Br. J. clin. Pharmac. (1987), **23**, 331–338

Intravenous infusion of adenosine but not inosine stimulates respiration in man

P. G. REID, A. H. WATT, P. A. ROUTLEDGE & A. PETER SMITH[1]
Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff and [1]Thoracic Unit, Llandough Hospital, Penarth, South Glamorgan

1 The effects on respiration of intravenous infusions of the endogenous nucleoside adenosine and its deaminated metabolite, inosine, administered in random order, single-blind, were compared in six healthy volunteers.
2 The infusion rate of each nucleoside was initially 3.1 mg min^{-1} and was increased stepwise every 2 min, as tolerated, up to a possible maximum of 23.4 mg ml^{-1}. The maximum dose rates received by all subjects were 8.5 mg min^{-1} for adenosine and 16.8 mg min^{-1} for inosine.
3 Adenosine infusion at rates of 6.1 mg min^{-1} and above caused a significant increase in minute ventilation, principally due to an increase in tidal volume, with an associated significant fall in end-tidal P_{CO_2}. Mean inspiratory flow rate increased and expiratory duration decreased during adenosine infusion, but there was no change in inspiratory duration.
4 Adenosine infusion also caused a significant increase in heart rate and a slight, but significant increase in systolic blood pressure.
5 Infusion of inosine at dose rates up to 16.8 mg min^{-1} produced no pharmacological effects.
6 This study shows that adenosine by infusion produces sustained respiratory stimulation in man and demonstrates that it does not depend on prior conversion of adenosine to inosine or related metabolites and that it is not secondary to systemic hypotension.

Keywords adenosine inosine respiration

Introduction

The endogenous nucleoside adenosine exerts a variety of physiological and pharmacological effects (Lancet, 1985). Recently, dose dependent stimulation of respiration in man in association with biphasic heart rate changes produced by intravenous boluses of adenosine has been described (Watt & Routledge, 1985, 1986). Adenosine is rapidly metabolised, either by re-incorporation into the nucleotide pool or by degradation initially to inosine (Klabunde, 1983) and has an *in vitro* half-life in human whole blood of less than 10 s (Klabunde, 1983). Significant metabolism of adenosine would therefore be expected during the observed 15–20 s interval between injection of adenosine and the onset of respiratory stimulation. It is therefore unclear whether the effects on respiration observed were due to adenosine itself or a metabolite.

Other effects of adenosine include hypotension when administered in large doses (Sollevi *et al.*,

Correspondence: Dr P. G. Reid, Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN

1984) and this itself might cause respiratory stimulation.

In this study we compared the effects on respiration, heart rate and blood pressure of intravenous infusions of adenosine and its metabolite inosine in order to clarify the mechanism of the previously reported respiratory stimulation produced by adenosine and to investigate whether the transitory effects seen after intravenous bolus doses of adenosine could be sustained by continuous infusion of the drug.

Methods

Eight healthy volunteers (seven male) aged 23 to 33 years gave informed, written consent to participate in the study which was approved by the Hospital Ethics Committee. All subjects were asked to abstain from caffeine-containing beverages for at least 12 h prior to the study. Adenosine and inosine were administered in random order, single-blind, by intravenous infusions separated by 30 min. This interval was chosen on the basis of our finding in a pilot study that the cardiorespiratory effects produced by adenosine infusion resolve within 1 to 2 min of stopping the infusion. The infusion rate of each nucleoside was initially 3.1 mg min^{-1} and was increased every 2 min up to a possible maximum of 23.4 mg min^{-1} (maximum possible number of stages: 7). Each infusion was discontinued following administration of a dose of 23.4 mg min^{-1} or earlier at the request of a subject. The maximum dose rates received ranged from 8.5 to 23.4 mg min^{-1} for adenosine and 16.8 to 23.4 mg min^{-1} for inosine.

