SINGLE-DOSE AND STEADY-STATE EFFECTS OF CONTROLLED-RELEASE SALBUTAMOL ON DRUG LEVEL AND AIRFLOW OBSTRUCTION IN PATIENTS WITH ASTHMA

W C Tan, T B Chan, S M Ang

ABSTRACT

Oral medication remains the mainstay of treatment for many asthmatics. We compared the single dose and steady-state effects of twice daily 4mg and 8mg controlled-release salbutamol(CRS) on plasma salbutamol and FEV1 in 10 asthmatic patients in a double-blind, double-dummy, cross-over study. On 5 separate days, one week apart, we measured FEV1 and plasma salbutamol hourly for 12 hours after a single dose and, after twice daily doses (4mg, 8 mg or placebo CRS) for one week. Controlled-release salbutamol showed controlled release properties and dose effect for the two doses. At steady-state, it provided relatively constant plasma levels for 12 hours. Significant and similar bronchodilatation occurred after both 4 mg and 8 mg CRS taken either as a single dose or a steady-state regime.

Keywords: Oral bronchodilator, Asian, Pulmonary Function.

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INTRODUCTION

Selective $ß_2$ adrenoreceptor agonists are currently the most widely used drugs for the treatment of asthma[1-4]. Ideally, inhaled therapy should be the route of administration for $ß_2$ agonists because of greater dose efficacy and minimal side-effects. In practice, many patients, especially the very young, the old and the handicapped are unable to use the inhaler even with the help of extension pieces such as spacers[5]. For them oral medication remains the only alternative. Because standard salbutamol are short-acting, frequent dosing is required. This reduces patient compliance[6]. Salbutamol is now available in a osmotic pressure mediated controlled-release(CRS) formulation (Volmax), which appears to be effective when administered twice daily[7-9].

There is much information on the effects of standard salbutamol on asthma in Caucasian patient[1-4]. Controlled-release salbutamol(CRS) has been shown to be as effective as standard salbutamol[7-9] and individually titrated oral sustained-release theophylline[10] in the control of asthmatic symptoms and in maintaining lung function. However, there has been no study of either the standard or controlled release formulations of this drug on plasma salbutamol and pulmonary function in Asian patients.

The aim of this study was to compare the single dose and steady-state effects of CRS 4 mg and 8 mg, on plasma salbutamol and pulmonary function in Asian patients with asthma.

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PATIENTS

Twelve adult men with bronchial asthma (as per the American Thoracic Society criteria) were recruited into the study[11]. All patients never smoked. They were clinically stable; medications were unchanged for at least one month before the study. Medications included inhaled $ß_2$ agonist in 10 patients, twice daily sustained-release oral theophylline in three, inhaled ipratropium bromide in one and low dose inhaled steroid in three patients . No patient was studied within six weeks of a respiratory tract infection and particular care was taken to exclude thyrotoxicosis, cardiovascular and hepatic disease. Although the patients were allowed to continue with their regular medications during the period of the study, they were instructed to withhold inhaled bronchodilators for 6 hours, and oral theophylline and antihistamine for 72 hours before the study days.

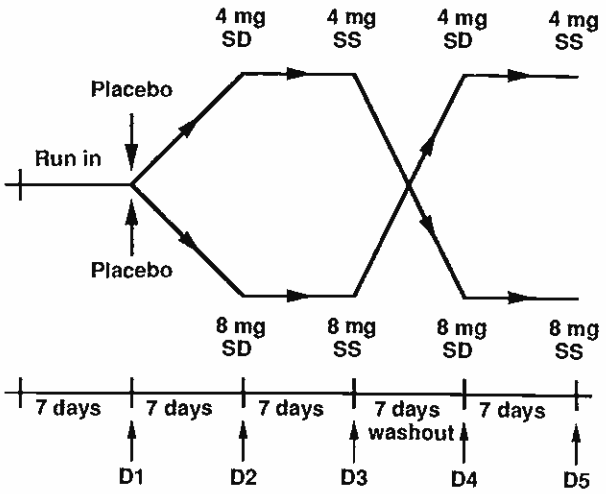
METHODS

A randomised, double blind, double placebo cross-over design was used in the study. Single dose and steady state responses were examined using two doses of CRS, 4 mg and 8 mg. The experimental conditions were kept constant on each study day: fixed starting time, standardised food and drinks, and pre-study variability in FEV1 was less than 15%.

