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Salbutamol induced hypokalaemia: the effect of theophylline alone and in combination with adrenaline

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1 We have previously shown that salbutamol induced hypokalaemia, like adrenaline induced hypokalaemia, is the result of stimulation of a membrane bound β_2-adrenoreceptor linked to Na^+/K^+ ATPase. We have also demonstrated that adrenaline induced hypokalaemia is potentiated by therapeutic concentrations of theophylline.

2 In a single-blind study of 14 normal volunteers, we infused salbutamol in doses used in clinical practice and examined the effects of the addition of theophylline alone or combined with (−)-adrenaline on plasma potassium levels, heart rate and blood pressure. The combinations studied were (i) salbutamol + vehicle control adrenaline infusion + placebo theophylline; (ii) salbutamol + vehicle control adrenaline infusion + theophylline; (iii) salbutamol + adrenaline + theophylline.

3 In a randomised, balanced placebo controlled design oral slow release theophylline or placebo was given for 9 days. Subjects were studied twice on the active limb (days 7 and 9) and once on the placebo limb (day 9) and the procedure was identical on each of the 3 study days except for the solutions administered.

4 Theophylline increased salbutamol induced hypokalaemia and in some individuals profound hypokalaemia (< 2.5 mmol l^{-1}) was observed with these relatively low doses of salbutamol and theophylline. Adrenaline did not further increase the magnitude of the fall in potassium observed. Combining theophylline with salbutamol increased the tachycardia resulting from the salbutamol infusion. Salbutamol infusion caused a fall in diastolic and rise in systolic blood pressure on all 3 study days and this was not altered by either theophylline or adrenaline alone or together.

5 We conclude that theophylline significantly increases salbutamol induced hypokalaemia and tachycardia and that the addition of adrenaline does not further increase hypokalaemia. Intensive bronchodilator therapy with these two agents in acutely ill, hypoxic patients with asthma or chronic obstructive lung disease may increase the risk of serious cardiac arrhythmias secondary to hypokalaemia.

Keywords hypokalaemia β_2-adrenoceptor agonists theophyllines adrenaline cardiac arrhythmias

Introduction

Although it is fifty years since D'Silva (1934) found that (−)-adrenaline reduces circulating potassium concentrations it has only recently been shown that it does so by stimulating a β_2-adrenergic receptor linked to a membrane-bound Na^+/K^+ ATPase pump which transfers potassium into the cells (Struthers & Reid, 1984).

In previous work we have confirmed that this

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mechanism is also the most likely explanation for the potassium lowering effect of the β_2-adrenoceptor agonist, salbutamol (Whyte *et al.*, 1987a). We have also previously demonstrated that the addition of theophylline increases (−)-adrenaline induced hypokalaemia (Whyte *et al.*, 1987b).

Combined treatment with both salbutamol, or other similar selective β_2-adrenoceptor agonists, and theophylline is common in acute attacks of asthma. In this study we have examined the changes in serum potassium and haemodynamics following the addition of therapeutic doses of theophylline to conventional doses of salbutamol.

Circulating (−)-adrenaline concentrations may be raised in asthma, although the literature is conflicting (Ind *et al.*, 1985; Barnes *et al.*, 1981; Griffiths *et al.*, 1972; Zielinske *et al.*, 1980). Therefore we have also examined the effect of raising circulating (−)-adrenaline concentrations on the hypokalaemia induced by salbutamol in combination with theophylline.

Methods

Fourteen healthy volunteers (seven males, seven females; age range 19–29 years) who had normal haematology, biochemistry and electrocardiographs were recruited. The protocol of the study was approved by the Research and Ethics Committee of the Northern District of Greater Glasgow Health Board and all subjects gave fully informed written consent.

