Intravenous Infusion of Prostacyclin Sodium in Man: Clinical Effects and Influence on Platelet Adenosine Diphosphate Sensitivity and Adenosine 3':5'-Cyclic Monophosphate Levels

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SUMMARY Clinical tolerance, inhibition of platelet aggregation and intracellular platelet adenosine 3':5'-cyclic monophosphate (cyclic AMP) levels were evaluated in normal volunteers given i.v. infusions of prostacyclin sodium at rates up to 15 ng/kg/min. Short-term infusions (30 and 60 minutes) were tolerated at rates up to 10.0 ng/kg/min; higher rates produced headaches, anxiety, nausea and vomiting. Six-hour and 24-hour infusions were tolerated at rates up to only 4.0 ng/kg/min. Twenty-four-hour infusions at 4 ng/kg/min produced a consistent 4-7-μM shift to the right in the platelet ADP dose-response curve; this platelet inhibitory activity did not diminish during the infusion. Prostacyclin sodium infusion elevated intracellular cyclic AMP levels, the increases corresponding to the onset of measurable inhibition of ADP-induced aggregation, although the magnitude of the increase did not necessarily reflect the degree of inhibition. Increased template bleeding times were seen with a greater than 10-μM shift in the ADP dose-response curve. We conclude that although prostacyclin sodium has a narrow safety margin, the drug does produce platelet inhibition at infusion rates generally tolerated by healthy volunteers.

PROSTACYCLIN is a biologic substance produced endogenously from arachidonic acid by various tissues, particularly by vascular endothelium. The chemical elucidation and total organic synthesis of prostaglandin X, since renamed prostacyclin or prostaglandin I₃, was achieved in 1976. The potent platelet antiaggregatory property of prostacyclin, as well as its vasodilatory activity, immediately suggested its potential usefulness in the therapy of thrombotic conditions.

Because prostacyclin is not readily metabolized by the lung, it should be clinically effective when given intravenously. Prostacyclin was first administered intravenously to man in 1978 and has subsequently been given intra-arterially, intravenously and by inhalation to small numbers of patients for peripheral vascular disease, persistent fetal circulation, asthma, chronic renal disease and thrombotic thrombocytopenia purpura. It has also been given to patients undergoing charcoal hemoperfusion and cardiopulmonary bypass (O'Grady J: personal communication). Prostacyclin's platelet antiaggregatory properties and its effects on the cardiovascular system and pulmonary function of humans have also been studied.

Although the overall exposure of human subjects to prostacyclin has been broad, there has been no systematic approach to dose-response relationships, correlation of side effects with platelet effects, or tolerance studies of infusions longer than 1 hour. Future controlled clinical studies will require prolonged prostacyclin infusions. Therefore, we initiated a tolerance study of prostacyclin to determine the minimal effective dose necessary to inhibit platelet aggregation and to establish the maximum tolerated dose for extended periods.

We wished to identify prostacyclin dosage levels at which platelet antiaggregatory activity and hypotensive activity are separated so that platelet-active doses of prostacyclin with no or minimal side effects can be defined.

Methods

Study Design

The study consisted of four trials based on the duration of i.v. prostacyclin sodium infusion: (1) 30 minutes (nine subjects); (2) 60 minutes (18 subjects); (3) 6 hours (four subjects); (4) 24 hours (nine subjects). Within each trial, infusion rates were increased as tolerance allowed. A heart rate greater than 120 beats/min or a decrease in mean arterial pressure greater than 25% of baseline values at any dosage level precluded administration of higher infusion rates to any subject. The trials of varying duration overlapped, but at least a 2-day lag time was allowed to en-
sure safety of a short infusion at each dosage level before proceeding to longer infusions at that level. Infusion rates of 0.5–15 ng/kg/min were used in the 30- and 60-minute trials and rates of 0.5–6 ng/kg/min were used for the longer infusion trials. Thirteen of the 27 subjects received two infusions. A minimum of 2 weeks separated the first and second infusion in a given subject.

