Platelet actions of stable carbocyclic analogues of prostacyclin

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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-Δ3PGF1,2 many synthetic prostacyclin analogues have been prepared and reported in the literature. Although prostacyclin (epoprostol) is now available for clinical use as a 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°C 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-PGI1,3,5 thia prostacyclins such as (5Z)-6,9-thia prostacyclin,6 nitrogen-containing analogues such as 9-deoxy-9α-6-nitrilo-PGF1,7 ring-expanded 5,9-epoxy derivatives such as 9-deoxy-5, 9α-epoxy-PGF1,7 and interphenylene analogues.8 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.9–16

Carbacyclin analogues. Carbacyclin, or (5E)-6α carbaprostaglandin 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.12–16 In our studies with carbacyclin,13 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,13,15 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.14

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.13 Likewise, this analogue was effective in vivo in reducing formation of thrombi in canine coronary arteries16 when infused intravenously. Studies with carbacyclin in anesthetized baboons have likewise shown inhibition of platelet aggregation determined ex vivo after intravenous or intragastric administration.17

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 isosteric15 with naturally occurring prostacyclin (5Z-PGL1). As expected, the (15R)-epimer had minimal activity, as did the 2-nor derivative (table 1). Substitution in the 9 position18 can also alter antiaggregating potency, with (5Z)-9β-ethyl and 9-cyano groupings 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.19

Studies using further derivatives of carbacyclin have been reported, and the 15-cyclopentyl-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, 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 carbacycl 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, 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 platelets was measured after infusion of ADP as an index of aggregation, showed antiaggregating activity after bolus injection.\textsuperscript{26}

Metabolic stability. Although the chemical half-life of prostacyclin at physiologic temperatures and pH is short, its antiplatelet activity, and particularly its cardiovascular activity in vivo, is often even more short-lived.\textsuperscript{13} This suggests that the pharmacologic effects of prostacyclin in vivo are limited by biological inactivation rather than solely by chemical breakdown. Furthermore, chemically stable prostacyclin analogues such as carbacyclin have only short-lived biological activity in vivo, as determined by cardiovascular actions and inhibition of platelet aggregation ex vivo, suggesting that like prostacyclin, these compounds are rapidly inactivated.\textsuperscript{13} The extent and duration of the biological actions of prostacyclin and its analogues

\begin{table}
\caption{Inhibition of ADP-induced platelet aggregation by stable 6a-carbocyclic prostacyclin analogues in vitro in human PRP}
\begin{tabular}{lcc}
\hline

& IC\textsubscript{50} (ng ml\textsuperscript{-1}) & Relative potency \\
\hline
Prostacyclin & 0.4 ± 0.1 & 1 \\
(5E)-carbacyclin & 11 ± 3 & 0.036 \\
(5Z)-carbacyclin & 700 ± 100 & 0.0006 \\
(5E)-carbacyclin-methyl ester & 140 ± 40 & 0.003 \\
6E-(15R)-carbacyclin & >1600 & 0.0003 \\
(5Z,9\B)-ethynyl-carbacyclin & 2.2 ± 0.3 & 0.18 \\
9β-cyano-carbacyclin & 7.1 ± 0.3 & 0.06 \\
9β-methyl-carbacyclin & 87 ± 11 & 0.005 \\
9β-pent-1-ynyl-carbacyclin & 475 ± 175 & 0.0008 \\
9β-ethyl-carbacyclin & 1348 ± 439 & 0.0003 \\
\hline
\end{tabular}
\end{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.
FIGURE 2. Structures of the chemically stable prostacyclin analogues: the β- and ω-modified carbacyclin derivative (A; CG 4305) and 9β-methyl carbacyclin (B; ciprostene).

