).

M&B 28,767 and each of its analogues (0.5–1.0 mg) were initially dissolved in 0.2 ml ethanol, converted to the sodium salt by addition of one equivalent of sodium carbonate and diluted with Krebs or physiological saline as required. The following agents were used: arachidonic acid (99% pure,

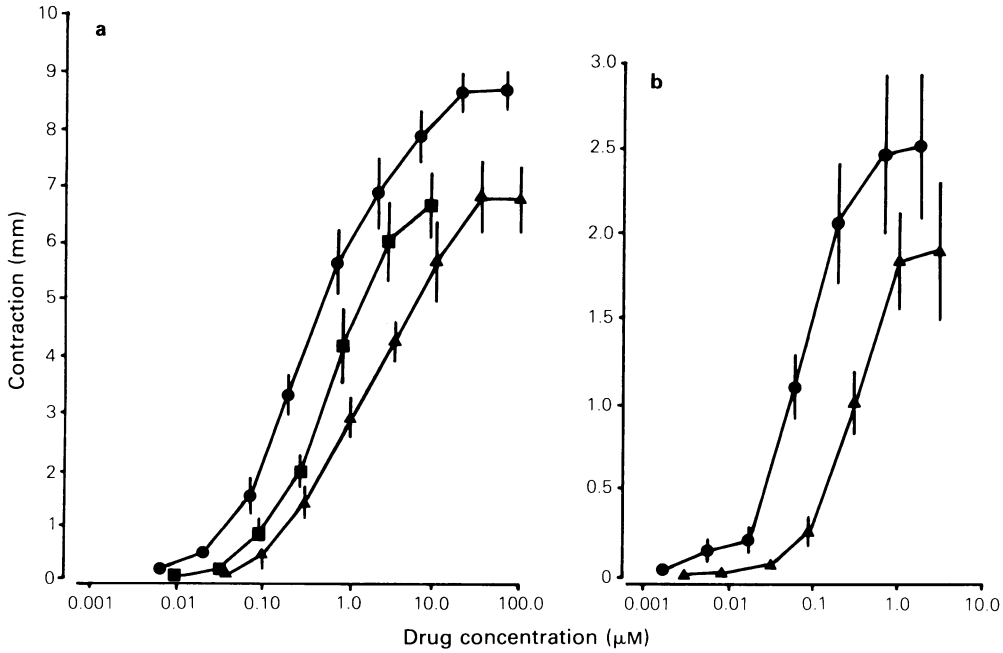

Figure 1 Log concentration-effect curves for the agonist activity of M&B 28,767 (▲), U-46619 (■) and noradrenaline (●) on superfused rabbit aorta (a) and mesenteric artery strips (b) *in vitro*. Each drug concentration was superfused for a tissue contact period of 2 min. The curves were constructed using pooled data derived from 3–8 experiments for each agonist; values are mean with vertical lines showing s.e.mean.

Sigma), adenosine diphosphate (BDH), 5,5′-diallyl barbituric acid (Sigma), noradrenaline (Koch Light Labs.), urethane (Sigma), PGI_2 (Ono Pharmaceutical Co.), and (15S)-hydroxy-11α-9α-(epoxymethano)-prosta-(5Z,13E)-dienoic acid (U-46619; Upjohn Co.).

Statistical analysis

Raw pharmacological data were analysed by Student's *t* test. Relative potency for M&B 28,767 analogues on rabbit aorta strip was estimated from dose-response data using a parallel line assay, EC_{100} not being achieved in all cases. Linear regression and correlation coefficient analysis (*r*) was carried out between *in vitro* and *in vivo* parameters as specified in the text. $P < 0.05$ was taken as indicating a significant result in each of the above statistical tests.

