Effect of indomethacin on cerebral blood flow, carbon dioxide reactivity and the response to epoprostenol (prostacyclin) infusion in man

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SUMMARY Cerebral blood flow (CBF) has been measured using a non-invasive Xenon clearance technique in six normal subjects after 2 days pretreatment with oral indomethacin at a dose of 100 mg/day. The results were compared with placebo given in a double blind balanced cross-over design. Indomethacin was found to result in a reduction in resting CBF of about 25% but the reactivity of the cerebrovascular circulation to carbon dioxide was preserved at normal levels. Infusions of epoprostenol (prostacyclin, PG1) at a dose of 5 ng/kg/min resulted in a reduction of CBF of about 10% after placebo but no significant change in CBF after indomethacin. The results suggest that prostaglandins are involved in the maintenance of cerebrovascular tone but not in the mechanism of cerebral vasodilation accompanying hypercapnia. The combination of indomethacin and PG1 has been proposed as a treatment of cerebral artery spasm and the findings suggest that the combination therapy would not be accompanied by undesirable intracerebral steal.

There is considerable evidence, recently reviewed by Pickard,† which suggests that prostaglandins and particularly prostacyclin (epoprostenol, PG1) are involved in the control of cerebral blood flow (CBF). The evidence comes from two separate lines, firstly experiments on the effects of indomethacin used as an inhibitor of prostaglandin synthesis, and secondly animal experiments on the direct effects of PG1, both in vitro and in vivo. Pickard and Mackenzie‡ first showed that in baboons intrarterial indomethacin reduced resting CBF, and almost abolished the rise in CBF that normally results from hypercapnia. Similar findings were recently reported in humans studied 1 hour after rectal indomethacin.³ These results were taken as evidence that some endogenous prostaglandin was involved in the CBF response to hypercapnia and from the very rapid onset of the effect of indomethacin it was concluded that a prostaglandin with a very rapid turnover was involved in CBF regulation. Prostacyclin (epoprostenol, PG1) appeared to have the required characteristics. It is formed by vascular endothelium⁴ and can be produced in vitro by cerebral vessels.⁵,⁶ It is a potent vasodilator, reducing vascular resistance when given systemically,⁷ and dilates human cerebral vessels in vitro.⁸ When given into the carotid artery of baboons in high concentrations, PG1 increases CBF.⁹ PG1 also has the required short half-life in vivo of only a few minutes. There has also been interest in PG1 as a potential therapeutic agent in ischaemic cerebral conditions. Cerebral artery spasm following subarachnoid haemorrhage may be a particular indication,³ as in animals PG1 can overcome this spasm in vitro⁹ and in vivo.¹⁰ The combination of indomethacin and PG1 was found to increase CBF after cerebral ischaemia in dogs.¹¹

There are a number of discrepancies in the evidence implicating PG1 in the control of CBF. Firstly agents other than indomethacin that also inhibit

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prostaglandin synthesis appear unable to block the CBF response to hypercapnia (eg aspirin given acutely\(^1\) or chronically\(^2\)). Secondly Brown and Pickles\(^3\) in an earlier study investigated the effect of intravenous PGI\(_2\) in normal subjects at the highest concentration that can be comfortably tolerated by conscious humans and, in contrast to the animal studies using higher concentrations, found that CBF was slightly reduced after PGI\(_2\). One explanation of this finding could be that the normal cerebral circulation did not dilate in response to exogenous PGI\(_2\) because of a rapid resetting of the normal balance between dilator and constrictor influences involving other prostaglandins. To investigate this possibility we have studied the effect of PGI\(_2\) on CBF in normal human subjects before and after indomethacin pretreatment. We have also investigated the effects of indomethacin on resting CBF and the CBF response to hypercapnia. A dose of oral indomethacin was used that is adequate to reduce endogenous prostaglandin synthesis\(^4\) without producing other toxic effects.

