The effect of dipyridamole and theophylline on hypercapnic ventilatory responses: the role of adenosine

T.L. Griffiths, J.M.L. Christie, S.T. Parsons, S.T. Holgate

The effect of dipyridamole and theophylline on hypercapnic ventilatory responses: the role of adenosine. T.L. Griffiths, J.M.L. Christie, S.T. Parsons, S.T. Holgate. ©ERS Journals Ltd 1997.

ABSTRACT: The purine nucleoside, adenosine, has been implicated as a neuromodulator in central respiratory depression during prolonged exposure to hypoxia. It may also be a mediator of hypoxic hyperpnoea, acting on the carotid bodies. As there may be adenosine-sensitive mechanisms of hypoxic respiratory control, we sought to determine whether adenosine might be involved as a respiratory modulator in another central but non-oxygen-related control mechanism, the ventilatory response to hyperoxic hypercapnia.

Twelve normal subjects were studied following 3 days of oral treatment with placebo, dipyridamole (which potentiates adenosine effects by inhibiting cellular uptake), and theophylline (a specific adenosine antagonist of cell surface receptors). The drugs were given in a random order, double-blind fashion. Resting end-tidal carbon dioxide tension (P_{ET,CO_2}) and the maximum rate of isometric inspiratory pressure change at the mouth ($(dP/dt)_{max}$), an index of respiratory drive, were determined in all subjects on each treatment. Hyperoxic, hypercapnic ventilatory responses were determined in seven of these subjects using a rebreathing technique. For each hypercapnic response, minute ventilation ($\dot{V}_E$) and $(dP/dt)_{max}$ were plotted against P_{ET,CO_2} breath-by-breath.

Resting P_{ET,CO_2} breathing room air was lower with theophylline (5.47 (SD 0.21) kPa) than with placebo (5.74 (0.26) kPa) or dipyridamole (5.86 (0.34) kPa), with no significant drug differences in resting $(dP/dt)_{max}$. However, neither the slope nor the P_{ET,CO_2} intercept of the relationship between ventilation or respiratory drive and P_{ET,CO_2} were altered by the study drugs under hyperoxic conditions.

We conclude that endogenous adenosine-related mechanisms are unlikely to be involved in determining either the sensitivity or the threshold of the ventilatory response to carbon dioxide under hyperoxic conditions. However, in normoxia, a centrally-acting, tonic, adenosine-mediated, respiratory modulation is not ruled out. *Eur Respir J*, 1997; 10: 156–160.

Dept of Medicine, University of Southampton, Southampton, UK.

Correspondence: T.L. Griffiths
Section of Respiratory Medicine
University of Wales College of Medicine
Llandough Hospital
Penarth CF64 2XX
UK

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The endogenous purine nucleoside, adenosine, has been implicated as a neuromodulator in the central nervous system (CNS), where one of its effects may be to depress ventilation, particularly under hypoxic conditions. This has been demonstrated in humans by pharmacological manipulation of the ventilatory response to prolonged hypoxia. Theophylline, a specific antagonist of extracellular adenosine receptors, attenuates hypoxic ventilatory depression [1, 2]. Dipyridamole, which blocks cellular uptake of adenosine thus raising extracellular adenosine concentrations, enhances hypoxic ventilatory depression [3]. GEORGOPOULOS *et al.* [2] have shown that, while the steady state level of ventilation in isocapnic hypoxia is increased by aminophylline, ventilation is not affected by this drug under hyperoxic isocapnic conditions.

As it appears that there are adenosine-sensitive central mechanisms of respiratory control in hypoxia, the aim of this study was to determine whether adenosine might be involved as a respiratory modulator in other

central but non-oxygen-related control mechanisms. In our investigation, therefore, we have studied the ventilatory response to progressive hyperoxic hypercapnia following oral treatment with dipyridamole and theophylline. These drugs would be expected to enhance and attenuate adenosine-related mechanisms, respectively. The presence of hyperoxia is important in these experiments as, under these conditions, afferent activity from the carotid bodies (a site at which exogenous [4, 5] and endogenous [3] adenosine may stimulate breathing) is attenuated.

Material and Methods

Subjects

The participants were 12 healthy male volunteers, aged 20–22 yrs, who abstained from xanthine containing drinks

for 12 h before the study and were at least 2 h post-prandial. The study was approved by the Southampton Joint Ethics Subcommittee, and all subjects gave their written informed consent.