The electrocardiogram (ECG) was monitored throughout each infusion. Recordings of the ECG and measurements of blood pressure (using an Accoson mercury sphygmomanometer, taking phase V as diastolic) were made at baseline and at 1 min intervals throughout each infusion. A respiratory trace was obtained from a Lectromed type 4320 respiration transducer (calibrated by a spirometer) secured around the chest. We have found this to give a linear response to increasing tidal volume in supine subjects. P_{CO_2} was measured continuously in gas sampled by a catheter, whose tip was clipped to the upper front teeth, using a PK Morgan Ltd. Type 901 MK.2 high speed response CO_2 analyser. The respiratory and P_{CO_2} traces were recorded on an Ormed MX 216 recorder. Respiratory variables (respiratory rate, tidal volume, minute ventilation, inspiratory duration, expiratory duration and total breath duration) and end-tidal P_{CO_2} were subsequently derived from the traces obtained. Subjects were asked to report any subjective sensations at 1 min intervals and were aware that an infusion would be stopped immediately at their request. In four subjects spirometry was performed prior to and immediately after each infusion using a Micromedical Instruments Pocket Spirometer (Chowienczyk & Lawson, 1982).

The solutions used were sterile preparations of adenosine (Sigma) or inosine (Sigma) in 0.9% sodium chloride at concentrations of 5 mg ml^{-1}. Infusion rates were regulated using a Harvard infusion pump, model 2681.

Comparisons of respiratory rate, tidal volume, minute ventilation, end-tidal P_{CO_2}, heart rate and blood pressure at different infusion rates, up to 8.5 mg min^{-1} for adenosine and 16.8 mg min^{-1} for inosine, were made using two-way analysis of variance and Student Newman-Keuls test. In one subject the study was stopped because of occipital headache and in one subject an inadequate respiratory trace was obtained. Data were therefore analysed for six subjects. Student's paired *t*-test was used to compare baseline values of the above variables as well as mean inspiratory flow, inspiratory duration, expiratory duration and inspiratory duration over total breath duration (T_I/T_{Tot}) with values at the maximum dose of each nucleoside tolerated, and to compare spirometric variables (peak expiratory flow rate (PFR), forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)) before and after each infusion.

Results

The effects of adenosine infusion on respiratory rate, tidal volume, minute ventilation and end-tidal P_{CO_2} and on heart rate and blood pressure are shown in Figures 1 and 2 respectively. All subjects received up to 8.5 mg min^{-1} of adenosine but the maximum infusion rate tolerated ranged from 8.5 to 23.1 mg min^{-1} (mean ± s.d.: 13.5 ± 5.7 mg min^{-1}). Data are therefore presented for infusion rates up to 8.5 mg min^{-1} and for the maximum infusion rate received by each subject.

Minute ventilation increased significantly during adenosine infusion from 6.6 ± 4.5 l min^{-1} at baseline to 13.0 ± 5.7 l min^{-1} at an infusion rate at 8.5 mg min^{-1}, and 19.2 ± 11.2 l min^{-1} at the maximum infusion rate ($P < 0.001$ and $P < 0.005$ respectively). These changes were predominantly due to an increase in tidal volume from 0.5 ± 0.4 l at baseline to 0.9 ± 0.4 l during adenosine infusion at 8.5 mg min^{-1}, and 1.2 ± 0.6 l at the maximum infusion rate ($P < 0.001$ and $P < 0.05$ respectively).

