PLATELETS AND VASCULAR OCCLUSION

Platelet actions of stable carbocyclic analogues of prostacyclin

BRENDAN J. R. WHITTLE, PH.D., AND SALVADOR MONCADA, M.D., Ds.C.

SINCE THE TIME of the discovery of prostacyclin and the elucidation of its chemical structure as prostaglandin (PG) (5Z)-9-deoxy-6, 9 α-epoxy-Δ³PGF₃, many synthetic prostacyclin analogues have been prepared and reported in the literature. Although prostacyclin (epoprostenol) is now available for clinical use as the freeze-dried sodium salt that, when mixed with the diluent buffer (sodium chloride 0.15% weight per volume [wt/vol] and glycine buffer solution 0.19% wt/vol; pH 10.5), results in a preparation that will remain stable over 24 hr when stored at 2° to 8° C, there is much interest in synthesizing a chemically stable analogue with a biological profile comparable to that of the parent prostacyclin. Furthermore, the definitive separation of the platelet and vascular activities in an orally active synthetic prostacyclin analogue, both for use as a research tool and as a clinically useful agent, is an ultimate objective in the development of prostacyclin mimetics.

Many structural variants of prostacyclin have been synthesized, including 5,6-dihydro analogues, exemplified by 6β-PGl₁, thia prostacyclins such as (5Z)-6,9-thia prostacyclin, nitrogen-containing analogues such as 9-deoxy-9α-6-nitro-PGF₄, ring-expanded 5,9-epoxy derivatives such as 9-deoxy-5, 9α-epoxy-PGF₄, and interphenylene analogues. However, the synthesis and biological actions of stable carbocyclic analogues of prostacyclin, in which the enol-ether oxygen atom is replaced by a methylene group, has attracted much attention and has been described by several groups.

Carbacyclin analogues. Carbacyclin, or (5E)-6α carboprostaglandin I₂ (figure 1, A), inhibits human platelet aggregation induced by a variety of agents including ADP, collagen, and arachidonic acid, while also inhibiting aggregation in platelet-rich plasma (PRP) obtained from several species, including the rabbit, rat, and dog. In our studies with carbacyclin, this stable analogue was 0.03 times as potent as prostacyclin as an inhibitor of aggregation induced by ADP (table 1), collagen, and arachidonic acid. As with prostacyclin, the antiaggregating activity of carbacyclin was enhanced by preincubation of platelets with theophylline, the phosphodiesterase inhibitor, indicating stimulation of cyclic AMP as its mechanism of inhibitory action. Indeed, other studies have shown an elevation of platelet cyclic AMP after incubation with the analogue.

Carbacyclin has been shown to be a potent inhibitor of platelet aggregation ex vivo when infused intravenously in the dog and rabbit, being 0.1 times as active as the parent, prostacyclin. Likewise, this analogue was effective in vivo in reducing formation of thrombi in canine coronary arteries when infused intravenously. Studies with carbacyclin in anesthetized baboons have likewise shown inhibition of platelet aggregation determined ex vivo after intravenous or intragastric administration.

In our studies in human PRP with analogues synthesized and supplied by the Upjohn Company, (5Z)-carbacyclin was less active than the (5E)-analogue, the latter being isosteric with naturally occurring prostacyclin (5Z-PGIl). As expected, the (15R)-epimer had minimal activity, as did the 2-nor derivative (table 1). Substitution in the 9 position can also alter antiaggregating potency, with (5Z)-9β-ethyl-9 cyanogroups enhancing activity and 9β-methyl, 9-pentyl-1-ynyl, and 9-ethyl groupings decreasing activity compared with that induced by carbacyclin itself (table 1).

Studies in human PRP with 9β-methyl-carbacyclin (ciprostene; figure 2, B) have shown it to have comparable potency as an antiaggregating agent against several aggregating agents (table 2). This compound is equipotent in vitro in human PRP and whole blood, and elevates platelet cyclic AMP levels.

