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CIGARETTE SMOKING DOES NOT ATTENUATE THE CARDIOVASCULAR EFFECTS OF EPOPROSTENOL (PROSTACYCLIN) IN HUMANS

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Infusion of epoprostenol (prostacyclin, PGI_2) in human subjects leads to a rise in pulse rate, a fall in diastolic pressure and a rise in pulse pressure. In three healthy subjects these responses to PGI_2 were identical before and after 30 min continuous cigarette smoking, and demonstrate that the attenuation of the PGI_2 response by smoking reported in rats does not occur in healthy humans.

Introduction

Epoprostenol (prostacyclin, PGI_2) is an endogenous product of vascular and other tissues in man and has vasodilator and platelet inhibitory properties. It has been suggested that some of the adverse cardiovascular complications of cigarette smoking could be related to PGI_2 insufficiency. Both acute and chronic smoking can reduce levels of circulatory PGI_2 (Masotti *et al.*, 1981), and smaller amounts of PGI_2 are produced by smokers in the lungs (Hensby, 1981) and in response to ischaemia (Masotti *et al.*, 1981) than by non-smokers. Recently, Boura *et al.* (1981) reported that in rats the cardiovascular response to exogenous PGI_2 was reduced dramatically 1 and 24 h following acute exposure to cigarette smoke. We have attempted to reproduce this effect in man.

Methods

Our subjects, two female and one male, aged 22 to 32 years, weight 54 to 91 kg, were all healthy ex-smokers, who had not smoked for at least 2 months. They gave their informed consent. During the experiment the subjects rested supine with an infusion running into a forearm vein. Radial pulse was monitored over 1 min at frequent intervals, and blood pressure was taken with a London School of Hygiene sphygmomanometer. Following a rest period, the infusion was changed from 0.9% saline to glycine buffer, then to PGI_2 in buffer for 10 min each at 2.5, 5, 7.5 and 10 ng kg^{-1} min^{-1}. The infusion was then changed back to saline, and when the cardiovascular variables had returned to baseline the subject smoked as many cigarettes as he could within a 30 min period (3 to 5 cigarettes, Senior Service, without filter, or Rothman's King size with filter, all middle tar). When the pulse and blood presure had returned to baseline, about 1 h later the PGI_2 infusion was repeated over the same time course as previously.

PGI_2 was synthesised by the Upjohn Company and formulated by the Wellcome Foundation Ltd. It was stored at 4°C and reconstituted in glycine buffer at pH. 10.5 immediately prior to use.

Results

Epoprostenol produced the same effects as seen previously (Warrington *et al.*, 1980), with tachycardia, a fall in diastolic blood pressure, headache and facial flushing. Cigarette smoking produced a marked tachycardia and rise in blood pressure in all three subjects. However, there was no difference at all in the rise in pulse rate or rise in pulse pressure in response to PGI_2 before and after smoking (see Figure 1). Mean baseline heart rate was 61.7 beats/min (range 44–75), increasing with 2.5 ng kg^{-1} min^{-1} PGI_2 by 1.3 (range 0–3), with 5 ng by 9.7

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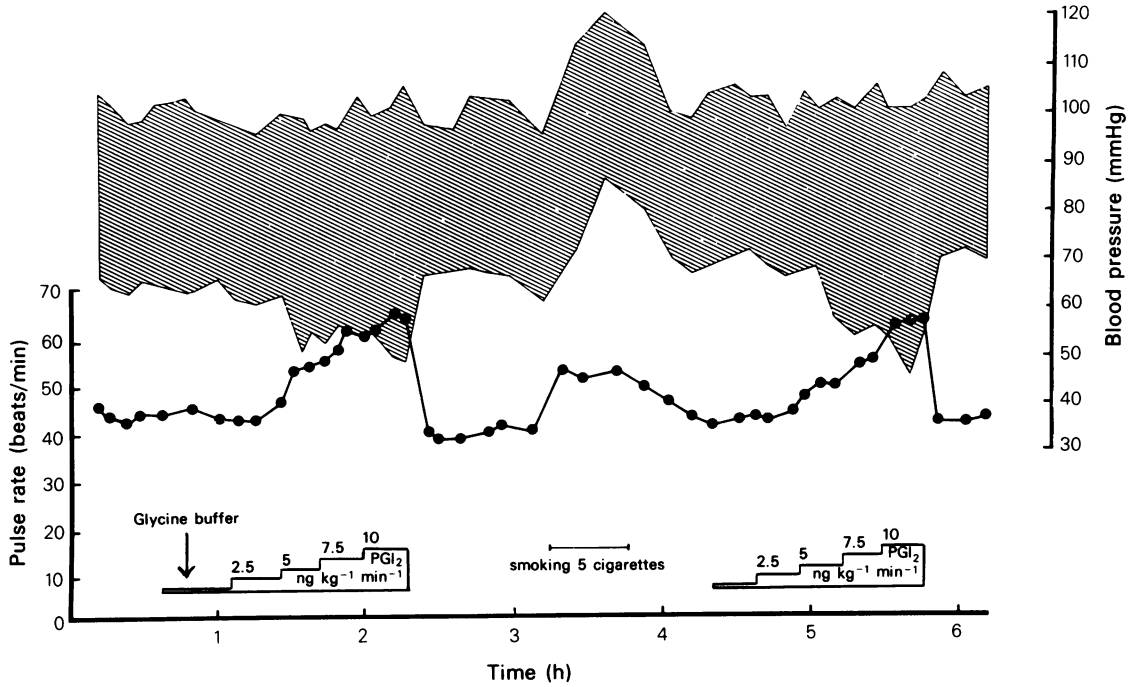

Figure 1 Pulse rate and blood pressure in a single subject during two infusions of PGI_2 separated by a smoking session. PGI_2 produces similar changes in heart rate and pulse pressure both before and after smoking.

(4–14), with 7.5 ng by 14.7 (10–18) and with 10 ng by 20.5 (20–21); following smoking the baseline heart rate was 62.8 (44–73) rising with 2.5 ng PGI_2 kg^{-1} min^{-1} by 2.2 (1.5–4) with 5 ng by 10.2 (6–13), with 7.5 ng by 14.9 (12–16.5) and with 10 ng by 24.5 (20–29). There was likewise no change in the increment in pulse pressure nor the fall in diastolic pressure in the two PGI_2 infusion periods. There was no difference in the rates of recovery following each PGI_2 infusion.

Discussion

We have been unable to demonstrate any reduction in the cardiovascular effects of PGI_2 following cigarette smoking. This study was designed as a pilot experiment, but in view of the completely negative results and the large number of subsequent experiments that would be required before a different conclusion could be reached, we felt it would not be ethical to continue. We attempted to reproduce the experimental conditions used by Boura *et al.* (1981), with 30 min exposure to cigarette smoke and with a subsequent test exposure to PGI_2 at least 1 h later, although the maximum dose of PGI_2 that could be given was substantially less than that possible in anaesthesized animals. Boura *et al.* (1981) were unable to conclude on the mechanism involved in the inhibitory effect of cigarette smoke on PGI_2 responses, considering both a direct action on the cardiovascular system and altered metabolic breakdown. Whatever this mechanism might be in rats, we have found no evidence that the response to exogenous PGI_2 is impaired in healthy humans following cigarette smoking.

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