THE METABOLIC ACTIONS OF INTRAVENOUS SALBUTAMOL AND AMINOPHYLLINE SINGLY AND IN COMBINATION

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1 The following four treatments were administered by constant intravenous infusion of four healthy volunteers in a balanced randomized study: 1) saline (30 min), salbutamol ($0.15 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 30 min) (sS), 2) saline, aminophylline ($0.2 \text{ mg kg}^{-1} \text{min}^{-1}$ for 30 min) (sA), 3) salbutamol, salbutamol (SS) and 4) aminophylline, salbutamol (AS).

2 Heart rate was recorded and venous blood taken for estimation of insulin, glucose, potassium and theophylline before and during the infusions (10, 20, 30, 40, 50 and 60 min).

3 The mean, peak heart rate increases from control, baseline values were 23.0 (sS), 3.5 (sA), 28.5 (SS) and 28.0 (AS) beats/min, the mean, peak insulin increases, 34.0 (sS), 0.5 (sA), 39.0 (SS) and 57.5 (AS) $\mu\text{U ml}^{-1}$, the mean, peak glucose increases, 1.4 (sS), 0.1 (sA), 2.6 (SS) and 2.0 (AS) mmol l^{-1} and the mean, peak potassium changes, -0.45 (sS), 0.58 (sA), -0.78 (SS) and -0.68 (AS) mmol l^{-1} .

4 The mean, peak serum theophylline levels were $48.1 \mu\text{mol l}^{-1}$ at 60 min in sA and $52.6 \mu\text{mol l}^{-1}$ at 50 min in AS ($39.1 \mu\text{mol l}^{-1}$ at 30 min).

5 Salbutamol stimulated significant insulin release and produced hypokalaemia and glycogenolysis, whereas aminophylline induced no metabolic effect.

6 A comparison of sS and AS indicated a trend for aminophylline to potentiate the metabolic effects of salbutamol.

Introduction

The metabolic actions of adrenergic drugs, e.g. adrenaline, isoprenaline, salbutamol, have been well documented in man (Goldberg, van As, Joffe, Knut, Bersohn & Seftel, 1975; Massara, Fassio, Camanni & Molinatti, 1975; Leitch, Clancy, Costello & Flenley, 1976; Neville, Palmer, Gaddie, May, Palmer & Murchison, 1977; Tickner, Cramp, Foo, Johnson, Bateman, Pidgeon, Spiro, Clarke & Wills, 1977; Berend & Marlin, 1978). These metabolic effects include insulin release, hypokalaemia, lipolysis and glycogenolysis, which have important clinical implications when these drugs are used for the treatment of asthma. Although insulin release is mediated by stimulation of pancreatic β -adrenoceptors, the subtype, i.e. β_1 or β_2 , has not been clearly defined (Porte, 1967; Goldberg *et al.*, 1975; Berend & Marlin, 1978; Harms, Gooren, Spoelstra, Hesse & Verschoor, 1978; William-Olsson, Fellenius, Bjorntorp & Smith, 1979).

Theophylline also stimulates insulin release in animals (Malaisse, Malaisse-Lagae & Mayhew, 1967; Turtle, Littleton & Kipnis, 1967; Gerich, Lovinger & Grodsky, 1975), but its effect in man has not been clearly established. The purpose of this work was to compare the insulin releasing action of intravenous salbutamol and aminophylline in man and to deter-

mine whether any synergistic activity existed with the two drugs in combination.

Methods

Observations were made in four healthy male volunteers, aged 27 to 35 years, who gave consent to the studies. Four treatments administered by constant intravenous infusion (Infusomat Pump, B. Braum Melsungen) as shown in Table 1 were given according to a single-blind, balanced, randomized design. If salbutamol and aminophylline produced equivalent responses, synergistic activity could be studied by comparing the salbutamol response in treatments SS and AS (Table 1). Alternatively, if aminophylline produced no demonstrable effect alone, synergistic activity could be studied by comparing the salbutamol response in treatments sS and AS (Table 1).

Following an overnight fast, the subjects rested for 15 min after which baseline, control heart rate was recorded with an electrocardiogram and a venous blood sample collected. The first 30 min infusion was then commenced followed by the second 30 min infusion and further heart rate recordings from a continuous trace and venous blood samples were

Table 1 The four treatments administered by constant intravenous infusion on four separate days to the four subjects.

