Effect of epoprostenol (prostacyclin, PGI₂) on cerebral blood flow in man

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SUMMARY Cerebral blood flow has been measured using the non-invasive Xenon¹³³ clearance technique in eight normal subjects during an infusion of epoprostenol (prostacyclin, PGI₂) at a dose of 5 ng/kg/min. The results were compared with a control infusion of saline given in a balanced order. PGI₂ was found to result in a reduction in cerebral blood flow of about 8%. PGI₁ also caused a small drop in diastolic blood pressure and it is proposed that the fall in cerebral blood flow may have been the result of disturbed autoregulation. The findings suggest that the therapeutic use of PGI₁ in patients with cerebral arterial spasm would not be accompanied by undesirable intracerebral steal.

It was proposed by Pickard and Mackenzie in 1973¹ that a vasodilatory endogenous prostaglandin with a rapid turnover was responsible for maintaining the normal level of cerebral blood flow. Epoprostenol (prostacyclin, PGI₁) is the most suitable candidate for such a role. A product of arachidonic acid metabolism, it is formed in vascular endothelium,² including that of cerebral vessels.³ ⁴ It is a potent dilator of cerebral blood vessels in vitro³ ⁵ ⁶ and has been found to increase cerebral blood flow (CBF) in baboons when infused into the carotid artery.⁷ It has been suggested that PGI₁ might have a therapeutic role in conditions associated with cerebral arterial spasm, such as subarachnoid haemorrhage.⁸ ⁹ In addition to its vasodilatory properties, PGI₁ is a potent inhibitor of platelet aggregation, and for this reason might also find application in a wider range of cerebrovascular conditions. We have therefore investigated the effects of exogenous PGI₁ on CBF in normal human subjects. PGI₁ is rapidly broken down in the circulation and therefore has to be given by infusion.

Methods

Eight clinically normal subjects, four male and four female, with a mean age of 22 years (range 19–33) were studied. The study was approved by the Ethics Committee of the National Hospital, Queen Square and the subjects gave their informed consent. Each subject had two estimations of CBF separated by about 1 h. During one CBF measurement, the subject received a control infusion of 0-9% saline into an indwelling catheter in a forearm vein, and during the other measurement an infusion of PGI₁ at a dose of 5 ng/kg/min. PGI₁ was synthesised by Upjohn and formulated by the Wellcome Foundation, was diluted in glycine buffer at pH 10·5 and given by constant infusion pump at a rate of 0·2 ml/min. This infusion was given for 10 min prior to the start of the CBF estimation, by which time other dynamic effects of PGI₁ were apparent, and continued throughout the flow measurement. The order of treatments was balanced so that four subjects received PGI₁ and four subjects saline as the first infusion. The infusions were not given blind, as we have found that characteristic facial flushing with PGI₁ makes it obvious which treatment has been given.

CBF was measured by the non-invasive intravenous Xenon¹³³ (Xe¹³³) clearance technique, details of which are given elsewhere.⁸ In brief, a bolus of approximately 7 mCi of Xe¹³³, dissolved in saline, was injected into a forearm vein and the clearance of the isotope from the cerebral hemispheres monitored for 15 minutes with six external 25 mm diameter scintillation detectors. Expired concentrations of Xe¹³³ were monitored with a seventh detector and the end-tidal levels used to estimate recirculating arterial Xe¹³³ concentrations. Regional CBF

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was calculated from a bicomartment analysis of 11.5 minutes of the clearance data and also from an initial slope analysis of the first minute of the clearance curves. These analyses resulted in figures for volumetric blood flow through the fast clearing tissues of the brain which are mainly grey matter (F fast), and a figure for flow to the whole brain (F initial). The CBF values presented for each subject are the means of the six regional measurements.

Blood pressure was recorded from the left arm with a standard mercury sphygmomanometer and the pulse rate measured over 30 seconds from the radial pulse on three occasions during the CBF measurement. Arterial partial pressure of carbon dioxide (pCO2) was estimated by monitoring expiratory CO2 concentration with a Datex CD 300 infra red analyser. The pCO2 levels were calculated from the mean end tidal concentration over the first 5 minutes of the blood flow measurement. Venous red cell haematocrit (PCV) was measured in a Hawksley microhaematocrit centrifuge.

