The dose-related hyper-and-hypokalaemic effects of salbutamol and its arrhythmogenic potential

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1 The hypokalaemic effect of salbutamol after more than 30 min of administration has been well described. A hyper-and-hypokalaemic effect for adrenaline has been reported, but no such hyperkalaemic effect for salbutamol.

2 The possible hyper-and-hypokalaemic effects of salbutamol with the concomitant potential for pro-arrhythmia were assessed in the baboon (*Papio ursinus*).

3 Male and female baboons were anaesthetized with ketamine (15 mg kg⁻¹) and maintained with 6% pentobarbitone as spontaneously breathing animals. Six baboons in each group received either 10, 100 or 500 µg kg⁻¹ salbutamol i.v. Lead II of the ECG and femoral i.a. blood pressure were recorded continuously for 10 min. Arterial blood samples were collected at 0 min and then after 3 and 10 min of salbutamol administration.

4 All the animals developed sinus tachycardia (above 200 beats min⁻¹) within 30 s of each dose of salbutamol administration and the high heart rate persisted throughout the experiment. All the animals were hyperkalaemic after 3 min and hypokalaemic after 10 min for each dose of salbutamol. Left ventricular conduction defects were seen in 3 animals during the hyperkalaemic phase. No arrhythmia was seen during the hypokalaemic phase.

5 Salbutamol has a transient hyperkalaemic and a more prolonged hypokalaemic effect in the baboon. The hypokalaemia could not be associated with arrhythmia although conduction defects were associated with the hyperkalaemia.

6 Since salbutamol is used as a bronchodilator in asthmatic patients and to treat acute hyperkalaemia, it is suggested that caution should be exercised when using salbutamol in high doses to treat acute asthma especially during the first few minutes of administration. The finding of hyperkalaemia with salbutamol questions its use in the treatment of hyperkalaemia.

Keywords: Salbutamol; hyperkalaemia; hypokalaemia; arrhythmia; asthma

Introduction

In 1971 the biphasic response of plasma potassium after stimulation with adrenaline was reported. The initial potassium increase occurred within 1 min of a continuous adrenaline infusion and kept on increasing for 6 min followed by a decrease to below control values within 14 min (Todd & Vick, 1971). The first response was shown to be a combined α -adrenoceptor and β -adrenoceptor effect and the second response a β -adrenoceptor effect. The hypokalaemic effect of the β_2 -adrenoceptor agonist, salbutamol, was reported in normal volunteers within 30, 60 and 120 min of administration respectively (Smith *et al.*, 1984; Whyte *et al.*, 1987; 1988), within 15 min in cats (Clapham & Hamilton, 1992), and within 15 min in asthmatics (Bremner *et al.*, 1992). However, no hypokalaemia was reported in asthmatics on long-term treatment (12 months) (Hock *et al.*, 1992). The incidence of hypokalaemia occurred irrespective of intravenous infusion, aerosol or nebulized delivery.

From the literature it was suggested that hypokalaemia might be a predisposing factor for tachyarrhythmia (Levy & Wiseman, 1991) but especially in asthmatics if they use β_2 -agonists (Leitch *et al.*, 1976). β -Adrenoceptor stimulant drugs are essential for the management of asthma. Yet, if used injudiciously it has been suggested they might be cardiotoxic and lead to death (Morild & Giertzen, 1989; Chazan *et al.*, 1993). This is true for both β_2 -selective and non-selective agents (Strunk *et al.*, 1985). However, it is still controversial whether arrhythmias are due to the reported hypokalaemia. In some studies where hypokalaemia was reported no arrhyth-

mias were seen (Smith *et al.*, 1984; Whyte *et al.*, 1987; Bremner *et al.*, 1992; Clapham & Hamilton, 1992). In another study hypokalaemia was reported after 2 h and only one subject had premature supraventricular beats (Whyte *et al.*, 1988). In contrast ventricular ectopic beats were reported in asthmatics who were on long-term (12 months) salbutamol therapy but no hypokalaemia was seen (Hoyer *et al.*, 1992). In none of the above mentioned reports was reference made to a possible dose-dependency of the effects of salbutamol although this has been described by others (Smith *et al.*, 1984; Crane *et al.*, 1989). No hyperkalaemic effects were reported.