Results

Arterial smooth muscle in vitro

M&B 28,767, U-46619 and noradrenaline each caused strong and dose-related contractions of rabbit aorta and rabbit mesenteric artery strips at concentrations in the range 10^{-8} to 10^{-4} M (Figure 1). In

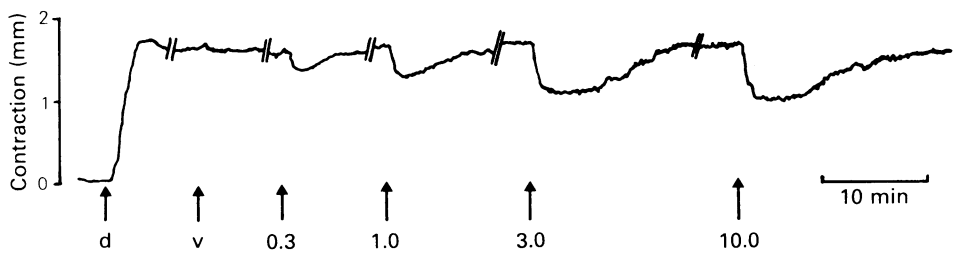

Figure 2 Effect of prostaglandin I_2 (PGI_2, 0.3–10.0 μM) on superfused rabbit mesenteric arterial strip tone induced by M&B 28,767 (1.0 μM). Superfusion of M&B 28,767 (d) was continued throughout the experiment. PGI_2 vehicle (v) and successive increasing concentrations of PGI_2 were added to the perfusate for tissue contact periods of 2 min.

contrast to noradrenaline, the responses of the rabbit aorta to M&B 28,767 and U-46619 were of long duration, with relaxation to baseline requiring at least 30–60 min at the high doses tested. A similar long-lasting response to M&B 28,767 was obtained with the rabbit mesenteric artery but U-46619 was not tested on this tissue. Mean EC_{50} values obtained for M&B 28,767 when full relaxation to baseline was allowed between doses were 2.0 μM on rabbit aorta (0.4 times the potency of U-46619; 0.2 times the potency of noradrenaline) and 0.2 μM on rabbit mesenteric artery (0.4 times the potency of noradrenaline), as shown in Figure 1. A similar result was obtained if dose-response curves were constructed in cumulative fashion, the mean EC_{50} for M&B 28,767 being in this case 1.2 μM (0.3 times the potency of U-46619).

A stable, increased level of tone was induced in both rabbit arterial strips by continual perfusion of 1.0 μM M&B 28,767 (causing a sub-maximal effect on aorta, and maximal response on mesenteric artery). Incorporation of PGI_2 (0.1–10.0 μM) into the perfusate produced dose-dependent, partial relaxation of rabbit mesenteric artery (34.8 ± 5.9% at

