Br. J. clin. Pharmac. (1987), **23**, 486–490

Adenosine-induced respiratory stimulation in man depends on site of infusion. Evidence for an action on the carotid body?

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Adenosine is an endogenous nucleoside which stimulates respiration in man and other mammals. In animals adenosine appears to initiate respiratory stimulation within the carotid body, but whether this is the site of action in man is not known. We administered adenosine by intra-aortic infusion to 12 subjects undergoing cardiac catheterisation. When adenosine was infused at three sites proximal to the carotid circulation, minute ventilation was significantly higher than baseline values or those during adenosine infusion at a more distal site. These results support the hypothesis that adenosine-induced respiratory stimulation in man is mediated in the carotid body.

Introduction

Adenosine is an endogenous nucleoside which exerts various pharmacological effects (Berne, 1980; Lancet, 1985; Newby, 1984), many of which appear to be related to the balance between energy (or oxygen) supply and demand (Newby, 1984).

We recently identified a dose-related respiratory stimulant effect of adenosine in man (Watt & Routledge, 1985), and suggested that this effect was likely to be carotid body mediated and that it might be relevant to the ventilatory stimulation produced by hypoxia which is carotid body dependent in man and some other mammals (Chalmers *et al.*, 1967; Lugliani *et al.*, 1971).

Adenosine has a half-life in human blood of less than 10 s (Klabunde, 1983). Therefore if adenosine-induced respiratory stimulation in man is carotid body mediated then it would be expected that administration of adenosine proximal to the carotid circulation would stimulate respiration whereas more distal administration of the nucleoside would have no such effect. We examined this hypothesis in 12 patients undergoing cardiac catheterisation.

Methods

Informed, written consent was obtained from 12 patients (10 male, aged 55 ± 7 years) scheduled to undergo cardiac catheterisation on clinical grounds for investigation of chest pain. Adenosine was administered according to a protocol approved by the hospital ethics committee. Careful consideration was given to the possibility of adverse cardiac events in such patients but it was considered that clinically significant adverse events were unlikely in view of the short half-life of adenosine, less than 10 s (Klabunde, 1983), and the ease of catheter withdrawal to a more distal part of the aorta.

Adenosine was administered by continuous intra-aortic infusion sequentially at five sites: (1) immediately above the aortic valve, (2) mid-ascending thoracic aorta, (3) top of the aortic arch, (4) mid-descending thoracic aorta and (5) just proximal to the top of the aortic arch (see Figure 1). Sites 1, 2 and 5 are proximal to the carotid circulation, site 3 is close to the origin of those vessels, and site 4 is situated distal to the carotid vessels. The initial rate of intra-aortic adenosine infusion was derived from our experi-

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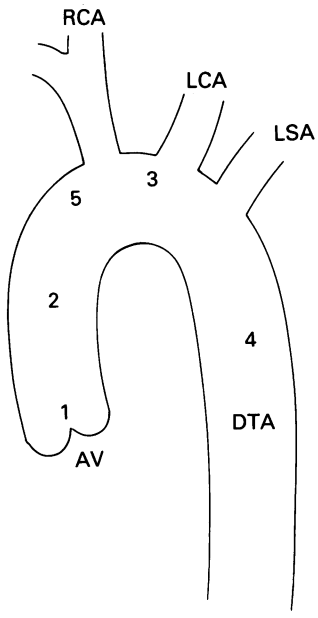

Figure 1 Schematic diagam showing infusion sites in the thoracic aorta in relation to the origin of the carotid circulation. Right common carotid artery (RCA), left common carotid artery (LCA), left subclavian artery (LSA), descending thoracic aorta (DTA) and aortic valve (AV).

ence of intravenous adenosine infusion: an intravenous infusion rate of 6 mg min^{-1} produced slight respiratory stimulation in man (Reid *et al.*, 1987). We assumed a half-life of adenosine in blood of about 10 s (Klabunde, 1983) and a circulation time of 20 s (from an antecubital vein). The infusion rate at site 1 was therefore initially 1.58 mg min^{-1}, and was increased as necessary to a level which produced a moderate increase in minute ventilation. In this group of patients the final dose was 2.86 ± 0.97 mg min^{-1} (mean ± s.d.), and the infusion was continued at a constant rate throughout the remainder of the study, as the cardiac catheter was moved at 1 min intervals from one site to the next. Patients were 'blind' to the timing and direction of catheter movements.

