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Adenosine stimulates respiration in man

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Respiratory effects produced by a series of intravenous boluses of adenosine were studied in nine healthy human subjects. Adenosine produced a significant dose-related increase in respiration, mostly due to increased depth of respiration. Possible mechanisms of this effect are discussed.

Keywords adenosine respiration

Introduction

Adenosine, an endogenous nucleoside, has recently been shown to be a potentially useful treatment for supraventricular tachycardia (Di Marco *et al.*, 1983). During our initial evaluation of adenosine for treatment of this arrhythmia in man (Watt *et al.*, 1985) we observed that adenosine produced hyperpnoea at about the time that it exerted its cardiac electrophysiological effects (unpublished observations). In a subsequent study of the negative chronotropic effects of adenosine on the hearts of normal volunteers we observed that adenosine was a powerful but short-lived subjective respiratory stimulant (unpublished observations). These observations led us to examine the respiratory stimulant effects of adenosine in healthy human volunteers.

Methods

Nine healthy subjects (five male), aged 21–39 years, gave written informed consent for the study. Adenosine was administered via an indwelling venous cannula by a series of rapid bolus injections, starting at 20 $\mu g\ kg^{-1}$, and increasing in steps of 20 $\mu g\ kg^{-1}$, as tolerated, to a maximum dose of 200 $\mu g\ kg^{-1}$. An individual study was stopped if the strength of respiratory stimulation became subjectively distressing. During the dose-titration of adenosine, placebo injections were given in volumes equivalent to doses of 80–200 $\mu g\ kg^{-1}$, at irregular intervals so that the subjects could not anticipate the effect or lack of it to be expected from an individual injection. The dose-titration of adenosine was approved by the hospital ethics committee.

The preparation of adenosine which we used was a sterile solution of adenosine (Sigma) in a final concentration of 5 mg ml^{-1}, dissolved in 0.9% sodium chloride with 0.1% sodium metabisulphite. Placebo solution was 0.1% sodium metabisulphite in 0.9% sodium chloride.

An electrocardiogram was recorded from three precordial electrodes simultaneously with a respiratory trace on an Ormed MX216 recorder. The respiratory trace was obtained from a Lectromed type 4320 respiration transducer, secured around the chest at the level of the xiphisternum by an elasticated strap with the subjects in a supine position. An index of ventilation expressed in arbitrary units was obtained from the product of respiratory rate (breaths min^{-1}) and respiratory depth (arbitrary units). In a preliminary study the Lectromed respiration transducer produced a linear response when compared to a spirometer.

Respiratory rate and depth were measured between the third and fourth breath after the onset of respiratory stimulation which occurred about 15–20 s after injection of adenosine. In traces where no respiratory change was discernable measurements were made at an equivalent time after the bolus injection. Baseline measure-

ments of these parameters were obtained immediately prior to each injection. Paper speed was 25 mm s^{-1}.

The respiratory parameters before and after each injection were compared using the Student's paired *t*-test. Correlation coefficients between the logarithm of adenosine dose and the change in respiratory parameters were calculated by the method of least squares. Statistical significance was assumed where $P < 0.05$.

Results

All subjects reported that adenosine produced a desire to breathe more deeply, often associated with a feeling of suffocation whereas placebo injections caused no such effects. The onset of this effect was approximately 20 s after injection. The lowest dose of adenosine producing a discernable subjective effect ranged from 20 μg kg^{-1} to 60 μg kg^{-1}. The maximum dose of adenosine tolerated ranged from 100 μg kg^{-1} to 200 μg kg^{-1}. The respiratory stimulant effect lasted about 20 s, varying both with the dose administered and between subjects. Facial flushing was a consistent subjective feeling and some subjects noticed chest, abdominal or neck discomfort lasting less than 15 s in all instances.

