SIDE EFFECTS OCCURRING DURING ADMINISTRATION OF EPOPROSTENOL (PROSTACYCLIN, PGI₂), IN MAN

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- 1 Fifty infusions of epoprostenol (PGI₂) were made, usually increasing the infusion rate until adverse effects were encountered. The volunteers were appraised that they might experience headache and facial flushing.
- 2 Facial flushing, headache, tachycardia and decrease in diastolic blood pressure were seen in almost all subjects. Erythema over the venous infusing site was also encountered in 13 infusions. Less common effects were sudden bradycardia, pallor and sweating—the vagal reflex—(seven times) and chest pain (twice). Other complaints included restlessness, abdominal discomfort, nausea and drowsiness.
- 3 The literature on side effects reported during PGI₂ infusion is reviewed and recommendations are made concerning administration of PGI₂.

Introduction

During the four years that epoprostenol (prosta-cyclin, PGI₂) has been available for experimental studies in humans, it has been tested in a wide range of disorders. A role is established in extracorporeal circulations, such as cardiopulmonary bypass (Longmore *et al.*, 1981; Rådegran & Papa-constantinou, 1980; Walker *et al.*, 1981), charcoal haemoperfusion (Gimson *et al.*, 1980) and haemodialysis (Turney *et al.*, 1980; Zusman *et al.*, 1981a). However, other potential applications for this compound include peripheral arterial disease (Hossman *et al.*, 1981; Szczeklik & Gryglewski, 1981; Olsson, 1980; Machin *et al.*, 1981a; Pardy *et al.*, 1980), acute or chronic coronary artery insufficiency (Bergman *et al.*, 1981; Szczeklik *et al.*, 1980e), haemolytic-uraemic syndrome (Beattie *et al.*, 1981; Webster *et al.*, 1981), thrombotic thrombocytopenic purpura (FitzGerald *et al.*, 1981), hypertension, especially in pregnancy (Fidler *et al.*, 1981) and also pulmonary hypertension (Szczeklik *et al.*, 1980c), Raynaud's disorder (Belch *et al.*, 1981; Dowd *et al.*, 1982) and persistent foetal circulation (Lock *et al.*, 1979). From knowledge of its potent action as a platelet inhibitor and as a vasodilator, activity in an even wider range of disorders could be predicted, and is currently being investigated. Many of the above conditions are associated with a high morbidity and mortality using conventional therapy.

Inevitably, however, an agent such as PGI₂ that is active in so many systems, will affect organs in the body other than those at which its therapy is directed,

leading to unwanted effects. It is important that these side effects should be carefully recorded and assessed in order that clinicians should be able to take pre-cautionary measures where applicable, give reassurances to patients and resolve difficulties of separating drug effects *per se* from general reactions attributable to anxiety on the part of the patient. In view of our own experience with PGI₂ in normal volunteers and that reported by some other groups, especially Data *et al.* (1981), we were concerned that there might have been unreporting of side effects during PGI₂ infusions in many clinical studies. We report here on our recent experience and review the available literature. We are aware that the infusions we describe took place in a potentially stressful situation and some of the reactions we report could equally have occurred during placebo infusions.

Methods

Fifty infusions of PGI₂ to 24 healthy volunteers were given over an 11-month period. Our subjects were ex- or non-smokers, aged 19–33 years, weighing 54 to 92 kg, 17 men, 7 women, and they all gave informed consent. Apart from a few pilot experiments, these infusions formed part of studies approved by the ethical committee of the appropriate hospital (St Bartholomew's or the National Hospital, Queen Square) (Fish *et al.*, 1982; Hassan *et al.*, 1982a,b; Pickles *et al.*, submitted for publication; Brown &

Pickles, submitted for publication). In one series, the subjects had received 0.2 mg/kg propranolol, 0.2 mg/kg atenolol or placebo intravenously 1.25 h prior to the PGI₂ infusion. In another study, the subjects had received dipyridamole 400 mg orally each day for 3 days, or placebo, prior to PGI₂. We have also studied 3 subjects immediately after receiving atropine 0.04 mg/kg i.v., and 3 further subjects immediately after cigarette smoking. None of these treatments appears to have made any quantitative or qualitative difference to the effects of PGI₂ infusion, except for the effect of atropine on the 'vagal reflex' (see below).

