The influence of tocolytic drugs on cardiac function, large arteries, and resistance vessels

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Short title: Cardiac and vascular effects of tocolytic drugs

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What this study adds

What is already known about the subject?

1. Mainly reports of ritodrine on the blood pressure and cardiovascular side effects are known;
2. Apart from blood pressure, no cardiovascular effects have been studied during atosiban-infusion;
3. Therefore, there is a need for in depth research on the effects of the two commonly used tocolytic drugs on the cardiovascular system to better understand their pharmacodynamic effects.

What this study adds:

Comparison of the effects of ritodrine and atosiban on macrocirculation (arterial stiffness and compliance), microcirculation (peripheral resistance) and cardiac function.

Abstract

Background: Beta-2 adrenoceptor agonistic drugs like ritodrine have been the reference tocolytic drugs but are associated with cardiovascular side-effects. Atosiban, a newer drug, is a competitive antagonist of oxytocin and has been claimed to have less cardiovascular side effects. Until now, there is mainly a subjective reporting of adverse reactions and little objective, cardiovascular data.

Aims: Evaluation of the acute effects of therapeutic doses of ritodrine and atosiban compared to placebo on cardiac function, large artery properties, blood pressure and resistance vessels.

Methods: A double-blind, randomized trial was carried out in twenty non-pregnant female volunteers. Hemodynamic measurements were done under standardized conditions during kinetic steady state. Cardiac output was measured with echocardiography, large artery properties with an echo-tracking device. The effect on the microcirculation was estimated using the total peripheral resistance index (TPRI).

Results: Atosiban did not differ from placebo. With ritodrine, cardiac function increased with 79% compared to placebo due to a rise in heart rate (91%). TPRI decreased with 48%. Ritodrine increased the distensibility of the common carotid artery with 62% and the compliance with 83%, independent from blood pressure. Compliance of the common femoral artery increased independently of pressure with 33% and the distensibility with 59%. Aortic pulse wave velocity was not influenced by either medication.

Conclusions: The present study shows potential beneficial vascular effects of ritodrine. which are counterbalanced by the cardiac effects. Atosiban has no clinically relevant cardiovascular effects and may be a good alternative for ritodrine in pregnant women at risk for cardiovascular complications.

List of Abbreviations (in order of appearance)

ICH: International Conference on Harmonisation

µg: microgram

min: minute

ml: milliliter

mmHg: millimeter Mercury

SBP: systolic blood pressure

DBP diastolic blood pressure

MAP: mean arterial pressure

HR: heart rate

CO: cardiac output

D: diameter

MHz: Mega Hertz

SV: stroke volume

CSA: cross-sectional area

Ao: aorta

FVI: flow velocity index

BSA: body surface area

CI: cardiac index

SI: stroke index

TPRI: total peripheral resistance index

PWV: pulse wave velocity

CCA: common carotid artery

CFA: common femoral artery

SSN: supra-sternal notch

CC: cross-sectional compliance

DC: distensibility coefficient

ΔA: systolic-diastolic change in arterial cross-section

ΔP: local change in pulse pressure

PP: pulse pressure

Δ_S: arterial diameter at end-systole

Δ_D: arterial diameter at end-diastole

A_D: arterial cross-section at end-diastole

PWF: pressure waveforms

DC_{ISO}: isobaric distensibility coefficient

CC_{ISO}: isobaric cross-sectional compliance

RAAS: Renin-Angiotensin-Aldosteron System

Introduction

Preterm labor is the most frequently reported cause of perinatal morbidity and mortality in the Western world.[1] Tocolytic medication can postpone delivery.[2]

Beta-2 adrenoceptor agonistic drugs have been the reference tocolytic drugs in most countries.[1;3] Their efficacy in prolonging pregnancy compared to placebo is proven although no benefit in neonatal morbidity or mortality has been demonstrated. Beta-mimetics are not highly selective and have many contraindications. Side-effects are frequent due to beta-1 and -2 adrenoceptor agonistic cardiovascular effects. Even serious complications such as pulmonary oedema and maternal death, though rare, have been reported.[4]

Oxytocin receptor blockers are a new class of tocolytic drugs. The oxytocin antagonist atosiban has less side effects than beta-agonists.[5] However, it is no more effective than ritodrine and the benefit of safety has to be balanced against that of cost.[6;7] A study of Ferriols et al. revealed that the cost-effectiveness obtained with the protocol including ritodrine as first-choice drug was three times less than when atosiban was used. In pregnant women where the likelihood of developing acute pulmonary oedema is high, or when cardiovascular risk is high (e.g. preeclampsia, cardiomyopathies, cardiovascular syndromes), atosiban may be an appropriate alternative option.[8] Although large studies using atosiban have been performed[4;9], there is mainly a subjective reporting of adverse reactions during infusion and objective data with regard to cardiovascular effects are scarce.

To the best of our knowledge, the hemodynamic effects on the heart and on the micro-and macro-circulation have not been studied before in a single study.[10] We evaluated the acute effects of therapeutic doses of ritodrine and atosiban on blood pressure, cardiac function, micro-circulation (total peripheral resistance) and macro-circulation (large artery stiffness) in healthy non-pregnant female volunteers.

Methods

Subjects

Twenty healthy non-pregnant female volunteers, either non-smokers or controlled smokers (≤10 cigarettes per day) with adequate non-uteral contraception were recruited from the local population. All participants gave written informed consent upon screening, organised within two weeks before the planned first drug administration. They were apparently healthy (no cardiovascular disease – arrhythmias included, obstructive lung disease, chronic kidney disease or diabetes mellitus). Breastfeeding women or women with a severe addiction were excluded.