Adenosine produced a significant increase in ventilation index over baseline, at doses in the range 60–200 μg kg^{-1}. A similar dose range (60–180 μg kg^{-1}) produced a significant increase in respiratory depth (Table 1). A slight but significant increase in respiratory rate was found between doses of 80 μg kg^{-1} and 140 μg kg^{-1} (Table 1). A trace recorded at a paper speed of 10 mm min^{-1} is shown in Figure 1.

The increase in respiratory depth and the increase in the ventilation index, product of respiratory depth and respiratory rate, were found to be significantly related to the logarithm of adenosine dose. Respective correlation coefficients were 0.612 ($P < 0.001$) and 0.698 ($P < 0.001$).

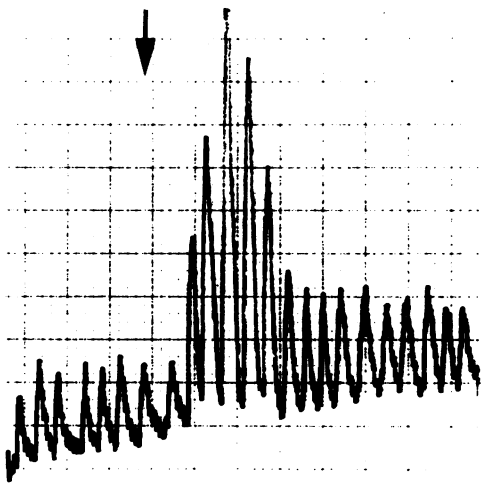

Figure 1 Respiratory trace at slow paper speed showing baseline ventilation and response to intravenous adenosine (injected at arrow).

Placebo injections did not change respiration as measured by ventilation index (128 ± 60 units at baseline, 118 ± 50 units after placebo, P = NS), nor did they cause any change in respiratory depth (9.9 ± 5.4 units at baseline, 9.3 ± 4.2 units after placebo, P = NS) or respiratory rate (13.7 ± 3.7 breaths min^{-1} at baseline, 13.3 ± 3.4 after placebo, P = NS).

Adenosine produced a slight, transient but statistically significant increase in R–R interval on the electrocardiogram in the dose range 60–140 μg kg^{-1}. For example at a dose of 140 μg kg^{-1}

Table 1 Respiratory depth and respiratory rate before and after intravenous boluses of adenosine

Adenosine dose (μg kg^{-1})	*Respiratory depth* *Baseline* (units)	*After adenosine* (units)	*Respiratory rate* *Baseline* (breaths min^{-1})	*After adenosine* (breaths min^{-1})
20	7.4 ± 3.9	9.9 ± 4.9	14.9 ± 3.7	14.2 ± 2.7
40	8.8 ± 4.7	14.1 ± 9.3	13.8 ± 3.8	16.3 ± 5.3*
60	8.9 ± 5.1	16.4 ± 6.4**	13.7 ± 4.5	18.2 ± 5.6
80	9.4 ± 6.3	16.2 ± 6.5**	12.5 ± 2.3	18.4 ± 7.1*
100	8.7 ± 6.8	19.8 ± 6.6***	12.6 ± 4.0	17.8 ± 4.3**
120	8.3 ± 4.2	20.8 ± 6.6***	12.9 ± 3.6	17.0 ± 2.3*
140	10.2 ± 4.3	23.5 ± 5.8***	13.2 ± 2.3	17.9 ± 2.4*
160	8.0 ± 4.7	26.0 ± 9.8**	15.7 ± 5.3	15.9 ± 2.5
180	9.0 ± 6.1	24.5 ± 12.9*	14.5 ± 3.9	16.0 ± 3.8
200	11.0 ± 11.1	29.0 ± 13.0	16.7 ± 7.1	18.3 ± 0.6

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

the baseline R–R interval was 810 ± 134 ms, and after adenosine was 1167 ± 271 ms ($P < 0.05$). The longest R–R interval occurred up to 2 s before the onset of the increase in ventilation. Placebo injections did not alter the R–R interval (787 ± 99 ms at baseline, 821 ± 140 ms after injections). The transient sinus bradycardia produced by adenosine was followed by a brief sinus tachycardia, possibly reflex in origin.

