DEVELOPMENT OF TOLERANCE TO ORAL SALBUTAMOL IN THE THIRD TRIMESTER OF PREGNANCY: A STUDY OF CIRCULATORY AND METABOLIC EFFECTS

JAN WAGER¹, BERTIL B. FREDHOLM², NILS-OLOV LUNELL¹
& BENGT PERSSON³

¹Department of Obstetrics and Gynaecology, Karolinska Institutet, Huddinge Hospital, 141 86 Huddinge, Sweden,

²Department of Pharmacology, Karolinska Institutet, 104 01 Stockholm, Sweden and

³Department of Paediatrics, Karolinska Institutet, St Görans Hospital, 112 81 Stockholm, Sweden

1 The purpose of the study was to investigate whether a development of tolerance does occur or not to salbutamol-induced cardiovascular and metabolic effects after oral long term treatment in pregnancy.

2 Twenty-three women in late pregnancy were given an oral dose of 4 mg salbutamol in the morning after an overnight fast. Ten of the women had not been exposed to β -adrenoceptor agonists earlier in their pregnancy (group A). Thirteen of the women had been treated with oral salbutamol in a dose of 4 mg four times a day for 12 to 33 days preceding the study (group B).

3 Blood samples were collected every 30 min for 120 min and analyzed for cyclic AMP, insulin, C-peptide, glucose, lactate, glycerol, non-esterified fatty acids (NEFA) and 3-hydroxybutyrate (3-HB). Heart rate and blood pressure were recorded simultaneously.

4 In group A there was significant increase in plasma cyclic AMP and increased glycogenolysis, lipolysis and insulin secretion. In this group there were also significant cardiovascular effects, that is, an increase of heart rate and decrease of diastolic blood pressure.

5 In group B the effects of salbutamol were significantly less pronounced, indicating a development of tolerance.

6 We conclude that the metabolic side-effects are not sufficient reason to withhold β -adrenoceptor agonists to healthy pregnant women with threatened premature labour, since tolerance rapidly develops to these actions.

Introduction

β_2 -selective adrenoceptor agonists, such as salbutamol, terbutaline, ritodrine and fenoterol, are widely used in obstetric practice to stop premature contractions. The administration, in most clinics, is generally started by an intravenous infusion of the drug for some 24 h, followed by oral medication for several weeks (Ingemarsson, 1976; Lauersen *et al.*, 1977; Richter, 1977; Ryden, 1977; Wallace *et al.*, 1978). These selective β_2 -adrenoceptor agonists have also been administered orally as prophylactic treatment in pregnant women with a history indicating high risk of premature birth (Walters & Wood, 1977) as well as in twin pregnancies (Marivate, Villiers & Fairbrother, 1977; O'Connor, Murphy & Dalrymple, 1979). In some clinics they have also been tried as growth promoting drugs in pregnancies with intra-uterine growth retardation of the foetus (Janisch, Leodolter & Reinold, 1974).

It is, however, becoming increasingly clear that β_2 -adrenoceptor agonists have pronounced circulatory and metabolic side-effects following intravenous

administration in late pregnancy (Thomas, Dove & Alberti, 1977; Kauppila *et al.*, 1978; Fredholm *et al.*, 1978; Spellacy *et al.*, 1978; Osler, 1979). Thus, it has been demonstrated that these drugs increase glycogenolysis and lipolysis. The most pronounced maternal circulatory effects were tachycardia and lowering of diastolic blood pressure.

We have also previously shown that a single oral dose of 4 mg salbutamol causes small but significant circulatory and metabolic effects (Lunell *et al.*, 1978). However, there was a large variability in response to salbutamol between the patients in that study. Since some of those patients were diabetics and many of them had previously been exposed to salbutamol we speculated that responses to β -adrenoceptor agonists may differ between diabetics and non-diabetics and that tolerance may develop towards these drugs. We have recently found that there are significantly more pronounced effects of salbutamol in juvenile diabetics than in non-diabetics (Wager *et al.*, unpublished observations). The

purpose of the present study was to investigate whether long term treatment with salbutamol in the last trimester of pregnancy would cause tolerance to β -receptor stimulation or not with regard to circulatory and metabolic side-effects.

Methods

Patients

Twenty-three women in the third trimester of pregnancy participated voluntarily in the study, which was approved by the local Ethical Committee. In all the women salbutamol (Ventolin, Glaxo Operations UK Ltd, Ware) was given to inhibit premature contractions. Ten of the women had not received salbutamol treatment earlier in their pregnancy (group A). Thirteen of the women had received salbutamol treatment in an oral dose of 4 mg four times a day for 12 to 33 days preceding the study (group B). The last salbutamol tablet was given 12 to 16 h before the study. There were no significant differences between the two groups with respect to age, pre-pregnancy weight or gestational age at testing and delivery. With the exception of the complicating premature contractions and pregnancies included in the study at the time of admittance been normal, and the mothers were all considered healthy.