It was therefore decided to investigate possible dose-related hyper-and-hypokalaemic effects of salbutamol and its arrhythmogenic potential in the baboon (*Papio ursinus*) as a primate model. The doses were chosen to correspond to that of a therapeutic bronchodilator dose (Hochhaus & Möllmann, 1992) and to a cardiotoxic dose (Chazan *et al.*, 1993).

Method

Male and female baboons with a body weight of between 10 and 15 kg were anaesthetized with ketamine (15 mg kg⁻¹, i.m.) and maintained with 6% pentobarbitone as spontaneously breathing animals. Lead II of the ECG and femoral intra-arterial blood pressure were recorded continuously for 10 min after an i.v. bolus injection of salbutamol. The recordings were made with a Hewlett Packard (HP) 7758 recording system and stored on magnetic tape (HP 3968 instrumentation recorder) for later analyses.

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Blood pressure was measured with an HP Quarts pressure transducer. Data were subsequently analysed with an HP computer. Three groups of baboons were used, each group consisting of six animals. The baboons in each group received either 10, 100 or 500 $\mu\text{g kg}^{-1}$ salbutamol (SA Drug-gists) respectively. Baseline values of the parameters measured before each dose served as control values. A placebo group of six baboons each received 2 ml saline which contained 100 μl 70% ethanol. The latter was also used as a solvent for salbutamol. Arterial serum electrolytes and blood gases were determined before drug administration, and 3 and 10 min thereafter. A CX 5 Analyzer (Beckman) and an ABL Blood Gas Analyzer (Radiometer) were used respectively for analyses.

The data were analysed and tested for significance by use of an ANOVA and performing Duncan's test. A *P* value of less than 0.05 was accepted as significant.

The protocol was approved by the Research and Animal Ethics Committee of the Medical University of Southern Africa. An independent veterinarian monitored the proceedings on random occasions.

Table 1 The dose-response of intravenously administered salbutamol on arterial serum potassium and arterial P_{O_2} in the baboon

	K^+ (mmol l ⁻¹)	P_{O_2} (kPa)
Placebo	3.35 $\pm$ 0.45	9.26 $\pm$ 0.41
Salbutamol 10 $\mu\text{g kg}^{-1}$		
Control	3.58 $\pm$ 0.33	10.38 $\pm$ 1.01
3 min	4.23 $\pm$ 0.57*	11.93 $\pm$ 1.37*
10 min	3.42 $\pm$ 0.21†	11.17 $\pm$ 0.99*
Salbutamol 100 $\mu\text{g kg}^{-1}$		
Control	3.65 $\pm$ 0.90	9.85 $\pm$ 1.23
3 min	4.13 $\pm$ 0.38*	11.63 $\pm$ 1.64*
10 min	3.25 $\pm$ 0.31†	11.71 $\pm$ 1.71*
Salbutamol 500 $\mu\text{g kg}^{-1}$		
Control	3.17 $\pm$ 0.41	9.74 $\pm$ 1.58
3 min	3.75 $\pm$ 0.62*	12.59 $\pm$ 1.78*
10 min	2.02 $\pm$ 0.29†	11.28 $\pm$ 1.30*

Values are given as means $\pm$ s.d. for *n* = 6.

*Significantly different from control values: *P* < 0.05.

†Significantly different from the 3 min interval: *P* < 0.05 (ANOVA, Duncan's test).

Results

Arterial serum potassium and electrolytes

The arterial serum potassium levels increased significantly (*P* < 0.05) at the 3 min interval for each of the salbutamol doses and returned to below base-line values at the 10 min interval. The largest increase was 0.65 mmol l⁻¹ (after administration of 10 $\mu\text{g kg}^{-1}$ salbutamol) and the largest decrease was 1.15 mmol l⁻¹ (after administration of 500 $\mu\text{g kg}^{-1}$ salbutamol). The potassium increase was not dose-related while the decrease was dose-related (Table 1). Serum Ca^{2+} , Mg^{2+} and Na^+ were unchanged.

T wave amplitude

The T wave amplitude started to increase within 10 s of salbutamol administration and reached a maximum after 30 s for each dose. The duration of the effect was dose-related. The magnitude of the effect after 500 $\mu\text{g kg}^{-1}$ salbutamol was almost the same at 30 s and 10 min, while the magnitude of the effect after 10 $\mu\text{g kg}^{-1}$ salbutamol was back to base-line values after 10 min (Table 2).