Discussion

Our results indicate that adenosine, given intravenously to healthy human subjects, produces a significant degree of respiratory stimulation which is dose-related. The observed effects are transient as the half-life of adenosine in human blood at 37° C is less than 10 s (Klabunde, 1983).

To our knowledge, there has been no other study examining the respiratory stimulant effects of intravenous adenosine in man. However, we believe that the respiratory stimulant effects of adenosine which we describe have been observed incidentally in other studies. Drury & Szent-Gyorgyi (1929) and Gustaffson (1981) mentioned such an effect in rabbits after the administration of adenosine. Honey *et al.* (1930) observed that the 'breathing became deeper and more rapid' in a patient given adenosine intravenously. None of these authors examined the respiratory changes in detail.

The effects which we have described might arise from a sensory reflex originating in the lungs, from respiratory areas in the brain, from the aortic chemoreceptors or from the carotid body. A pulmonary reflex is unlikely to be involved as Gustafsson (1981) demonstrated respiratory stimulation in rabbits given adenosine into the left ventricle. The effects which we describe are also unlikely to be mediated by effects on the central nervous system. Adenosine (Kattwinkel & Darnall, 1982), and its synthetic analogues (Lagercrantz *et al.*, 1984; Wessberg *et al.*, 1984; Hedner *et al.*, 1982; Mueller *et al.*, 1982) inhibit respiration when applied directly to the brain, and adenosine administered intravascularly appears to cross the blood-brain barrier slowly, if at all (Berne *et al.*, 1974). The aortic chemoreceptors appear to play a significant role in the control of respiration in some species but in man they appear to be relatively unimportant (Whipp & Wassermann, 1980).

The most likely site of respiratory stimulation by adenosine would appear to be the carotid bodies. The timing of the respiratory stimulant effect in relation to the transient sinus bradycardia would be consistent with this suggestion. Furthermore adenosine has been shown to increase chemoreceptor discharges from the denervated carotid body (McQueen & Ribeiro, 1981), which would be expected to increase ventilation in the intact animal (Eyzaguirre & Zapata, 1984). The adenosine receptor within the carotid body has been characterised as 'P1' receptor (McQueen & Ribeiro, 1983) according to the classification of Burnstock (1978).

Some may interpret this respiratory stimulant effect of adenosine to be due to hypotension. However, McQueen & Ribeiro (1981) observed no change in blood pressure in their study in cats, nor did Di Marco *et al.* (1983) in man using the same techniques and doses of adenosine as we used. Therefore, arterial hypotension is unlikely to play an essential part in the causation of the effects of adenosine which we describe.

The identification of an adenosine receptor in the carotid body (McQueen & Ribeiro, 1981, 1983) and the observation of the effects of adenosine which we have described raise the question of whether adenosine has any physiological role in the regulation of respiration particularly in response to hypoxia. Hypoxia leads to increased adenosine production in a number of organs (Fox *et al.*, 1974; Winn *et al.*, 1979; Dobson *et al.*, 1971) but it is not known if this occurs in the carotid body. Hypoxia may cause adenosine triphosphate stored in the carotid body (Böck, 1980) to be released and degraded to adenosine and so stimulate respiration. If such released ATP were not degraded then depression of neural discharges, and hence of respiration, would be expected (McQueen & Ribeiro, 1983). The partial pressure of oxygen is low in the parenchyma of the carotid body (Weigelt *et al.*, 1980) and this local hypoxia may play a role in the control of the postulated release of adenosine within the carotid body as occurs in other organs. Alternatively systemic hypoxia may lead to an increase in circulating adenosine levels and so stimulate the carotid body.

We would speculate that adenosine is a mediator in the carotid body of the ventilatory response to hypoxia. If this suggestion is correct then adenosine's role as a 'retaliatory metabolite' (Newby, 1984) may extend beyond the level of blood and oxygen delivery to individual organs to the level of control of oxygen delivery to the whole organism.

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