Fenoterol increases erythropoietin concentrations during tocolysis

C. H. Gleiter,[1] K. H. Schreeb,[1] S. Goldbach,[1] S. Herzog,[2] T. Cunze[2] & W. Kuhn[2]

[1]*Abteilung Klinische Pharmakologie and* [2]*Klinik für Gynäkologie und Geburtshilfe, Georg-August-Universität, Göttingen, Germany*

Aims The present study was carried out to assess the effect of the selective β_2-adrenoceptor agonists on erythropoietin (EPO) production.

Methods Routine tocolysis with fenoterol (using the regular rate of 2 μg min^{-1}) was used as a clinically easily accessible model.

Results EPO concentrations had doubled 24 h after the start of tocolysis ($P<0.001$). This increase lasted over the entire observation period of 48 h. Potassium concentrations fell significantly during the first hours of fenoterol infusion. There was no increase of human placenta lactogen during the period of EPO increase.

Conclusions The data confirm our earlier results that fenoterol increases EPO concentrations following haemorrhage. In this model it was not necessary to stimulate EPO production prior to pharmacological treatment.

Keywords: erythropoietin, fenoterol, tocolysis, pregnancy, metoprolol, human placenta lactogen

Introduction

Our earlier experiments have lead to the hypothesis that adrenergic transmission may play a role in the control of erythropoietin (EPO) production [1]. In an experiment which used phlebotomy in healthy volunteers as a controlled physiological stimulation paradigm, we were able to show that the selective β_2-adrenoceptor agonist fenoterol increased EPO production significantly by 40% [2].

Based on these data the present trial used routine tocolytic treatment with the β_2-adrenoceptor agonist fenoterol as an easily accessible model for the modulation of EPO production *without* prior stimulation as e.g. in our earlier investigations [1–3]. To our knowledge, the effect of β_2-adrenoceptor agonists on EPO production during tocolysis has never been systematically investigated. Ibrahim *et al.* [4]. showed that application of the selective β_2-adrenoceptor agonist ritodrine to murine dams *decreased* EPO concentrations in dams and their fetuses. From a single observation, Coates & Canning concluded that salbutamol would not increase EPO significantly during tocolysis [5].

Methods and patients

Patients

Eight Caucasian pregnant women were included in this protocol (Table 1). Prior to tocolysis they underwent a standard medical examination comprising physical status, blood chemistry (including transferrin and iron), urinalysis and ECG. Inclusion criteria were: Pregnant women, age 18–35 years, with a medical indication for standard tocolysis and otherwise healthy (e.g., no EPH gestosis or pregnancy-related hypertension). Exclusion criteria were smoking, the intake of medication other than vitamins, thyroid hormone, iodine, magnesium or iron supplementation, a stay at an altitude of 1000 m or higher (including air travel), blood loss of more than 100 ml within 4 weeks prior to the investigation. The trial was approved by the Ethics Committee of the University of Göttingen. Written informed consent was obtained from each participant.

Correspondence: Dr C. H. Gleiter, Abteilung Klinische Pharmakologie, Georg-August-Universität Göttingen, Robert-Koch-Strasse 40, D-37075 Göttingen, Germany.

Protocol

Women who were to receive tocolysis for medical reasons (Table 1) were subjected to the standard regimen using a continuous infusion of fenoterol (Partusisten®) at a rate of 2 μg min^{-1} in an open manner. Blood was collected for EPO, human placenta lactogen (HPL), potassium, iron, transferrin and haematological status before the start of fenoterol infusion. Blood samples for measurement of EPO, HPL and potassium were taken after the beginning of fenoterol administration (for collection times see Figure 1). When heart rate rose higher than 100 beats min^{-1} within 1 h after the fenoterol infusion was started, the selective β_1-adrenoceptor antagonist metoprolol (Beloc mite®) was administered at a dose of 50 mg twice daily (Table 1).

Analytical methods and statistics

Haemoglobin, haematocrit, electrolytes and other standard clinical chemistry parameters were measured in the Dept. of Clinical Chemistry, University of Göttingen. Human placenta lactogen was measured using a solid-phase ^{125}I-RIA (Coat-A-Count® HPL, Diagnostic Products Corporation, Los Angeles, CA, USA). EPO in plasma was analysed using a monoclonal enzyme-linked immunosorbent assay (Kat.-Nr. 500, medac GmBH, Hamburg, Germany). Values are expressed as mean $\pm$ s.e.mean. Primary parameters were analysed by ANOVA followed by a *t*-test with a correction

Table 1 Patient characteristics (PL = preterm labour; CI = cervix incompetence; PRM = preterm rupture of membrane).