Time	Treatments		Code
	Infusion 1	Infusion 2	
1	30 min Saline (s)	30 min Salbutamol (S)	sS
2	Saline (s)	0.15 $\mu\text{g kg}^{-1} \text{min}^{-1}$ Aminophylline (A)	sA
3	Salbutamol (S)	0.2 $\text{mg kg}^{-1} \text{min}^{-1}$ Salbutamol (S)	SS
4	0.15 $\mu\text{g kg}^{-1} \text{min}^{-1}$ Aminophylline (A)	0.15 $\mu\text{g kg}^{-1} \text{min}^{-1}$ Salbutamol (S)	AS
	0.2 $\text{mg kg}^{-1} \text{min}^{-1}$	0.15 $\mu\text{g kg}^{-1} \text{min}^{-1}$	

taken at 10, 20, 30, 40, 50 and 60 min. All venous blood samples were assayed for theophylline (radioimmunoassay, Clinical Assays), insulin (radioimmunoassay) and glucose and potassium (auto-analyser method). The results were submitted to statistical analysis using the paired Student's *t*-test.

Results

The mean $\pm$ s.e. mean control, baseline values before the treatments for the four subjects are shown in Table 2. There were no significant differences between these mean control values for the four parameters. The treatment results were expressed as changes from control, baseline values and the mean $\pm$ s.e. mean heart rate, insulin, glucose and potassium changes from control for the four subjects are shown in Table 3. A summary of the statistical analysis when positive statistical significance was obtained for the various treatment comparisons for each parameter is shown in Table 4. Salbutamol significantly increased heart rate and glucose compared with saline ($\text{sS} \nu \text{SS}$, $\text{sA} \nu \text{SS}$) but there was no significant dif-

Table 2 The mean $\pm$ s.e. mean control, baseline values before each treatment for heart rate, insulin, glucose and potassium in the four subjects.

	Treatments			
	sS	sA	SS	AS
Heart rate (beats min^{-1})	63 $\pm$ 3	61 $\pm$ 5	62 $\pm$ 4	64 $\pm$ 3
Insulin ($\mu\text{U ml}^{-1}$)	22 $\pm$ 5	17 $\pm$ 3	23 $\pm$ 3	17 $\pm$ 4
Glucose (mmol l^{-1})	5.2 $\pm$ 0.1	5.2 $\pm$ 0.5	4.9 $\pm$ 0.2	5.7 $\pm$ 0.3
Potassium (nmol l^{-1})	3.6 $\pm$ 0.1	3.6 $\pm$ 0.1	3.7 $\pm$ 0.1	3.7 $\pm$ 0.1

Treatments (Table 1): sS — saline, salbutamol
sA — saline aminophylline
SS — salbutamol, salbutamol
AS — aminophylline, salbutamol

ference between aminophylline and saline for any parameter ($\text{sS} \nu \text{AS}$, $\text{sA} \nu \text{AS}$). In treatment sS the effects of salbutamol for all parameters at 60 min were significantly greater than saline at 30 min ($P < 0.05$). The salbutamol responses for all parameters were significantly greater than those for aminophylline ($\text{sS} \nu \text{sA}$, $\text{SS} \nu \text{AS}$, $\text{SS} \nu \text{sA}$). A comparison of the salbutamol responses in sS and AS showed no significant differences, although at 60 min the effect of salbutamol for all parameters in AS was greater than in sS. The insulin increase with salbutamol in AS was also greater than in SS.

The mean $\pm$ s.e. mean serum theophylline levels in sA and AS are shown in Table 5. There were no significant differences between the peak levels in both treatments.

Discussion

This study confirmed that salbutamol by the intravenous route stimulates insulin release from the pancreas and produces hypokalaemia and glycogenolysis. However, aminophylline did not induce any metabolic effect with mean serum theophylline levels which reached 48.1 $\mu\text{mol l}^{-1}$ in sA and 39.1 $\mu\text{mol l}^{-1}$ in AS (peak individual level; 55.0 $\mu\text{mol l}^{-1}$). The dose of aminophylline administered to produce these levels ranged from 13.6 to 17.0 mg/min for 30 min according to the weight of the subject. Cathcart-Rake, Kyner & Azarnoff (1979) have recently shown that serum theophylline levels between 55 and 110 $\mu\text{mol l}^{-1}$ produced no change in insulin but a rise in glucose. Several workers have demonstrated variable insulin and glucose increases with higher doses or rates of infusion of aminophylline than in the present study but with no serum level monitoring (500 mg at 25 mg/min, 250 mg at 25 mg/min, 1000 mg at 100 mg/min, 250 mg bolus) (Ensinck, Stoll, Gale, Santen, Touber & Williams, 1970; Marco, Diaz-Fierros, Baroja, Villanueva & Valverde, 1972; Arnman, Carlstrom & Thorell, 1975; Gedik & Zileli, 1977). Thus, high serum theophylline levels which may exceed the therapeutic range for bronchodilatation (55–110 $\mu\text{mol l}^{-1}$) and produce unwanted effects may be required for consistent insulin stimulation.