The study was a single-blind, randomised, placebo controlled, balanced Latin square cross-over design arranged so that the active agents adrenaline, salbutamol and theophylline with appropriate placebos, could be compared in the combinations of interest in the course of 3 study days after a preliminary period to establish the appropriate dose of theophylline for each subject. The combinations studied were:

(1) intravenous salbutamol + placebo theophylline + vehicle control adrenaline;
(2) intravenous salbutamol + theophylline +

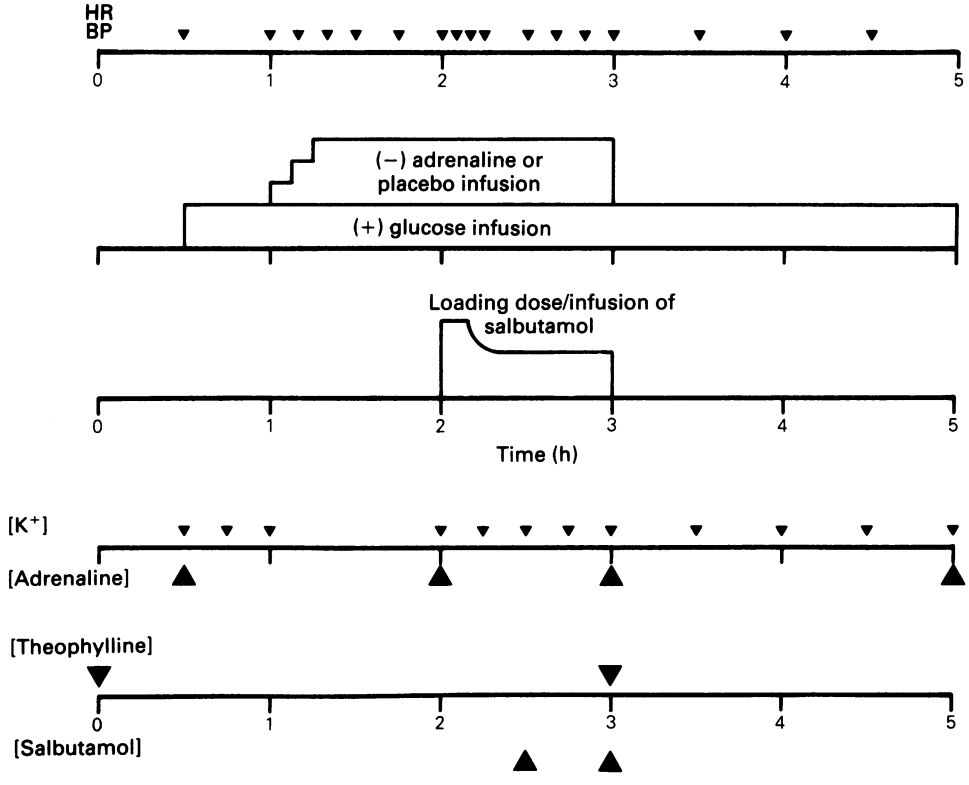

Figure 1 Detailed outline of study day, all study days were identical except for the infusion solutions administered.

vehicle control adrenaline;

(3) intravenous salbutamol + theophylline + (−)-adrenaline;

A diagram of the study design is given in Figure 1.

In the run-in phase to determine the individual subject's theophylline dose requirement a slow release theophylline preparation (Uniphyllin Tablets, Napp Laboratories, Cambridge, U.K.) was taken in twice daily dosage at a rate of 5-7.5 mg kg^{-1} day^{-1} for 2 days then 10–15 mg kg^{-1} day^{-1} for 5 days. If tolerated then a trough theophylline level was measured by h.p.l.c. and the required daily dose to achieve a therapeutic plasma level throughout was calculated using a microcomputer based optimisation programme (OPT, Nodecrest Ltd., Byfleet, Surrey, U.K.). This dose was used for the remainder of the study.

Subjects attended the Research Laboratory on the seventh and ninth day of active theophylline treatment period and on only the seventh day of their placebo phase, having fasted for 10 h and abstained from caffeine, alcohol and smoking for 12 h. By careful conduct of the procedure it was possible to do this without breaking the blind. A light standard breakfast was given along with the morning dose of the drug. Intravenous cannulae were inserted into each forearm for withdrawal of blood samples and the administration of infusions respectively. Subjects were studied supine throughout the study period. The procedure on each separate study day was identical except for the infusions administered. A control 5% (+)-glucose infusion was administered by a Braun IV perfusor pump for 60 min and this was followed by a 5% (+)-glucose infusion containing (−)-adrenaline or an identical control adrenaline vehicle solution and after 1 h salbutamol was added.