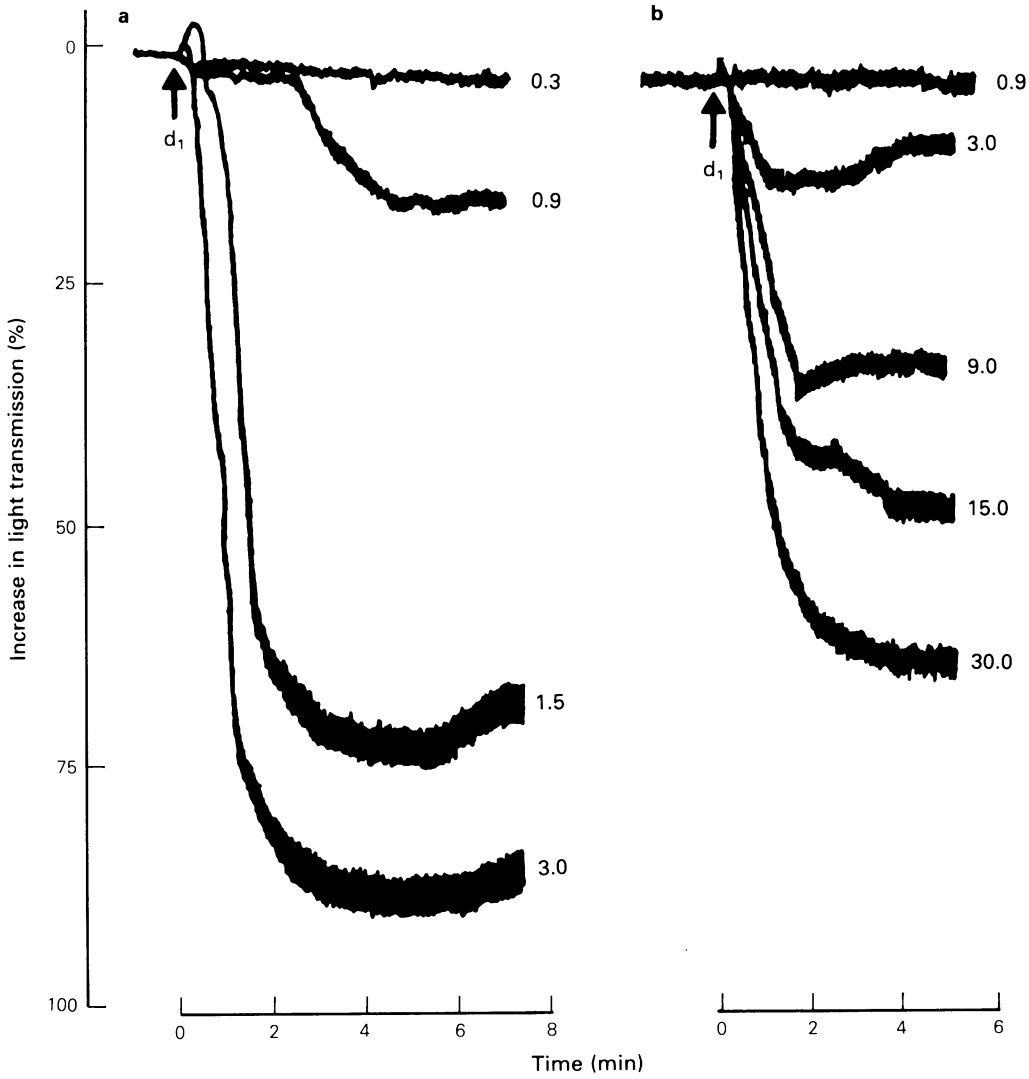

Figure 3 Pro-aggregatory effect of M&B 28,767 on rat (a) and human (b) platelet rich plasma (PRP) *in vitro*. Doses of M&B 28,767 are expressed as final plasma concentration (μM). Aggregation curves are superimposed to the point of addition of M&B 28,767 (d_1).

3.9 μM; Figure 2) but was without effect on the contraction of rabbit aorta.

Platelet aggregation in vitro

M&B 28,767 demonstrated potent, irreversible pro-aggregatory activity on both rat (Figure 3a) and human (Figure 3b) PRP *in vitro*. The mean EC_{min} and ΔT_{50} values obtained for M&B 28,767 in experiments with rat and human PRP are compared with those for U-46619, arachidonic acid (AA), collagen and ADP in Table 1.

M&B 28,767 was approximately equiactive with U-46619 and ADP on rat PRP (0.9 times potency of both U-46619 and ADP), less active than U-46619 but approximately equiactive with ADP on human PRP (0.2 times potency of U-46619; 0.8 times potency of ADP), and substantially more active than arachidonic acid on both rat (486 times potency of AA) and human (55 times potency of AA) PRP *in vitro*. However, whereas U-46619 appeared equipotent as a pro-aggregatory agent in PRP from both species, M&B 28,767 was about six fold less active in human compared to rat PRP.