Patient Population

Twenty-seven normal, healthy males, ages 18–43 years, gave informed consent and participated in The Upjohn Company Protocol 1059. This protocol was approved by the Bronson Methodist Hospital Human Use Committee in February 1979. Volunteers had the following screening studies done before the prostacyclin sodium infusion: history; physical examination; laboratory tests, including biochemical profile (glucose, triglycerides, cholesterol, total bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, uric acid, albumin, calcium, phosphorus, creatinine, urea nitrogen), complete blood count (CBC) with differential, platelet counts and platelet aggregation studies, plasma fibrinogen, prothrombin time (Pro-time) and partial thromboplastin time (PTT), template bleeding time, and urinalysis; pulmonary function tests, including vital capacity, 1-second forced expiratory volume, total lung capacity and a flow-volume study; chest x-ray; and an ECG. Results had to satisfy predetermined criteria for safe conduct of the study. Subjects with bleeding tendencies or petechiae, those with hypertension and those with clinical, biochemical or other evidence of organ malfunction or dysfunction of an acute or chronic nature were excluded from the study. Subjects were requested to abstain from all drugs, including over-the-counter preparations, for 2 weeks before the study.

Drug

Freeze-dried, sterile prostacyclin sodium, hereafter called prostacyclin, was dissolved in sterile glycerine buffer (pH 10.5). Both drug and diluent were supplied by The Upjohn Company. The amount selected for infusion was delivered by means of a Harvard pump (model 940). Fresh prostacyclin solution was prepared on each day of administration and refrigerated (2–8°C) until it was used. Drug solution was at room temperature for the infusions and was replaced every 6 hours for the 24-hour infusions. The biologic potency in platelets was established by comparison with a primary standard before and after infusion. Subsequent analysis has indicated that prostacyclin in glycerine buffer is stable for at least 8 hours at room temperature.

Protocol

Subjects were admitted to the Bronson Clinical Investigational Unit the night before the study. The 30- and 60-minute infusions were conducted with the subjects in a fasting state. Subjects received fat-free diets during the longer infusion trials to minimize lipid interference with platelet aggregation studies.

A 19-gauge butterfly needle (Abbott Laboratories), fitted with a three-way stopcock, was inserted into a forearm vein 45 minutes before drug infusion to eliminate need of frequent venipunctures. This system was kept patent with 0.6 ml of heparinized saline (100 U/ml), which was withdrawn before each blood drawing. Ten minutes before drug infusion, a second needle was inserted into a vein in the opposite forearm and normal saline was infused at 125 ml/hour by means of an Abbott/Shaw Life Care Pump. At zero time, the prostacyclin solution was “piggybacked” into the saline line and infused at a rate of 0.02 ml/min by means of the Harvard infusion pump. After 2 minutes the saline infusion was reduced to a rate of 25 ml/hour for the duration of the study.

Clinical Assessment

Vital signs, continuous electrocardiographic monitoring and pulmonary function studies were done by nursing personnel at frequent intervals during the study. Mean arterial blood pressure was calculated and followed throughout the study. Before and after infusion, thoracic gas volume at functional residual capacity, airway resistance and specific conductance were measured using a body plethysmograph system (Warren E. Collins). A wedge spirometer (Model 570, Med Science) was used to assess forced expiratory flow and forced vital capacity. Pulmonary function studies done during the 30- and 60-minute infusions included forced vital capacity (Cavitron, KDC Cardiopulmonary Sales) and peak flow (Wright Peak Flow Meter, Air Med Limited). Ear oximeter (Model 47201A, Hewlett-Packard) readings were also made before, during and after the infusion.

Biochemical Variables

Plasma glucose levels were measured immediately after blood samples were drawn, using a glucose analyzer (Model 23A, Yellow Springs Instruments). Glucose measurements were also performed as part of the biochemical profile.