Salbutamol (Allen & Hanbury's Ltd, Greenfield, Middlesex, U.K.) 4 μg kg^{-1} (16 nmol kg^{-1}) was administered as an intravenous loading dose over 5 min followed by a maintenance infusion 8 μg kg^{-1} h^{-1} (32 nmol kg^{-1} h^{-1}) and this was continued for 55 min.

The (−)-adrenaline (Antigen Ltd, Roscrea, Ireland) infusion was commenced at a rate of 0.015 μg kg^{-1} min^{-1} (0.08 nmol kg^{-1} min^{-1}) for 10 min and if tolerated the infusion rate was increased at 10 min intervals to 0.03 μg kg^{-1} min^{-1} (0.16 nmol kg^{-1} min^{-1}) and then to 0.06 μg kg^{-1} min^{-1} (0.33 nmol kg^{-1} min^{-1}) if there were no side effects. This dose (0.06 μg kg^{-1} min^{-1}) was continued for a further 100 min. Both the (−)-adrenaline infusion and the control adrenaline vehicle infusion contained ascorbic acid in a concentration of 1 mg ml^{-1} to prevent oxidation of the adrenaline.

At the end of the second hour of active infusions both the salbutamol and (−)-adrenaline infusions were discontinued and a 5% (+)-glucose infusion was continued for a further 2 h.

Throughout the study period heart rate and blood pressure were measured at frequent intervals (see Figure 1) by a semi-automated sphygmomanometer (Sentron, Bard Medical Division, Lombard, Illinois, U.S.A.). Cardiac rhythm was monitored throughout by precordial electrodes and the electrocardiogram was displayed continuously on an oscilloscope and stored on a computer (Nodecrest Varian, VT17, Nodecrest Ltd, Byfleet, Surrey, U.K.).

Venous blood samples for potassium levels were taken at the indicated intervals (see Figure 1), centrifuged within 30 min and analysed by standard methods on an autoanalyser (Technicon SMA-C, Technicon Instrument Corpn., New York, U.S.A.). At frequent intervals (see Figure 1) venous blood was aspirated into chilled syringes, centrifuged at 4° C and the plasma stored at −20° C for later assay for adrenaline by an h.p.l.c. method employing electrochemical detection (Howes *et al.*, 1985).

Prior to the start of the study and at 180 min serum was taken for assay of serum theophylline trough and peak concentrations by a competitive binding assay based on fluorescence polarization (T.D.X. system, Abbot Laboratories Ltd, Wokingham, Berkshire, U.K.). Blood was also collected at 150 and 180 min for measurement of plasma salbutamol concentrations by an h.p.l.c. method in the Clinical Research Unit of Glaxo Laboratories (Glaxo Laboratories, Greenford, Middlesex).

All results are presented as mean ± s.d. Statistical analysis was by analysis of variance as applied to repeated measures comparing individual parameters on separate study days and 95% confidence intervals for differences between treatments at each time point were calculated (Bryce, 1980; Winer, 1971).

Results

Tolerance

One volunteer withdrew during the initial treatment period because of nausea, her plasma theophylline level was 14.6 μg ml^{-1}. Two volunteers withdrew during the main study. One subject was unable to tolerate the salbutamol infusions on two occasions due to salbutamol induced vomiting. One subject was withdrawn as a result of developing premature supraventricular beats at a rate of 6–8 beats min^{-1} during the (−)-

adrenaline and salbutamol infusions whilst receiving active therapy. These extrasystoles persisted for 4 h after cessation of the infusions and the subject then made an uneventful recovery. Data from these subjects is not presented in this paper which includes the results from the remaining 11 subjects who completed the study.

All subjects reported palpitations during the salbutamol loading dose. No dysrhythmias were noted but heart rate increased. Two volunteers reported tremor of their hands during the salbutamol infusion. All the other subjects tolerated both the oral theophylline and the active infusions without any other side-effects.