Heart rate and arrhythmia

The initial sinus tachycardia after each dose of salbutamol remained relatively high throughout the experiment (10 min). A maximum of 202 $\pm$ 7, 206 $\pm$ 10, and 221 $\pm$ 15 beats min⁻¹ was reached after 10, 100 and 500 $\mu\text{g kg}^{-1}$ salbutamol respectively. Except for the 10 $\mu\text{g kg}^{-1}$ dose for which the maximum effect was reached after 30 s, the maxima for the 100 and 500 μg doses were reached after 3 min (Table 2). Despite the tachycardia, only two baboons developed isolated aberrant ventricular conduction defects after 100 $\mu\text{g kg}^{-1}$ salbutamol at the 1 min (3 complexes) and 2 min (1 complex) intervals respectively and one baboon developed 46 successive such complexes after 500 $\mu\text{g kg}^{-1}$ salbutamol at the 3 min interval. All the animals were hyperkalaemic at that stage. However, for each dose of salbutamol, all the animals were hypokalaemic at the 10 min interval but no arrhythmia was seen.

Table 2 The dose-response of intravenously administered salbutamol on heart rate, blood pressure and T wave amplitude in the baboon

	Heart rate (beats min ⁻¹)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	T wave (mV)
Placebo	141 $\pm$ 6	175 $\pm$ 12	114 $\pm$ 7	0.077 $\pm$ 0.043
Salbutamol 10 $\mu\text{g kg}^{-1}$				
Control	129 $\pm$ 8	172 $\pm$ 14	102 $\pm$ 11	0.076 $\pm$ 0.052
30 s	202 $\pm$ 7*	164 $\pm$ 13*	79 $\pm$ 18*	0.196 $\pm$ 0.089*
3 min	183 $\pm$ 12*	184 $\pm$ 9	107 $\pm$ 8	0.093 $\pm$ 0.074*
10 min	160 $\pm$ 17*	189 $\pm$ 11	107 $\pm$ 8	0.057 $\pm$ 0.083
Salbutamol 100 $\mu\text{g kg}^{-1}$				
Control	128 $\pm$ 13	158 $\pm$ 15	91 $\pm$ 16	0.050 $\pm$ 0.095
30 s	203 $\pm$ 13*	119 $\pm$ 26*	46 $\pm$ 14*	0.257 $\pm$ 0.127
3 min	206 $\pm$ 10*	158 $\pm$ 32	77 $\pm$ 24	0.250 $\pm$ 0.121*
10 min	192 $\pm$ 11*	172 $\pm$ 24	92 $\pm$ 13	0.156 $\pm$ 0.131
Salbutamol 500 $\mu\text{g kg}^{-1}$				
Control	146 $\pm$ 4	179 $\pm$ 14	107 $\pm$ 13	0.090 $\pm$ 0.023
30 s	218 $\pm$ 13*	114 $\pm$ 30	46 $\pm$ 17*	0.245 $\pm$ 0.082
3 min	221 $\pm$ 15*	149 $\pm$ 30	74 $\pm$ 25*	0.253 $\pm$ 0.039*
10 min	211 $\pm$ 13*	177 $\pm$ 10	87 $\pm$ 14*	0.240 $\pm$ 0.132

Values are given as means $\pm$ s.d. for *n* = 6.

*Significantly different from control values: *P* < 0.05 (ANOVA, Duncan's test).

Blood pressure

In all cases blood pressure decreased rapidly and dose-dependently within the first 10 s and reached a maximum after 30 s after which it returned to base-line values. The difference between 100 and 500 $\mu\text{g kg}^{-1}$ salbutamol on the maximum decrease in diastolic pressure was not significant, indicating that a maximal decrease was reached after 100 $\mu\text{g kg}^{-1}$ salbutamol (Table 2). The diastolic pressure changed more in magnitude than the systolic pressure and was dose-related (Table 2).

Arterial blood gases

The PO_2 increased significantly for each of the doses and was only slightly lower at the 10 min interval compared to the 3 min interval. No other blood gas parameters showed any change (Table 1).

The data were compared to control values. The placebo had no effect.

