Metabolic effects of salbutamol: comparison of aerosol and intravenous administration

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Summary

The effects of intravenous salbutamol (4 µg/kg) were compared with those of aerosol salbutamol (200 µg) in 10 asthmatic patients in a double-blind placebo-controlled study. Both methods of administration produced equal bronchodilatation. Intravenous salbutamol caused significant increases in plasma insulin and glucose levels and a fall in serum potassium concentration in addition to tachycardia and tremor, whereas aerosol salbutamol produced only a small transient increase in the plasma glucose level. The initially raised non-esterified fatty acid levels decreased significantly after aerosol and placebo but not after intravenous salbutamol.

Introduction

The beta₂-adrenoceptor agonist salbutamol is often used to relieve airways obstruction and may be administered orally, by aerosol, or intravenously. In addition to its bronchodilator action salbutamol has been shown to cause increases in plasma glucose, non-esterified fatty acids (NEFA), and insulin levels

when given intravenously¹ and orally² to normal subjects. We compared these metabolic effects when the drug was given in equivalent bronchodilator doses by aerosol and intravenously to asthmatic subjects in a double-blind randomised study.

Patients and methods

Ten subjects (eight men and two women aged 18-60 years (mean 38 years)) with mild chronic bronchial asthma volunteered for the study. Each patient attended after a 12-hour fast at 9 am on three separate mornings at least 48 hours apart, and bronchodilators were discontinued during this period. An indwelling intravenous cannula was inserted, and patients rested semirecumbent for 30 minutes before two basal recordings of pulse, blood pressure, forced vital capacity (FVC), and forced expiratory volume in one second (FEV₁) were made using a dry wedge spirometer and two basal blood samples were obtained at 10-minute intervals. On three separate occasions each patient received either salbutamol intravenously (4 µg/kg over five minutes) and placebo aerosol; placebo injection and salbutamol aerosol (200 µg); or placebo injection and placebo aerosol. The order of treatments was double-blind and randomised. The pulse rate was recorded during the injection. Further blood samples were obtained after 2, 4, 10, 15, 30, and 60 minutes, and pulse, blood pressure, and ventilatory function were recorded 15 minutes after the injection. Heparinised blood samples were separated immediately and analyses carried out on plasma concentrations of insulin (by radioimmunoassay), potassium (flame photometry), free glycerol and triglyceride (enzymatic method), and NEFA (Duncombe colorimetric technique). A glucose oxidase method was used to measure plasma glucose. The results were analysed statistically using Student's paired *t* test, and the NEFA changes in the three groups were analysed by analysis of variance.

Results

Changes in ventilatory function are shown in table I. There was an equivalent and significant increase after intravenous and aerosol salbutamol compared with placebo. Intravenous salbutamol produced a significant increase in the mean resting pulse rate from 73 beats/min to 104 beats/min at the completion of injection (*P* < 0.001), and 15

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TABLE I—Ventilatory function tests. Results are means ± SE of mean

	Placebo		Salbutamol			
			Aerosol		Intravenous	
	Basal	15 Minutes	Basal	15 Minutes	Basal	15 Minutes
FEV ₁	1.34 ± 0.20	1.25 ± 0.20	1.46 ± 0.27	1.93*** ± 0.27	1.33 ± 0.28	1.72*** ± 0.28
FVC	2.67 ± 0.31	2.50* ± 0.30	2.78 ± 0.34	3.48* ± 0.30	2.50 ± 0.33	3.10** ± 0.34

Significant difference from mean basal level: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

TABLE II—Effects of intravenous salbutamol. Results are means ± SE of mean

	Basal	2 Minutes	4 Minutes	10 Minutes	15 Minutes	30 Minutes	60 Minutes
Insulin (mU/l)	17 ± 3	49** ± 11	43*** ± 9	37** ± 7	33* ± 5	27* ± 5	16 ± 3
Glucose (mmol/l)	5.1 ± 0.1	5.7*** ± 0.1	5.8*** ± 0.1	5.8*** ± 0.1	5.7** ± 0.1	5.5* ± 0.1	5.2 ± 0.1
Potassium (mmol/l)	3.9 ± 0.1	3.7 ± 0.1	3.7* ± 0.1	3.5*** ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.8 ± 0.2
Free glycerol (µmol/l)	380 ± 49	376 ± 37	412 ± 46	361 ± 35	383 ± 40	288* ± 29	240* ± 30
Triglyceride (mmol/l)	0.465 ± 0.058	0.521 ± 0.080	0.353 ± 0.053	0.406 ± 0.062	0.395 ± 0.076	0.482 ± 0.057	0.422 ± 0.072
NEFA (µmol/l)	1255 ± 138	1351 ± 175	1379 ± 167	1358 ± 164			

Significant difference from mean basal level: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Potassium: 1 mmol/l = 1 mEq/l. Glycerol: 1 µmol/l ≈ 0.0092 mg/100 ml. Triglyceride: 1 mmol/l ≈ 88.5 mg/100 ml. NEFA: 1 µmol/l ≈ 0.26 mg/l.