Patient#	*Age (years)*	*Gestation week*	*Reason for tocolysis*	*Concomitant treatment*	*Metoprolol coadministration*
1	33	19	PL, CI	—	+
2	27	16	PL, CI	iron, magnesium	+
3	24	23	PL, CI	iron, magnesium, iodine	+
4	28	24	PL, PRM	magnesium	—
5	26	33	PL, CI	iron, magnesium, iodine	+
6	28	24	PL, CI	iron, magnesium, iodine	+
7	32	33	PL	iron, magnesium, iodine	+
8	26	34	PL, PRM	—	+

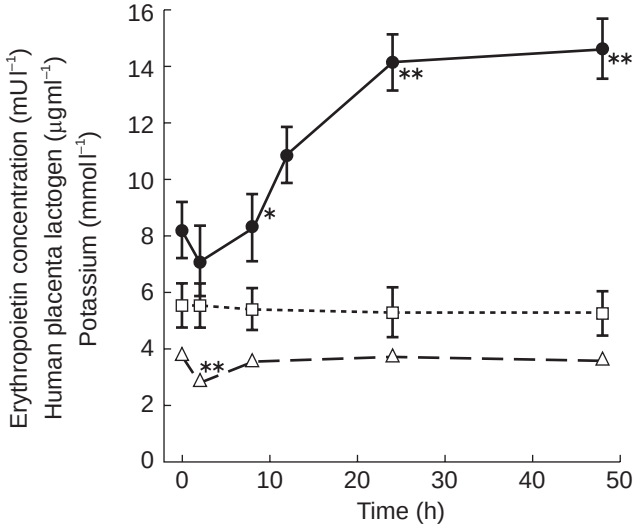

Figure 1 Time course of erythropoietin concentrations (●), human placenta lactogen (□) and potassium (△) in pregnant women under routine tocolysis with fenoterol at a rate of 2 μg min^{-1} (mean ± s.e.mean; $n = 8$; time point 0 h = before start of tocolysis; ⋆$P < 0.05$; ⋆⋆$P < 0.001$).

according to Bonferroni-Holm. $P < 0.05$ was considered statistically significant.

Results

Mean haemoglobin before inclusion in the study was 11.1 ± 0.2 g dl^{-1}, mean haematocrit 31.6 ± 0.6%. Clinical chemistry parameters including iron and transferrin concentrations were within the normal range in all participants. Potassium concentrations fell significantly during the first hours of fenoterol infusion (Figure 1). There was no change of HPL concentrations during the observation period (Figure 1). All HPL concentrations were in the normal, gestation-related range [6]. EPO baseline (0 h concentrations) and time course are given in Figure 1 Baseline values were within the normal range of the assay used. EPO concentrations doubled within 24 h after start of tocolysis and remained elevated during the entire observation period.

Discussion

Based on earlier results we hypothesized that adrenergic activity may lead to an increase of EPO concentrations in humans [1]. This hypothesis was further investigated using phlebotomy as a model of controlled, physiological stimulation of EPO production: We were able to show that the selective β_2-adrenoceptor agonist fenoterol (at a rate of 1.5 μg h^{-1} over 6 h) did significantly increase EPO concentrations [2]. The present investigation confirms these previous observations in healthy volunteers. It should be noted that the current experiment used routine tocolytic treatment with fenoterol as a model for the investigation of EPO production *without* prior stimulation. We observed a doubling of EPO concentrations under tocolysis. To our knowledge, this is the first report on a pharmacologically induced increase of EPO production in humans without preceeding stimulation by other means. It is interesting to note that coadministration of the selective $beta_1$-adrenoceptor antagonist metoprolol did not grossly influence or suppress the reponse of EPO to fenoterol. This is in agreement with the observation that the predominant β_1-adrenoceptor agonist dobutamine did not increase EPO production after phlebotomy [2].

As it has been described that EPO baseline levels rise during a regular course of pregnancy almost until to term [5, 7], pregnancy as such may represent a state of facilitated EPO production. Even though there were marked differences in gestation in our group of patients there were no clear differences in baseline EPO concentrations. Coates & Canning presented a single case in which higher EPO concentrations during tocolysis were measured over the entire course of pregnancy [5]. The EPO concentrations of that case were, however, within the range of normal pregnant women without tocolysis so that the authors concluded that there was no additional effect on EPO concentrations by salbutamol.

Our finding is in contrast to animal data by Ibrahim *et al.* [4]. These investigators showed that the selective β_2-adrenoceptor agonist ritodrine, given on the last day of gestation, 4 h before the fetuses were removed, had an EPO *lowering* effect in dams and their offspring. This effect may resemble the initial declining course of EPO values in our study. However, this can also be interpreted as an initial dilution effect by the infusion of fluid after the start of tocolysis.

The administration of fenoterol caused the expected transient decrease of potassium levels. It is, as discussed earlier [2], difficult to decide whether hypokalaemia can be considered as a mechanism for the increase of EPO levels. One argument against this explanation may be the sustained higher level of EPO in the present experiment when

potassium levels were normalised. Our earlier trial in healthy humans did not allow such an observation as fenoterol was administered only for 6 h [2]. Further, a change of renal haemodynamics may be a reason for this increase. However, in our earlier study fenoterol did not increase glomerular filtration rate (GFR). In contrast, dobutamine led to a higher GFR but no change of EPO concentrations [2].

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