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 β- and ω-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 ω-tail, e.g., by insertion of a 15-cyclohexyl grouping, while protection against β-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

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>25; 20</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>9β-methyl-carbacyclin</td>
<td>Human</td>
<td>0.01</td>
<td>19</td>
</tr>
</tbody>
</table>

| TABLE 2
Comparison of the ID50 values of prostacyclin and ciprostene (9β-methyl-carbacyclin) in human PRP aggregated with different aggregating agents, ADP, collagen, U-46619 (epoxy-methano PGH2), and arachidonic acid

<table>
<thead>
<tr>
<th>Aggregating agent</th>
<th>ID50 (ng ml⁻¹)</th>
<th>Prostacyclin</th>
<th>Ciprostene</th>
<th>Potency ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>0.55 ± 0.1</td>
<td>86.6 ± 11</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>0.91 ± 0.08</td>
<td>123 ± 32</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>1.8 ± 0.7</td>
<td>55.8 ± 17.6</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>U-46619</td>
<td>0.15 ± 0.03</td>
<td>15.4 ± 1</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 4 to 13).

*Dose producing 50% inhibition of platelet aggregation.
fully elucidated and some mechanism of controlling the distribution of the analogue from the blood to the various tissue compartments is developed, metabolically stable prostacyclin 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>
<thead>
<tr>
<th>TABLE 4</th>
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<tbody>
<tr>
<td><strong>Inhibition of ADP-induced platelet aggregation in vitro in PRP by prostacyclin and carbacyclin after 1 min incubation, and ex vivo after intravenous infusion in various species</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>ID_{50}^{A}</th>
<th>Dose</th>
<th>Submax.</th>
<th>Maximum</th>
<th>ΔABP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostacyclin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in vitro (ng ml^{-1})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ex vivo (μg kg^{-1} min^{-1})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>0.3</td>
<td>0.008^{A}</td>
<td>11</td>
<td>0.2–0.8^{A}</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>0.7</td>
<td>0.015</td>
<td>20</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>2.0</td>
<td>0.28</td>
<td>25</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td><strong>Carbacyclin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in vitro (ng ml^{-1})</td>
<td></td>
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<tr>
<td>ex vivo (μg kg^{-1} min^{-1})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>0.4</td>
<td>0.012</td>
<td>10</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>0.3</td>
<td>0.006</td>
<td>9</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.2</td>
<td>0.04</td>
<td>30</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

^{A}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. (1983).
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 suggested that inhibition of platelet aggregation ex vivo could be achieved after intravenous infusion of doses having minimal action on blood pressure (table 5). While carbacyclin 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. Cardiovascular studies in the anesthetized baboon and determination 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 administration 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 prostacyclin. At higher rates of infusion, however, carbacyclin, 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 carbacyclin 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 difference 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 hence selectivity of the compounds (table 6).

Since the potency and intrinsic selectivity of prostacyclin 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 prostacyclin or carbacyclin is tested in the same experimental preparation. Thus, selectivity of action may be more readily demonstrated in certain species and preparations of platelet aggregation.

Studies with the 16-substituted carbacyclin derivative 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 selectivity of action of iloprost away from the cardiovascular actions of carbacyclin. Comparative studies with this analogue and with prostacyclin on formation of thrombi in an extracorporeal circuit in the anesthetized rat could not, however, demonstrate any disassociation between the antiaggregatory and vasodepressor actions.

Studies in man. In a preliminary evaluation in human volunteers, intravenous infusion of carbacyclin inhibited platelet aggregation ex vivo yet had no effect on blood pressure or heart rate. Since concurrent studies with prostacyclin in these subjects were not undertaken, the extent of this selectivity of action in man could not be assessed. After oral administration of carbacyclin (25 mg) in two subjects in a dose sufficient to cause approximately 68% inhibition of platelet aggregation 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),

<table>
<thead>
<tr>
<th>TABLE 6</th>
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<tbody>
<tr>
<td>Comparison of the hypotensive and platelet antiaggregating effects of prostacyclin and 9β-methyl-carbacyclin (9β-Me) after intravenous infusion in the anesthetized greyhound and the patas monkey</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Dog</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Monkey</td>
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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 ID₃₀ (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.³⁴
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 kallikrein 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 epoprostanol (prostacyclin) and the analogue 9β-methyl-carbacyclin (figure 2, B; ciprostene) in healthy volunteers, the two drugs exhibited comparable profiles of pharmacologic activity.³⁹ 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.⁴⁰ 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 longer 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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