Procedure

All 23 women were studied in the morning after an overnight fast. Blood samples were drawn from an indwelling catheter placed in a brachial vein and used for the measurement of cyclic adenosine mono-

phosphate (cyclic AMP), insulin, C-peptide, glucose, lactate, glycerol, non-esterified fatty acids (NEFA) and 3-hydroxybutyrate (3-HB). When blood samples at -20 and 0 min had been collected the patient received an oral dose of 4 mg salbutamol. Blood samples were then drawn at 30, 60, 90 and 120 min. Maternal blood pressure and pulse rate were registered simultaneously. NEFA was analyzed in only seven of the thirteen women in the salbutamol treated group (group B). For lactic acid determination samples were drawn directly into ice-cooled 0.6 M perchloric acid. Cyclic AMP was determined in blood samples drawn into tubes containing EDTA. Blood samples for the other parameters were drawn into heparin-containing tubes. After centrifugation the plasma or the protein free supernatant was stored frozen until assay.

Chemical determinations

All determinations were done in duplicate. Lactic acid was measured according to Cramp (1968), glucose with a glucose-oxidase method (Glox®, AB Kabi, Stockholm, Sweden), glycerol fluorimetrically (Laurell & Tibbling, 1966), NEFA colorimetrically (Laurell & Tibbling, 1967), 3-HB fluorimetrically (Persson, 1969), insulin and C-peptide by radioimmunoassay (Heding, 1972, 1975) with reagents obtained from Novo Research Institute (Copenhagen, Denmark). Cyclic AMP was determined according to Brown, Ekins & Albano (1972) as described elsewhere (Fredholm *et al.*, 1978).

Calculations and statistical methods

Basal values were obtained as the mean of the values at -20 and 0 min. The response of salbutamol of each

Table 1 Basal values for heart rate, blood pressure, plasma levels of cyclic AMP, insulin, C-peptide, carbohydrate and lipid metabolites in group A and B.

Parameter	Group A	Group B	Significance
Heart rate (beats/min)	81 $\pm$ 2	87 $\pm$ 3	—
Diastolic BP (mm Hg)	69 $\pm$ 3	62 $\pm$ 4	—
Systolic BP (mm Hg)	104 $\pm$ 2	95 $\pm$ 3	$P < 0.05$
Cyclic AMP (nmol/l)	14.5 $\pm$ 2.5	18.3 $\pm$ 1.7	—
Insulin (nmol/l)	0.18 $\pm$ 0.04	0.11 $\pm$ 0.01	$P < 0.05$
C-peptide (nmol/l)	0.88 $\pm$ 0.14	0.62 $\pm$ 0.04	—
Glucose (mmol/l)	4.27 $\pm$ 0.14	4.09 $\pm$ 0.11	—
Lactate (mmol/l)	1.11 $\pm$ 0.11	1.08 $\pm$ 0.10	—
Glycerol (mmol/l)	0.07 $\pm$ 0.01	0.06 $\pm$ 0.01	—
NEFA (mmol/l)	0.56 $\pm$ 0.05	0.40 $\pm$ 0.04	$P < 0.05$
3-HB (mmol/l)	0.13 $\pm$ 0.02	0.09 $\pm$ 0.02	—

Basal values were obtained as the mean of the values at -20 and 0 min before salbutamol administration. Group A consists of ten women with no prior exposure to salbutamol and group B of thirteen women that had been treated with the drug for 12–33 days preceding the study. Values are given as mean $\pm$ s.e. mean.

cardiovascular and metabolic parameter was calculated as the difference between the basal value and the values at 30, 60, 90 and 120 min for every patient. The responses were tested statistically by the Wilcoxon test for paired variates. Differences in magnitude of the responses between groups were tested by the Mann-Whitney U-test for unpaired variates (Snedecor & Cochran, 1976). Unless otherwise stated the figures given are means and standard errors of the mean (s.e. mean), computed with conventional methods. In the figures significant changes are marked with * for $P < 0.05$ and ** $P < 0.01$.

Results

Basal values

Basal values for the circulatory and metabolic parameters in group A and B are shown in Table 1. The basal values of systolic blood pressure, insulin and NEFA were significantly lower in the salbutamol treated group ($P < 0.05$), otherwise there were no significant differences.

Heart rate and blood pressure (Figure 1)

In the women with no prior exposure to salbutamol (group A) salbutamol caused significant increase of heart rate and systolic blood pressure. However, in the women with prior exposure (group B) salbutamol had no significant effect on these parameters. The difference in response between the two groups were significant for heart rate at 30 and 60 min ($P < 0.05$) and at 90 and 120 min ($P < 0.01$). Diastolic blood pressure decreased significantly after salbutamol in both groups, but this decrease was significantly more pronounced in group A at 60 min ($P < 0.01$) and at 90 min ($P < 0.05$). Since the diastolic blood pressure under basal conditions tended to be lower in group B than in group A (Table 1) the absolute level of diastolic blood pressure at 90 min after salbutamol was identical in the two groups, despite the difference in the magnitude of the fall.