Study design

The subjects took each of the three study drugs orally, in a randomized, double-blind fashion. At the end of each drug period, the resting end-tidal carbon dioxide tension (P_{ET,CO_2}) and maximum rate of isometric inspiratory pressure change $(dP/dt)_{max}$ were determined. In seven of the subjects, the ventilatory and respiratory responses to progressive hypercapnia under hyperoxic conditions were determined using a rebreathing technique. Breath-by-breath ventilation ($\dot{V}_E$) and $(dP/dt)_{max}$, taken as an index of the neuromuscular drive to breathe, were plotted against P_{ET,CO_2} and regression lines were drawn. The responses were characterized by the P_{ET,CO_2} intercept (threshold) and slope (sensitivity) of the regression lines. Effects of the study drugs on these variables were then sought.

Methods - drugs

Subjects took placebo (ascorbic acid 50 mg), dipyrindamole (Persantin 100 mg tablets; Boehringer Ingelheim, Bracknell, Berks, UK) or theophylline (Nuelin SA; Riker Laboratories, Loughborough, Leics, UK) 6 hourly for 3 days, before each of the three sets of hypercapnic studies. Drugs were enclosed in identical opaque rice-paper cachets and given in a double-blind, randomized fashion. The dose of theophylline given was determined as the dose required to give a plasma concentration of 10–20 $mg \cdot L^{-1}$, as predicted from a preliminary study, when the plasma concentration achieved by test dosing with 175 mg of the same theophylline preparation was analysed using a computer model of second order kinetics, according to the equations derived by PATERSON *et al.* [6]. Plasma concentrations of dipyrindamole and theophylline were determined by high performance liquid chromatography in blood sampled at the end of each experimental session. The dose of theophylline was: 350 $mg \cdot 6 h^{-1}$ in five subjects; 250 $mg \cdot 6 h^{-1}$ in five subjects; and 175 $mg \cdot 6 h^{-1}$ in two subjects. The mean (SD) plasma concentrations of the study drugs were: theophylline 12.9 (4.0) $mg \cdot L^{-1}$; dipyrindamole 0.59 (0.37) $mg \cdot L^{-1}$.

Methods - study design

Each subject underwent three study sequences consisting of 3 days of oral drug administration followed by the assessment of resting P_{ET,CO_2} and $(dP/dt)_{max}$. Subjects were acclimatized to the apparatus by breathing through a mouthpiece with a breathing valve of 40 mL volume for 15 min. Carbon dioxide concentration at the mouth was measured by a continuously sampling, fast responding infra-red gas analyser (LB; Beckman, High Wycombe, Bucks, UK). P_{ET,CO_2} and $(dP/dt)_{max}$ were determined over a 30–60 s period. Estimations were performed on two occasions at least 30 min apart, and these values were averaged.

Subsequently, in seven of the subjects, ventilatory and respiratory drive responses to progressive hypercapnia

were determined. Subjects breathed from air for 15 min; then at end-expiration a rebreathing bag of starting volume 6–8 L and containing 5% CO_2 in oxygen (one subject) or pure oxygen (six subjects) was switched into the circuit. All rebreathing for each individual was carried out using the same starting gas composition, and terminated when an end-tidal CO_2 concentration of 9% was reached. Ventilation was recorded by placing the rebreathing bag in a rigid box, attached to a water-sealed spirometer (Expirograph; Godart Stratham, Rugby, Warks, UK). Changes in the bell position were registered potentiometrically from its supporting pulley. After analogue-to-digital conversion, this signal passed to a BBC microcomputer for determination of breath-by-breath tidal volume, breath duration and, hence, ventilation. P_{ET,CO_2} was monitored breath-by-breath, as described previously. Pressure at the mouth was monitored continuously (Pressure Transducer; Lectromed UK Ltd., Letchworth, Herts, UK). The amplified output was differentiated and the resulting signal (the rate of change of mouth pressure (dP/dt)) displayed on a pen recorder (MX4; Devices). The response of this system was linear from 0 to 60 $cmH_2O \cdot s^{-1}$. The peak rate of inspiratory pressure development $((dP/dt)_{max})$ was read from the paper trace and entered into the computer breath-by-breath. $\dot{V}_E$ and $(dP/dt)_{max}$ were and plotted against P_{ET,CO_2} breath-by-breath. Gas volumes and partial pressures were corrected to body temperature, atmospheric pressure and saturation with water vapour (BTPS).

Data were analysed for breaths corresponding to P_{ET,CO_2} between 6 and 9 kPa. The mean (SD) duration of data recording was 4.32 (1.03) min. Open loop conditions were not a feature of this study.