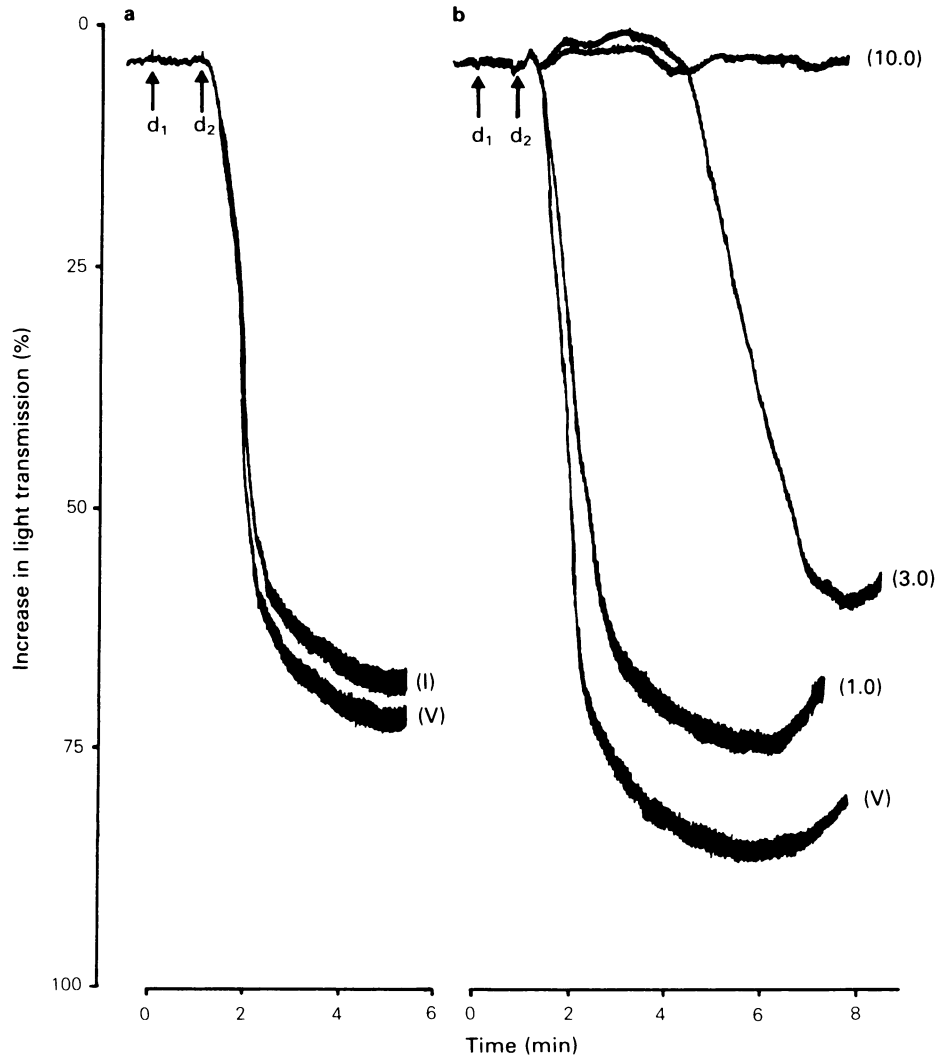

Figure 4 Effect of indomethacin (a) and prostaglandin I_2 (PGI_2) (b) on M&B 28,767-induced aggregation of rat PRP *in vitro*. Indomethacin (I) at a concentration of 84 μM, PGI_2 at concentrations of 1, 3 and 10 nM, or the respective vehicles (V) were added to rat PRP (d_1) 1 min before 3 μM M&B 28,767 (d_2). The resulting aggregation curves are shown superimposed to the point of addition of M&B 28,767.

Table 1 Comparison of pro-aggregatory activity on rat and human platelet-rich plasma (PRP) *in vitro*

	Rat PRP		*Human PRP*	
Pro-aggregatory agent	EC_{min} (μM) mean	ΔT_{50} (μM) mean ± s.e.mean	EC_{min} (μM) mean	ΔT_{50} (μM) mean ± s.e.mean
M&B 28,767	0.8	1.4 ±0.21	2.7	8.1 ±2.2
U-46619	0.7	1.3 ±0.15	0.3	2.0 ±0.3
Arach. Acid	550	680 ±49	394	443 ±33
ADP	0.2	1.2 ±0.13	0.5	6.1 ±0.8
Collagen*	1.0	4.1 ±0.3	0.3	1.4 ±0.2

Dose-response curves were constructed from pooled data for each pro-aggregatory agent on rat and human PRP to determine the concentration causing threshold aggregation (EC_{min}) and 50% increase in light transmission (ΔT_{50}) at 4 min after addition to PRP.
The data shown are pooled from 5–8 occasions with the exception of U-46619 on human PRP ($n = 3$). Relative activities quoted in the text are derived from ΔT_{50} values.
*Concentrations expressed as $\mu g\ ml^{-1}$.

Indomethacin (3–84 μM) was inactive against the M&B 28,767-induced aggregatory response (Figure 4a). PGI_2 methyl ester (1–30 nM) inhibited M&B 28,767-induced aggregation of rat PRP in dose-related fashion ($P < 0.02$), with progressive increases in delay time prior to onset of aggregation being recorded in conjunction with significantly reduced responses (Figure 4b).