Serum theophylline concentrations

Theophylline levels are shown in Table 1. The mean (± s.d.) theophylline concentration on active therapy at time 0 min (trough) was 11.9 ± 3.1 μg ml^{-1} (range −6.3–17.9 μg ml^{-1}) and 13.5 μg ml^{-1} (range −8.3–23.5 μg ml^{-1}) at time 180 min (peak). The therapeutic range for our laboratory is 10–20 μg ml^{-1}. On placebo therapy theophylline was not detected.

Plasma salbutamol concentrations

Plasma salbutamol levels were between 5.0–12.0 ng ml^{-1} (Table 1). With this infusion regimen some subjects demonstrated a small fall in salbutamol concentrations between the first and second measurement and others modest rises. There was no significant difference between salbutamol levels with or without theophylline or with the adrenaline infusion (see Table 1).

Plasma adrenaline concentrations

Baseline plasma adrenaline levels were not significantly different between study days (see Table 1) and did not increase on either of the control infusions of the adrenaline vehicle. On the active adrenaline infusion plasma adrenaline concentration increased from 1.55 ± 3.34 nmol l^{-1} to 4.28 ± 4.23 nmol l^{-1} at the end of the (−)-adrenaline infusion falling to 0.88 ± 1.01 nmol l^{-1} by the end of the study period (see Table 1).

Plasma potassium concentrations

Baseline plasma potassium concentrations were not significantly different on the 3 study days. Salbutamol infusion (8 μg kg^{-1} h^{-1}), in the absence of an active (−)-adrenaline infusion and without theophylline, from 120 min to 180 min (see Figure 1) resulted in a fall in plasma potassium from 4.0 ± 0.3 mmol l^{-1} to 3.0 ± 0.3 mmol l^{-1}. Salbutamol induced hypokalaemia was significantly greater following chronic pretreatment with theophylline, plasma potassium falling from 3.9 ± 0.3 mmol l^{-1} to 2.6 ± 0.3 mmol l^{-1} ($P < 0.05$). The addition of the (−)-adrenaline infusion (0.06 μg kg^{-1} min^{-1}) on the active theophylline study day did not result in a further fall of potassium, the nadir being similar, 2.6 ± 0.3 mmol l^{-1}. By the end of the study plasma potassium levels were not significantly different on each of the study days. Plasma potassium concentrations had still not however returned to baseline levels at 360 min (see Figure 2).

Table 1 Plasma adrenaline and noradrenaline concentrations following either active theophylline [T] or placebo prior to (30 min) and at the end of the active or placebo (−)-adrenaline [A] infusion period (180 min); salbutamol concentrations during (150 min) and at the end of the salbutamol infusion period (180 min) on each study day, salbutamol was infused in an identical regimen on all 3 study days (mean ± s.d., $n = 11$).

Treatment	*Adrenaline concentration (nmol l^{-1})*		*Noradrenaline concentration (nmol l^{-1})*		*Salbutamol concentration (ng ml^{-1})*	
	30 min	*180 min*	*30 min*	*180 min*	*150 min*	*180 min*
Placebo T + Placebo A	1.44 ± 2.96	1.48 ± 3.37	1.97 ± 0.91	3.15 ± 0.97	6.74 ± 0.90	7.74 ± 1.14
Active T + Placebo A	0.77 ± 1.05	0.78 ± 1.28	3.75 ± 1.97	4.70 ± 2.25	7.34 ± 0.64	7.71 ± 1.70
Active T + Active A	1.55 ± 3.34	4.28 ± 4.23	3.47 ± 1.84	4.45 ± 1.85	7.12 ± 1.01	7.58 ± 1.10