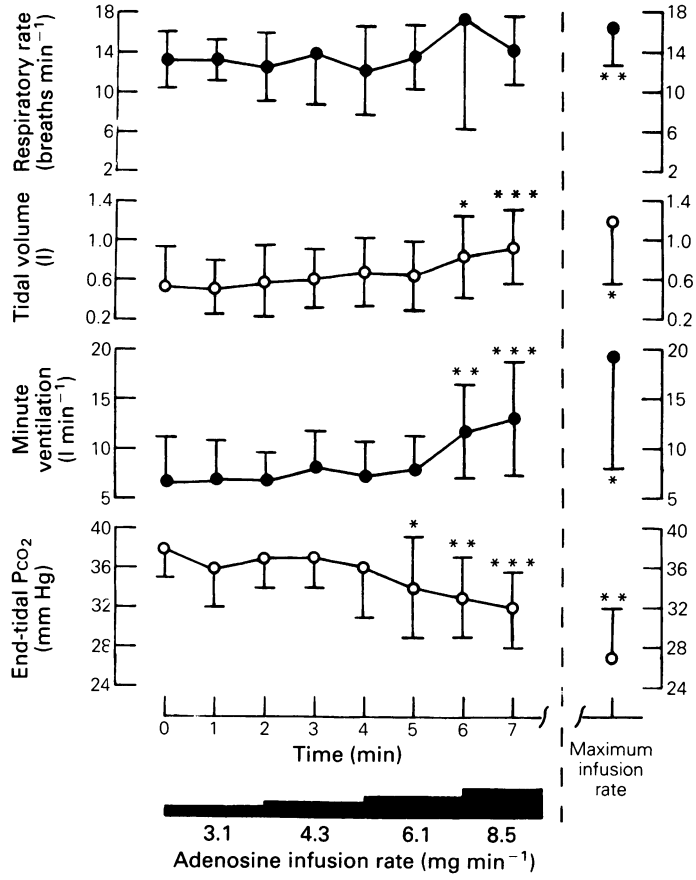

Figure 1 Respiratory rate, tidal volume, minute ventilation and end-tidal P_{CO_2} during adenosine infusion. Data are shown as mean ± s.d., $n = 6$ except for 3.1 mg min^{-1} where $n = 5$. For explanation of maximum dose please see text.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for comparisons with baseline.

The changes in respiratory rate were only significant at the maximum infusion rate (16 ± 4 breaths min^{-1} *vs* 13 ± 3 breaths min^{-1} at baseline; $P < 0.01$).

The increase in ventilation during adenosine infusion was accompanied by an increase in mean inspiratory flow (tidal volume/inspiratory duration) from 16.8 ± 9.6 l min^{-1} at baseline to 46.8 ± 21.0 l min^{-1} at the maximum infusion rate ($P < 0.05$). The expiratory duration fell from 3.1 ± 1.0 s at baseline to 2.4 ± 0.9 s at the maximum infusion rate ($P < 0.01$) but there was no change in inspiratory duration (1.7 ± 0.5 s at baseline *vs* 1.5 ± 0.5 s at the maximum infusion rate; $0.1 < P < 0.2$) or T_I/T_{Tot} (0.4 ± 0.1 at baseline and at the maximum infusion rate).

End-tidal P_{CO_2} fell significantly during adenosine infusion from 38 ± 3 mm Hg at baseline to 32 ± 4 mm Hg at an infusion rate of 8.5 mg min^{-1}, and 27 ± 5 mm Hg at the maximum infusion rate ($P < 0.001$ and $P < 0.01$ respectively).

Heart rate increased during adenosine infusion from 67 ± 7 beats min^{-1} at baseline to 86 ± 15 beats min^{-1} at an infusion rate of 8.5 mg min^{-1}, and 105 ± 9 beats min^{-1} at the maximum infusion rate ($P < 0.01$ and $P < 0.001$ respectively). One subject developed a transient bradycardia of 30 min^{-1} with second degree heart block for a few beats during breath-holding immediately after discontinuing adenosine infusion at a rate of 16.8 mg min^{-1}. Rhythm in this subject quickly reverted to sinus tachycardia. In no other subject was a bradycardia seen.

Systolic blood pressure increased significantly during adenosine infusion from 120 ± 10 mm Hg at baseline to 131 ± 11 mm Hg at an infusion rate