Analysis

The plots of $\dot{V}_E$ against P_{ET,CO_2} and $(dP/dt)_{max}$ against P_{ET,CO_2} were well-fitted by computer-drawn straight lines using simple linear regression. These lines were characterized by their slope and intercept on the P_{ET,CO_2} axis. Analysis of variance (ANOVA) with repeated observations was used to determine an effect of the study drugs on these slopes and intercepts, and on resting P_{ET,CO_2} and $(dP/dt)_{max}$. Where a significant effect was indicated, multiple comparisons were made between specific treatments using Student's paired t-tests with a Bonferroni correction. A p-value of less than 0.05 for ANOVA and of less than 0.016 for multiple comparisons was regarded as significant. Simple linear regression was used to examine the relationship between drug plasma concentrations and CO_2 response variables.

Using data from the placebo run, the study had approximately 80% power to detect a 20% change in P_{ET,CO_2} intercept at a two sided significance level of 0.05. However, the characteristically large intersubject variability in the slope of the relationship between $\dot{V}_E$ and P_{ET,CO_2} seen in rebreathing studies, such as this, makes it impossible to rule out a type II error resulting in the negative finding with respect to this variable. Unless otherwise stated, the values given are mean (SD).

Although the minimum *in vivo* plasma concentration of theophylline required to inhibit the CNS actions of adenosine has not been established, modulation of the peripheral respiratory effects of exogenous adenosine

Table 1. – Details of subjects and their ventilatory responses to progressive hypercapnia

		Starting gas mixture CO ₂ :O ₂ %								
Subject	No.	5:95 1	0:100 2	0:100 3	0:100 4	0:100 5	0:100 6	0:100 7	Mean	(sd)
Placebo										
Resting P_{ET,CO_2} kPa		5.55	5.56	5.34	6.15	5.56	-	-	5.63	(0.30)
Slope $\Delta V'E/\Delta P_{ET,CO_2}$ L·kPa ⁻¹		19.51	8.48	10.45	21.37	17.90	10.52	14.70	14.70	(5.04)
Intercept $\Delta V'E/\Delta P_{ET,CO_2}$ kPa		6.49	5.07	4.36	5.84	5.35	4.82	5.31	5.32	(0.69)
Dipyridamole										
Drug concentration mg·L ⁻¹		0.64	0.88	0.35	1.23	-	0.45	0.30	0.64	(0.36)
Resting P_{ET,CO_2} kPa		5.30	5.93	6.06	6.17	5.93	5.70	5.26	5.76	(0.36)
Slope $\Delta V'E/\Delta P_{ET,CO_2}$ L·kPa		35.12	12.03	16.23	13.37	26.55	10.62	14.02	18.27	(9.09)
Intercept $\Delta V'E/\Delta P_{ET,CO_2}$ kPa		5.83	5.80	5.70	5.82	6.11	5.25	4.97	5.64	(0.39)
Theophylline										
Drug concentration mg·L ⁻¹		15.9	7.8	14.7	19.9	8.5	15.7	12.9	13.63	(4.30)
Resting P_{ET,CO_2} kPa		5.18	5.70	5.36	5.51	5.23	-	5.12	5.35	(0.22)
Slope $\Delta V'E/\Delta P_{ET,CO_2}$ L·kPa ⁻¹		31.36	15.77	17.03	20.35	19.33	13.25	17.90	19.28	(5.81)
Intercept $\Delta V'E/\Delta P_{ET,CO_2}$ kPa		5.24	5.36	4.63	5.29	5.50	5.33	4.66	5.14	(0.35)

P_{ET,CO_2} : end-tidal carbon dioxide tension; $V'E$: minute ventilation; Δ : change in.

has been demonstrated at plasma theophylline concentrations of 9.4–9.5 mg·L⁻¹ [7]. We, therefore, examined the responses of the three subjects with plasma theophylline concentration less than 9.5 mg·L⁻¹, and found that they were not qualitatively or quantitatively different from those with plasma concentrations above this level. Moreover, excluding them from analysis did not alter the overall results. Thus, the findings reported below are for the whole group of subjects.

Results

For the group of 12 subjects, resting P_{ET,CO_2} (kPa) was: placebo 5.74 (0.26); dipyridamole 5.86 (0.34); and theophylline 5.47 (0.21). ANOVA indicated a significant drug effect ($p=0.032$), with P_{ET,CO_2} being significantly lower on theophylline than on placebo ($p=0.01$) or dipyridamole ($p<0.0004$). Values for the resting (dP/dt)_{max} (cmH₂O·s⁻¹) were: placebo 8.27 (1.87); dipyridamole 7.49 (2.41); and theophylline 7.96 (1.84). There was no significant drug effect on resting (dP/dt)_{max}.