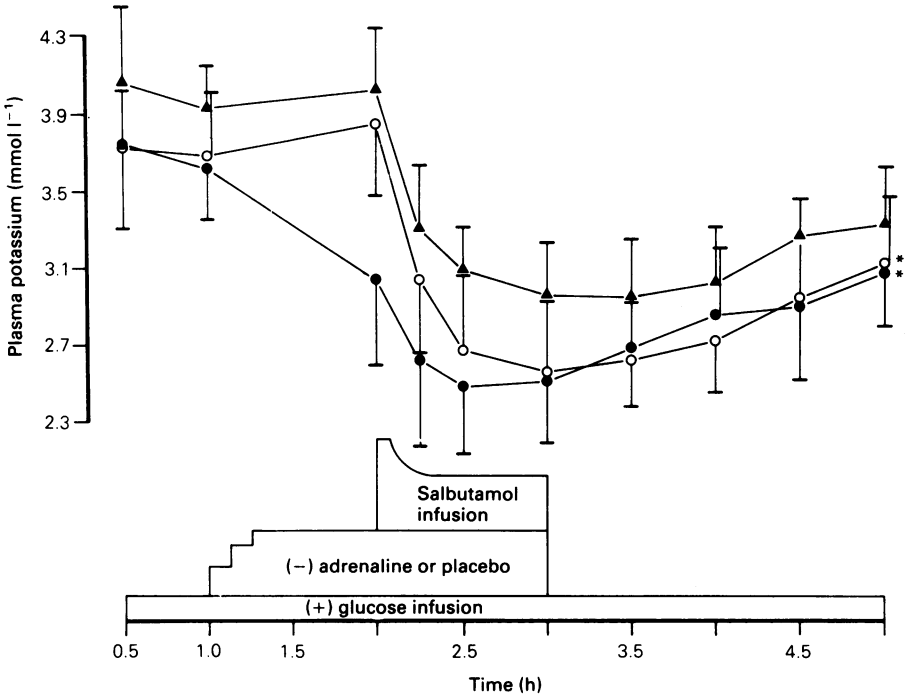

Figure 2 Changes in plasma potassium on each of the 3 study days, salbutamol + placebo theophylline + vehicle control adrenaline (▲---▲); salbutamol + theophylline + vehicle control adrenaline (○---○); and salbutamol + theophylline + (−)-adrenaline (●---●). Mean ± s.d., $n = 11$, * = $P < 0.05$ when active study day is compared with the salbutamol + placebo theophylline + vehicle control adrenaline study day by analysis of variance as applied to repeated measures.

Haemodynamic measurements

Baseline heart rate at 60 min was not significantly different on the 3 study days (see Figure 3). There was a rise in heart rate during the salbutamol infusion on all 3 study days and this rise was significantly higher on the 2 study days when theophylline was administered compared with the placebo theophylline day ($P < 0.05$, ANOVA). The addition of the (−)-adrenaline infusion to the combination of theophylline and salbutamol caused only a further small rise in heart rate (see Figure 3). Heart rate fell following the cessation of the active infusions but remained elevated at the end of the study period on all treatments compared to baseline values (see Figure 3).

Diastolic and systolic blood pressures throughout the study periods are shown in Figure 3. Salbutamol consistently lowered diastolic blood pressure and increased systolic blood pressure (see Figure 3) on all 3 study days. There was no significant difference between the 3 different study days.

Discussion

Our results demonstrate that theophylline adds to the potassium lowering effect of salbutamol but (−)-adrenaline makes no further difference. The theophylline concentrations were well within the established therapeutic range and achieved by an oral slow release formulation employed in conventional doses. The intravenous infusion rate of salbutamol used was in the lower half of the recommended intravenous dosage schedule for the treatment of severe asthma (A.B.P.I., 1985). A previous study has demonstrated that theophylline potentiated the hypokalaemic action of intravenous terbutaline (Smith & Kendall, 1986). We have confirmed and extended these observations.

The high concentrations of adrenaline reached did not significantly alter the absolute extent of hypokalaemia we observed with the salbutamol and theophylline combination. This suggests the β_2-receptor linked to the Na^+/K^+ ATPase pump was already maximally stimulated. Alternatively rapid changes in β_2-receptor affinity or