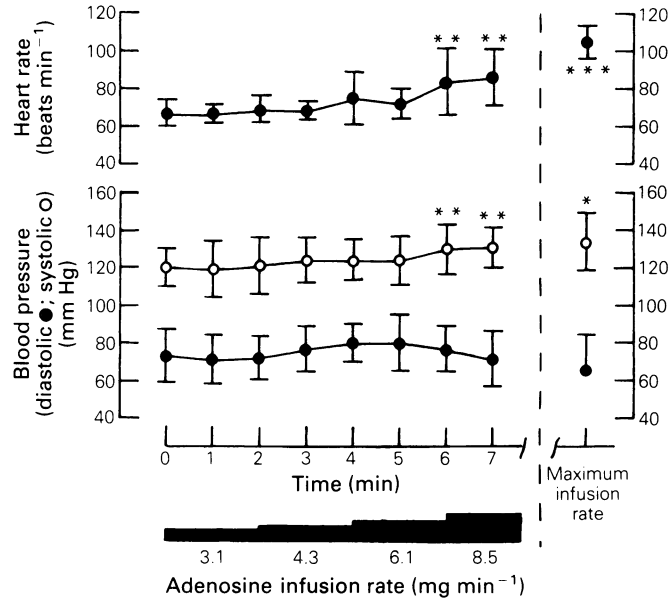

Figure 2 Heart rate and blood pressure during adenosine infusion. Data are shown as mean ± s.d., $n = 6$ except for 3.1 mg min^{-1} where $n = 5$. For explanation of maximum dose please see text.
$*P < 0.05$, $**P < 0.01$, $***P < 0.001$ for comparisons with baseline.

of 8.5 mg min^{-1}, and 134 ± ± 15 mm Hg at the maximum infusion rate ($P < 0.01$ and $P < 0.05$ respectively). Diastolic blood pressure changed biphasically increasing from 73 ± 14 mm Hg at baseline to 80 ± 10 mm Hg during adenosine infusion at 4.3 mg min^{-1}, with a fall at higher infusion rates, to 66 ± 19 mm Hg at the maximum infusion rate. These changes were, however, not statistically significant ($P > 0.2$). Significant hypotension did not occur during adenosine infusion at any of the doses used in this study.

In contrast to the changes observed during adenosine infusion, no significant changes in the above variables were observed during inosine infusion, despite the higher maximum infusion rate (16.8 mg min^{-1}) received by all subjects. Respiratory rate, tidal volume and minute ventilation during inosine infusion are shown in Figure 3 and heart rate and blood pressure in Figure 4. Results for mean respiratory flow, inspiratory duration, expiratory duration, and T_I/T_{Tot} (baseline *vs* infusion at 16.75 mg min^{-1} were 21.0 ± 9.6 *vs* 20.4 ± 7.2 l min^{-1}, 1.5 ± 0.6 *vs* 1.7 ± 0.6 s, 3.4 ± 0.7 *vs* 3.0 ± 1.3 s, and 0.3 ± 0.1 *vs* 0.4 ± 0.1 respectively ($P > 0.2$ for all comparisons).

During adenosine infusion facial flushing was reported by all eight subjects, dyspnoea by seven, throat discomfort by five, epigastric discomfort by four, headache by four and retrosternal discomfort by two. One subject was able to tolerate the maximum dose of adenosine infused (23.4 mg min^{-1}). In all other subjects the infusion was stopped at a lower dose rate because of the degree of dyspnoea and other sensations experienced. Three subjects experienced paraesthesiae in the hands at the end of the study. All sensations resolved within 1 to 2 min after stopping the infusion.

During inosine infusion one subject reported lightheadedness but all other subjects were asymptomatic.

No subject reported wheeziness and spirometry showed no significant changes in the four subjects tested. In this group FEV_1, PEFR and FVC (best of three readings; mean ± s.d.) were 4.25 (± 0.50) l, 635 (± 65) l min^{-1} and 5.24 (± 0.63) l respectively at baseline and 4.10 (± 0.47) l, 594 (± 48) l min^{-1} and 5.27 (± 0.56) l respectively immediately following adenosine infusion. Values for FEV_1, PFR and FVC prior to inosine infusion were 4.12 (± 0.45) l, 572 (± 60) l min^{-1} and 5.20 (± 0.72) l respectively, and immediately following inosine infusion were 4.19 (± 0.49) l, 588 (± 73) l min^{-1} and 5.30 (± 0.63) l respectively.