The PGI₂ used was synthesized by The Upjohn Company and formulated by The Wellcome Foundation Limited as a freeze-dried preparation in vials containing 0.5 mg, was dissolved in glycine buffer, pH 10.5, at room temperature, and given by slow infusion into a forearm vein. The infusion rate varied from 0.05 to 0.5 ml/min. In 44 experiments, PGI₂ was given first at a low dose for 10–20 min (2 or 2.5 ng kg⁻¹ min⁻¹) and then the dose was increased at 10–20 min intervals to 4, 6 and perhaps 8 and 10 ng kg⁻¹ min⁻¹, or to 5, 7.5 and 10 ng kg⁻¹ min⁻¹. In some of these experiments, the dose was increased to the maximum tolerated dose. The maximum total duration of PGI₂ infusion was 100 min. In the remaining 6 experiments, PGI₂ was given for about 30 min at 5 ng kg⁻¹ min⁻¹. All our subjects knew when they were receiving PGI₂ for the characteristic facial flushing (see below) destroys any attempt at concealment and all our subjects were warned that they might experience headache and facial flushing. All experiments took place with the subject semi-supine or supine.

Results (see Table 1)

Facial flushing

All the subjects showed flushing of the face, accompanied by a sensation of warmth. The flush in

some subjects was apparent at 2 ng kg⁻¹ min⁻¹ and in all at 6 ng kg⁻¹ min⁻¹. In 30 of the infusions facial colour was recorded photographically, later rated blind by an independent observer and a significant effect of PGI₂ on facial flush was confirmed (Pickles *et al.*, submitted for publication; Hassan *et al.*, 1982b). For most subjects, the affected area involved not only the face, but also the ears and neck in a collar fashion, and sometimes also the upper back and a V-shaped patch on the upper chest. A rise in forehead temperature, measured by skin thermocouple, accompanied the facial flush. Palmar erythema was a less frequent occurrence.

Headache

All our subjects developed a headache, but it should be noted they were all questioned directly about this, some with an analogue rating scale, and none of our infusions were double-blind. Nevertheless, headache was the limiting factor in most of the experiments in which we were attempting to increase the PGI₂ dose, and some subjects described the headache as the most severe they had ever experienced. The headache was variously described as frontal or overall, throbbing or constant, as a heaviness or a constriction. One subject, who also suffered from migraine, found the PGI₂ headache was distinctly different.

Venous reaction

In previous experiments at St Bartholomew's Hospital, PGI₂ had been infused directly into an antecubital vein, and no local reaction had ever been seen (O'Grady *et al.*, 1980; Warrington *et al.*, 1980). In many of the present experiments, the indwelling cannula was inserted into a more peripheral vein in the forearm. With the cannula in such a site, in 13 separate experiments a reaction became apparent in the infusing vein. On each occasion it appeared after at least 30 min of infusion and consisted of a bright redness over the line of the vein, sometimes spreading to interconnecting veins upstream as well as downstream. The vein felt indurated and was tender. On discontinuing the infusion this reaction outlasted the other effects of PGI₂ subsiding within about 30 min.

'Vagal reflex'

On 7 occasions in 5 subjects the usual tachycardia in response to PGI₂ rapidly reversed to a bradycardia, accompanied by pallor, sweating, nausea and sometimes abdominal discomfort. Unlike in a classical faint, there were no warning signs or symptoms such as overbreathing, anxiety or visual disturbances. This reaction occurred once immediately after stopping the PGI₂ infusion; in the remaining instances the infusion was promptly discontinued. One subject reacted in this manner on each of the 3 occasions he

Table 1 Incidence of adverse effects during 50 infusions of PGI₂ into 24 normal volunteers

Adverse effects	Occasions seen	Number of subjects
Flushing	50	24
Headache	50	24
Erythema over vein	13	9
Bradycardia 'vagal reflex'	7	5
Chest pain or tightness	2	1
Nausea without bradycardia	1	1
Abdominal discomfort	5	4
Drowsiness	2	2
Restlessness	?	?

received PGI₂. Another had received atropine 0.04 mg/kg i.v. 2 h 20 min prior to this reaction: his response was identical to that seen previously with other subjects except that he did not sweat.

Restlessness/unease

In one of our studies, an observer rated the 6 subjects for restlessness on an analogue scale, and a significant increase in the restlessness was found at 4 and 6 ng kg⁻¹ min⁻¹ ($P < 0.01$). Nevertheless, it was concluded that this effect was not necessarily attributable to PGI₂ and an accurate assessment of its incidence could not be given.