Plasma insulin levels were measured before, during and after the 30-minute prostacyclin infusion only. The measurements were performed by radioimmunoassay with a previously described modification of an immunoassay using cellulose powder.17

Biochemical profile, CBC, Pro-time, PTT, plasma fibrinogen and urinalysis determinations were performed at the Clinical Research Laboratory at The Upjohn Company or at the Bronson Methodist Hospital Laboratory, Kalamazoo, Michigan, using standard methods.

Bleeding Times

The template bleeding time was performed by means of the Simplate-II method (General Diagnostics, Division of Warner-Lambert). Before the
start of the drug infusion, bleeding times were performed simultaneously on the anterior aspect of the midforearm and the outer aspect of the midcalf. Cuts were made along the longitudinal axis of the limb parallel to Langer's lines of tension. These two measurements were used to compare bleeding times of the arm and leg, as standards had been established only for the arm. During the infusion, bleeding times were performed only on the leg, because needles inserted into forearm veins of both arms precluded application of the blood pressure cuff necessary for bleeding time measurements. In most instances, the baseline times of the arm and leg were similar.

Platelet Aggregation Studies

At scheduled times during the study, platelet-rich plasma (PRP) was prepared from whole blood anticoagulated with citrate (one part 3.8% citrate/nine parts blood). The blood was immediately centrifuged for 10 minutes at 200 g at room temperature. As soon as the centrifuge stopped, samples of PRP were taken for platelet counts, adenosine 3':5'-cyclic monophosphate (cyclic AMP) measurements, and measurement of adenosine diphosphate (ADP)-induced platelet aggregation. Several concentrations of ADP were used to generate dose-response curves at sampling times before, during and after prostacyclin infusion.

Aggregometry was done according to published methods. PRP was prewarmed to 37°C before the addition of ADP (Sigma Chemical Co.). The time from the drawing of blood to the completion of the ADP dose-response curves was 18–24 minutes.

For a given subject, aggregation data obtained during the prostacyclin infusion are reported as shifts to the right (μM) in the linear portion of the ADP dose-response curve compared with the baseline response, each subject serving as his own control. In all cases the sensitivity to ADP returned to the control (baseline) levels after termination of the prostacyclin infusion.

Cyclic AMP Measurements

Iodine-125-labeled 2'-0-Succinyl cyclic AMP tyrosine methyl ester and cyclic AMP antiserum were purchased from Collaborative Research. To measure cyclic AMP levels, 1.0 ml of PRP was added to 0.8 ml of 5% trichloroacetic acid within 11 minutes of the initial blood draw. To determine recoveries, [3H] cyclic AMP (Amersham-Searle) was added to each sample; the acidified samples were immediately frozen in liquid nitrogen. The cyclic AMP in the aqueous extracts was measured by radioimmunoassay as previously described. Data are presented as the mean of duplicate samples and expressed as pmoles cyclic AMP/10⁶ platelets.

A significant portion of the cyclic AMP (60–80%) is in the plasma (unpublished experiments). Calculation of changes of cyclic AMP levels without subtracting plasma levels tends to diminish the “apparent” increase in cyclic AMP in the platelets themselves. Therefore, when we had the background plasma levels available, we plotted the cyclic AMP data both with and without subtraction of the background values.

Results

Clinical Symptoms

Table 1 outlines the side effects and relative changes in bleeding time during the 30- and 60-minute infusions. The observed clinical effects and their time of occurrence for the 6- and 24-hour infusions are shown in Figure 1. Most of the prostacyclin infusions induced flushing of varying degrees. Low doses produced transient periods of flushing late in the infusion, whereas higher doses produced intense, constant flushing within 4–10 minutes. Before their infusions were terminated, subjects 16A, 34 and 24 showed a transient pallor that lasted up to 30 minutes after infusion. In general, the number, intensity and severity of side effects increased with increasing infusion rates. Four of the subjects who received longer infusions required early termination. An infusion rate of 6 ng/kg/min was not tolerated for longer than 9 hours because of the number and severity of side effects. Subject 4A experienced significant orthostatic hypotension and bradycardia twice, finally necessitating cessation of his 6-ng/kg/min infusion. Anxiety contributed to the discomfort that prompted early termination of the planned 24-hour infusions in subjects 29A (5.0 ng/kg/min) and 33 (6.0 ng/kg/min); subject 33 also had slight slurring of his speech. Subject 32A (4.0 ng/kg/min) had palpitations, heat sensation, and an increase in blood pressure, along with anxiety, beginning at 2.5 hours and ending at 5 hours, but the symptoms did not necessitate early termination of the scheduled 6-hour infusion.