Platelet aggregation and cardiovascular effects in vivo

In the anaesthetized rat intravenous injection of veh-

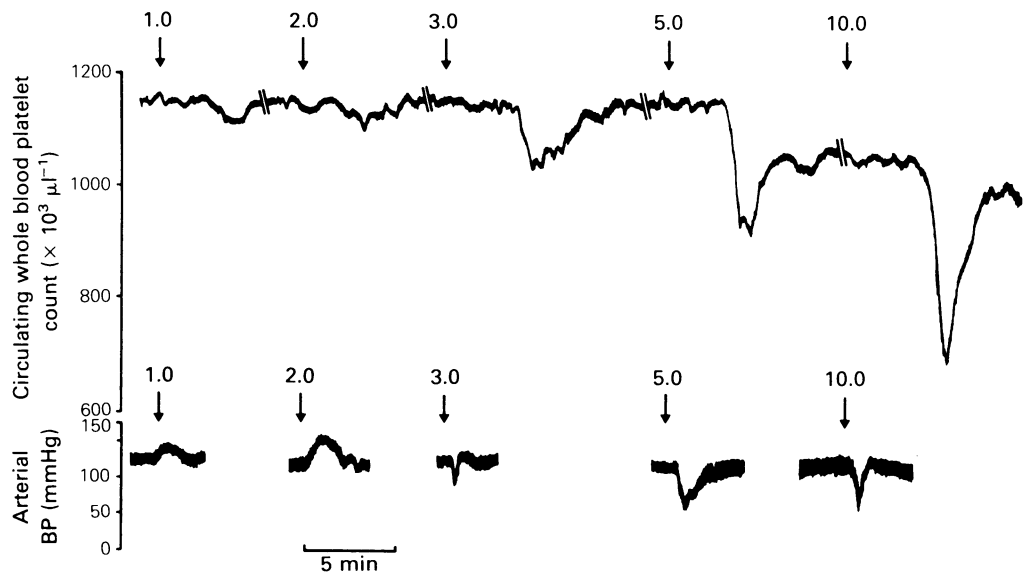

Figure 5 Effect of M&B 28,767 on circulating whole blood platelet count and arterial blood pressure in the anaesthetized rat. The drug was administered intravenously in bolus doses via a femoral vein indwelling cannula. Doses shown are $\mu g\ kg^{-1}$. Platelet responses occurred simultaneously with effects on arterial BP, but are offset on the trace due to a 3 min lag-phase in the platelet autoanalyser.

icle in volumes up to 0.1 ml had no effect on either platelet count or arterial blood pressure. Progressively increasing intravenous bolus doses of M&B 28,767 (range 1–10 $\mu g\,kg^{-1}$) administered at 15 min intervals caused sharp, dose-related falls in circulating platelet count (22.7 ± 4.2% at 10 $\mu g\,kg^{-1}$). Low doses (< 2 $\mu g\,kg^{-1}$) induced transient pressor effects in four out of seven animals, whereas doses > 2 $\mu g\,kg^{-1}$ always caused substantial decreases in arterial blood pressure (42.7 ± 4.3% at 10 $\mu g\,kg^{-1}$) (Figures 5 and 6). All changes in BP and platelet count were significant ($P < 0.05$) with intravenous M&B 28,767 at 3, 5 and 10 $\mu g\,kg^{-1}$. The effects at 3–10 $\mu g\,kg^{-1}$ were invariably accompanied by severe respiratory distress (requiring ventilation if respiration ceased completely) and doses > 10 $\mu g\,kg^{-1}$ were frequently fatal.

U-46619 demonstrated very similar dose-related effects on circulating platelet count (Figure 6), but in direct contrast to M&B 28,767, these responses were always accompanied by moderate and transient (1–3 min duration) increases in arterial blood pressure. The pressor effects observed with U-46619 were not apparently dose-related. Severe respiratory distress was also observed with high doses (3–10 $\mu g\,kg^{-1}$) of U-46619.

Analogues of M&B 28,767

Thirteen selected analogues of M&B 28,767 were compared with the parent compound under identical experimental conditions (Table 2). Agonist responses of the rabbit aortic strip preparation were without exception similar in nature to those observed with M&B 28,767, being slow in onset particularly at lower doses, and of long duration. In all cases threshold concentrations for agonist activity in this test did not correlate with relative activity to the parent compound, as determined by parallel line assay of log dose-response curves (Table 2).