Studies using further derivatives of carbacyclin have been reported, and the 15-cyclopropyl-ω-pentanor carbacyclin derivative (ONO 41483, figure 1, B) has been shown to have 0.1 times the activity of prostacyclin as
an inhibitor of human platelet aggregation in vitro,\textsuperscript{20, 21} as shown in table 3. In addition, this analogue inhibited platelet aggregation, determined ex vivo after intravenous infusion or oral administration in the baboon, and exhibited vasodepressor actions after bolus intravenous administration.\textsuperscript{20}

Further chemically stable analogues based on the carbacyclin structure have been reported. The 16-methyl, 18-19-didehydro derivative (figure 1, \textit{D}) has been shown to have potent antiaggregating properties, inhibiting human platelet aggregation in vitro induced by a variety of agents\textsuperscript{22} in a concentration range similar to that of prostacyclin (table 3). This analogue (ZK 36374 or iloprost) also induced disaggregation of platelets in vitro in cat whole blood, such platelet aggregates being formed in vivo after surgery.\textsuperscript{23} In addition, intravenous infusion reversed the fall in platelet number after coronary artery ligation in the cat.\textsuperscript{23} Other studies conducted in the rat have shown this carbacyclin derivative to inhibit platelet aggregation in vitro in PRP, and to have 0.3 times the activity of prostacyclin. This potency ratio is similar to that observed in the rat in vivo with respect to prolonging bleeding time in an extracorporeal circuit after intravenous infusion.\textsuperscript{24} Potent relaxation of bovine coronary artery strips in vitro and vasodepressor actions in the cat and rat have also been observed with this carbacyclin derivative.\textsuperscript{23}

A series of 13,14-didehydro carbacyclin analogues has also been reported.\textsuperscript{25} One such compound (figure 1, \textit{C}), like its 20-carbon homologue, inhibited rabbit platelet aggregation in vitro, while studies in vivo in the guinea pig, in which pulmonary accumulation of indium-labeled iloprost (D; 13,14-didehydro derivative (ONO 41483)) has also been observed,\textsuperscript{25} suggested that like prostacyclin, these compounds are rapidly inactivated.\textsuperscript{13} The extent and duration of the biological actions of prostacyclin and its analogues

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>IC\textsubscript{50} (ng ml\textsuperscript{-1})</th>
<th>Relative potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin</td>
<td>0.4 ± 0.1</td>
<td>1</td>
</tr>
<tr>
<td>(5E)-carbacyclin</td>
<td>11 ± 3</td>
<td>0.036</td>
</tr>
<tr>
<td>(5Z)-carbacyclin</td>
<td>700 ± 100</td>
<td>0.0006</td>
</tr>
<tr>
<td>(5E)-carbacyclin-methyl ester</td>
<td>140 ± 40</td>
<td>0.003</td>
</tr>
<tr>
<td>5E-{15}R}-carbacyclin</td>
<td>&gt;1600</td>
<td>0.0003</td>
</tr>
<tr>
<td>(5Z,9}B}-ethynyl-carbacyclin</td>
<td>2.2 ± 0.3</td>
<td>0.18</td>
</tr>
<tr>
<td>9}β-cyano-carbacyclin</td>
<td>7.1 ± 0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>9}β-methyl-carbacyclin</td>
<td>87 ± 11</td>
<td>0.005</td>
</tr>
<tr>
<td>9}β-pent-1-ynyl-carbacyclin</td>
<td>475 ± 175</td>
<td>0.0008</td>
</tr>
<tr>
<td>9}β-ethyl-carbacyclin</td>
<td>1348 ± 439</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Results given as the IC\textsubscript{50} value (concentration causing 50\% inhibition of platelet aggregation) after 1 min incubation at 37° C in PRP and as potency relative to prostacyclin, are the mean ± SEM from at least four experiments. Carbacyclin and its derivatives were synthesized as described\textsuperscript{11, 12, 19} and supplied by the Upjohn Company, Kalamazoo, MI.
in vivo may also be attenuated by the release of endogenous vasoactive substances, including renin and vasopressin.27-30

Like prostacyclin, carbacyclin has comparable vasodepressor activity when administered by the intravenous or intra-arterial route, indicating minimal pulmonary inactivation of this analogue.13 The finding that carbacyclin is a good substrate for the purified 15-hydroxy prostaglandin dehydrogenase derived from monkey lung31 lends support to the concept that these analogues fail to gain access to the enzyme in the intact lung. Like prostacyclin, these analogues will presum-
ably undergo metabolism elsewhere, including in the liver.