TABLE III—Effects of aerosol salbutamol. Results are means $\pm$ SE of mean

	Basal	2 Minutes	4 Minutes	10 Minutes	15 Minutes	30 Minutes	60 Minutes
Insulin (mU/l)	13 $\pm$ 2	16 $\pm$ 3	14 $\pm$ 2	16 $\pm$ 4	18 $\pm$ 3	14 $\pm$ 3	13 $\pm$ 3
Glucose (mmol/l)	5.1 $\pm$ 0.01	5.3** $\pm$ 0.01	5.2 $\pm$ 0.1	5.1 $\pm$ 0.1	5.2 $\pm$ 0.1	5.1 $\pm$ 0.1	5.1 $\pm$ 0.1
Potassium (mmol/l)	3.8 $\pm$ 0.1	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1	4.0 $\pm$ 0.1	4.1 $\pm$ 0.1
Free glycerol (μ mol/l)	378 $\pm$ 60	342 $\pm$ 58	350 $\pm$ 64	357 $\pm$ 53	302** $\pm$ 49	269** $\pm$ 39	222** $\pm$ 33
Triglyceride (mmol/l)	0.677 $\pm$ 0.074	0.515** $\pm$ 0.097	0.584 $\pm$ 0.109	0.434*** $\pm$ 0.097	0.503** $\pm$ 0.083	0.573 $\pm$ 0.112	0.617 $\pm$ 0.077
NEFA (μ mol/l)	1179 $\pm$ 129	940** $\pm$ 87	1039 $\pm$ 105	932 $\pm$ 81			

Significant difference from mean basal level: *P < 0.05; **P < 0.01; ***P < 0.001.

TABLE IV—Effects of placebo. Results are means $\pm$ SE of mean

	Basal	2 Minutes	4 Minutes	10 Minutes	15 Minutes	30 Minutes	60 Minutes
Insulin (mU/l)	14 $\pm$ 3	12 $\pm$ 3	12 $\pm$ 3	15 $\pm$ 3	15 $\pm$ 3	14 $\pm$ 3	15 $\pm$ 3
Glucose (mmol/l)	4.9 $\pm$ 0.2	5.0 $\pm$ 0.1	5.0 $\pm$ 0.1	5.0 $\pm$ 0.1	5.0 $\pm$ 0.1	5.0 $\pm$ 0.1	5.1 $\pm$ 0.1
Potassium (mmol/l)	3.8 $\pm$ 0.1	3.8 $\pm$ 0.1	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1	3.8 $\pm$ 0.1	4.0 $\pm$ 0.2	4.2 $\pm$ 0.3
Free glycerol (μ mol/l)	341 $\pm$ 57	308 $\pm$ 54	316 $\pm$ 66	287 $\pm$ 70	285 $\pm$ 47	280 $\pm$ 47	198** $\pm$ 29
Triglyceride (mmol/l)	0.626 $\pm$ 0.107	0.495** $\pm$ 0.079	0.556 $\pm$ 0.097	0.495 $\pm$ 0.084	0.466** $\pm$ 0.081	0.499* $\pm$ 0.077	0.547 $\pm$ 0.082
NEFA (μ mol/l)	1548 $\pm$ 335	1269* $\pm$ 374	1349 $\pm$ 356	1260** $\pm$ 312			

Significant difference from mean basal level: *P < 0.05; **P < 0.01.

minutes after injection it was still raised at 84 beats/min ($P < 0.01$). The pulse rate did not change after aerosol salbutamol or placebo, and the blood pressure was unaltered in all three treatment groups. During and after the intravenous salbutamol seven of the 10 patients had finger tremor, four had transient palpitations associated with sinus tachycardia, and two, one of whom also complained of facial flushing, had headache.