Cyclic AMP (Figure 2)

Salbutamol caused a significant increase in cyclic AMP in group A, but no changes in group B. The difference in response between the two groups was significant at 60 min ($P < 0.01$), at 90 and 120 min ($P < 0.05$).

Insulin and C-peptide (Figure 2)

Both insulin and C-peptide increased significantly after salbutamol in group A. In group B insulin was unchanged but C-peptide decreased significantly at

Figure 1 Changes in heart rate, diastolic and systolic blood pressure after 4 mg oral salbutamol in a group of ten women who had not received salbutamol earlier in their pregnancy, group A (●—●) and in another group of thirteen women who had been treated with salbutamol for 12 to 33 days preceding the study, group B (▲—▲). Values are mean $\pm$ s.e. mean. Asterisks denote significance of changes from basal value following salbutamol within group A and B respectively. * = $P < 0.05$ and ** = $P < 0.01$.

Figure 2 Changes in plasma cyclic AMP, insulin and C-peptide after 4 mg oral salbutamol in a group of ten women who had not received salbutamol earlier in their pregnancy, group A (●—●) and in another group of thirteen women who had been treated with salbutamol for 12 to 33 days preceding the study, group B (▲—▲). Values are mean $\pm$ s.e. mean. Asterisks denote significance of changes from basal value following salbutamol within group A and B respectively. * = $P < 0.05$ and ** = $P < 0.01$.

120 min. The differences in responses between the two groups were significant for both insulin and C-peptide at 30, 60, 90 and 120 min ($P < 0.05$). The level in group B of insulin and C-peptide at 90 min after salbutamol was less than half that seen in the drug naive group, group A. The molar ratio between insulin and C-peptide was similar in both groups which indicates that salbutamol stimulates insulin secretion rather than disturbs the metabolism of insulin.

Glucose (Figure 3)

The plasma glucose level also rose significantly after salbutamol in group A, but was unaffected in group B. The difference in response between the two groups was significant at 60, 90 and 120 min ($P < 0.01$).

Lactate and glycerol

Neither lactate nor glycerol were significantly altered by salbutamol in the two groups. However, the levels tended to be higher in group A than in group B and in fact the absolute level of glycerol after 90 min was significantly higher in group A than in group B ($P < 0.05$).

NEFA and 3-HB (Figure 3)

There were significant increases in NEFA and 3-HB in both group A and B. It was a tendency towards more pronounced responses of both parameters in group A but these differences were not significant.

Discussion

The major finding of the present study is that for several parameters measured the responses to salbutamol were much less pronounced in the group which had been treated with salbutamol, indicating development of tolerance. The time interval between onset of the salbutamol treatment and delivery was the same in both groups. Therefore, it is not likely that the two groups of women were different in their innate response to salbutamol.

Many β -adrenergic receptor effects are mediated by the formation of cyclic AMP (Robinson, Butcher & Sutherland, 1971). There was no change in plasma cyclic AMP after salbutamol in the treated group which is consistent with reports showing a diminished cyclic AMP generation in asthmatics after β -adrenoceptor agonist therapy (Conolly & Greenacre, 1976; Morris *et al.*, 1977). The mechanism for the development of resistance of β -adrenoceptors to β -adrenergic receptor stimulants is unknown. However, a reversible uncoupling of β -adrenoceptors and the enzyme adenylate cyclase (Harden, Su & Perkins,

Figure 3 Changes in plasma glucose, NEFA and 3-HB after 4 mg oral salbutamol in a group of ten women who had not received salbutamol earlier in their pregnancy, group A (●—●) and in another group of thirteen women who had been treated with salbutamol for 12 to 33 days preceding the study, group B (▲—▲). Values are mean $\pm$ s.e. mean. Asterisks denote significance of changes from basal value following salbutamol within group A and B respectively. * = $P < 0.05$ and ** = $P < 0.01$.

1979) and/or a diminished number of β -adrenoceptors after adrenergic therapy (Wolfe *et al.*, 1977) may be involved.

