Br. J. clin. Pharmac. (1978), **5**, 127–129

THE METABOLIC EFFECTS OF INHALED SALBUTAMOL

S.M. BATEMAN[1], J. PIDGEON[1], S.G. SPIRO[1] & A.J. JOHNSON[2]

Department of Medicine[1] and Department of Clinical Pharmacology[2],
Cardiothoracic Institute, Brompton Hospital, Fulham Road,
London SW3 6HP

1 The metabolic effects of salbutamol (5 mg) given by intermittent positive pressure breathing have been studied in eight patients with airflow obstruction.

2 No changes in plasma nonesterified fatty acids, triglyceride, glucose, insulin or cortisol were seen 1 and 4 h after administration.

3 It is concluded that inhaled salbutamol does not cause the unwanted metabolic effects reported with oral or parenteral administration, and that this is a further indication for this route of administration.

Introduction

There has been considerable recent interest in the metabolic effects of the β_2-adrenergic receptor agonist salbutamol on plasma constituents. Intravenous administration as a bolus or a short duration infusion to normal subjects caused a marked rise in nonesterified fatty acids (NEFA) and lactate, and smaller increases in insulin and glucose concentrations (Goldberg, Joffe, Bersohn, Van As, Krut & Seftel, 1976). A single 4 mg tablet of salbutamol given to normal subjects was associated with an elevation of insulin and glucose and a fall in potassium concentration (Taylor, Gaddie, Murchison & Palmer, 1976). The rise in NEFA and free glycerol following this route of administration also occurred with a placebo. A recent study has shown that acute asthma itself causes a marked rise in NEFA as a result of the 'stress' involved (Tickner, Cramp, Foo, Johnson, Bateman, Pidgeon, Spiro, Clarke & Wills, 1977). With administration of salbutamol by infusion to treat the asthma, no further rise in NEFA occurred, but there were rises in insulin and glucose, and a fall in potassium concentration.

Salbutamol is frequently administered by the inhaled route to minimize cardiovascular and muscle side effects. Choo-Kang & Grant (1975) showed that intermittent positive pressure breathing (IPPB) is an effective method of administration, presumably because a larger dose of drug is delivered to the patient than by dry pressurized aerosol (Shenfield, Evans & Paterson, 1974). In view of the previously documented metabolic effects of salbutamol when given by other routes, we have used IPPB administration to patients with airways obstruction to determine the metabolic effects of inhaled salbutamol.

Method

Eight patients convalescing after an acute attack of asthma or exacerbation of chronic bronchitis gave their informed consent to participate in the study. Details of the patients and their treatment prior to the study are given in Table 1. All were receiving regular salbutamol both by IPPB and by tablets as part of their clinical management, but all preparations of bronchodilator were withheld for 12 h prior to the study. Other medication was continued. Peak expiratory flow rate was measured using a Wright peak flow gauge (Airmed Ltd) at commencement of the study.

The patients were studied supine at 06.00 h following an overnight fast. An initial venous blood sample was withdrawn into a lithium heparin tube, centrifuged and the plasma separated and frozen to −20°C. Salbutamol (5 mg) was then administered by IPPB (Bird Mk 7 respirator). Further blood samples were taken 1 and 4 h after completion of the treatment. NEFA was measured by the method of Carruthers & Young (1973), triglyceride by the method of Cramp & Robertson (1968), glucose using an automated glucose oxidation method (Trinder, 1969), insulin by single antibody radio immunoassay (Lepetit), and cortisol by competitive protein binding. Analysis of results was undertaken using Student's *t*-test.

Results

The mean observed PEFR before salbutamol was significantly reduced compared to the mean predicted ($P < 0.001$, Table 1). Mean baseline plasma con-

centrations of NEFA, triglyceride and cortisol were within the normal range for this laboratory, and plasma glucose just above the upper limit (Table 2). There was a rise in NEFA and fall in insulin and cortisol mean concentrations 1 h after administration, but these and further small changes 4 h after administration were not statistically significant from the mean pre-treatment values. The elevation of plasma insulin concentration compared to the normal range was due to one subject (patient 3) who had an initial value of 120 μU/l falling to 66 μU/l at 1 h and 40 μU/l at 4 hours. With this subject excluded the mean plasma insulin concentration remained within the normal range, and did not alter significantly with treatment.

Discussion

Bronchodilator drugs are often administered for long periods to patients suffering from asthma or chronic bronchitis. The β_2-adrenoceptor agonists have been developed in order to minimize unwanted cardiovascular side effects. However, it has been claimed that the marked rise in NEFA concentration associated with intravenous administration of salbutamol, when combined with hypoxia, tachycardia and raised catecholamines due to the stress of the disease, may be a danger in acute asthma by provoking dysrythmias (Oliver, 1972; Leading Article, 1975). Whilst parenteral salbutamol is reserved for the acute phase of asthma, the associated rise in NEFA,