In rat PRP *in vitro*, aggregation induced by all of the analogues which possessed activity was of the irreversible monophasic type, whereas *in vivo*, the responses were reversible, and circulating platelet counts generally returned to near pre-dose levels within 5–7 min of the maximum fall being observed. No structure-activity relationship emerged from measurement of arterial blood pressure, apart from characteristic sharp falls simultaneous with aggregation observed with all of the pro-aggregatory prostaglandin analogues except the 2-chloro derivative (X).

The 15-β-hydroxy derivative of M&B 28,767 (I) appeared significantly less pro-aggregatory on rat platelets *in vitro* and *in vivo* ($P < 0.05$ in both cases), but proved an equipotent agonist on rabbit aortic strip *in vitro*. The 17-phenyl (II) and 9α-hydroxy (IV) analogues were substantially less active in all tests, whereas the 13,14-dihydro compound (III) retained moderate pro-aggregatory activity *in vitro* and *in vivo*.

Incorporation of substituent groups in the 16-phenoxy moiety at the 4-position led in some cases to reduction or loss of *in vitro* pharmacological activity in these tests, as evidenced by the 4-methyl (V), 4-methoxy (VI), 4-cyano (VII) and 4-hydroxy (VIII)

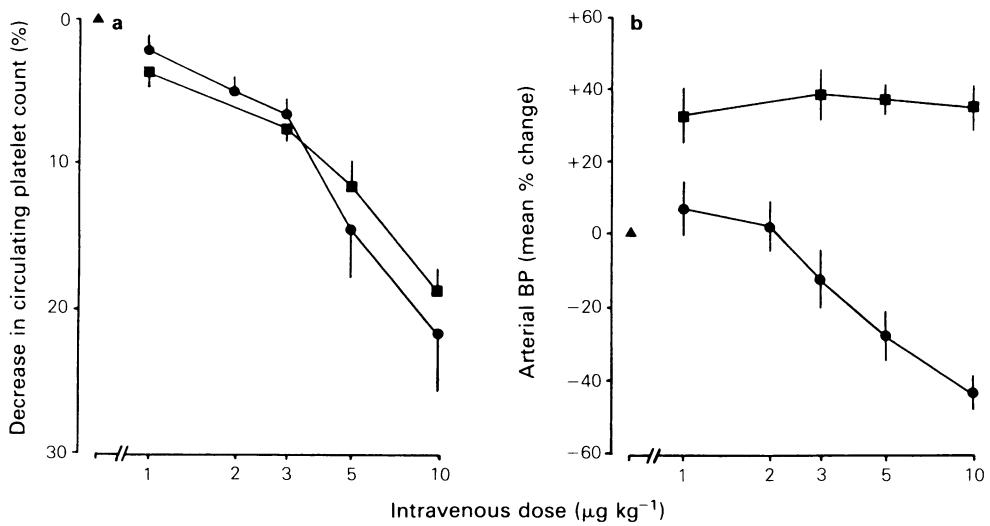

Figure 6 Effect of M&B 28,767 (●) and U-46619 (■) on circulating whole blood platelet count (a) and arterial blood pressure (b) in the anaesthetized rat. Vehicle (V) at equivalent dose volumes (0.05–0.2 ml) had no effect on either parameter. Each data point is the mean result from seven experiments; vertical lines show s.e.mean.

Table 2 A comparison of the proaggregatory and vascular smooth muscle agonist activity of M&B 28,767 and a series of structural analogues, *in vitro* and *in vivo*