An electrocardiogram was recorded throughout the study. A respiratory trace was recorded at 1 min intervals from a Lectromed type 4320 respiration transducer (which had been calibrated against a spirometer) on an Ormed MX216 recorder. Minute ventilation was calculated from the product of tidal volume and respiratory rate. Intra-aortic pressure was measured in eight subjects via the cardiac catheter before and immediately after the adenosine infusion. In four patients right femoral artery pressure was measured at 1 min intervals from a side-arm of a sheath through which the cardiac catheter had been inserted. Patients were asked at 1 min intervals to report any subjective sensations.

The adenosine solution used was a sterile preparation of adenosine (Sigma) in 0.9% sodium chloride at a final adenosine concentration of 5 mg ml^{-1}. Infusion rates were controlled using a Harvard model 2681 infusion pump.

Eight patients were taking oral β-adrenoceptor blockers, seven oral or dermal nitrate preparations and five oral calcium antagonists. One patient was receiving amiodarone, one bendrofluazide, and one frusemide (20 mg daily). All therapy, other than sublingual nitrates, was stopped at least 12 h prior to the study.

Comparisons of log-transformed minute ventilation, heart rate and blood pressure at different sites were made using two-way analysis of variance and Student Newman-Keuls test. Blood pressure before and after the adenosine infusion was compared using Student's paired *t*-test.

Results

Respiratory, heart rate and blood pressure data are summarised in Table 1. In one patient the trace recorded at position 4 could not be measured and in one patient the study was stopped prematurely because of epigastric discomfort. Data were therefore analysed for the remaining 10 patients.

There was a significant difference in minute ventilation at different infusion sites ($F = 5.444$, Num d.f. = 5, Den d.f. = 45, $P < 0.002$). Minute ventilation at baseline and site 4 did not differ from each other ($Q = 0.989$, $P > 0.50$) but were significantly less than minute ventilation at sites 1, 2 or 5 ($P < 0.025$ for each comparison). Minute ventilation at site 3 was intermediate and did not differ significantly from that at any other site. There were no other significant inter-site differences in minute ventilation.

The difference in minute ventilation was attributable to inter-site differences in tidal volume ($F = 3.886$, Num d.f. = 5, Den d.f. = 45, $P < 0.02$). Tidal volume during adenosine infusion at sites 1, 2 and 5 was higher than at baseline ($P < 0.05$ for each comparison). Tidal volume at site 4 did not differ from baseline ($Q = 0.711$, $P > 0.50$), but approached a significant difference from sites 1, 2 and 5 ($0.05 < P < 0.10$ for each comparison). There was no difference in respiratory rate at different infusion sites ($F = 1.482$, Num d.f. = 5, Den d.f. = 45, $P > 0.20$).

Table 1 Respiration, heart rate and mean blood pressure during adenosine infusion at the sites described. Data are shown as mean ± s.d.

Variable	n	*Baseline*	*Site 1*	*Site 2*	*Site 3*	*Site 4*	*Site 5*
Minute ventilation ($l\ min^{-1}$)	10	5.31 ± 1.68	8.78 ± 3.53	10.13 ± 8.93	6.83 ± 2.26	5.05 ± 2.53	9.71 ± 6.21
Respiratory rate (min^{-1})	10	16.1 ± 3.6	16.3 ± 3.6	16.6 ± 5.0	15.1 ± 2.4	13.8 ± 3.4	16.7 ± 3.0
Tidal volume (l)	10	0.35 ± 0.14	0.57 ± 0.29	0.60 ± 0.34	0.46 ± 0.18	0.38 ± 0.18	0.62 ± 0.45
Heart rate (beats min^{-1})	10	59 ± 10	63 ± 12	68 ± 14	70 ± 13	69 ± 14	73 ± 15
Mean right femoral artery pressure (mm Hg)	4	92 ± 10	94 ± 16	99 ± 12	94 ± 14	92 ± 12	102 ± 13

There was also a significant difference in heart rate at different infusion sites ($F = 13.974$, Num d.f. = 5, Den d.f. = 45, $P < 0.001$). Heart rate at baseline and at site 1 was significantly less ($P < 0.01$ for each comparison) than heart rate at sites 2, 3, 4 or 5 which were not significantly different from one another.