Discussion

This study confirms the respiratory stimulant property of adenosine in man, which was first

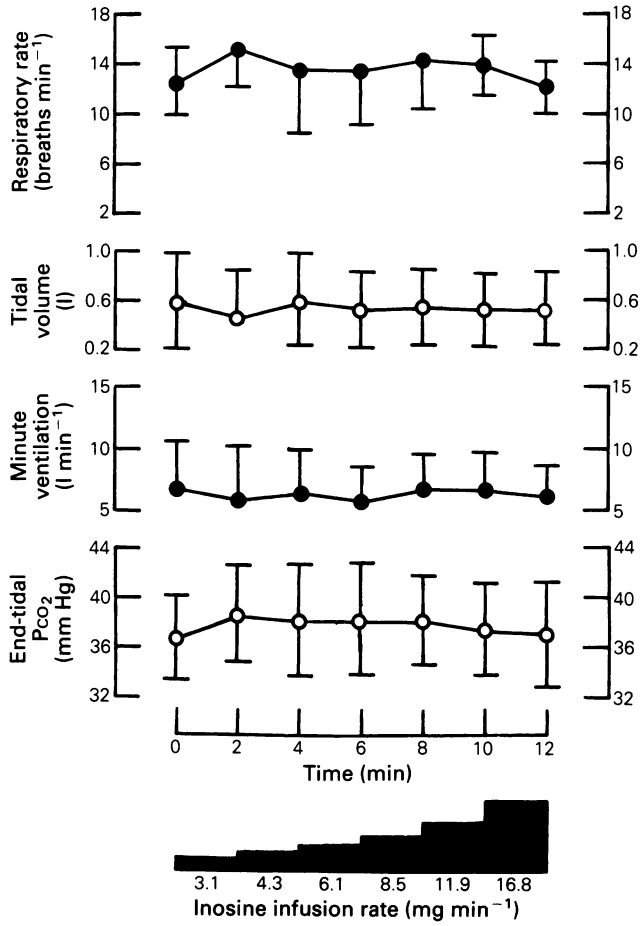

Figure 3 Respiratory rate, tidal volume, minute ventilation and end-tidal P_{CO_2} during inosine infusion. Data are shown as mean ± s.d.

demonstrated as a transient effect following intravenous boluses of adenosine (Watt & Routledge, 1985), and shows that respiratory stimulation is sustained during infusion of the nucleoside. Similar findings have recently been reported in abstract form by Biaggioni *et al.* (1986).

Adenosine is rapidly removed from the circulation principally by cellular uptake and then either metabolised by deamination to inosine or reincorporated into the nucleotide pool (Klabunde, 1983). The present study has shown that intravenous inosine is without effect on respiration in the dose range studied and therefore the respiratory stimulation produced by adenosine in this dose range does not depend on prior metabolism to inosine.

Our data do not exclude the possibility that phosphorylation of adenosine is a prerequisite for its respiratory stimulant effect. However, it has been shown in the cat that adenosine increases neural discharges from the carotid body (McQueen & Ribeiro, 1981), whereas a stable analogue of adenosine triphosphate (ATP) was without effect (McQueen & Ribeiro, 1983). In addition studies using long acting analogues of adenosine suggest that it acts via cell surface receptors of the A2 subtype in the carotid body (Ribeiro & McQueen, 1986).

Mean inspiratory flow can provide an index of 'inspiratory drive' provided the mechanical properties of the respiratory system are fixed (Remmers, 1976). The changes observed in this study during adenosine infusion, namely an increase in mean inspiratory flow and a reduction in expiratory duration are qualitatively similar to those produced by a number of respiratory stimuli, including hypoxia and hypercapnia

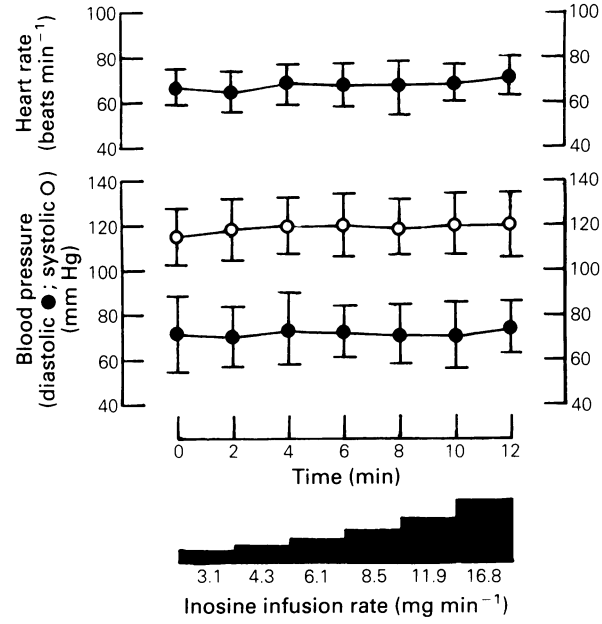

Figure 4 Heart rate and blood pressure during inosine infusion. Data are shown as mean ± s.d.