**Methods**

Six normal subjects, three male, three female, aged 20–23 years part in this study which had been approved by the Ethics Committee of the National Hospital, Queen Square. Each subject was studied on two occasions, which were separated by at least 2 weeks. Prior to attending the laboratory the subjects took either oral indomethacin 100 mg daily for 3 days in divided doses, with 50 mg on the morning of the experimental day, or matching placebo capsules according to a double-blind, balanced cross-over design. On each experimental day the subjects had three measurements of CBF separated by at least 40 minutes and in the same sequence (1) at rest during normocapnia, (2) while breathing 5% or 8% carbon dioxide (CO\(_2\)) in air and (3) during an infusion of PGI\(_2\). PGI\(_2\), synthesised by Upjohn and formulated by the Wellcome Foundation was diluted in glycine buffer at pH 10-5 and given by constant infusion pump into a forearm vein at a dose of 5 ng/kg/min for 5–10 minutes prior to and throughout the third CBF estimation.

CBF was measured by the non-invasive intravenous Xenon\(^{133}\) (Xe\(^{133}\)) clearance technique, details of which are given elsewhere.\(^5\) In brief, a bolus of approximately 7 mCi of Xe\(^{133}\), 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 Xe\(^{133}\) were monitored with a seventh detector and the end-tidal levels used to estimate recirculating arterial Xe\(^{133}\) concentrations. Regional CBF was calculated from a bicompartiment analysis of 11.5 minutes of the clearance data and also from an initial slope analysis of the first 1 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 init). To reduce the subjects’ exposure to CO\(_2\) isotope clearance during hypercapnia was monitored for only five minutes and the measurements of CBF while breathing CO\(_2\) were therefore limited to an initial slope analysis only. The CBF values used for each subject were 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 (pCO\(_2\)) was estimated by monitoring expiratory CO\(_2\) concentration with a Datex CD 300 infra red analyser. The pCO\(_2\) levels were calculated from the mean end tidal concentration over the first 5 minutes of each study. Samples were taken for estimation of indomethacin blood levels at the start of the first and third CBF estimations on each study day, and were analysed by a modification of the spectrofluorometric method of Hucker.\(^6\)

**Results**

The CBF results are shown in the table. Baseline resting CBF was found to be reduced by about 25% following indomethacin pretreatment compared to placebo (p < 0-02). These results and the response to hypercapnia are illustrated in the figure. Hypercapnia caused a significant rise in CBF (p < 0-01) both after indomethacin and placebo pretreatments but there was no significant difference in the responses with the two pretreatments. The mean % reactivity to CO\(_2\) (% rise in CBF with each kPa rise in pCO\(_2\)) was 34-7 on placebo and 33-7 on indomethacin.

The infusion of PGI\(_2\) resulted in a small reduction in CBF of about 10% following placebo treatment compared to the baseline levels (p < 0-05). In contrast, following indomethacin treatment there was no significant change in CBF. There was no significant difference in the pCO\(_2\) measurements between indomethacin and placebo pretreatment either during the resting measurement or after PGI\(_2\). The patterns of end-tidal Xe\(^{133}\) concentration were not significantly altered by the PGI\(_2\) infusions and it is therefore unlikely that there were significant alterations in the ratio of arterial to expired Xe\(^{133}\) concentrations that might have influenced the accuracy of the correction for arterial recirculation.

Indomethacin produced no significant differences in heart rate or blood pressure compared to placebo at normocapnia, hypercapnia or during PGI\(_2\). However, within each treatment group, PGI\(_2\) infusion caused a small rise in heart rate, mean increase 9-4 beats/min on placebo, 6-8 on indomethacin (p < 0-05 cf baseline). There was no significant change in systolic blood pressure during PGI\(_2\), but diastolic
Effect of indomethacin on cerebral blood flow and carbon dioxide reactivity

Table  Effect of indomethacin on cerebral blood flow in six subjects

<table>
<thead>
<tr>
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<th>Placebo mean ± SEM</th>
<th>Indomethacin mean ± SEM</th>
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<tr>
<td></td>
<td>Cerebral blood flow</td>
<td>pCO₂</td>
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<td>ml/100 mg/min</td>
<td>kPa</td>
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<td>(1) Baseline normocapnia</td>
<td>81.6 ± 4.4</td>
<td>58.3 ± 4.1</td>
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<td>(2) Hypercapnia</td>
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<td>88.0 ± 5.24</td>
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<tr>
<td>(3) PGI₂ infusion (normocapnia)</td>
<td>73.7 ± 3.6*</td>
<td>53.3 ± 3.5</td>
</tr>
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</table>

*p < 0.05 paired t test, cf baseline placebo.
†p < 0.02 paired t test, cf baseline placebo.
‡p < 0.01 paired t test, cf normocapnia.
Ø Finit not obtained during hypercapnia.