The prevention of enzymatic inactivation of prostacyclin analogues in vivo has been attempted by substitution in both $\beta$- and $\omega$-chains. Studies of the kinetics of 16-methyl-18,19-didehydro-carbacyclin (figure 1, D) after bolus intravenous injection in the rat have indicated a biphasic decline in plasma concentrations, with an initial half-life of 5 min.32 Although the kinetics of prostacyclin under comparable conditions was not investigated, these results suggest that the analogue does not exhibit a biologically significant longer duration of activity than prostacyclin, despite protection of the 15-hydroxy grouping from enzymatic attack. Studies in the baboon also suggest that this compound did not exhibit enhanced metabolic stability as compared with carbacyclin.33

In a further series of carbocyclic analogues, the 15-hydroxy group was protected by modification of the $\omega$-tail, e.g., by insertion of a 15-cyclohexyl grouping, while protection against $\beta$-oxidation was afforded by insertion of an $m$-carboxyphenylene residue.8 Despite such modifications (figure 2, A), these prostacyclin analogues still exhibited only a short duration of action, with the hypotensive effects ranging from 0.25 to 1.2 min. Only with supramaximal doses were any differences between the duration of biological action of the analogues detected, and thus such properties have no real clinical or experimental application.

These observations with chemically stable prostacyclin analogues thus suggest that a rapid elimination of the analogues, largely independent of the rate of metabolism of the compound, is of major importance in determining the plasma levels of active drug and hence the duration of cardiovascular and antiaggregating activity in vivo. It would therefore appear that until the pharmacokinetic parameters of these analogues are

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**TABLE 2**

Comparison of the ID$_{50}$ values$^a$ of prostacyclin and ciprostene (9$\beta$-methyl-carbacyclin) in human PRP aggregated with different aggregating agents, ADP, collagen, U-46619 (epoxy-methano PGH$_2$), and arachidonic acid.

<table>
<thead>
<tr>
<th>Aggregating agent</th>
<th>Prostacyclin (ng ml$^{-1}$)</th>
<th>Ciprostene (ng ml$^{-1}$)</th>
<th>Potency ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>$0.55 \pm 0.1$</td>
<td>$86.6 \pm 11$</td>
<td>0.01</td>
</tr>
<tr>
<td>Collagen</td>
<td>$0.91 \pm 0.08$</td>
<td>$123 \pm 32$</td>
<td>0.01</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>$1.8 \pm 0.7$</td>
<td>$55.8 \pm 17.6$</td>
<td>0.03</td>
</tr>
<tr>
<td>U-46619</td>
<td>$0.15 \pm 0.03$</td>
<td>$15.4 \pm 1$</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 4 to 13).

$^a$Dose producing 50% inhibition of platelet aggregation.

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**TABLE 3**

Inhibition of platelet aggregation in vitro in PRP from various species by carbocyclic prostacyclin analogues and their potency relative to prostacyclin.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Potency ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbacyclin</td>
<td>Human</td>
<td>0.03</td>
<td>13</td>
</tr>
<tr>
<td>13,14-didehydro-carbacyclin</td>
<td>Rabbit</td>
<td>0.09</td>
<td>26</td>
</tr>
<tr>
<td>20 methyl-didehydro-carbacyclin</td>
<td>Rabbit</td>
<td>0.11</td>
<td>26</td>
</tr>
<tr>
<td>15-cyclopentyl-carbacyclin</td>
<td>Human; baboon</td>
<td>0.11</td>
<td>21</td>
</tr>
<tr>
<td>16-methyl-18,19-didehydro-</td>
<td>Human</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>carbacyclin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9$\beta$-methyl-carbacyclin</td>
<td>Human</td>
<td>0.01</td>
<td>19</td>
</tr>
</tbody>
</table>

---

**FIGURE 2.** Structures of the chemically stable prostacyclin analogues: the $\beta$- and $\omega$-modified carbacyclin derivative (A; CG 4305) and 9$\beta$-methyl carbacyclin (B; ciprostene).

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fully elucidated and some mechanism of controlling the distribution of the analogue from the blood to the various tissue compartments is developed, metabolically stable prostacyclins analogues with long durations of action in vivo will remain to be identified.