In the eight patients in whom mean intra-aortic pressure was measured before (89 ± 8 mm Hg) and immediately after (84 ± 12 mm Hg) adenosine infusion, there was no significant change ($t = 1.754$, d.f. = 7, $P > 0.10$). In the four patients in whom right femoral artery pressure was measured at each infusion site no significant changes were demonstrable ($F = 1.054$, Num d.f. = 5, Den d.f. = 15, $P > 0.50$).

Adverse effects were reported by a number of patients during adenosine infusion but these were mild with one exception. That patient, who had a symptomatic hiatus hernia, experienced epigastric pain during adenosine infusion at site 4 and the study was promptly terminated at the patient's request. While no other subject requested that the study be terminated (although all were aware that they might do so) eight reported dyspnoea, eight had chest discomfort (six at site 4), eight experienced epigastric discomfort (one at site 1, six at site 4), two reported nausea, six mentioned facial flushing and four described discomfort in the neck or throat. All subjective sensations resolved within 60 s of stopping the adenosine infusion.

Discussion

The present study confirms the respiratory-stimulant effect of adenosine in man which we reported previously (Watt & Routledge, 1985; Reid *et al.*, 1987). Further the results demonstrate that the respiratory-stimulant effect of intravenous adenosine depends on the site of administration. Adenosine infused distal to the carotid circulation (site 4) caused no respiratory stimulation, but infusion of adenosine proximal to the carotid circulation caused a respiratory stimulation both before (sites 1 and 2) and after (site 5) more distal adenosine infusion.

These findings raise the question of why adenosine-induced respiratory stimulation should depend on perfusion of the carotid circulation. The effect could be mediated by the carotid bodies or brain chemoreceptors. The latter alternative appears unlikely because adenosine analogues depress respiration when applied locally to the brain (Eldridge *et al.*, 1984; Mueller *et al.*, 1984). We found that adenosine-induced respiratory stimulation in the rabbit was abolished by bilateral division of the afferent nerve supply to the carotid bodies (Buss *et al.*, 1986) and others have demonstrated the same finding in the rat (Monteiro & Ribeiro, 1986). This suggests that adenosine stimulates respiration by an action on the carotid body in those species. The data presented above support but do not prove the hypothesis that adenosine-induced respiratory stimulation in man is also carotid body mediated.

The pattern of site-dependent changes in heart rate differed from that of minute ventilation. Heart rate increased after adenosine infusion was started; the increase over baseline values being apparent during infusion at sites 2, 3, 4 and 5. We did not identify any fall in blood pressure to account for the changes in heart rate. It is not clear why heart rate did not increase at site 1, but it may partly be because a sufficiently high concentration of adenosine might be per-

fusing the coronary circulation, to exert a negative chromotropic effect on the sinoatrial node (Szentmiklosi *et al.*, 1980) to oppose any increase in heart rate produced by other mechanisms. The increase in heart rate seen at other sites may be a reflex, perhaps secondary to the increase in ventilation produced by carotid body stimulation, as has been observed in the dog (Daly & Scott, 1958). If this is the case it is unclear why the changes in heart rate show a pattern different from the respiratory changes. Heart rate does not return rapidly to baseline following boluses of adenosine (see figure in Watt & Routledge, 1986) so it is possible that in the present study there was insufficient time during the period of infusion at site 4 for a return to baseline heart rate to occur. Alternatively a sympathetic reflex secondary to the adverse effects experienced may have contributed to the tachycardia and hence its persistence during infusion at site 4 where some adverse effects were more common. Evidence of sympathetic stimulation by adenosine has been provided by Biaggioni *et al.* (1985) who reported elevated plasma adrenaline and noradrenaline levels in association with increased heart rate and systolic blood pressure during peripheral infusion of adenosine. The mechanism of this sympathetic activation remains to be elucidated.