Clinical Signs

A few subjects experienced slight, inconstant and insignificant decreases in diastolic blood pressure with little or no change in systolic blood pressure. Heart rate increased to some extent in almost all subjects during the short-term infusions. Increases in heart rate of 25% over baseline, classified as tachycardias, were present in nine subjects (table 1). In each, the tachycardia was apparent by 8–10 minutes of infusion and persisted with minimal change until 5–10 minutes after infusion. There was a gradual return to baseline by 15–20 minutes after infusion.

ECGs recorded as part of the screening physical and again 24 hours after termination of the infusion showed no drug-related changes. The ECG was continuously monitored during the infusion period, and five subjects who received infusion rates of 6 ng/kg/min or more had some nonspecific T-wave flattening that reverted to normal upon termination of the infusion.

No significant changes were observed in pulmonary function, which was tested as part of the screening physical and during and after the 30- and 60-minute infusion trials. The prostacyclin infusion had no effect on the subjects' temperatures or ear oximeter read-
TABLE 1. Side Effects and Changes in Bleeding Times During 30- and 60-minute Infusions of Prostacyclin Sodium

<table>
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<tr>
<th>Infusion rate (ng/kg/min)</th>
<th>Duration</th>
<th>Subject</th>
<th>Flushing</th>
<th>Pressure in Head</th>
<th>Nausea and Abdominal pain</th>
<th>Tachycardia</th>
<th>Diaphoresis</th>
<th>Restlessness</th>
<th>Sighing</th>
<th>Increase in Bleeding time</th>
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Blanks indicate that no effect was observed.
Abbreviations: A = second infusion (same subject); + = mild-to-moderate effect; ++ = moderate-to-severe effect; *= emesis.

ings, although at higher infusion rates, blood for platelet aggregation studies was bright red, suggesting arterialization.

Biochemical Variables

Plasma glucose levels were measured before and at frequent intervals during the 30- and 60-minute infusions. Five of the 27 subjects in the 30- and 60-minute infusion trials, had minor elevations (about 10 mg/dl) in plasma glucose levels. These levels returned to baseline levels after the infusion was stopped. In the longer infusion trials, plasma glucose levels measured 2 hours after each meal returned to baseline. There were no significant changes observed in plasma insulin levels during the 30-minute trials.

The biochemical profiles, CBCs, and urinalyses done before and after each infusion, as well as coagulation tests (Pro-time, PTT and plasma fibrinogen) revealed no drug-related changes.

Bleeding Times

Table 1 lists the relative changes in bleeding times for the volunteers receiving prostacyclin for the shorter infusion times. Rates of 0.5–4 ng/kg/min had little effect on bleeding times, but at rates of 6–15 ng/kg/min, inconsistent prolongation of bleeding sometimes occurred. When prolonged, bleeding times returned to baseline within 60 minutes after infusion. Unexpectedly, subjects 15, 12A and 18A, who received infusions at rates of 10 ng/kg/min or more, had absolutely no bleeding for various periods of time after cessation of the infusion, when platelets still showed marked insensitivity to ADP. Bleeding times returned to baseline within 60 minutes in two of the three sub-
jects. Longer infusions at rates of 0.5-5 ng/kg/min produced little effect upon bleeding time. The two subjects who received 6.0 ng/kg/min (subjects 9A and 33), however, did have prolonged bleeding times during the infusion. Subject 9A's bleeding time increased from 9 minutes baseline to 17½ minutes during infusion, while subject 33's bleeding time increased from 6½ minutes baseline to 17 minutes during infusion.