Each subject was studied five times, at weekly intervals. After an initial run-in familiarisation period of seven days during which the subject received double placebo, each subject was first studied on Day 1 (D1). The subjects were then randomised into two groups. Both groups of subjects received double placebo for another week. At the end of this period the subject was studied on two occasions: an acute study after a single dose on day D2, and a steady-state study after seven days of twice daily administration of the dose on day D3. After a washout period of seven days during which the subjects again received double placebo, the same sequence was repeated for single dose on day D4 and steady-state on day D5, using the alternate dose(4 mg or 8 mg). (Fig 1)

On each study day timed measurements were made before the drug was administered and at 1,2,3,4,6,8 and 12 hours

Fig 1 - Schematic representation of the design of the study.



SD=single dose; SS=steady-state;
D1, D2, D3, D4, D5 are the separate study days.

thereafter. Spirometry was performed by standard techniques[12] using a dry rolling seal spirometer (Gould USA). Venous blood was withdrawn on study days D2 to D6, immediately centrifuged at 3,000 rev/min, stored at -20°C. At the end of the study the venous samples were packed in dry-ice and airflown to BIOS [Consultancy & Contract Research Ltd. (Surrey, UK)] for plasma salbutamol assay using a high performance liquid chromatographic (HPLC) and solid phase extraction method developed by Glaxo, Ware, and validated by BIOS. The coefficient of variation of the assay at 2ng/ml was 13.81%. The detection limit of of the assay was 1 ng/ml, which was the effective zero for the method[13, 14]. Pulse rate and blood pressure were recorded by one investigator.

A count of tablets was made at each clinic visit. Twice daily recordings of PEFR Peak expiratory flow rate was measured with a Mini Wright peak flow meter throughout the period of the study. Informed written consent was obtained from all the patients before the study.

ANALYSIS OF DATA

The data from the clinic visits and the diary cards were analysed separately. All values were expressed as mean±se. Spirometric data and plasma salbutamol data and diary recordings of PEFR were compared by Student's t-test. Significance was assumed at $p < 0.05$.

RESULTS

Patient data

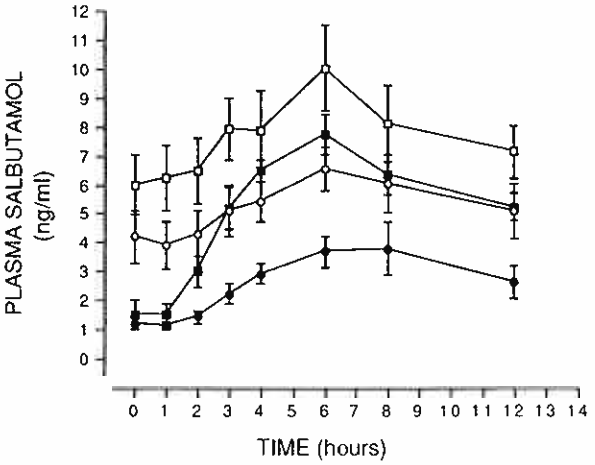
Ten patients out of twelve completed the study. Two patients were withdrawn from the study because of intercurrent upper respiratory tract infection, which occurred after the first visit. Hence the data from the ten remaining patients were analysed. The age was 29± 4.6 [mean (se)], (range 17 to 56 years), height 169(2.4)[mean(se)] cm, weight 58(2.0) kg. Mean FEV1 was 76.0(5.2), and FVC 95.6(4.7) both expressed as % predicted. The percentage improvement in FEV1 after 400µg of inhaled salbutamol was 24(2.1). The mean duration of historical asthma was 14.7(4.4) years before the study.

Plasma salbutamol

We found that the response in plasma salbutamol over time was graded from 4 mg single dose(SD) to 8mg SD, to 4 mg steady state(SS) to 8 mg SS. The peak concentration of salbutamol was attained at 6 hours after administration of the drug with both SD and SS regimens. The basal plasma concentration was higher for the steady state regimes than for the single dose regimes. At 12 hours plasma salbutamol remained elevated above basal level in all 4 regimens. Plasma salbutamol varied little over the course of 12 hours during steady state regimens. (Fig 2 and 3)

Spirometry

Fig 2 - Single Dose(SD) and Steady-State(SS) Plasma Salbultamol-Time Profiles after 4mg and 8mg controlled-release salbutamol in 10 asthmatic patients. The detection limit of the assay was 1 ng/ml, which was the effective zero for the method.