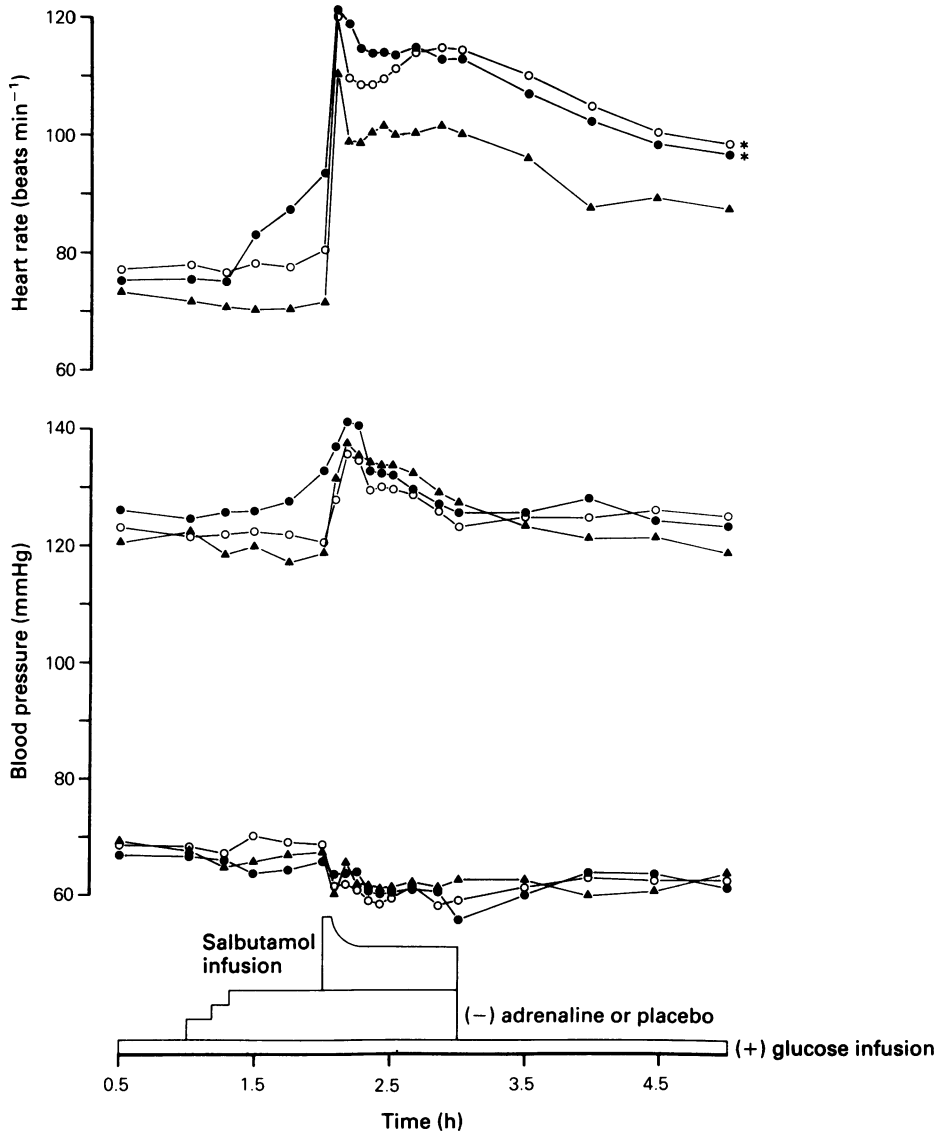

Figure 3 Changes in heart rate and blood pressure on each of the 3 study days, salbutamol + placebo theophylline + vehicle control adrenaline (▲---▲); salbutamol + theophylline + vehicle control adrenaline (○---○) and salbutamol + theophylline + (−)-adrenaline (●---●). Mean values, $n = 11$, * = $P <$ 0.05 when active study day is compared with the salbutamol + placebo theophylline + vehicle control adrenaline study day by analysis of variance as applied to repeated measures.

number may have occurred even in the short time of these experiments with agonist induced receptor down regulation limiting the extent of the response. These explanations are clearly not mutually exclusive. Recent studies with radioligand binding to guinea pig skeletal muscle membranes suggest that agonists do indeed cause down regulation of β-receptors (Elfellah & Reid, 1987) and that such changes may occur relatively rapidly (Snaveley *et al.*, 1985).

We have previously demonstrated that theophylline potentiates (−)-adrenaline induced hypokalaemia. The mechanism is unknown. We were unable to demonstrate any enhanced vasodilator effect of adrenaline or salbutamol which would be the result of stimulation of β_2-adreno-

ceptors on peripheral vascular smooth muscle. We detected no significant differences between the fall in diastolic blood pressure during the salbutamol infusion on the placebo or active theophylline study days. It is possible that other cardiovascular homeostatic responses were recruited to assist in the maintenance of blood pressure.