Results

The results are presented in this table. Compared with the saline infusion, PGI2 resulted in small but significant reduction in mean CBF of 7.3 ml/100g/min (F fast) and 5.1 ml/100g/min (F initial). There was no significant change in PCV or arterial pCO2 that might have influenced the results. The pattern of end tidal Xe13 concentration was not altered by the PGI1 infusion and it is therefore unlikely that there were alterations in the ratio of arterial to expired Xe concentrations that might have influenced the accuracy of the correction for arterial recirculation.

During the infusion of PGI1, all subjects developed a marked facial flush, a moderate tachycardia (mean rise in pulse rate = 12.3, p < 0.01) and a small fall in diastolic blood pressure (mean fall = 9.4 mmHg, p = < 0.01). Systolic blood pressure rose in five out of the eight subjects but the mean rise of 3.4 mmHg was not statistically significant. Four subjects complained of headache, and three others a slight heaviness in the head, 3 had palmar flushing and 1 suffered from nausea and restlessness.

Discussion

This study has demonstrated that, contrary to expectations, epoprostelenol (prostacyclin, PGI1) given intravenously results in a slight fall in mean CBF in normal subjects. Since completing our work another group has briefly reported similar findings in man using a dose of 4 ng/kg/min.19 The dose of 5 ng/kg/min used in the current study is the highest intravenous infusion rate that can be readily tolerated by conscious humans and even this dose is greatly in excess of normal circulating endogenous PGI2.10 The findings contrast with the effects of giving PGI1 in relatively enormous doses (5,000 ng/kg/min) directly into the carotid arteries of anaesthetised baboons, when an increase in CBF has been reported.7 We note that the lowest dose at which dilator effects of PGI2 has been seen on cerebral vessels in vitro exceeds both the normal circulating level and that we might expect to attain during an infusion.10 The blood brain barrier might reduce the effective dose delivered by an intravenous infusion even further.

The effects of PGI2 on blood pressure, pulse and the symptoms experienced by the subjects in the current study were similar to those found in previous work12-14 and are discussed in more detail elsewhere.15 It seems likely that the headache frequently reported during PGI2 infusion is the result of vasodilation occurring in the external carotid circulation (as demonstrated by the facial flush), although the current results do not exclude the possibility that the headache results from changes in the calibre of larger intracranial vessels that are not reflected by alterations in cerebral perfusion.

One possible explanation for the fall in CBF recorded in man lies in the effects of PGI2 elsewhere in the body. The large drop in peripheral resistance during PGI2 infusion is only partly compensated by the rise in cardiac output.1617 and a fall in diastolic pressure is usually recorded. PGI2 has a differing effect on the various vascular beds, and it is probable that this is responsible for the fall in peripheral resistance that is not reflected by changes in cerebral perfusion.