Table 1 Anthropometric data

Patient	*Diagnosis*	*Drugs*	*Age (years)*	*Sex*	*Weight (kg)*	*Predicted PEFR (l/min)*	*Observed PEFR (l/min)*
1	Intrinsic asthma	Prednisolone Beclomethasone Ampicillin	50	M	63.5	550	–
2	Extrinsic asthma Chronic bronchitis	Beclomethasone Tetracosactrin Frusemide Amiloride	52	M	79	535	110
3	Intrinsic asthma	Betamethazone tabs. Beclomethasone Cromoglycate Amoxycillin Erythromycin	53	M	39	–	60
4	Intrinsic asthma	Prednisone Beclomethasone Cromoglycate	50	F	59	380	250
5	Intrinsic asthma	Beclomethasone	35	F	40	380	325
6	Chronic bronchitis	Frusemide	67	M	69	530	115
7	Chronic bronchitis	Amoxycillin	58	F	101.5	400	130
8	Intrinsic asthma	Prednisone Cyclopenthiazide	61	F	55.5	310	95
		Mean	53.3		63.3	440.7	155.0
		± s.e. mean	3.4		7.3	36.3	36.1

Predicted PEFR derived from Cotes (1975).

Table 2 Mean ± s.e. mean plasma constituents before and after salbutamol (5 mg) administered by IPPB

	Initial level	*1 h after drug*	*4 h after drug*	*Normal fasting range*
NEFA (μmol/l)	431.4 ± 55.3	456.3 ± 56.5	510.6 ± 58.2	300–700
Triglyceride (mmol/l)	1.7 ± 0.2	1.8 ± 0.3	1.7 ± 0.2	0.6–2.0
Glucose (mmol/l)	5.9 ± 0.4	5.8 ± 0.6	6.0 ± 0.3	3.4–5.8
Insulin (μU/l)	24.9 ± 15.9	17.1 ± 7.1	12.1 ± 4.2	<10.0
Cortisol (μg/100 ml)	17.6 ± 4.1	14.3 ± 3.8	12.7 ± 3.1	8–25

insulin and glucose, and the fall in potassium concentration, may be important if it occurred with chronic administration by other routes. In this study administration of a single large dose of nebulized salbutamol, by a technique which delivers proportionately more of a dose to the lung than a dry pressurized aerosol (Shenfield *et al.*, 1974), caused no significant changes in NEFA, glucose or insulin. Although plasma potassium was not measured, the small fall in insulin and unchanged glucose suggest that hypokalaemia was unlikely. In view of these findings the dry pressurized aerosol, which delivers a much smaller dose (100 μg per actuation), is even less likely to cause any metabolic disturbances.

Most of the documented metabolic changes following salbutamol administration have been measured in small groups, and the effects of tablet administration confined to normal subjects (Taylor *et al.*, 1976). However, it would appear preferable to prescribe the aerosol of salbutamol as it is both rapidly effective and without any short term unwanted metabolic effects.

We wish to thank the Physicians of Brompton Hospital for permission to study patients under their care, Dr T.R. Tickner and Miss A.Y. Foo of the Department of Chemical Pathology, Royal Free Hospital, for the estimation of plasma constituents, and Mrs C.A. Inkpen for typing the manuscript. A.J. is supported by the Asthma Research Council.

References

CARRUTHERS, M. & YOUNG, D.A.B. (1973). Free fatty acid estimation by a semi-automated fluorimetric method. *Clinica Chim. Acta,* **49**, 341–348.

CHOO-KANG, Y.F.J. & GRANT, I.W.B. (1975). Comparison of two methods of administering bronchodilator aerosol to asthmatic patients. *Br. med. J.,* **1**, 119–120.

COTES, J.E. (1975). Lung function. Assessment and application in medicine, p. 377, 3rd edition. London: Blackwell Scientific Publications.

CRAMP, D.G. & ROBERTSON, G. (1968). The fluorimetric assay of triglyceride by a semi-automated method. *Analyt. Biochem.,* **25**, 246–251.

GOLDBERG, R., JOFFE, B.I., BERSOHN, I., VAN AS, M., KRUT, L. & SEFTEL, M.C. (1976). Metabolic responses to selective adrenergic stimulation in man. *Postgrad. med. J.,* **51**, 53–58.

LEADING ARTICLE (1975). Management of acute asthma. *Br. med. J.,* **4**, 65–66.

OLIVER, M.F. (1972). Metabolic responses during impending myocardial infarction, ii. clinical implications. *Circulation,* **45**, 491–500.

SHENFIELD, G.M., EVANS, M.E. & PATERSON, J.W. (1974). The effect of different nebulizers with and without positive pressure breathing on the absorption and metabolism of salbutamol. *Br. J. clin. Pharmac.,* **1**, 295–300.

TAYLOR, M.W., GADDIE, J., MURCHISON, L.E. & PALMER, K.N.V. (1976). Metabolic effects of oral salbutamol. *Br. med. J.,* **1**, 22.

TICKNER, T.R., CRAMP, D.G., FOO, A.Y., JOHNSON, A.J., BATEMAN, S.M., PIDGEON, J., SPIRO, S.G., CLARKE, S.W. & WILLS, M.R. (1977). Metabolic response to intravenous salbutamol in acute asthma. *Thorax,* **32**, 182–184.

TRINDER, P. (1969). Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. *Ann. clin. Biochem.,* **6**, 24–27.

(Received February 28, 1977)