The positive chronotropic effect of β_2 -selective adrenoceptor stimulants appears to be partly a result of a direct stimulation of the β_1 -adrenoceptors of the heart but perhaps mainly a consequence of reflex activation secondary to the decreased resistance of the peripheral blood vessels following stimulation of their β_2 -adrenoceptors. Thus, the present finding that there was a significantly smaller decrease of diastolic blood pressure in the salbutamol treated group could explain the lack of response of heart rate to salbutamol in that group. The question is if the decreased fall in diastolic blood pressure in the salbutamol treated group is due to development of resistance in the peripheral blood vessels to β_2 -adrenoceptor stimulants. The results of Larsson, Svedmyr & Thiringer (1977) that six out of eight asthmatic patients did not develop tolerance to the blood pressure effect of terbutaline argue against this possibility. Even our own finding of a decreased salbutamol effect does not constitute definite evidence for the development of tolerance since the basal level of the diastolic blood pressure was lower in the group of patients previously given salbutamol. Moreover, the absolute levels of diastolic blood pressure at 90 min after salbutamol were similar in the two groups. Irrespective of whether a true tolerance at the receptor level does develop or not the important fact remains that the absolute level of drug-induced fall in diastolic blood pressure may be decreased following salbutamol treatment. This may be the reason for the clinically important tolerance to the positive chronotropic effect of salbutamol.

The β -adrenoceptors mediating lipolysis in adipose tissue are mainly of the β_1 -type (Lands, Luduena & Buzzo, 1967; Frisk-Holmberg & Östman, 1977). It is also known that noradrenaline released from nerve endings is the major lipolytic stimulus (Fredholm, 1970). It is possible that at least part of the lipolytic stimulation caused by salbutamol is due to enhanced sympathetic tone. Therefore, some of the attenuated salbutamol effect on glycerol and NEFA after prolonged salbutamol treatment could be due to diminished sympathetic activation. This would then be analogous to the decreased chronotropic response. However, it is possible that there is also an impairment in the β -adrenoceptor function in adipose tissue.

Salbutamol caused a marked increase of insulin secretion in the non-treated women. It is not known whether the effect of salbutamol on insulin secretion is a direct action of the drug on the pancreatic beta-cell as described especially in animal experiments (Kaneto, Miki & Kosaka, 1975) or if it is solely secondary to the salbutamol induced rise in plasma glucose levels. The fact that the rise in insulin

secretion was large despite the relatively moderate rise in plasma glucose could indicate that a direct effect of the β -adrenoceptor agonist does play a role. Hence, the finding that prior salbutamol exposure decreased the rise in insulin secretion may be taken as an argument for tolerance at the level of the β_2 -adrenoceptors in pancreas. The rise in plasma glucose observed following salbutamol treatment in drug naive subjects (group A) was completely eliminated after prolonged salbutamol treatment (group B). Since glucose tolerance is unimpaired following previous salbutamol treatment (Wager *et al.*, 1981) the lack of glucose increase in group B indicates tolerance to the glycogenolytic effect of the drug in the liver.

Thus, the present results have shown that tolerance does develop for certain actions of salbutamol. Most clearly this is shown for cyclic AMP and glucose. Other effects, notably the cardiovascular ones, may or may not show tolerance at the receptor level. The important question now rises: are all effects equally susceptible to the development of tolerance?

There may be a difference in the development of tolerance between β -adrenoceptors of the uterus, bronchi and peripheral blood vessels causing relaxation of the smooth muscle cells and the β -adrenoceptors of other tissues causing metabolic changes. Such differential development of tolerance to prolonged treatment with β_2 -adrenoceptor agonists could be due to tissue differences as regards the number of spare receptors in various tissues. Prolonged treatment with stimulating drugs leads to a loss of receptors. Such a loss in the number of receptors manifests itself as a shift to the right of the dose-response curve (Williams & Lefkowitz, 1978). However, this will be evident only if the number of spare receptors is small. On the other hand, if the

number of spare receptors is large even a major loss of receptors will have minor consequences. There are considerable tissue differences in the number of spare receptors (Nahorski, 1978). Thus, it seems of interest to find out whether the tissues mediating metabolic effects have a small number of spare receptors while the smooth muscle cells of bronchi and uterus are richly endowed with spare receptors.

The clinical study by Larsson *et al.* (1977) indicates that there might be a difference in the development of tolerance to β_2 -adrenoceptor agonists between β_2 -adrenoceptors in different tissues. They showed that there was no sign of resistance of the β_2 -adrenoceptors of the bronchi in asthmatics during a 1 year period of oral treatment with terbutaline, but within 1 month resistance developed to the β_2 -tremorogenic effect of the drug. Unfortunately, nothing is known about the development of resistance to β -adrenergic receptor stimulants of the myometrium due to considerable methodological and ethical problems in evaluating the human uterine activity response to β -adrenoceptor agonists during pregnancy. However, our clinical impression is that no significant tolerance develops in the utero-relaxing effect of salbutamol during treatment with that drug. Even if this would be the case, our studies suggest that the metabolic side-effects, which theoretically might be of considerable concern to obstetric practice (Fredholm *et al.*, 1978) are not sufficient reason to withhold β_2 -adrenoceptor agonists to pregnant women, since tolerance rapidly develops to these actions.

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