A comparison of treatments sS and AS enabled the effects of pre-treatment with saline and aminophylline on the subsequent salbutamol responses to be studied. The results indicated a trend for aminophylline to potentiate the metabolic effects of salbutamol, particularly the insulin response which in AS was greater than in both sS and SS. It is known that the bronchodilator effect of theophylline is directly related to the logarithm of the serum concentration (Marlin, Harris, Klumpp & Rutland, 1979). Aminophylline itself may have contributed to the increased salbutamol response in AS without

Table 3 The mean $\pm$ s.e. mean heart rate, insulin, glucose and potassium changes from control, baseline values before each treatment for the four subjects for sS, sA, SS and AS.

Time (min)	Treatments			
	sS	sA	SS	AS
<i>Heart rate change from control (beats min⁻¹)</i>				
10	0 $\pm$ 0.8	0 $\pm$ 0.8	12.8 $\pm$ 4.3	0.3 $\pm$ 1.3
20	1.0 $\pm$ 1.7	1.5 $\pm$ 1.7	18.5 $\pm$ 3.9	1.5 $\pm$ 1.0
30	0.8 $\pm$ 1.1	1.0 $\pm$ 3.3	19.5 $\pm$ 3.8	0.8 $\pm$ 1.5
40	12.5 $\pm$ 1.0	2.5 $\pm$ 2.6	23.0 $\pm$ 3.7	7.5 $\pm$ 1.5
50	17.0 $\pm$ 0.6	3.0 $\pm$ 4.0	25.0 $\pm$ 3.3	22.0 $\pm$ 2.9
60	23.0 $\pm$ 3.1	3.5 $\pm$ 3.6	28.5 $\pm$ 3.1	28.0 $\pm$ 5.7
<i>Insulin change from control (μU ml⁻¹)</i>				
10	-1.3 $\pm$ 2.0	1.3 $\pm$ 2.0	0.8 $\pm$ 5.4	0.8 $\pm$ 1.4
20	-3.8 $\pm$ 2.3	-2.0 $\pm$ 1.9	18.0 $\pm$ 7.8	2.8 $\pm$ 1.4
30	-4.0 $\pm$ 2.8	-2.5 $\pm$ 0.9	20.8 $\pm$ 9.6	2.8 $\pm$ 1.5
40	12.3 $\pm$ 6.5	-1.5 $\pm$ 0.5	29.3 $\pm$ 8.9	18.3 $\pm$ 3.1
50	16.0 $\pm$ 7.8	-1.0 $\pm$ 1.4	37.0 $\pm$ 7.3	35.5 $\pm$ 10.2
60	34.0 $\pm$ 11.7	0.5 $\pm$ 2.1	39.0 $\pm$ 2.7	57.5 $\pm$ 17.6
<i>Glucose change from control (mmol l⁻¹)</i>				
10	-0.3 $\pm$ 0.4	0 $\pm$ 0.4	0.5 $\pm$ 0.1	0.1 $\pm$ 0.1
20	-0.3 $\pm$ 0.3	-0.1 $\pm$ 0.3	1.2 $\pm$ 0.3	-0.1 $\pm$ 0.1
30	-0.2 $\pm$ 0.4	-0.3 $\pm$ 0.4	1.8 $\pm$ 0.5	-0.2 $\pm$ 0.2
40	0.1 $\pm$ 0.4	-0.3 $\pm$ 0.4	2.1 $\pm$ 0.5	0.6 $\pm$ 0.4
50	0.8 $\pm$ 0.3	0.1 $\pm$ 0.4	2.4 $\pm$ 0.6	1.1 $\pm$ 0.5
60	1.4 $\pm$ 0.5	0 $\pm$ 0.4	2.6 $\pm$ 0.4	2.0 $\pm$ 0.3
<i>Potassium change from control (mmol l⁻¹)</i>				
10	0.03 $\pm$ 0.05	-0.05 $\pm$ 0.03	0.08 $\pm$ 0.08	0 $\pm$ 0.04
20	1.10 $\pm$ 0.04	-0.05 $\pm$ 0.10	-0.25 $\pm$ 0.17	0.10 $\pm$ 0.04
30	0.15 $\pm$ 0.07	0.15 $\pm$ 0.03	-0.18 $\pm$ 0.19	0.20 $\pm$ 0.06
40	0.13 $\pm$ 0.06	0.58 $\pm$ 0.18	-0.40 $\pm$ 0.16	0.05 $\pm$ 0.09
50	-0.23 $\pm$ 0.09	0.38 $\pm$ 0.10	-0.45 $\pm$ 0.05	-0.30 $\pm$ 0.11
60	-0.45 $\pm$ 0.07	0.38 $\pm$ 0.08	-0.78 $\pm$ 0.05	-0.68 $\pm$ 0.05