**Selectivity of action.** A preliminary indication of the separation between platelet antiaggregating and cardiovascular actions within a particular prostacyclin analogue series can be gained from consideration of the selectivity ratio. Studies on the potency of such analogues in inhibiting human platelet aggregation in vitro and in lowering blood pressure in the anesthetized rat can be employed as primary screens for biological activity of analogues and thus, the ratio of the relative potency of effects on these parameters can readily be obtained. With the use of this ratio, it has been calculated that carbacyclin has a selectivity ratio close to that of prostacyclin. A favorable ratio of activity for carbacyclin has also been reported by others, whereas the (5Z) and (15R)-hydroxy derivatives of carbacyclin appeared less selective than carbacyclin itself. This selectivity ratio must be interpreted with caution, since it is derived from studies in two species, and importantly, from a comparison of data obtained in vitro with that obtained in vivo. Thus, for example, modification of a structure to prevent metabolism in the body may reduce its activity in vitro compared with its parent, yet in vivo it may appear more potent as a consequence of reduced metabolism giving a seemingly high ratio and apparent low selectivity. However, platelet studies in vitro of the effects of prostacyclin and carbacyclin in PRP from man, dog, and rabbit have been predictive of the potency as an inhibitor of platelet aggregation ex vivo (table 4).

It is clear that the most valid determination of selectivity between cardiovascular and platelet antiaggregating actions of prostacyclin analogues is obtained from studies in which the compounds are administered in vivo and in which both parameters are measured simultaneously. For this purpose the inhibition of platelet aggregation ex vivo and concurrent cardiovascular changes have been determined in anesthetized rabbits, dogs, and monkeys. To enable a more rapid preparation of samples of PRP so that platelet function could readily and continually be assessed, a rapid-spin method for the centrifugation of blood samples was developed. With this technique, blood samples (3.0 ml) are slowly collected from a cannula inserted into a femoral vein into a plastic syringe containing trisodium citrate (3.18%, 1 volume to 9 volumes of blood), shaken gently, and transferred to two Eppendorf plastic tubes (1.5 ml). Each sample is then spun separately in a modified Eppendorf centrifuge for 2 sec (maximum centrifuge force, 10,000 g). The PRP from each tube is collected separately and 0.4 ml aliquots are transferred to the aggregometer and incubated at 37°C for 1 min before addition of sufficient ADP to produce near-maximal aggregation (table 5). The time interval between removal of blood samples and the transference of the PRP to the aggregometer is only 1 min. This technique, which allows continual monitoring of platelet aggregation throughout periods of drug infusion, appears particularly useful in the study of labile or rapidly metabolized substances, the plasma half-

**TABLE 4**

<table>
<thead>
<tr>
<th>Species</th>
<th>Platelet aggregation</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Submax.</td>
<td>Maximum</td>
</tr>
<tr>
<td></td>
<td>(mg kg)</td>
<td>(mg kg)</td>
</tr>
<tr>
<td>Human</td>
<td>0.3</td>
<td>0.008c</td>
</tr>
<tr>
<td>Dog</td>
<td>0.7</td>
<td>0.015</td>
</tr>
<tr>
<td>Rabbit</td>
<td>2.0</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Dose producing 50% inhibition of platelet aggregation.

Experimental data taken from Whittle et al. and ex vivo human data from O'Grady et al. or Adaikan et al.

**TABLE 5**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Submax.</th>
<th>Maximum</th>
<th>ΔBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>0.01</td>
<td>40 ± 15</td>
<td>37 ± 15</td>
<td>-6 ± 2</td>
</tr>
<tr>
<td>Carbacyclin</td>
<td>0.2</td>
<td>67 ± 24</td>
<td>64 ± 22</td>
<td>-4 ± 2</td>
</tr>
<tr>
<td>Monkey</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>0.01</td>
<td>50 ± 10</td>
<td>17 ± 4</td>
<td>-6 ± 5</td>
</tr>
<tr>
<td>Carbacyclin</td>
<td>0.4</td>
<td>56 ± 7</td>
<td>22 ± 7</td>
<td>-1 ± 0.5</td>
</tr>
</tbody>
</table>

Results are mean ± SEM from three or four experiments during a 15 min period of intravenous infusion.

Platelet aggregation ex vivo was induced by ADP in doses causing submaximum aggregation (3 and 5 μM in monkey and dog, respectively) and maximum aggregation (10 and 20 μM, respectively).
lives of which may be far shorter than the time taken to 
prepare PRP by conventional methods (15 to 20 min). 