Chest pain

During an infusion of PGI₂ at 4 ng kg⁻¹ min⁻¹, one 21-year-old male subject complained of an 'indigestion like' post sternal pressure. A few minutes later, his phonocardiogram revealed frequent added heart sounds, sometimes 3rd, sometimes 4th, and these were confirmed on auscultation. He then developed tightness across his chest, and difficulty with breathing. The jugular venous pressure was elevated by about 3 cm, and there were basal crepitations. There was no disturbance of ECG rhythm, a 12-lead ECG was not taken and the subject was not investigated further. All his symptoms subsided within 15 min of discontinuing the infusion. He stated that during an infusion of the same dose of PGI₂ 2 weeks previously, he had also experienced some tightness in his chest but had not revealed this to the investigators.

Other effects

Abdominal discomfort was volunteered on 4 occasions, apart from those in which it was seen as part of the 'vagal reflex', and nausea was experienced once. Drowsiness or sleepiness was seen twice. A significant rise in pulse rate and drop in diastolic blood pressure was found: some subjects were aware of the tachycardia but none of them found it distressing. Ventricular ectopics were noted in one subject receiving 10 ng PGI₂ kg⁻¹ min⁻¹.

Timing of events

There was variation between subjects in their susceptibility to PGI₂, but the same sequence of events was usually present. A change in pre-ejection period and facial flushing was often apparent at PGI₂ 2–2.5 ng kg⁻¹ min⁻¹. A rise in heart rate and change in other cardiovascular variables together with a subjective awareness of cardiac effects and facial warmth was present by 4–5 ng kg⁻¹ min⁻¹. Headache was usually present at this dose and increased as did the other measures if the dose was raised. The venous

reaction and the 'vagal reflex' might have been dependent on the total duration of infusion as well as the dose, and only appeared after at least 1 h of infusion. In most of our experiments the dose was increased every 15–20 min, and the effects of each dose increased throughout this infusion period (e.g. see Figure 1, Hassan *et al.*, 1982a).

Discussion and literature review

Flushing

We have found that the dilatation of small blood vessels in the face leading to a facial flush is the most consistent guide to the activity of PGI₂, and occurs at a lower dose than that at which a clear effect on the pulse, blood pressure or platelets can be demonstrated. All our subjects showed this effect and it is reported consistently in other studies (Bergman *et al.*, 1981; Data *et al.*, 1981; Eklund *et al.*, 1981; FitzGerald *et al.*, 1979; O'Grady *et al.*, 1979; Olsson, 1980; Pardy *et al.*, 1980; Szczeklik *et al.*, 1978a,b; Warrington *et al.*, 1980; Wilhelmsson *et al.*, 1981). This effect has been looked for but not seen consistently in patients undergoing cardiopulmonary bypass (Bennett *et al.*, 1981; Longmore *et al.*, 1981; Walker *et al.*, 1981) or charcoal haemoperfusion; this may be because the agent responsible is being destroyed or removed (Gimson *et al.*, 1980), or because in these circumstances flushing seems too minor an effect to warrant comment. Facial flushing can also occur during haemodialysis with PGI₂ (Turney *et al.*, 1980; Zusman *et al.*, 1981b) and has also been seen following inhalation of PGI₂ (Bianco *et al.*, 1979; Szczeklik *et al.*, 1978b). Flushing is seen in the affected limb when PGI₂ is infused intra-arterially (Machin *et al.*, 1981b). Szczeklik & Gryglewski (1979) and Bianco *et al.* (1979) reported flushing of the palms and feet, as well as on the face.

We do not know why the vessels of the face should show this particular sensitivity to PGI₂, but this area is prone to flushing in other circumstances such as embarrassment, oestrogen withdrawal and the alcohol-chlorpropamide interaction. This last effect involves both endogenous prostaglandins and a naloxone-sensitive component (Medbak *et al.*, 1981) and we are currently investigating whether the PGI₂ flush is also naloxone-sensitive.

Headache

As in other studies with PGI₂ involving normal volunteers, we found that headache was a common feature (Data *et al.*, 1981; Eklund *et al.*, 1981; FitzGerald *et al.*, 1979; O'Grady *et al.*, 1979, 1980; Szczeklik & Gryglewski, 1979, 1981; Wilhelmsson *et al.*, 1981). After flushing, this is usually the most

frequent adverse effect in patient studies also (Bergman *et al.*, 1981; Dowd *et al.*, 1982; Olsson, 1980; Pardy *et al.*, 1980; Szczeklik, *et al.*, 1980a; Zusman *et al.*, 1981b). Again, the mechanism is unknown but a similar headache often develops with other vasodilators. PGI₂ headache is dissimilar from that experienced in migraine or cluster headaches (Peatfield *et al.*, 1981). We would agree with Data *et al.* (1981) that it is the headache that prevents normal volunteers from tolerating the higher doses of PGI₂ for long periods.