Discussion

Arterial serum potassium and arrhythmia

It was clearly shown that an i.v. bolus injection of salbutamol had a biphasic effect on arterial serum potassium: first a transient hyperkalaemic effect followed by a more prolonged hypokalaemic effect. The hyperkalaemic effect was not dose-dependent since no significant differences could be found between the different doses. However, the hypokalaemic effect appeared to be dose-dependent. Although no difference could be found in effect between 10 and 100 $\mu\text{g kg}^{-1}$ salbutamol, both differed significantly from the 500 $\mu\text{g kg}^{-1}$ dose. A similar biphasic response has been reported for adrenaline (Todd & Vick, 1971; Vick *et al.*, 1972) but only a hypokalaemic effect has been reported for salbutamol (Smith *et al.*, 1984; Whyte *et al.*, 1987; 1988) perhaps because the blood samples were taken after the occurrence of the earlier hyperkalaemia. The present results show that the hyperkalaemic effect occurs within 3 min after salbutamol administration. It occurred within 1 min after adrenaline as reported by others (Todd & Vick, 1971; Vick *et al.*, 1972).

Although we did not measure potassium levels within 1 min the possibility exists that the hyperkalaemic effect of salbutamol might also occur within a minute as reported for adrenaline. To support this possibility the results show that the T wave amplitude began to increase within 30 s after salbutamol administration (Table 2) (Mudge & Weiner, 1990).

Our study shows that salbutamol causes hypokalaemia after 10 min in the baboon, while other studies showed the hypokalaemic effect only after 15 min (Bremner *et al.*, 1992; Clapham & Hamilton, 1992) and longer (Whyte *et al.*, 1987; 1988). The hypokalaemic effect could conceivably be mediated by the stimulation of β -adrenoceptors in the liver and skeletal muscle through the activation of $\text{Na}^+\text{-K}^+$ -

ATPase, which increased the uptake of potassium (Vick *et al.*, 1972; Clapham & Hamilton, 1992) and more specifically by β_2 -receptors (Brown *et al.*, 1983).

Although it has been shown that sympathomimetic hyperkalaemia is mediated through α -adrenoceptors (Williams *et al.*, 1984), a hyperkalaemic effect after salbutamol administration was shown to be dependent on β_2 -adrenoceptor stimulation, but no reference was made to the origin of the potassium (Reverte *et al.*, 1993). This dual mechanism remains unexplained. In addition it is speculated that the increase in potassium might be the result of potassium release from skeletal muscle after β_2 -adrenoceptor stimulation similar to that seen during exercise (Hutchinson *et al.*, 1992).

The suggested use of salbutamol to treat hyperkalaemia during dialysis (Leanza *et al.*, 1992) or renal failure (Mocan *et al.*, 1993) could therefore be extremely dangerous if induction of hyperkalaemia occurs in man also, since this study suggests that salbutamol, although only transiently, causes hyperkalaemia.

Furthermore it was suggested that hypokalaemia might be a predisposing factor for tachyarrhythmia (Steinfath *et al.*, 1992) but our study showed only an aberrant ventricular conduction defect during the hyperkalaemic phase and tachycardia during all the phases. The aberrant ventricular conduction could be secondary to the hyperkalaemia but the possibility that the precipitous decrease in afterload could lead to myocardial ischaemia, and in turn to arrhythmia cannot be excluded. The tachycardia is probably a combined result of reflex-mediation due to the drop in blood pressure and a direct β_2 -adrenoceptor stimulation (Steinfath *et al.*, 1992).

T wave amplitude

Since the T wave amplitude followed more or less the same pattern as the changes in the potassium concentrations, with an initial increase followed by a decrease in amplitude, it is suggested that the T wave changes reflect the changes in the serum potassium concentration.

Blood pressure and blood gases

The fall in diastolic and systolic pressure recovered within 2 min due in part to a reflex-mediated tachycardia. However, after 10 min the blood pressure was back to base-line values while the tachycardia persisted. This latter response could be a direct β_2 -mediated chronotropy (Steinfath *et al.*, 1992) together with a sustained reflex response.

In conclusion, salbutamol has a transient hyperkalaemic effect as well as a more prolonged hypokalaemic effect, both of which could be responsible for cardiotoxic effects. Conduction defects might occur during the transient hyperkalaemia. It would therefore be extremely important to monitor an asthmatic patient especially during the first few minutes of emergency treatment with β_2 -agonists. Furthermore, caution should be taken when treating acute hyperkalaemia with β_2 -agonists.

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