(11, deoxy, 16-phenoxy PGE_1 analogues

		In vitro *studies*				In vivo *studies* (Rat)			
		Agonist activity on rabbit aortic strip		*Proaggregatory activity rat PRP*		*Fall in circulating platelet count*		*Arterial blood pressure† (mean % change)*	
	R	EC_{min} (nM)	Relative activity (M&B 28,767 = 1)	ΔT_{50} (μM)	Relative activity (M&B 28,767 = 1)	ED_{20} ($\mu g\,kg^{-1}$)	Relative activity (M&B 28,767 = 1)	$10\,\mu g\,kg^{-1}$	$100\,\mu g\,kg^{-1}$
M&B 28,767	CH=CH.CH(OH).CH_2O-Ph	104.3	1.00	1.6	1.00	7.8	1.00	−42.7	ND
I	CH=CH.CH(OH).CH_2O-Ph	76.9	1.30	4.0	0.40	39.5	0.19	+5.4	ND
II	CH=CH.CH(OH).CH_2CH_2-Ph	805.4	0.07	>25.0	>0.05	>100.0	<0.10	+6.9	+34.6
III	CH_2CH_2.CH(OH).CH_2O-Ph	53.1	0.11	4.0	0.40	18.0	0.43	−42.2	ND
IV*	CH=CH.CH(OH).CH_2O-Ph	284.5	0.18	>25.0	<0.05	>100.0	<0.10	+38.8	+47.6
V	CH=CH.CH(OH).CH_2O-Ph-CH_3	185.6	0.38	7.7	0.21	>100.0	<0.10	+29.8	+26.7
VI	CH=CH.CH(OH).CH_2O-Ph-OCH_3	802.1	0.04	>25.0	<0.05	>100.0	<0.10	+5.6	+31.3
VII	CH=CH.CH(OH).CH_2O-Ph-CN	450.6	0.31	>25.0	<0.05	>100.0	<0.10	+4.1	−13.7
VIII	CH=CH.CH(OH).CH_2O-Ph-OH	25641.0	0.01	>25.0	<0.05	>100.0	<0.10	+16.8	+6.6
IX	CH=CH.CH(OH).CH_2O-Ph-Br	33.1	0.79	17.9	0.09	>100.0	<0.10	+45.4	+29.3
X	CH=CH.CH(OH).CH_2O-Ph(Cl)	39.2	1.24	4.8	0.33	30.0	0.26	+47.7	+12.7
XI	CH=CH.CH(OH).CH_2O-Ph(Cl)	489.6	0.08	>25.0	<0.05	>100.0	<0.10	+13.5	+22.9
XII	CH=CH.CH(OH).CH_2O-Ph-Cl	11.5	4.75	8.4	0.19	30.0	0.26	+22.8	−59.4
XIII	CH=CH.CH(OH).CH_2O-Ph-F	8.9	2.85	0.4	4.00	7.2	1.08	−49.4	ND

All compounds tested as the Na salt, exactly as described for M&B 28,767, ($n > 6$) for all compound treatment groups. ND = not determined.
Rabbit aorta: EC_{min} = response threshold concentration (nM).
Rat platelets: ΔT_{50} = concentration causing a 50% increase in light transmission *in vitro* (μM).
Rat platelets: ED_{20} = i.v. dose causing a 20% fall in circulating platelet count ($\mu g\,kg^{-1}$).
* = 9α-hydroxy.
† + signifies increase, − decrease in arterial blood pressure.

examples shown, although substitution in the 4-position retained or improved activity *in vitro* and *in vivo* in some cases, with an overall activity trend F > Cl > Br (XIII, XII and IX respectively). Interestingly, the 3-chloro analogue (XI) was much less active than the 2 or 4-chloro substituted derivatives (X and XII) *in vitro* and *in vivo*.

Linear regression analysis of the full data from which Table 2 is derived showed a highly significant correlation between *in vitro* agonist activity on rabbit aorta strip and *in vitro* pro-aggregatory activity on rat PRP ($r = 0.81$; $P < 0.02$). Similarly, a high degree of correlation resulted from comparison of pro-aggregatory activity on rat platelets *in vitro* and *in vivo* for the series ($r = 0.90$; $P < 0.01$). No correlation was obtained between the effects observed on arterial blood pressure and any other *in vitro* or *in vivo* parameter.

Discussion

These results demonstrate that the 11-deoxy, 16-phenoxy-PGE$_1$ derivative, M&B 28,767, possesses significant agonist activity on rabbit arterial smooth muscle and rat or human platelets *in vitro*, and is a potent pro-aggregatory agent when administered intravenously *in vivo*. This compound has also previously been shown to cause powerful contraction of guinea-pig tracheal smooth muscle preparations *in vitro* (Tuffin *et al.*, 1980).