Using this technique, studies of both prostacyclin 
and carbacyclin in the anesthetized dog have suggest-
ed that inhibition of platelet aggregation ex vivo could 
be achieved after intravenous infusion of doses having 
minimal action on blood pressure (table 5). While car-

bacyclin appeared more selective than prostacyclin, 
producing a greater degree of platelet inhibition for a 
given vasodepressor response, this selectivity of action 
cannot be considered of great magnitude. Cardiovas-
cular studies in the anesthetized baboon and determi-
nation of platelet inhibition in vitro with carbacyclin 
and prostacyclin have also suggested that effects of 
carbacyclin may be more selective than prostacyclin in 
this species. Studies ex vivo of carbacyclin in the baboon 
have indicated that near-maximal inhibition of 
platelet aggregation could be achieved by doses with 
minimal hypotensive action. However, after oral ad-
ministration of carbacyclin in the baboon at a dose 
causing 70% inhibition of platelet aggregation, a rise 
in the heart rate was observed without a fall in blood 
pressure. In our studies in the anesthetized monkey, 
intravenous infusion of carbacyclin in intermediate 
doses inhibited platelet aggregation with a minimal 
hypotensive effect, in contrast to the effects of pros-
tacyclin. At higher rates of infusion, however, carba-
cyclin, like prostacyclin, did lower blood pressure 
(table 5).

Further studies have been conducted with the stable 
analogue 9β-methyl-carbacyclin in both anesthetized 
patas monkeys and greyhounds. After intravenous 
infusion in the dog, at doses having minimal action on 
blood pressure, both prostacyclin and 9β-methyl car-
bacyclin inhibited platelet aggregation, which was 
determined ex vivo in samples of PRP prepared by the 
rapid-spin procedure (table 6). Comparison of the 
potency ratio for either action suggests a minimal differ-
ence between the selectivity of 9β-methyl-carbacyclin 
and that of prostacyclin in this species. Likewise, in 
the monkey, in which both prostacyclin and 9β-methyl-
carbacyclin were less potent with respect to both 
parameters compared with in the dog, there was no 
significant difference between the potency ratios and 
here selectivity of the compounds (table 6).

Since the potency and intrinsic selectivity of prosta-
cyclin for either parameter can vary between species, it 
is clear that any claim for selective cardiovascular or 
antiaggregating actions in a series of analogues must 
be supported by a direct comparison in which prosta-
cyclin or carbacyclin is tested in the same experimental 
preparation. Thus, selectivity of action may be more

| Table 6 |
|---|---|---|---|
| Blood pressure | Platelets |
| Potency | Potency | Potency |
| ID50 | ED30 | ratio | ED30 | ID50 | ratio |

| Dog | PGI2 | 0.05 | 1 | 0.013 | 1 |
| 9β-Me | 1.9 | 0.03 | 0.31 | 0.04 |

| Monkey | PGI2 | 0.2 | 1 | 0.13 | 1 |
| 9β-Me | 14.3 | 0.014 | 9.1 | 0.014 |

Results, shown as mean from four experiments for each species, are 
expressed as the ED30 (the dose causing a 30 mm Hg fall in diastolic 
blood pressure) and the ID50 (the dose causing a 50% inhibition of ex 
vivo platelet aggregation induced by ADP) and as the potency ratio to 
prostacyclin. Data is derived from Allan et al.

readily demonstrated in certain species and prepara-
tions of platelet aggregation.

Studies with the 16-substituted carbacyclin deriva-
tive iloprost (figure 1, D) in the anesthetized cat indicate 
that the decrease in peripheral platelet count after 
coronary ligation can be abolished by doses having no 
effect on blood pressure. Results of studies with this 
derivative in the baboon during intravenous infusion 
have indicated that platelet aggregation ex vivo could 
be inhibited with variable effects on blood pressure and 
heart rate. Investigation of the hypotensive activity 
after bolus injection in the baboon have suggested se-
lectivity of action of iloprost away from the cardiovas-
cular actions of carbacyclin. Comparative studies 
with this analogue and with prostacyclin on formation 
of thrombi in an extracorporeal circuit in the anes-
ethetized rat could not, however, demonstrate any disas-
sociation between the antiaggregatory and vasodepressor 
actions.