Treatments (Table 1): sS — saline, salbutamol
sA — saline, aminophylline
SS — salbutamol, salbutamol
AS — aminophylline, salbutamol

invoking synergy as a mechanism for this observation. However, serum theophylline levels remained constant during the salbutamol infusion in AS and would not be expected to contribute any further to the metabolic response. This possible synergistic effect occurred with serum theophylline levels only reaching the low therapeutic range. If similar potentiating activity of low doses of theophylline could be demonstrated in the lung, this would provide a therapeutic advantage if high doses of theophylline could be avoided when given with β -adrenoceptor agonists. However, some studies have shown that theophylline and β -adrenoceptor agonists in combination produce only additive bronchodilator effects (Marlin, Hartnett, Berend & Hackett, 1978; Wolfe, Tashkin, Calvarese & Simmons, 1978), although Campbell, Middleton, McHardy, Shotton, McKenzie & Kay (1977) showed transient synergy between intravenous aminophylline and aerosol isoprenaline. The possi-

bility of synergy of unwanted effects, e.g. metabolic, cardiovascular, must also be considered.

Hypokalaemia may be present in patients with untreated acute, severe asthma and may worsen with parenteral β -adrenoceptor agonists (Shires, Joffe, Heding & Seftel, 1979). Intravenous aminophylline and aerosol β -adrenoceptor agonist by wet nebulization are often given together in acute asthma, but will both produce significant drug blood levels (Shenfield, Evans & Paterson, 1974) which may result in metabolic effects. This study emphasizes the necessity for regular monitoring of serum potassium in acute, severe asthma when β -adrenoceptor agonists and aminophylline are administered.

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Table 4 The results of the statistical analysis when positive statistical significance was obtained for the various treatment comparisons for the heart rate, insulin, glucose and potassium changes from control, baseline values in the four subjects.

Time (min)	Significance value					
	10	20	30	40	50	60
<i>Heart rate increase control</i>						
sS > sA	—	—	—	—	*	***
SS > sS	—	**	**	*	—	—
SS > sA	—	*	—	*	*	***
SS > AS	—	**	***	*	—	—
AS > sA	—	—	—	—	*	*
<i>Insulin increase from control</i>						
SS > sS	—	***	**	*	—	—
AS > sA	—	—	—	***	*	—
<i>Glucose increase from control</i>						
SS > sS	—	***	**	*	—	—
SS > sA	—	—	—	*	—	*
SS > AS	*	**	*	—	—	—
AS > sA	—	—	—	—	—	***
<i>Potassium decrease from control</i>						
sS > sA	—	—	—	—	**	***
SS > sS	—	—	—	—	—	***
SS > sA	—	—	—	*	***	***
SS > AS	—	***	—	—	—	—
AS > sA	—	—	—	—	*	***

Significant value: * $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$
 — not significant

Treatments (Table 1): sS — saline, salbutamol
 sA — saline, aminophylline
 SS — salbutamol, salbutamol
 AS — aminophylline, salbutamol

Table 5 The mean $\pm$ s.e. mean serum theophylline levels for the four subjects in treatments sA and AS.

Time (min)	Serum theophylline ($\mu\text{mol l}^{-1}$)	
	sA	AS
10	0	7.6 ± 3.2
20	0	26.7 ± 8.7
30	0	39.1 ± 9.9
40	5.5 ± 3.2	45.7 ± 7.2
50	21.8 ± 2.5	52.6 ± 10.0
60	48.1 ± 2.5	43.7 ± 8.4

Treatments (Table 1): sA — saline, aminophylline
 AS — aminophylline, salbutamol

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