For each rebreathing subject, the drug concentrations measured, resting P_{ET,CO_2} , and slopes and intercepts of the ventilatory response to CO₂ are presented in table 1. No statistically significant effects of the study drugs on the ventilatory response to CO₂ were found. For the relationship of (dP/dt)_{max} to P_{ET,CO_2} , the mean slope (cmH₂O·s⁻¹·kPa⁻¹) was: placebo 5.10 (1.13); dipyridamole 5.99 (3.43); theophylline 7.11 (3.51). The mean intercept (kPa) was: placebo 5.31 (0.27); dipyridamole 5.67 (0.28); and theophylline 5.36 (0.45). No significant effect of the study drugs was found for either parameter with ANOVA.

There was no correlation between resting P_{ET,CO_2} or (dP/dt)_{max} and the plasma concentration of either drug. Neither was there a significant relationship between plasma drug concentrations and the magnitude of changes in the slope or intercept of the hypercapnic ventilatory response.

Discussion

There are two main findings of this study. Firstly, the oral administration of neither the adenosine uptake blocker,

dipyridamole, nor the adenosine antagonist, theophylline, modulated the ventilatory response to hyperoxic hypercapnia. Secondly, while breathing room air, resting P_{ET,CO_2} was lower on theophylline than with placebo or dipyridamole.

The hypercapnic ventilatory response has been delineated in normal subjects. The value calculated on placebo for the mean slope of the regression of ventilation upon P_{ET,CO_2} of 14.7 (SD 5.04; SE 1.90) L·min⁻¹·kPa⁻¹ is similar to that reported by previous investigators using various rebreathing techniques. The distribution of values is also similar (L·min⁻¹·kPa⁻¹): GODFREY *et al.* [8] 1971 (15.35; SD 7.28); READ [9], 1967 (20.4; SE 1.96); MATTHEWS and HOWELL [10], 1976 (14.7; SE 1.24); and JAVAHERI and GUERRA [11], 1990 (21.75; SD 6.75). The mean P_{ET,CO_2} intercept, which was found to be 5.32 (SD 0.69) kPa, is also similar to that found by GODFREY *et al.* [8] (6.13 (1.1) kPa); and JAVAHERI and GUERRA [11] (5.27; (0.35) kPa).

Hyperoxic, hypercapnic responses were studied in an attempt to elucidate central adenosine-related mechanisms. The carotid bodies in animals [12, 13], and also probably in humans [4, 5], are stimulated directly by adenosine. Centrally-mediated respiratory depression by adenosine has also been observed in animals [14]. We argued that, if peripheral adenosine-related mechanisms could be silenced, central mechanisms might be elucidated. Hyperoxia has been reported to render human carotid bodies refractory to stimulation by hypercapnia [15–18], suggesting that under these conditions peripheral chemoreceptor mechanisms might be silenced. However, the concept of carotid body silencing by hyperoxia has been challenged. DAHAN *et al.* [19] (1990) observed that, in 3 of their 9 subjects, evidence of a reduced carotid body response to CO₂ could be found in hyperoxia. They suggested, using modelling considerations, that evidence previously held to rule out hyperoxic CO₂ stimulation of peripheral chemoreceptors was unreliable, as slow time constant responses might have been overlooked. Thus, whilst it is not certain that the carotid bodies are completely silenced in all subjects by hyperoxia, the response is attenuated in the minority who demonstrate some responsiveness.

In this study, a rebreathing method was used to determine the ventilatory response to CO₂. However, as

pointed out by BOURKE and WARLEY [20], under certain circumstances, steady state methods may yield different results compared with rebreathing. Steady state methods may be less susceptible to changes in cerebral blood flow, rate of carbon dioxide production, and chemoreceptor response time constant, and, thus, may give a result reliant more specifically on chemoreceptor sensitivity. Our finding of a lack of effect using a rebreathing method could possibly be due to confounding effects of other drug actions; but, as no effect was seen in either direction, it is likely that neither of the study drugs had an overall effect on mechanisms related to the ventilatory response to CO_2 .