Studies in man. In a preliminary evaluation in human 
volunteers, intravenous infusion of carbacyclin inhib-
ited platelet aggregation ex vivo yet had no effect on 
blood pressure or heart rate. Since concurrent studies 
with prostacyclin in these subjects were not undertak-
en, the extent of this selectivity of action in man could 
not be assessed. After oral administration of carbacy-
clin (25 mg) in two subjects in a dose sufficient to 
cause approximately 68% inhibition of platelet aggrega-
tion ex vivo (determined 30 to 90 min later), a 
marked rise in heart rate was observed, along with 
headache and flushing of rapid onset.

In studies in human volunteers, the analogue 15-
cyclopentyl carbacyclin (ONO 41483; figure 1, B),
infused intravenously in the maximum tolerated dose (2.5 ng kg\(^{-1}\) min\(^{-1}\)), caused a 27% inhibition of platelet aggregation ex vivo.\(^{21}\) Higher doses, both by the intravenous and oral route, produced more substantial inhibition of platelet aggregation, but also induced side effects including flushing of the face and limbs, headache, and phlebitis,\(^{21}\) effects similar to those observed with high doses of prostacyclin.\(^{36}\)

In a placebo-controlled study in six patients with peripheral vascular disease, intravenous infusion of the 16-methyl derivative iloprost (figure 1, A) in doses of 0.5 to 3 ng kg\(^{-1}\) min\(^{-1}\) for 2 to 4 hr did not alter systemic arterial blood pressure or heart rate, nor did it increase blood flow in the calf muscle or extremities.\(^{37}\) At higher doses that inhibited platelet aggregation ex vivo, side effects of facial flushing and headache were observed.\(^{37}\) In a further study during intravenous infusion of iloprost (4 to 8 ng kg\(^{-1}\) min\(^{-1}\)) for 72 hr in nine patients with peripheral vascular disease, marked vasodilation but only a small fall in blood pressure was reported, but a high incidence of side effects (including headache and vomiting) was noted. An increase in urine output, glomerular filtration, and kaliuretic excretion was also found, with a decrease in tubular reabsorptions of sodium and water and serum angiotensin-converting activity after infusion of iloprost.\(^{38}\)

In a double-blind placebo-controlled comparison of the effects of epoprostenol (prostacyclin) and the analogue 9β-methyl-carbacyclin (figure 2, B; ciprostene) in healthy volunteers, the two drugs exhibited comparable profiles of pharmacologic activity.\(^{19}\) During intravenous infusion, 9β-methyl-carbacyclin (150 to 600 ng kg\(^{-1}\) min\(^{-1}\)) significantly displaced the dose-response curve for ADP-induced platelet aggregation ex vivo, being 0.01 times as active as prostacyclin. As with prostacyclin, elevation in heart rate was only observed at the highest rate of infusion, while no change in systolic or diastolic blood pressure or left ventricular ejection time was observed with either compound in the dose range studied. A greater incidence of facial flushing was observed with prostacyclin than with 9β-methyl-carbacyclin in the lower dose range, while headache was only noted at the highest rate of infusion of 9β-methyl-carbacyclin.\(^{10}\) The pharmacodynamic effects and duration of action of 9β-methyl-carbacyclin and prostacyclin in man are thus comparable, with the analogue being 100 times less active.

The mechanisms underlying peripheral vasodilation, as demonstrated by facial flushing or increased blood flow to the extremities in the absence of a marked fall in blood pressure, as seen with prostacyclin, 9β-methyl-carbacyclin, or other analogues, warrant further investigation and point to potential therapeutic utilities of these compounds, including the treatment of peripheral vascular diseases. Although the carbacyclin analogues described thus far offer the advantage of being more chemically stable than prostacyclin, the development of well-tolerated, orally effective compounds of long duration of activity for use in man is still awaited. Although there is some evidence from experimental studies of a change in selectivity away from the vasodepressor actions of prostacyclin, there is as yet no stable analogue that has a highly selective action on platelets in vivo. Claims for such selectivity in an analogue will require support from rigorous comparisons with prostacyclin in several experimental preparations in different species. The definitive separation of the platelet and cardiovascular properties in further analogues, if demonstrated in man, will have extensive therapeutic possibilities and will also allow a closer analysis of the mechanism of action of prostacyclin in such clinical situations as peripheral vascular disease. The rational design of the pharmacologic profile of such analogues will, however, depend on the clinical experience gained with prostacyclin itself.

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References


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