(Remmers, 1976). We found no change in inspiratory duration during adenosine infusion. It has been suggested that whereas inspiratory duration may remain constant during hypercapnia until tidal volume is increased to 3–5 times the resting value, there is a progressive shortening of inspiratory duration during progressive isocapnic hypoxia (Rebuck *et al.*, 1976). Others, however, have found no change in inspiratory duration during ventilatory stimulation by hypoxia, hypercapnia and exercise (Cunningham & Gardner, 1972; Jennett *et al.*, 1974). In any case a reduction in inspiratory duration when it occurs is considerably less than the reduction in expiratory duration.

The present results together with our finding in man that perfusion of the carotid circulation by adenosine-rich blood is necessary to produce respiratory stimulation (Watt *et al.*, 1986) and the findings of Dixon *et al.* (1986) that adenosine potentiates ventilatory responses to hypoxia but not hypercapnia in man are consistent with the hypothesis that adenosine stimulates respiration by an action in the carotid body. This is supported by findings in the rabbit (Buss *et al.*, 1986) and the rat (Monteiro & Ribeiro, 1986) that stimulation of respiration by adenosine is abolished by section of the nerve supply to the carotid body and the finding in a number of species that various adenosine analogues act centrally as respiratory depressants (Hedner *et al.*, 1982; Eldridge *et al.*, 1984 and Wessberg *et al.*, 1985). Studies using adenosine antagonists at cell surface receptors, e.g. aminophylline, or inhibitors of nucleoside transport e.g. dipyridamole, would further characterise the mechanism(s) involved.

Adenosine acts as a vasodilator in several vascular beds (Berne, 1980; Berne *et al.*, 1974; Proctor, 1984) and both ATP, which is rapidly hydrolysed to adenosine *in vivo*, and adenosine have been used as hypotensive agents in man (Fukunaga *et al.*, 1982; Sollevi *et al.*, 1984). In the present study hypotension was not an effect of adenosine infusion, but on the contrary a mild, but statistically significant increase in systolic blood pressure was observed. The observed respiratory stimulation is therefore not attributable to hypotension which has only been reported during adenosine infusion to anaesthetised subjects who were pretreated with dipyridamole (Sollevi *et al.*, 1984). A rise in systolic blood pressure in association with a decreased diastolic blood pressure and increased heart rate has been reported by others (Biaggioni *et al.*, 1985) who found plasma noradrenaline and adrenaline levels to be elevated during adenosine infusion. The pressor effect of adenosine may represent a non-specific sympathetic response to the subjective sensations experienced or alternatively may be secondary to stimulation of the carotid body which has been described in animals (Daly & Scott, 1962). Further studies

are necessary to clarify the mechanism(s) of the observed blood pressure changes.

Adenosine administered by intravenous bolus produces a biphasic heart rate response: an initial transient bradycardia followed by a more sustained tachycardia (Watt & Routledge, 1986). The initial bradycardia is seen in isolated hearts and probably represents a direct negative chronotropic effect of adenosine on the sinoatrial and atrioventricular nodes (Szentmiklosi *et al.*, 1980). In the present study only an increase in heart rate was seen during adenosine infusion, as has been reported by others (Biaggioni *et al.*, 1985). The mechanism of this requires elucidation. In dogs a tachycardia following carotid body stimulation has been seen as a reflex secondary to increased ventilation (Daly & Scott, 1958). A similar mechanism may in part explain the heart rate changes seen in the present study. Negative chronotropic effects of intravenous adenosine boluses are probably exerted in the heart before other responses that may have a positive chronotropic effect, e.g. carotid body stimulation, can begin to take effect. Absence of a 'bolus effect' may explain why only an increase in heart rate was seen in this study using an intravenous infusion of adenosine.