U-46619 is considered to be a selective thromboxane A$_2$ (TXA$_2$) mimetic, acting at PGH$_2$/TXA$_2$ receptors. The potent *in vitro* pro-aggregatory and vascular smooth muscle agonist activity of U-46619 observed here is in close agreement with that widely reported elsewhere (Malmsten, 1976; Jones & Wilson, 1978; Best *et al.*, 1979; Coleman *et al.*, 1980a; 1981; Di Minno *et al.*, 1981). In contrast, the rapid falls in rat circulating platelet count observed in our experiments following intravenous administration of U-46619 were not observed by Smith & Duncan (1981) using an identical model.

The type of prostanoid receptor stimulated by U-46619, M&B 28,767, and other previously reported PGD and PGF$_{2\alpha}$ derivatives in which the C17-C20 group has been replaced by a 16-phenoxy moiety is of considerable interest. Although this will not be resolved without further investigation, the similar characteristic activity and comparable order of potency of U-46619 and M&B 28,767 in the majority of our test systems, *in vitro* and *in vivo*, indicates that both agents may activate a common receptor. The only difference between the activities of M&B 28,767 and U-46619 was the vasodepressor effect of the former at doses $> 2\ \mu g\ kg^{-1}$ i.v. Vasopressor effects of U46619 in the guinea-pig and dog have previously been reported (Jones & Marr, 1977; Jones & Wilson, 1981). The reason for the contrasting effects of M&B 28,767 and U-46619 on arterial BP is not clear, but in this model, cardiovascular changes are difficult to interpret. Contributory factors are certain to include direct agonist actions on the pulmonary circulation and peripheral resistance vessels, together with vascular effects secondary to platelet aggregation and the release of additional pharmacologically active agents. In addition to its thromboxane-like activities, M&B 28,767 ressembles E type prostaglandins in that it causes emesis and diarrhoea in dogs, inhibits gastric acid secretion and reduces gastric ulceration induced by indomethacin in rats (Banerjee *et al.*, 1981b). This suggests that M&B 28,767, unlike U46619, can also stimulate a second prostanoid (PGE type) receptor which may account for its observed vasodepressor action in rats. A prostanoid receptor with praticularly high sensitivity to the natural prostaglandin endoperoxides and U-46619, present in vascular and bronchial smooth muscle, has recently been described (Coleman *et al.*, 1980b). Furthermore, TXA$_2$, PGH$_2$, 9,11azo PGH$_2$, 9,11-epoxymethano PGH$_2$, 11,9-epoxymethano PGH$_2$ (U-46619), 9,11-ethano PGH$_2$, ICI 79939 (rac 17,18,19,20 - tetranor - 16 - *p* - fluorophenoxy PGF$_{2\alpha}$), compounds with partial agonist activity on the platelet thromboxane system (e.g. CTA$_2$), and thromboxane/endoperoxide analogues which specifically antagonize thromboxane-like actions on the human platelet (e.g. PTA$_2$ and EP045) have been shown to displace [15-^{3}H-9,11-epoxy-methano]-PGH$_2$ from human platelet receptor sites using an *in vitro* ligand binding assay (Jones *et al.*, 1981; Amstrong *et al.*, 1983).

Amongst the close analogues of M&B 28,767 examined here, those with 4-halogen substituted 16-phenoxy groups showed a similar pharmacological profile, the 4-fluoro compound being particularly active in this respect. These findings agree with published data for 16-aryloxy PGF$_{2\alpha}$ derivatives, where the equivalent compound ICI 79939 (above) was also particularly potent (Jones & Marr, 1977). Nevertheless, there appears to be an opportunity for structural variation within the 11-deoxy, 16-phenoxy PGE$_1$ series to decrease selectively the undesirable pro-aggregatory and smooth muscle agonist properties while maintaining the desirable therapeutic activity in other areas. In several analogues with alternative substituents in the 16-phenoxy group, prostaglandin endoperoxide-like properties were either substantially reduced or abolished. Studies are in progress to develop this possibility, but it is clear that careful evaluation of novel prostaglandin derivatives of this type in a wide spectrum of tests is essential in the search for safe and selective therapeutic agents.

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