The vagal reflex

Bradycardia and nausea are features of excess vagal activity and so the sudden occurrence of these symptoms together with pallor and sweating we have called the 'vagal reflex'. The frequency with which we saw this effect, especially at the mid range of the doses we employed, was unexpected as was the suddenness (a few seconds) it took to develop. Although some very early human studies led to similar reactions (Szczeklik *et al.*, 1978a,b; Szczeklik & Gryglewski, 1979) it appeared that this effect would occur only at doses over 20 ng kg⁻¹ min⁻¹ (Szczeklik & Gryglewski, 1981). However, other groups of workers have also seen bradycardia infrequently at lower doses in both patients (Budd *et al.*, 1980; Zusman *et al.*, 1981a,b) and normals (Eklund *et al.*, 1981), as well as at higher doses in patients (Beattie *et al.*, 1981). Data *et al.* (1981) reported two episodes of bradycardia and orthostatic hypotension in one normal subject at 6 ng PGI₂ kg⁻¹ min⁻¹. Foetal bradycardia during PGI₂ infusion has been noted (Fidler *et al.*, 1980) and might be related.

A Bezold-Jarisch-type vagal reflex initiated by pulmonary (Armstrong & Miller, 1980) or cardiac (Roberts *et al.*, 1980) C-fibres is now recognized in animals (Hintze *et al.*, 1981) and it seems likely that we have seen in humans a reflex with a similar mechanism. Although much of the efferent side of the reflex is cholinergic, atropine does not completely abolish it (Chapple *et al.*, 1980), in keeping with the findings in our atropinized subject. This means that discontinuing the infusion or reducing the infusion rate becomes the only sensible response to this reaction.

Gastrointestinal upset

We have recorded a lower incidence of nausea, vomiting and abdominal discomfort with PGI₂ than in other volunteer studies (Data *et al.*, 1981; Eklund *et al.*, 1981; FitzGerald *et al.*, 1980). When the Cracow group reviewed their adverse effects from 110 infusions (Szczeklik & Gryglewski, 1981), gastrointestinal complaints did not feature. Whilst most studies with patients have recorded nausea, vomiting,

abdominal cramps or pains infrequently (Olsson & Nilsson, 1981; Machin *et al.*, 1981b; Pardy *et al.*, 1980; Zusman *et al.*, 1981b), in some studies the great majority of patients have suffered such complaints (Belch *et al.*, 1981; Dowd *et al.*, 1981; Guadagni *et al.*, 1981).

Restlessness/unease

Excessive restlessness and fidgeting, not necessarily associated with anxiety, is an unusual drug response and has been noted with PGI₂ right from the earliest studies (Szczeklik *et al.*, 1978a; FitzGerald *et al.*, 1979; O'Grady *et al.*, 1980; Chierchia *et al.*, 1979; Szczeklik & Gryglewski, 1979; Olsson, 1980; Guadagni *et al.*, 1981; Data *et al.*, 1981; Hensby *et al.*, 1979). The mechanism is unknown.

Local venous reaction

In view of the frequency with which we have seen a local reaction in the vein into which the PGI₂ was being infused, we were surprised that this had been reported previously by only one group of workers (Olsson, 1980; Olsson & Nilsson, 1981). As was mentioned by them, this reaction was very similar to that which is recognized with PGE₁ infusion (Beitner *et al.*, 1980). The high pH (10.5) of the buffer could have been responsible for this reaction, rather than the PGI₂ *per se*. In all our subjects, the reaction resolved spontaneously.

Chest pain and ECG changes

One normal male volunteer suffered an attack of tightness in his chest during PGI₂ at 4 ng kg⁻¹ min⁻¹. Other workers have seen chest pain in normal volunteers receiving PGI₂ (Kaijser & Wennmalm, personal communication) and T-wave flattening has also been noted (Data *et al.*, 1981). In patients, Fidler *et al.* (1980) and Zusman *et al.* (1981a) have reported chest pain during PGI₂ infusions. Dargie & Lewis (1981), when studying the effect of PGI₂ in patients with angina at rest, produced ischaemic symptoms and ECG changes; β -adrenoceptor blockade reduced the absolute heart rate and suppressed these symptoms during a subsequent PGI₂ trial. Ventricular ectopics, palpitations and ECG changes have also been noted by other groups (Pardy *et al.*, 1980; Gryglewski & Szczeklik, 1981; Guadagni *et al.*, 1981), and have been predicted from certain animal experiments (Karmazyn *et al.*, 1978).