After intravenous salbutamol there were significant increases in plasma glucose and insulin concentrations, with a small but statistically significant decrease in serum potassium levels (table II). The only change after aerosol salbutamol was a transient increase in plasma glucose at 2 minutes (table III). No such changes were seen after placebo. In all three groups pretreatment fasting levels of free glycerol and NEFA were raised, and serum triglyceride levels were low. After aerosol salbutamol and placebo, free glycerol, triglyceride, and NEFA levels fell (tables III and IV), whereas NEFA levels tended to increase, though not significantly, after intravenous salbutamol. The mean change in NEFA concentration after intravenous salbutamol (+108 μ mol/l (+28 mg/l), however, was significantly different from that after both aerosol salbutamol (−209 μ mol/l (−54.3 mg/l); $P < 0.01$) and placebo (−255 μ mol/l (−66.3 mg/l); $P < 0.01$).

Discussion

Theoretically the metabolic changes caused by salbutamol may be harmful to the asthmatic patient. We have shown that a standard dose of aerosol salbutamol produced only a minor transient increase in plasma glucose levels and caused no change in plasma insulin or potassium levels, whereas an equivalent bronchodilator dose of intravenous salbutamol did. When salbutamol is given by aerosol, however, the plasma levels of salbutamol are negligible.³ We have previously shown that similar changes in glucose, insulin, and potassium occur after oral salbutamol in normal subjects. We have not yet compared the metabolic responses of normal and asthmatic subjects to sympathomimetic amines, but there is evidence that the changes in glucose⁴ and possibly NEFA⁵ may be smaller in asthmatics during periods of airways obstruction.⁶

Our patients had only mild to moderate airways obstruction. Intravenous salbutamol is used in patients with severe airways obstruction unresponsive to aerosol treatment. In these patients hypoxia, acidosis, and high catecholamine levels increase the risk of dysrhythmias,⁷ and this may be further aggravated by the metabolic changes after intravenous salbutamol. It has been suggested that after myocardial infarction high levels of NEFA are cardiotoxic,⁸ but the concept that high NEFA levels predispose to cardiac arrhythmias is controversial.⁹

Another factor that may predispose to the development of dysrhythmias in asthmatics treated by salbutamol is hypokalaemia, resulting from a shift of potassium from the extracellular to the intracellular space due to the action of insulin or to a direct effect of salbutamol on potassium transport into muscle.¹⁰ A significant fall in serum potassium from 3.99 to 3.10 mmol(mEq)/l during a one-hour infusion of 600 μ g of salbutamol has been found,¹¹ and we have shown a smaller but statistically significant decrease after a lower intravenous dose of salbutamol, although the clinical significance of this is uncertain. The risk of dysrhythmias in salbutamol-induced hypokalaemia is probably determined mainly by two factors: the rapidity with which the intracellular concentration of potassium rises and the extracellular concentration falls, and by the degree of hypoxia of the myocardium.^{12, 13} An additional possible cause of hypokalaemia in patients with severe airways obstruction is the concomitant administration of parenteral corticosteroids in high doses. Although no one has yet shown that the administration of parenteral salbutamol results in cardiac dysrhythmias, it would be prudent to carry out cardiac monitoring of patients who receive intravenous salbutamol for status asthmaticus until it is established whether or not these theoretical hazards are clinically important.

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References

- Goldberg, R, *et al*, *Postgraduate Medical Journal*, 1975, **51**, 53.
- Taylor, M W, *et al*, *British Medical Journal*, 1976, **1**, 22.
- Paterson, J W, and Shenfield, G M, *BTTA Review*, 1974, **4**, 25.
- Lockey, S D, *et al*, *Journal of Allergy*, 1967, **40**, 349.
- Middleton, E, *et al*, and Finke, S R, *Journal of Allergy*, 1968, **42**, 288.
- Inoue, S, *Journal of Allergy*, 1967, **40**, 337.
- Collins, J M, *et al*, *British Journal of Pharmacology*, 1969, **36**, 35.
- Oliver, M F, *Circulation*, 1972, **45**, 491.
- Opie, L H, *Circulation*, 1972, **45**, 483.
- Wang, P, and Clausen, T, *Lancet*, 1976, **1**, 221.
- Leitch, A G, *et al*, *British Medical Journal*, 1976, **1**, 365.
- Hoffman, B F, and Cranefield, P F, *American Journal of Medicine*, 1964, **37**, 670.
- Gelband, H, *et al*, *Circulation Research*, 1972, **30**, 293.

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