Table 1 Effect of epoprostelenol (prostacyclin, PGI1) infusion on cerebral blood flow (F fast & F initial) in 8 normal subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Arterial BP systolic/diastolic mmHg Saline</th>
<th>Arterial pCO2 kPa Saline</th>
<th>PGI1</th>
<th>F fast ml/100g/min Saline</th>
<th>PGI1</th>
<th>F initial ml/100g/min Saline</th>
<th>PGI1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115/70</td>
<td>117.65</td>
<td>5.4</td>
<td>5.3</td>
<td>100.5</td>
<td>92.3</td>
<td>69.0</td>
</tr>
<tr>
<td>2</td>
<td>130/88</td>
<td>125/82</td>
<td>5.0</td>
<td>5.1</td>
<td>82.5</td>
<td>72.6</td>
<td>63.5</td>
</tr>
<tr>
<td>3</td>
<td>132/87</td>
<td>152/85</td>
<td>4.6</td>
<td>4.7</td>
<td>74.5</td>
<td>74.9</td>
<td>53.8</td>
</tr>
<tr>
<td>4</td>
<td>138/83</td>
<td>140/80</td>
<td>5.9</td>
<td>5.8</td>
<td>116.0</td>
<td>102.9</td>
<td>76.0</td>
</tr>
<tr>
<td>5</td>
<td>136/82</td>
<td>144/68</td>
<td>5.3</td>
<td>4.7</td>
<td>74.1</td>
<td>59.5</td>
<td>54.0</td>
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<tr>
<td>6</td>
<td>110/72</td>
<td>106/58</td>
<td>5.3</td>
<td>5.4</td>
<td>87.5</td>
<td>95.6</td>
<td>66.5</td>
</tr>
<tr>
<td>7</td>
<td>110/67</td>
<td>115/57</td>
<td>5.7</td>
<td>5.6</td>
<td>107.1</td>
<td>91.2</td>
<td>70.6</td>
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<tr>
<td>8</td>
<td>128/85</td>
<td>127/64</td>
<td>6.1</td>
<td>5.6</td>
<td>100.6</td>
<td>95.4</td>
<td>64.7</td>
</tr>
<tr>
<td>Mean</td>
<td>125.79</td>
<td>128.70</td>
<td>5.4</td>
<td>5.34</td>
<td>92.9</td>
<td>85.6*</td>
<td>64.8</td>
</tr>
</tbody>
</table>

Results during PGI1 compared with saline using paired t tests: * p = < 0.05 † p = < 0.01 ‡ = NS.
Effect of epoprostenol (prostacyclin, PG\textsubscript{I\textsubscript{2}}) on cerebral blood flow in man

that the increased cardiac output is directed mostly into vasodilated splanchic and liver blood vessels\textsuperscript{18} rather than into muscle,\textsuperscript{17} renal\textsuperscript{19} or cerebral vessels. Clearly PG\textsubscript{I\textsubscript{2}} does not have a marked vasodilator effect on the human cerebrovascular bed at the dose we used and could have a slight vasoconstrictor effect. Alternatively, the fall in CBF recorded may have been the result of the excessive shunting of blood into organs of reduced vascular resistance and the small drop in perfusion pressure. However, CBF is normally maintained in the face of much larger changes in perfusion pressure by the process of autoregulation\textsuperscript{20} and the current results suggest that this autoregulation may have been disturbed by the presence of exogenous PG\textsubscript{I\textsubscript{2}}.

It has been suggested that PG\textsubscript{I\textsubscript{2}} could be a useful therapeutic agent in cerebrovascular disease particularly subarachnoid haemorrhage\textsuperscript{6} because of its ability to overcome arterial spasm in vitro.\textsuperscript{7} The current results suggest that if used to treat cerebral artery spasm, PG\textsubscript{I\textsubscript{2}} would not result in vasodilation in normal areas of the brain and would therefore be unlikely to cause undesirable intracerebral diversion (intracerebral steal) of blood from ischaemic to normal areas. At the dose used in the present study, an effect on platelet aggregation would be expected,\textsuperscript{14} and thus PG\textsubscript{I\textsubscript{2}} may be able to prevent constrictor agents being released from platelets at sites of endothelial disruption and thus reduce cerebral artery spasm through this separate mechanism.

Failure to demonstrate an increase in CBF with PG\textsubscript{I\textsubscript{2}} does not necessarily exclude a role for PG\textsubscript{I\textsubscript{2}} in the normal regulation of CBF. Rapid resetting of the normal balance between endogenous dilator and constrictor influences in our subjects may have prevented a dilator effect of exogenous PG\textsubscript{I\textsubscript{2}}. Pretreatment with salicylate or indomethacin, which is thought to inhibit the synthesis of endogenous prostaglandins such as PG\textsubscript{I\textsubscript{2}}, causes an impaired dilatary response to hypercapnia,\textsuperscript{21-23} and permits moderate doses of PG\textsubscript{I\textsubscript{2}} to increase cerebral blood flow after cerebral ischaemia in dogs.\textsuperscript{8} Acute pretreatment with indomethacin or salicylate may therefore provide conditions in man under which PG\textsubscript{I\textsubscript{2}} infusions will increase rather than decrease CBF and we are currently investigating this possibility.

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