Drowsiness

Drowsiness and lassitude have been infrequent complaints with PGI₂ in our experience, and in that of

other workers (Beattie *et al.*, 1981; Dowd *et al.*, 1982; Olsson, 1980). Light-headedness has been reported by Szczeklik *et al.* (1978a) and Zusman *et al.* (1981b) and although blurred vision was reported by O'Grady *et al.* (1980) they saw no change in mental state. Sighing and yawning were seen in 6 of the 27 infusions of Data *et al.* (1981) and slurring of speech once.

Pain in limbs and jaw

Although PGI₂ has also been reported to relieve rest pain in ischaemic limbs most investigators who have used intra-arterial injections of PGI₂ have produced limb pains at times (Szczeklik *et al.*, 1979, 1980d; Gryglewski & Szczeklik, 1981; Olsson & Nilsson, 1981; Machin *et al.*, 1981b; Vermeylen *et al.*, 1980). Machin *et al.* (1981b) also report one case of intolerable burning sensation in the toes. The mechanism is likely to be either 'steal' from the ischaemic areas or conversely intense local vasodilatation.

It is less easy to understand other local pains unrelated to the site of infusion, in particular the jaw pain described by Gryglewski & Szczeklik (1981) and described in 18 of the 25 patients with Raynaud's phenomenon complicating systemic sclerosis studied by Dowd *et al.* (1982). As this pain was aggravated by chewing, it could originate from salivary glands affected by Sjogren's syndrome.

Hypotension and tachycardia

PGI₂ usually produces a modest tachycardia and fall in diastolic pressure. The hypotension results from peripheral vasodilation (Eklund, *et al.*, 1981) and the cause of the tachycardia is not yet clear (Hassan *et al.*, 1982b). Although the hypotension is usually asymptomatic, it was listed as a side effect by Dowd *et al.* (1982) and by Guadagni *et al.* (1981). When occurring during dialysis, it responds to extra fluid replacement (Zusman *et al.*, 1981a) or reduction in PGI₂ dose (Smith *et al.*, 1981). Turney & Weston (1981) in over 50 haemodialyses with PGI₂ have not yet observed clinically significant hypotension. When PGI₂ is used during coronary bypass, some workers have reported a need for extra fluid replacement (Bunting *et al.*, 1981; Fabiani *et al.*, 1981). In 3 of the 110 subjects studied by Szczeklik & Gryglewski (1981) a paradoxical rise in blood pressure was recorded.

Bleeding

In view of its well-known effect on platelets, subjects with pre-existing lesions run the theoretical risk of increased bleeding whilst receiving PGI₂, and prolongation of cutaneous bleeding time can be recorded (Data *et al.*, 1981; Szczeklik & Gryglewski,

1979; Pickles *et al.*, submitted for publication). Pre-existing uterine bleeding was made more brisk in one of the patients studied by Olsson (1980), and unusually brisk bleeding was seen at caesarian section by Fidler *et al.* (1980). Although the events were almost certainly unrelated to the use of PGI₂ a patient with thrombotic thrombocytopenic purpura suffered a fatal cerebral haemorrhage when on PGI₂ (Budd *et al.*, 1980) and vitreous haemorrhages developed in one of the cases of central retinal vein occlusion given PGI₂ by Zygulska-Mach *et al.* (1980). However PGI₂ is safer than heparin when an actively bleeding patient requires haemodialysis (Arze & Ward, 1981; Zusman *et al.*, 1981). Data *et al.* (1981) also reported a complete inhibition of template bleeding after discontinuing PGI₂ in 3 of their subjects, and were unable to give an explanation for this. Increased platelet activity on discontinuing PGI₂ has been reported by Dembinska-Kiec *et al.* (1981b).