Platelet Aggregation

The effect of infusions of various amounts of prostacyclin on ADP-induced platelet aggregation is summarized in figures 2, 3 and 4. Figure 2 shows the pooled data from all subjects at the 30-minute point of infusion. Except for subject 1 who received 2.0 ng/kg/min, the ADP dose-response curve was not shifted more than 0.5 µM at 30 minutes until the 5.0 ng/kg/min rate was reached. Between 5.0 and 8.0 ng/kg/min, the shift in the ADP dose response was variable. For 10.0-15.0 ng/kg/min, the shifts in the dose-response curve clustered around 10.0 µM. The data from the 60-minute point from all subjects receiving 1-, 6- and 24-hour infusions were also pooled (fig. 3). The shifts to the right in the ADP dose-response curves were less variable at 60 minutes of infusion than at 30 minutes. At rates between 0.5 and 4.0 ng/kg/min, 1-2-µM shifts in the curves were observed. At rates of 5.0-10.0 ng/kg/min, the shifts in the ADP dose-response curve were from 5-8 µM. The two highest rates of infusion, 12.5 and 15.0 ng/kg/min, shifted the ADP dose-response 11 and 26 µM, respectively.

Infusion of 0.5, 4.0, 5.0 or 6.0 ng/kg/min over several hours produced no evidence of tachyphylaxis or desensitization to prostacyclin (fig. 4).
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0.5 ng/kg/min for 24 hours induced a consistent 1–2-µM shift in the ADP dose-response curve. The 2.5-ng/kg/min rate of infusion gave comparable shifts in the ADP dose-response curve (data not shown). When the rate was increased to 4.0 ng/kg/min, there was a consistent 4–7-µM shift in the ADP dose-response curve throughout the 24-hour infusion (fig. 4). Infusion rates of 5 and 6.0 ng/kg/min were not administered for longer than 9 hours owing to patient discomfort, but both of the higher levels induced shifts in the ADP dose-response curve of more than 10 µM (fig. 4). In these infusions, when shifts of 10 µM or greater were observed in the response to ADP, bleeding times were also prolonged.

**Cyclic AMP**

Prostacyclin inhibits platelet aggregation in vitro by stimulating intracellular cyclic AMP levels. We therefore monitored cyclic AMP levels in most of the subjects. There were no significant changes in cyclic AMP in any subject until we reached an infusion rate of 4.0 ng/kg/min. At this rate, one of two subjects had slightly elevated cyclic AMP levels (data not shown). We measured cyclic AMP in 18 subjects during 30- and 60-minute infusions at 4.0–15.0 ng/kg/min. Of these, 14 subjects showed elevations in cyclic AMP during the infusion, though there was no clear correlation between cyclic AMP elevations and shifts in the ADP response curves. Figure 5 shows a representative pattern for total and intracellular cyclic AMP for a
60-minute infusion. Although plots of both sets of data are qualitatively similar, the intracellular levels give a clearer representation of actual changes in cyclic AMP levels. In general, the peak cyclic AMP level during the 60-minute infusions was reached within the first 20 minutes. After 20 minutes the cyclic AMP levels either reached a plateau or began to decline slightly. Two exceptions to this pattern were seen. Subjects 16A and 33, who experienced severe clinical intolerance to prostacyclin, had a progressive increase in cyclic AMP through 40 minutes of infusion with a plateau thereafter until the infusion was stopped because of intolerance. Immediately after termination of the infusions, there was a dramatic decrease of cyclic AMP to control levels. Generally, the cyclic AMP levels returned to control levels within 30 minutes of cessation of the infusion.