Inhaled adenosine causes bronchonstriction in asthmatics, but not normal subjects (Cushley *et al.*, 1983). The mechanism is unclear (Cushley & Holgate, 1985). In the rat intravenous adenosine has been found to cause bronchoconstriction (Pauwels & Van Der Straeten, 1983). In the present study no subject reported a sensation of wheeze and in the four subjects in whom spirometry was performed there were no significant changes. Biaggioni *et al.* (1986) observed no change in spirometry in 12 subjects receiving adenosine infusion. Unlike the bronchoconstriction produced by inhaled adenosine in asthmatics, which had not fully abated within 30 min (Cushley *et al.*, 1983), the increased respiration produced by intravenous adenosine in the present study was observed to resolve within 1 min. These observations suggest that the respiratory stimulation is not secondary to airflow limitation. Further studies are necessary to examine the effects of intravenous adenosine on airway calibre in normal subjects and those with reversible airways obstruction.

The finding that intravenous adenosine infusions stimulate respiration raises two important questions: (1) Does adenosine have a physiological role in the control of respiration, possibly by mediating the ventilatory response to hypoxia within the carotid body, as has been suggested (Watt & Routledge, 1985)? (2) Can the respiratory stimulant property of intravenous adenosine be usefully applied, e.g. in patients with respiratory failure? With regard to a potential therapeutic role for adenosine, the adverse subjective sensations we have noted in this study in which we examined the dose-response relationship between ventilation and adenosine infusion rate up to the limit of each subject's tolerance may not be relevant to longer term use of lower dose infusion of the nucleoside. If adenosine were to adversely affect airway calibre, this may be a limiting factor in patients with airways obstruction. Further studies are required to answer these questions.

A.H.W. is 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 preparations of adenosine and inosine. We are grateful to Mrs Sue Forster for typing the manuscript.

References

Berne, R. M., Rubio, R. & Curnish, R. R. (1974). Release of adenosine from ischemic brain: effect on cerebral vascular resistance and incorporation into cerebral adenine nucleotides. *Circ. Res.*, **35**, 262–271.

Berne, R. M. (1980). The role of adenosine in the regulation of coronary blood flow. *Circ. Res.*, **47**, 807–813.

Biaggioni, I. O., Onrot, J., Kincaid, D., Hollister, A. S. & Robertson, D. (1985). Humoral and hemodynamic effects of adenosine infusion in man. *Clin. Res.*, **33**, 280A.

Biaggioni, I. O., Olafsson, B., Robertson, R., Hollister, A. S. & Robertson, D. (1986). Characteristics of adenosine-induced stimulation of respiration in man. *Pflügers Arch.*, **407**, S55.

Buss, D. C., Routledge, P. A. & Watt, A. H. (1986). Intravenous adenosine stimulates respiration in conscious adult rabbits. *Br. J. Pharmac.*, **87**, 182P.

Chowienczyk, P. J. & Lawson, C. P. (1982). Pocket-sized device for measuring forced expiratory volume in 1 second and forced vital capacity. *Br. med. J.*, **285**, 15–17.

Cunningham, D. J. C. & Gardner, W. N. (1972). The relation between tidal volume and inspiratory and expiratory times during steady-state CO_2 inhalation in man. *J. Physiol.*, **227**, 50–51P.

Cushley, M. J. & Holgate, S. T. (1985). Adenosine-induced bronchconstriction in asthma: Role of mast cell-mediator release. *J. Allergy clin. Immunol.*, **75**, 272–278.

Cushley, M. J., Tattersfield, A. E. & Holgate, S. T.

(1983). Inhaled adenosine and guanosine on airway resistance in normal and asthmatic subjects. *Br. J. clin. Pharmac.*, **15**, 161–165.

Daly, M. DeB. & Scott, M. J. (1958). The effects of stimulation of the carotid body chemoreceptors on heart rate in the dog. *J. Physiol.*, **144**, 148–166.

Daly, M. DeB. & Scott, M. J. (1962). An analysis of the primary cardiovascular reflex effects of stimulation of the carotid body chemoreceptors in the dog. *J. Physiol.*, **162**, 555–573.

Dixon, C. M. S., Fuller, R. W., Hughes, J. M. B., Maxwell, D. L., Nolop, K. B. (1986). Hypoxic and hypercapnic ventilatory responses during adenosine infusion in man. *J. Physiol.*, **376**, 51P.