Miscellaneous

Moderate hyperglycaemia during PGI₂ therapy in diabetic patients was reported by Gryglewski & Szczeklik (1981), and studied in more detail by Szczeklik *et al.* (1980b), and by Dembinska-Kiec *et al.* (1981a). Non-diabetic subjects may not be subject to this effect (Data *et al.*, 1981; Eklund *et al.*, 1981; Patrono *et al.*, 1981). Sweating has been reported by both Dowd *et al.* (1982) and Data *et al.* (1981), and occurred a few hours after one of the very first human PGI₂ infusions (Szczeklik *et al.*, 1978a). As has been found with other vasodilators, arterial pO₂ may fall with PGI₂ (Gimson *et al.*, 1981; Tricot *et al.*, 1980; Williams *et al.*, 1980). When delivered by inhalation, PGI₂ can cause pharyngeal irritation and coughing, probably due to the high pH of the inhalate (Bianco *et al.*, 1979; Szczeklik *et al.*, 1978b). Hypotonia was mentioned by Gryglewski & Szczeklik (1981), anxiety by Data *et al.* (1981) and a brisk diuresis seen by FitzGerald *et al.* (1979), and Fidler *et al.* (1981), all in relation to PGI₂ infusions.

Conclusions and recommendations

Clinicians should be aware of the incidence, nature and severity of adverse events reported after infusion of PGI₂, and we have described some of the events we have seen in healthy volunteers infused with PGI₂ on an open basis.

(1) PGI₂ dose

In many of the early experiments, relatively high doses of PGI₂ (e.g. 20 ng kg⁻¹ min⁻¹) were given without mishap. It appears probable that the PGI₂ currently available from Upjohn Wellcome is up to

twice as potent as that which was available from other sources some years ago. We would agree with Data *et al.* (1981) that $4 \text{ ng kg}^{-1} \text{ min}^{-1}$ should in general be the maximum infusion rate for prolonged infusions and this dose would be expected to produce circulating PGI_2 considerably in excess of the normal physiological level (Christ-Hazelhof & Nugteren, 1981). Patients who are anaesthetized, especially if there is an extracorporeal circulation which could lead to a more rapid breakdown of PGI_2 , are known to tolerate higher infusion rates. It was noted that patients receiving PGI_2 $12.5 \text{ ng kg}^{-1} \text{ min}^{-1}$ did not show a tachycardia when they were anaesthetized (Bunting *et al.*, 1981) and some cardiovascular responses to PGI_2 are known to be reduced by anaesthesia in dogs (Hintze *et al.*, 1981).

Data *et al.* (1981) recommend that $10 \text{ ng kg}^{-1} \text{ min}^{-1}$ should be the maximum rate for infusions lasting up to 60 min: although undoubtedly many subjects could tolerate this dose, all our adverse effects occurred at a lower dose than this.

It has been suggested that female subjects are more susceptible to the cardiovascular effects of PGI_2 than are male (Bianco *et al.*, 1980). This needs confirmation.

(2) Infusion technique

PGI_2 in solution needs to be kept at pH 10.5 but it is now known that it is not necessary to keep the solution cooled, as at least 90% of activity is preserved for 12 h in such solutions at room temperature. However, because of the high pH, it is usual for a small volume of the PGI_2 solution to be given by infusion pump at a very slow rate. With this arrangement, accidental injection of a bolus of a higher dose of PGI_2 can occur readily, and has been reported (Data *et al.*, 1981). Syringe changes should not be left to staff unfamiliar with the infusion apparatus. The dose of PGI_2 is very small in comparison with that of any other drug so those unfamiliar with PGI_2 could readily make a mis-

calculation in preparing the solution (the bottle is labelled in mg, the dose is calculated in ng). Again, these procedures should not be delegated to untrained or inexperienced staff.

(3) Patient monitoring

In view of the suddenness with which the 'vagal reflex' can occur, heart rate monitoring is advisable as a fall in pulse rate is an early guide that the 'vagal reflex' is occurring.

Most of the events reported here have responded to a reduction in PGI_2 dosage, although this hardly seems necessary for the minor ones. If more serious reactions occur, or the patient becomes distressed with headache, none of the present indications for PGI_2 are such that the infusion has to continue without a dose reduction (with the possible exception of haemodialysis of a bleeding patient).

(4) Conclusion

Awareness of the possible range of side effects, and careful attention to infusion technique, will allow further safe exploration of the therapeutic potential of PGI_2 , and an extended assessment of its risk-benefit ratio. The latter must be considered in relation to potential therapeutic expectations for prostacyclin. In several conditions in which the use of prostacyclin is currently under investigation, either the prognosis with conventional treatment is poor, as in fulminant hepatic failure, or the use of conventional medication, such as heparin, may itself be hazardous, as in the haemodialysis of patients with haemorrhagic complications.

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