Eight of the 10 patients were receiving treatment with β-adrenoceptor blockers and this is likely to have reduced the magnitude of the heart rate changes in those patients. In the two patients who were not receiving β-adrenoceptor blockers heart rate increased by up to 34 beats min^{-1}, while in the β-adrenoceptor blocked patients heart rate increased by up to 19 beats min^{-1} from baseline.

Intravenous adenosine in high doses is known to lower blood pressure in anaesthetised man (Sollevi *et al.*, 1984) and in laboratory mammals (Fukunaga *et al.*, 1982). At the doses used in the present study no changes in arterial blood pressure were detected. Numbers were small, therefore a Type II error is a possibility but in other studies using intravenous adenosine infusion we and others observed respiratory stimulation without hypotension and with an increase in systolic blood pressure (Reid *et al.*, 1987; Biaggioni *et al.*, 1986). Therefore it is unlikely that hypotension is a necessary factor contributing to the observed adenosine-induced respiratory stimulation.

The occurrence of chest discomfort in some patients during intra-aortic infusion is of interest in the context of the adenosine-induced retrosternal discomfort reported recently by Sylven *et al.* (1986). They proposed that exogenous adenosine produced such transient chest discomfort by directly stimulating afferent cardiac nerves, and further proposed that adenosine released spontaneously during cardiac ischaemia contributes to the pain of angina pectoris. They provided no information as to changes in coronary flow associated with such sensations or whether such sensations are ever cardiac in origin. We have shown that adenosine increases coronary flow in man (Watt *et al.*, 1986) and in 9 of those 10 patients transient retrosternal discomfort occurred in association with doubled coronary flow. Thus retrosternal discomfort is not attributable in those patients with normal coronary arteries to a fall in coronary blood flow. The present study provides information on the site of origin of adenosine-induced chest discomfort. In seven of the eight patients reporting such discomfort, it occurred during adenosine infusion at sites 3 and 4. When one considers that the half-life of adenosine in human blood is less than 10 s (Klabunde, 1983), it is unlikely that such chest sensations in those patients are cardiac in origin. In the single patient who reported 'chest tightness' during adenosine infusion at site 1 but at no other site, the heart might appear to be the source of adenosine-induced discomfort. That patient had a 50% left anterior descending coronary artery stenosis. Coronary flow increases distal to stenoses of that degree in animal hearts in response to vasodilators (Knabb *et al.*, 1985) so a fall in absolute coronary flow distal to the stenosis is unlikely in that patient. The occurrence of 'chest tightness' in that patient would therefore appear to provide support for a possible cardiac origin of adenosine-induced retrosternal discomfort in some circumstances.

Adenosine reproduces the epigastric pain of duodenal ulceration (Watt *et al.*, 1987). While epigastric discomfort of some degree occurred in 8 of 10 patients in this study, in only the patient with a hiatus hernia was the discomfort marked. It may be, therefore, that not only duodenal ulceration but also other inflammatory lesions of the upper gastrointestinal tract may predispose to adenosine-induced epigastric discomfort by mechanisms as yet undefined.

We previously suggested that adenosine stimulates respiration in man by an action on the carotid body (Watt & Routledge, 1985). The results of the present study support this suggestion and are consonant with the data supporting the carotid body as being the site of adenosine-induced respiratory stimulation in the rabbit (Buss *et al.*, 1986) and rat (Monteiro & Ribeiro, 1986). The ventilatory response to hypoxia in man is also carotid body dependent (Lugliani *et al.*, 1971). It remains to be established whether

adenosine plays a role in the mechanisms by which the ventilatory response to hypoxia is initiated in the carotid body.

A.H.W. was supported by the Welsh Scheme for the Development of Health and Social Research. We thank the Sterile Products Unit, Pharmacy Department, University Hospital of Wales for supplying the sterile preparation of adenosine. We are grateful to Mrs Sue Forster for typing the manuscript.

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(Received 21 October 1986, accepted 9 December 1986)