We measured total cyclic AMP several times during the longer prostacyclin infusions, 6–24-hours, in five subjects. Two subjects receiving 6.0 ng/kg/min had slight increases in cyclic AMP at 6 and 9 hours of infusion. Two other subjects who received 0.5 and 6.0 ng/kg/min actually had small decreases in cyclic AMP. One subject given 2.5 ng/kg/min had slightly elevated cyclic AMP levels at 9 hours, but his cyclic AMP was markedly elevated at 12 hours, immediately after an accidental bolus of prostacyclin was given.

Clinical Intolerance in Two Subjects

The symptoms of subjects 16A and 24 clearly show the clinical intolerance produced by prostacyclin. Concurrent platelet effects are given to emphasize the narrow margin of safety. Clinical intolerance was associated with marked elevations in cyclic AMP levels in both subjects.

After 10 minutes of a 10-ng/kg/min infusion, subject 16A developed a pressure headache that became progressively worse during the remainder of the infusion. Diaphoresis appeared at about 30 minutes, followed by nausea, yawning, restlessness, anxiety, abdominal pain and finally emesis (table I). The infusion was terminated prematurely at 56.6 minutes, just before the emesis occurred. All side effects resolved within 30 minutes. Six-micromolar shifts in the ADP aggregation curves were present at 20 and 40 minutes and a 4-μM shift was present at 60 minutes. His cyclic AMP levels increased from 92 to 160 pmol/10⁹ platelets by 40 minutes and remained at this level until the infusion was stopped.

Subject 24 tolerated the first 12 hours of his 2.5-ng/kg/min infusion satisfactorily, experiencing only transient flushing and a slight pressure headache early in the infusion (fig. 1). At 12 hours he inadvertently received a bolus of an undetermined amount of prostacyclin during syringe change. He rapidly developed increasing diaphoresis, nausea, and tachycardia. The infusion was immediately terminated. The cyclic AMP levels were 64, 61, and 78 pmol/10⁹ platelets at 0, 6 and 9 hours into the infusion with 0-, 2- and 0-μM shifts in the ADP aggregation curve. Immediately after the bolus of drug was given, his cyclic AMP level rose to 199 pmol/10⁹ platelets and the ADP aggregation curve shifted by more than 16 μM.

In these two subjects, inhibition of platelet aggregation as evidenced by a shift in the ADP response curve greater than 2 μM was also associated with elevations of cyclic AMP. Clinical intolerance was noted when marked cyclic AMP elevations were present.

Discussion

In this study in normal men, short infusions of prostacyclin sodium were generally tolerated at rates up to a maximum of 10 ng/kg/min, though some subjects could tolerate slightly higher rates. Because of significant complaints of headache, anxiety, nausea and vomiting, these higher doses would not be advisable even for short periods of time in unanesthetized patients. In general, side effects were linearly related to infusion rate. The highest tolerated 24-hour infusion rate in our study was 4 ng/kg/min. Attempts to administer 24-hour infusions at 5 and 6 ng/kg/min were unsuccessful because of intolerable gastrointestinal complaints, restlessness, anxiety and headaches.

Figure 5. Influence of 6-ng/kg/min infusion of prostacyclin sodium on human platelet cyclic AMP levels. At time 0 and at 20, 40 and 60 minutes during the infusion of prostacyclin, cyclic AMP levels were determined in platelet-rich plasma as described in the Methods. Both the total (platelets and plasma) and intracellular (platelets) levels of cyclic AMP are plotted against time. Dotted lines show levels of cyclic AMP after infusion. Data are reported as pmol cyclic AMP/10⁹ platelets (average of two determinations).
I.V. PROSTACYCLIN SODIUM IN MAN/Data et al.

Prostacyclin infusion in these normal men resulted in a dose-dependent inhibition of ADP-induced platelet aggregation. As clinical effects were observed when platelet effects were minimal, some recovery of the platelets from the effects of prostacyclin may have occurred during centrifugation of blood. Therefore, both the shift in the ADP dose-response curve and the cyclic AMP data reported may underestimate the actual changes that occurred in vivo.