Eldridge, L. F., Millhorn, D. E., Kiley, J. P. (1984). Respiratory effects of a long-acting analog of adenosine. *Brain Res.*, **301**, 273–280.

Fukunaga, A. F., Ikeda, K. & Matsuda, I. (1982). ATP-induced hypotensive anaesthesia during surgery. *Anesthesiol.*, **57**, A65.

Hedner, T., Hedner, J., Wessberg, P., Jonason, J. (1982). Regulation of breathing in the rat: indication for a role of central adenosine mechanisms. *Neurosci. Lett.*, **33**, 147–51.

Jennett, S., Russel, T., Warnock, K. A. (1973). The duration of inspiration during changing states of ventilation in man. *J. Physiol.*, **238**, 54P–55P.

Klabunde, R. E. (1983). Dipyridamole inhibition of adenosine metabolism in human blood. *Eur. J. Pharmac.*, **93**, 21–26.

Lancet (1985). Adenosine revisited. *Lancet*, **ii**, 927–928.

McQueen, D. S. & Ribeiro, J. A. (1981). Effect of adenosine on carotid chemoreceptor activity in the cat. *Br. J. Pharmac.*, **74**, 129–136.

McQueen, D. S. & Ribeiro, J. A. (1983). On the specificity and type of receptor involved in carotid body chemoreceptor activation by adenosine in the cat. *Br. J. Pharmac.*, **80**, 347–354.

Monteiro, E. C. & Ribeiro, J. A. (1986). Adenosine modulation of respiration mediated by carotid body chemoreceptors in the rat. In *Chemoreceptors and respiratory control*, ed. Pallot, D. J. & Ribeiro, J. A. (in press).

Pauwels, R. A. R. & Van Der Straeten, M. E. R. Ph. (1983). The *in vivo* bronchoconstrictory effect of adenosine. *J. Allergy clin. Immunol.*, **71** (Suppl.), 103.

Proctor, K. G. (1984). Reduction of contraction-induced arteriolar vasodilation be adenosine deaminase or theophylline. *Am. J. Physiol.*, **247**, H195–H205.

Rebuck, A. S., Rigg, J. R. A. & Saunders, N. A. (1976). Respiratory frequency response to progressive isocapnic hypoxia. *J. Physiol.*, **258**, 19–31.

Remmers, J. E. (1976). Analysis of ventilatory response. *Chest*, **70** (Supplement), 134–137.

Ribeiro, J. A. & McQueen, D. S. (1986). Chemoexcitation evoked by adenosine: pharmacological characterization of the receptor. In *Chemoreceptors and respiratory control*, eds Pallot, D. J. & Ribeiro, J. A. (in press).

Sollevi, A., Lagerkranser, M., Irestedt, L., Gordon, E. & Lindquist, C. (1984). Controlled hypotension with adenosine in cerebral aneurysm surgery. *Anesthesiology*, **61**, 400–405.

Szentmiklosi, A. J., Nemeth, M., Szegi, J., Papp, J. G. & Szekeres, L. (1980). Effect of adenosine on sinoatrial and ventricular automaticity of the guinea pig. *Arch. Pharmac.*, **311**, 147–149.

Watt, A. H., Reid, P. G., Stephens, M. R. & Routledge, P. A. (1986). Adenosine-induced respiratory stimulation depends on site of infusion. Evidence for an action on the carotid body? *Br. J. clin. Pharmac.*, **22**, 238P–239P.

Watt, A. H. & Routledge, P. A. (1985). Adenosine stimulates respiration in man. *Br. J. clin. Pharmac.*, **20**, 503–506.

Watt, A. H. & Routledge, P. A. (1986). Transient bradycardia and subsequent sinus tachycardia produced by intravenous adenosine in healthy adult subjects. *Br. J. clin. Pharmac.*, **21**, 533–536.

Wessberg, P., Hedner, J., Hedner, T., Persson, B., Jonason, J. (1985). Adenosine mechanisms in the regulation of breathing in the rat. *Eur. J. Pharmac.*, **106**, 59–67.

(Received 11 July 1986, accepted 16 October 1986)