The question arises: were the drug dosages adequate to affect potential adenosine-related mechanisms? The effect of theophylline on resting PET,CO_2 suggests that plasma theophylline concentrations were adequate to have physiological effects. The majority of the subjects in the present study demonstrated levels found to antagonize the respiratory effects of exogenous adenosine [7]. The mean (SD) plasma theophylline concentration in these rebreathing subjects was $13.62 (4.3) \text{ mg}\cdot\text{L}^{-1}$, which is similar to that previously found to inhibit central hypoxic respiratory depression in normal humans following intravenous infusion of aminophylline [1]. Thus, it does seem likely that effective concentrations of theophylline were present in the cerebrospinal fluid (CSF) of these subjects.

The dipyrindamole dosage regimen used in this study has previously been reported to modulate the respiratory effects of exogenous adenosine [21] and to raise the plasma adenosine concentration maximally after 48 h of treatment [22]. In only one of the present subjects was the plasma dipyrindamole concentration lower than the range reported in the latter study. However, the relationship between plasma concentration of dipyrindamole and adenosine has not been fully established. A recent study [3] has shown effects on central hypoxic respiratory depression with intravenous doses of dipyrindamole that would have produced significantly (100%) higher plasma concentrations than were achieved in the present study. Thus, it is possible that higher plasma concentrations might have altered the results.

The finding of a lack of effect of theophylline on the ventilatory response to hyperoxic hypercapnia is similar to results of previous studies using intravenous [23, 24] and oral [11, 25] aminophylline. This finding in relation to the overall ventilatory response is supported by the observation of lack of effect on the respiratory drive response to hypercapnia, as determined from $(dP/dt)_{\text{max}}$ using the technique of MATTHEWS and HOWELL [10, 26].

Thus, the lack of effect of the trial drugs on the ventilatory response to hypercapnia under hyperoxic conditions suggests that adenosine-related mechanisms are probably not important in the central response to progressive hypercapnia against a background of supranormal oxygenation. The situation in hypoxic or normoxic conditions may, however, be different.

The finding of a reduction in resting PET,CO_2 with theophylline administration is similar to observations made previously [11, 25]. It has been suggested that this may be due to antagonism of tonic adenosine-mediated downregulation of breathing under normoxic conditions. However, the failure to demonstrate an effect of theo-

phylline on $(dP/dt)_{\text{max}}$ does not allow us to confirm this effect.

Indeed other mechanisms for the reduction in PET,CO_2 should be considered. Possible effects could be a reduction in carbon dioxide production, an increase in airway calibre, or a reduction in the relative contribution of dead space ventilation. The first is unlikely, as theophylline has actually been shown to increase carbon dioxide production alongside an elevated resting ventilation [23]. Changes in airway calibre would have been small in the normal subjects. Finally, in this study, resting ventilation and dead space to tidal volume ratios were not recorded, and it is therefore possible that changes in the pattern of breathing could have led to increases in effective alveolar ventilation, even with unaltered intensity of neuromuscular drive.

Thus, there may indeed have been an increase in alveolar ventilation related to an effect of theophylline on respiratory control in normoxia. If this were to be true, what is the explanation for a lack of effect of dipyrindamole on normoxic PET,CO_2 ? Dipyrindamole, although it does not cross the blood/brain barrier [27, 28], may affect adenosine concentrations in the CNS by impairing adenosine clearance from the CSF by the vascular endothelium [29]. Physiological effects of dipyrindamole may, therefore, depend on an enhanced rate of adenosine production, as seen in hypoxia [30–35]. The finding that dipyrindamole does not significantly elevate resting normoxic PET,CO_2 is in agreement with a previous study using high doses of intravenous dipyrindamole [3], and suggests that mechanisms related to increased adenosine production may be more susceptible to manipulation by inhibition of adenosine uptake than situations in which the ongoing adenosine production rate may be low.

In humans, the evidence for the activity of adenosine in hypoxic ventilatory modulation is indirect [1, 3]. The present study suggests that these effects of endogenous adenosine could be the result of the brain's response to hypoxia, rather than suggesting that adenosine is integral to the chemosensory function of the brain stem. GEORGOPOULOS *et al.* [2] have studied the effect of aminophylline on ventilation in steady state hypoxia, normoxia and hyperoxia and over switches between them, and concluded that, whilst there may be adenosine-related modulation of breathing in hypoxia, none is demonstrable in hyperoxia. The present findings support this view.

We conclude that whilst adenosine might play a neuromodulatory role in the control of breathing in normoxia, it is unlikely to be involved in the mechanism of the ventilatory response to progressive hypercapnia under hyperoxic conditions.

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