Key: Values are mean(se)
SD(4mg): SD(8mg); SS(4mg); SS(8mg).

Table I – Comparison of the Bronchodilator response after placebo, 4mg and 8mg of salbutamol controlled-release in 10 asthmatic patients.

	Placebo	Single dose		Steady-state	
		4mg	8mg	4mg	8mg
FEV1pre(B)(L)	2.40±.25	2.28±.24*	2.40±.19**	2.25±.21†	2.31±.22††
FEV1post(A)(L)	2.51±.21	2.65±.26*	2.65±.23**	2.50±.21†	2.57±.21††
BD/init.FEV1(%)	5±2	18±4	12±3	12±4	13±5
BD AFEV1-BFEV1	150±70	374±100	250±80	250±60	260±80

Definition of abbreviations:
BD = bronchodilator response;
AFEV1 = after bronchodilator FEV1;
BFEV1 = before bronchodilator FEV1.

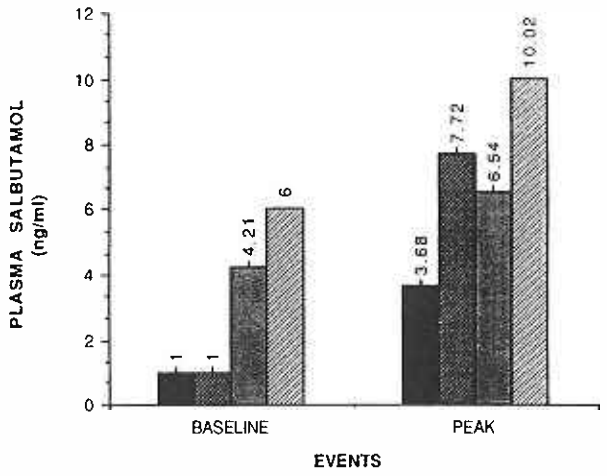
* p<.005;
** p<.004;
† p<.02;
†† p<.007 (FEV1 before and after each dose regimen of controlled-release salbutamol.

Table II – Comparison of the baseline and maximum pulse rate and blood pressure after placebo, 4mg and 8mg of salbutamol controlled-release in 10 asthmatic patients.

	Placebo	Single dose		Steady-state	
		4mg	8mg	4mg	8mg
Pulse(B)#/min	70±3.4	71±3.5	72±6.3	75±6.3	83±6.7
Pulse(A)#/min	71±2.5	72±5.2	80±4.7	77±2.9	84±3.6
SystolicBP(B)	110±5.0	116±6.0	120±4.5	116±8.1	116±6.8
SystolicBP(P)	112±4.0	120±6.3	120±3.2	116±8.1	122±6.6
DiastolicBP(B)	72±4.0	72±4.9	78±3.7	74±2.5	74±2.5
DiastolicBP(P)	71±2.1	76±2.5	78±2.0	74±2.5	76±2.5

Definition of abbreviations:
BP = blood pressure,
B = Baseline;
P = peak.

Fig 3 - Single Dose(SD) and Steady-State(SS) Baseline and peak plasma salbutamol after 4mg and 8mg controlled-release salbutamol in 10 asthmatic patients.



Key: Values for Mean ±se are shown.

SD(4mg); SD(8mg); SS(4mg); SS(8mg).

There is no significant difference between 4mg and 8mg after correction for dose. The detection limit of the assay was 1 ng/ml, which was the effective zero for the method.

The maximum responses in FEV1 to the 4 dosing regimens were all significantly greater than that with placebo. However these responses were not dose-dependent as was observed with plasma salbutamol. (Table I)

Side Effects

Side effects were few: one patient complained of headache and another had mild tremor of the hands, neither requiring the discontinuation of the test drug. The baseline and peak pulse rate, systolic and diastolic blood pressures during the study were not significantly different between the 4 dosing regimens. (Table II)

Diary card results

Home measurements of twice daily PEFR showed wide variations. The values during treatment with 4 mg or 8 mg twice daily for a week were higher than that during placebo but the differences did not reach statistical significance. The PEFR [mean (se)] for one week were: for 4 mg , 453(32.3) L/min (am) and 471(32.3) L/min (pm) ; for 8 mg, 446(38.7) L/min(am) and 443(33.8) L/min (pm); for placebo 431(34.2) L/min (am) and 438(34.7) L/min (pm).