Discussion

This study has confirmed that oral indomethacin reduces resting CBF in man. Since Vane's discovery of its effect as an inhibitor of prostaglandin synthesis, indomethacin has been used as a standard pharmacological tool in prostaglandin research. If an action is blocked or inhibited by indomethacin, this is often taken as suggestive evidence that endogenous prostaglandins are involved in the reaction. On this basis we could conclude that a vasodilatory endogenous prostaglandin is involved in the regulation of normal human CBF, and CBF falls following indomethacin because the dominant dilator prostaglandin tone is removed. This has been the argument put forward by Pickard and others based on similar work on the effects of acute indomethacin administration to man and animals. However, some other inhibitors of prostaglandin synthesis such as aspirin and naproxen are without effect on resting CBF when given chronically, and Eriksson et al reported that a week of oral indomethacin does not reduce resting CBF in man. The position is thus unclear and although our results are compatible with the prostaglandin hypothesis, further evidence is required.

The current study has also demonstrated that pre-treatment with oral indomethacin does not alter the normal cerebrovascular response to an increase in arterial pCO₂. This is in contrast to the conclusions of two previous studies, which have suggested that indomethacin reduces cerebral vasodilation during hypercapnia in man and the baboon. However, both these studies examined the effects of acute administration of indomethacin, rather than two days pretreatment, and this may explain the results. There are also other methodological differences between the studies which may be relevant. The normal CBF response to an increase in arterial pCO₂ is exponential and also varies considerably.
from one individual to another.\textsuperscript{22} It is therefore essential to express CO\textsubscript{2} reactivity for each subject as a percentage of baseline values. It is not possible to calculate CO\textsubscript{2} reactivity accurately in the previous human study\textsuperscript{1} because of different numbers of subjects in the normocapnic and hypercapnic groups and therefore the results cannot be directly compared to ours. In the baboon study\textsuperscript{2} much higher doses of indomethacin were given directly into the circulation and the results could have been due to a toxic effect of the drug. Our current study suggests that prostaglandins are not directly involved in the mechanism of cerebral vasodilation accompanying hypercapnia and this is supported by the recent demonstration that an increase in PGI\textsubscript{1} metabolites is not found in the cerebral circulation during hypercapnia.\textsuperscript{20} The mediator of the dilatory response to hypercapnia is still unknown and suitable alternatives should be sought.

The finding that PGI\textsubscript{1} reduces CBF slightly after placebo pretreatment in normal individuals confirms previous studies.\textsuperscript{14,23} Exogenous PGI\textsubscript{1} greatly reduces peripheral resistance\textsuperscript{7} and there is considerable shunting of blood through the GI tract.\textsuperscript{24,25} The increase in cardiac output\textsuperscript{12} does not match this fully, and a small drop in blood pressure usually results, which could result in reduced CBF. However, the cerebral circulation is normally protected by the process of autoregulation from fluctuations in perfusion pressure and we have therefore previously suggested\textsuperscript{14} that PGI\textsubscript{1} may result in a disturbance of autoregulation. However, the finding that CBF remained unchanged and if anything rose in response to PGI\textsubscript{1} infusion after indomethacin pretreatment despite equivalent falls in blood pressure makes this suggestion less likely. Taken together the results suggest that exogenous PGI\textsubscript{1} has a direct effect on cerebrovascular tone which is dependent on the overall level of other prostaglandins.

Although PGI\textsubscript{1} in doses acceptable to conscious humans does not appear to increase the normal level of CBF this does not exclude a therapeutic vasodilator role in pathological areas of the circulation. PGI\textsubscript{1} is able to overcome cerebral artery spasm in vitro\textsuperscript{3} and in vivo\textsuperscript{10} and may therefore have a place in the treatment of subarachnoid haemorrhage. In dogs modest doses of PGI\textsubscript{1} increase CBF to ischaemic areas of brain only after indomethacin pretreatment.\textsuperscript{11} The current studies have shown that combined treatment with PGI\textsubscript{1} and indomethacin in patients with cerebrovascular disease would not result in significant vasodilation in normal areas of the brain and would therefore be unlikely to cause undesirable intra cerebral steal of blood away from ischaemic to normal areas.

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