It has been previously suggested that theophylline has a β-adrenoceptor agonist action but this has never been confirmed (Mackay *et al.*, 1983). The enhancement of the chronotropic effects of salbutamol, a β_1-adrenoceptor action, by theophylline which we found in this study suggests that the action of theophylline is not specific to β_2-adrenoceptors. As theophylline and not adrenaline increased salbutamol effects it appears that the former is either exerting its action independently of the β-adrenoceptors or by activating second or subsequent messengers in the cell membrane or intracellularly. We have previously demonstrated that chronic theophylline therapy, unlike acute dosing, does not result in increased adrenaline or noradrenaline concentrations (Whyte *et al.*, 1987b). This action is therefore not the result of theophylline increasing circulating adrenaline levels.

Methylxanthines have previously been demonstrated to increase the action of sympathomimetic agonists, Rall & West (1963) reported that the addition of theophylline produced a dose related increase in the inotropic response to noradrenaline. The original hypothesis offered for this observation was the inhibition of phosphodiesterase by theophylline. In recent years it has been demonstrated that theophylline, in therapeutic concentrations, produces only a minor degree of phosphodiesterase inhibition (Rall, 1982). Currently increasing evidence is accumulating that theophylline's principal site of action is by competitive antagonism of adenosine receptors. Adenosine, an autocoid, acts on intracellular adenyl cyclase via two receptors, A_1 which inhibits adenyl cyclase and A_2 which stimulates adenyl cyclase. Some tissues have only one type of adenosine receptor and thus, methylxanthines which are equally powerful antagonists of both the adenosine receptors will have different effects on adenyl cyclase in different tissues (Rall, 1982). It is thought that the membrane bound β_2-adrenoceptor linked Na^+/K^+ ATPase is principally on skeletal muscle cells (Struthers & Reid, 1984) and blockade of A_2 receptors on these cells would result in increased intracellular ATP. An alternative mechanism is suggested by recent evidence that purines such as adenosine and ATP may exert a co-transmitter role at sympathetic effector sites via purinergic receptors on cell membranes. Originally it was thought that methylxanthines had no effect on purinergic receptors (Rall, 1982). Recent evidence has suggested that in sympathetic nerves supplying blood vessels ATP and adenosine inhibit pre-junctional P_1-purinoceptors decreasing noradrenaline release and this effect is blocked by methylxanthines (Burnstock, 1985).

Though the mechanism of action, at a cellular level, of theophylline remains unclear, this study clearly demonstrates that therapeutic theophylline levels potentiate the chronotropic and hypokalaemic effects of therapeutic doses of salbutamol. The clinical consequences of this interaction are unknown. It has been reported that the combination of theophylline and a sympathomimetic agent increases the incidence of side-effects (Weinberger & Bronsky, 1975). On the other hand combinations of sympathomimetics and theophyllines have been widely used for many years and there have been few reports of serious toxicity with these combinations. These oral preparations do not, however, contain enough theophylline to achieve adequate plasma theophylline concentrations. The more recently introduced slow release theophylline preparations have resulted in increasing numbers of patients achieving sustained higher theophylline concentrations.

There is evidence from experimental studies in animals that the combination lowers the threshold for the initiation of cardiac dysrhythmias (Green *et al.*, 1980; Joseph *et al.*, 1981) and hypokalaemia may predispose to cardiac dysrhythmias but it is unlikely that life threatening hypokalaemia would result at the low plasma salbutamol levels achieved with inhaled therapy even in the presence of therapeutic theophylline levels.

The administration of high doses of β_2-adrenoceptor-agonists during the treatment of severe episodes of asthma, to patients already receiving adequate theophylline therapy, could result in serious dysrhythmias from the combination of hypokalaemia and co-existent hypoxaemia and acidosis.

In patients taking long term β_2-adrenoceptor agonists with or without theophylline it will be of interest to determine whether there is adaption or tolerance to the hypokalaemia and the time course and mechanism of any such 'down regulation'.

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