Aiken et al.22 showed in the canine coronary occlusion model that a shift of 2 μM to the right in the ADP dose-response curve is needed to slow the rate of coronary occlusion. During our 24-hour infusions at 4.0 ng/kg/min, there was a consistent 4–7 μM shift to the right in the platelet ADP dose-response curve. When one considers that the total amount of releasable ADP in human platelets is 8–10 μM,22 the inhibition mediated by even 4.0 ng/kg/min is likely to be clinically significant. Twenty-four-hour infusions also showed no evidence of desensitization of the platelet to prostacyclin, as the platelet inhibitory activity of prostacyclin was maintained at a relatively stable level.

We and others4–18 have found a variable effect of prostacyclin on bleeding time. In our study, prolongation of bleeding time occurred in some subjects who received 4 ng/kg/min, while others showed no effect at 12.5 ng/kg/min. The most striking increases in bleeding time were seen during the longer 6-ng/kg/min infusions. When shifts of 10 μM or greater were observed in the platelet response to ADP, bleeding times were prolonged. In only one subject was the bleeding time prolonged enough to suggest an increased risk of hemorrhage. This subject did not bleed at all for the bleeding time at the end of the infusion, despite continued inhibition of platelets to ADP. This lack of bleeding in three of our subjects could not be explained. Platelets from these subjects were not hypersensitive to ADP at the time, nor was Pro-time or PTT shortened in the 60-minute subject in whom these measurements were made.

In addition to inhibiting ADP-induced platelet aggregation and in some cases prolonging template bleeding time, prostacyclin infusion elevated intracellular platelet cyclic AMP levels. The increases in cyclic AMP corresponded well to the onset of measurable inhibition of ADP-induced aggregation, but the magnitude of the increase did not necessarily reflect the degree of inhibition. The sensitivity of human platelets to prostacyclin appears to vary widely. Because cyclic AMP is constantly metabolized by the cyclic AMP-dependent phosphodiesterase, variations in the specific activity of this enzyme would also be a factor in the ultimate ability of prostacyclin to elevate platelet cyclic AMP. Subjects 16A and 33, who had marked clinical intolerance that necessitated premature termination of the shorter infusion, maintained rather constant levels of cyclic AMP until the infusion was terminated, unlike most subjects (fig. 5).

We speculate that inability to tolerate higher concentrations of prostacyclin may be linked to these elevations in cyclic AMP.

Although our findings support those of others, that prostacyclin sodium can produce a significant effect in vitro platelet aggregation studies when given intravenously to man,5,10 we emphasize that there is a rather small margin between significant in vitro platelet effects and undesirable side effects. Our study suggests poor tolerance to moderate doses of longer infusions of prostacyclin. Volunteers were unable to tolerate the headache alone for long. Most disease states will require prolonged infusions to have clinical utility. Because the desired platelet effects do not appear to be cumulative (fig. 4), the safety index for prostacyclin is low. As facial flushing is observed at even low rates of infusion, it is more likely that more in vivo platelet effects are present than can be assessed with the current method.

Szczeklik et al.6 reported that infusion rates of up to 10 ng/kg/min for 72 hours were given to patients with peripheral vascular diseases. The use of concomitant medication and/or the severity of the disease state in these patients might well have masked the side effects experienced by our subjects. It would be interesting to know whether there was any correlation between the beneficial therapeutic effects and cyclic AMP levels in the study of Szczeklik et al.

In conclusion, although prostacyclin can safely be given to man, extreme care must be taken. We recommend that 10 ng/kg/min be the maximum allowable rate infused for up to 60 minutes and that 4 ng/kg/min be the maximum 24-hour infusion rate to conscious subjects. These infusion rates were generally tolerated by our healthy volunteers and produced platelet inhibitory effects that have been associated with beneficial antithrombotic effects in the dog.22 Infusion of prostacyclin at rates that are well tolerated does induce marked inhibition of platelet sensitivity to aggregating agents; therefore, prostacyclin may well be a beneficial agent for the therapy of various types of thromboembolic disease.

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