DISCUSSION

The results show that twice daily administration of oral controlled-release salbutamol(CRS) at 4 mg or 8 mg produced significant bronchodilatation when compared with placebo, in patients with mild to moderate asthma. Controlled-release salbutamol showed sustained release properties and produced a dose response in the plasma levels of the drug. With steady-state dosing, small variations in plasma level occurred over the course of the dosing interval of 12 hours. These features are characteristic of effective controlled-release formulations of oral drugs[15]. These small fluctuations in drug level together with the wide therapeutic/toxic margins of salbutamol give CRS a distinct advantage over sustained-release theophylline which requires individual titration according to blood level response[16].

Body mass does not appear to significantly influence the effective dose of CRS. It is surprising that inspite of the smaller body build of our subjects, the mean peak and trough plasma concentrations of salbutamol during steady-state dosing with 4 mg and 8 mg of the drug are similar to[7] or lower than[9, 17] the levels found in Caucasian patients. We do not feel that this can be attributed to poor compliance as the administration of all single doses of the drug was supervised and a close record kept of all tablets taken during the week of the steady-state study.

A significant bronchodilator response as shown by FEV1, was observed for all four CRS dosing regimens when compared to that for placebo. We did not observe a close temporal relationship between the bronchodilator response and the plasma salbutamol. The maximum response for all 4 dosing regimens were significantly greater than that for placebo. However the magnitude of the bronchodilator response was not dose-dependent.

There are several possible explanations for these observations. First, there are well-recognised problems in the use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. There is no consensus on the ideal definition for reversibility and on the expression and the clinical interpretation of response to bronchodilators. Conventionally, this response is expressed as a percentage change in FEV1 of the baseline or of the predicted normal[18, 19]. Expressed in this way, it is well known that a small bronchodilator response in FEV1 may be seen either in mild asthmatics when the function is virtually normal, because of the "ceiling effect" or in the most severe asthmatics where the obstruction is usually due to inflammatory changes and mucous plugging rather than to bronchoconstriction. In between these extremes the largest

responses are seen[20]. Since most of the patients in this study have mild airway obstruction with almost normal baseline spirometry, a 4 mg dose of CRS could have produced maximum bronchodilatation with little potential for further improvement. It is therefore not surprising that we failed to find a clear separation in the bronchodilator FEV1 response similar to that observed with plasma levels of salbutamol.

Other potential confounding factors may include: (1) the small number of patients studied. This together with large individual variations in FEV1 response could produce a type 2 error by masking any real difference between the treatments[21]. However, we felt that with this double-blind cross-over design, the size of the patients studied is statistically adequate and is unlikely to be the sole explanation for the lack of difference between the treatment regimens. (2) Our patients were allowed to continue with their regular supplementary medication in the intervals between the study days provided medications were withdrawn at a specific interval before the study as stated in the section on methods. We were aware of the potential carry-over effect of other medications such as theophylline and inhaled steroids on the observed bronchodilator response. However, since the patients were clinically stable on their regular medication it was felt that total drug withdrawal was not justified. Instead the patients were carefully instructed to continue with the same medication with a fixed dosing schedule until a defined interval just before each study. In this way we felt we have minimised the carry-over effect of the maintenance therapy.

We were also unable to demonstrate any significant change in the morning and evening PEFR measured at home by the patients. The same reasons could explain this observation. Furthermore, PEFR is a more variable measure of airflow limitation than FEV1[12].

Side effects were few and transient and consisted of headache in one patient and tremor in another, both of which were not troublesome and subsided with continued medication. No cardiovascular adverse effects were recorded during the studies. Tolerance to side effects has been well documented with β_2 agonist[22].

It would appear that oral twice daily administration of controlled-release salbutamol provides steady blood levels, effective bronchodilatation, and is a well-tolerated option in the control of mild to moderate asthma in Asian patients. The impression in this study is that lower dose of CRS is adequate and that the higher dose of CRS may not produce additional improvement in pulmonary function. This impression may be further clarified when the study is repeated in asthmatic patients with more severe airway obstruction .

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