Subjects were asked not to eat, smoke and drink caffeine-containing beverages for at least 3 hours before and during the measurements. They also had to refrain from drinking alcohol for at least 10 hours before measurements.[11]

Design

A double-blind, randomised trial was carried out at the Drug Research Unit Ghent of the Ghent University Hospital, Belgium. The study was approved by the Ethics Committee of Ghent University and conducted according to ICH Good Clinical Practice and the Declaration of Helsinki (last amended in 2008 in Seoul).

Twenty female volunteers were given atosiban (Tractocile®, Ferring, Sweden) and placebo (Glucose 5%) intravenously, in random order. Eight of them were randomly chosen to also get ritodrine (PrePar®, Eumedica, Belgium) in a single-blind way. The effects of drugs were compared after 95 minutes of infusion when kinetic steady state was reached for atosiban and ritodrine, being 15 minutes after starting the highest dose (400µg/min) of ritodrine. Hemodynamic measurements were done by one investigator with the subjects in supine position and under standardized conditions (derived from the Task Force III, clinical applications for arterial stiffness[11]) including a temperature controlled room (22 ± 1 °C).

Medication

Each medication and placebo were infused for 120 minutes. Both atosiban and ritodrine were given with glucose 5% as vehiculum. Atosiban was given at a constant dose of 300µg/min at a constant infusion rate of 0.4ml/min. Ritodrine was given in a dose escalation scheme starting with a dose of 100µg/min gradually upgraded to a dose of 400µg/min. The infusion rate varied with each dosing step (from 0.23 to 0.53ml/min). Glucose 5% was given as placebo at a constant infusion rate of 0.4ml/min. Dosing was based on previous studies using atosiban or ritodrine[1;12-15] and on the manufacturers prescriptions. Each period, the subjects received a total volume of 48ml.

Stopping criteria for dosing were: a heart rate increase above 75% of the age-based maximal heart rate or blood pressure changes from baseline of more than 30 mmHg for systolic (SBP) and 15 mmHg for diastolic blood pressure (DBP); a SBP above 180 mmHg or less than 90 mmHg and DBP more than 110 mmHg. The infusion was also ended when the subject suffered intolerable side effects.

Measurements

Brachial blood pressure and heart rate

Semi-recumbent brachial SBP and DBP and heart rate (HR) were recorded at the right upper arm opposite to the arm with the intravenous infusion line with a validated semi-automated oscillometric device (OMRON 705IT, OMRON Healthcare, Hoofddorp, The Netherlands).[16] Mean arterial pressure (MAP) was calculated by adding 40% of the pulse pressure (PP) to the measured DBP.[17]

Cardiac Output

Cardiac output (CO) was measured using echocardiography (AU5, Esaote, Genoa, Italy). Measurements were performed in the left lateral position. Aortic diameter (D) was measured at least three times using pulsed ultrasound at 2.5 MHz from a standard two-dimensional long-axis parasternal view at the site of the aortic annulus; the median of these readings was

used in the subsequent calculations. Aortic blood velocity profiles (at least 5 beats) were measured across the aortic valve with continuous ultrasound using an apical window. Stroke volume (SV) was calculated from aortic cross-sectional area (CSA_{ao}) multiplied by the flow velocity integral (FVI).

$CSA_{ao}$was calculated as $\pi D^2/4$

$SV = FVI \times CSA_{ao}$

CO = SV x HR (heart rate).

HR, as determined from the duration of the cardiac cycle on the FVI.[18] In our hands, reproducibility of aortic diameter and the FVI expressed as coefficient of variation was 4% and 6% respectively.

To relate the heart function to body size, CO and SV were divided by the body surface area (BSA) which was calculated by the Dubois & Dubois formula[19] to get the cardiac index (CI) and the stroke index (SI).

Microcirculation

The effects on the microcirculation were estimated using total peripheral resistance index (TPRI) which was calculated as MAP divided by the CI.

Macro-circulation

Large artery wall properties were assessed for the aorta using carotid-femoral pulse wave velocity (PWV), and local distensibility and compliance were measured at the right common carotid artery (CCA) and right common femoral artery (CFA).

PWV was measured using a Sphygmocor® (AtCor Medical, Sydney, Australia) system. [20;21] Surface distance between the two recording sites was measured in supine position using an anthropometer and the supra-sternal notch (SSN) as reference point: the distance CCA-to-SSN was subtracted from the distance SSN-to-CFA.

Arterial cross-sectional compliance (CC), a measure of buffering capacity and distensibility coefficient (DC), a measure of elasticity, were calculated as follows:[22]

$$CC = \frac{\Delta A}{\Delta P} = \frac{\Pi(D_s^2 - D_d^2)}{4\Delta P}$$

$$DC = \frac{\Delta A / A_d}{\Delta P} = \frac{(D_s^2 - D_d^2)}{D_d^2 \Delta P}$$

Where ΔA is the systolic-diastolic change in arterial cross-section at a given location; ΔP is the local pulse pressure (PP) at a given location; D_s is the arterial diameter at end-systole; D_d is the arterial diameter at end-diastole; A_d is the arterial cross-section at end-diastole.

Arterial diameter distension waveforms were assessed with a wall-tracking vascular echoscanner (Wall Track System, Esaote, Genoa, Italy) [23] equipped with a 7.5-10 MHz linear-array. Wall motion was tracked at the interface between media and adventitia at both (near and far) walls, at 1-2 cm proximal to the bifurcation of the CCA and the CFA. Per location, the median of tree recordings, each lasting for 5-6 seconds, was used for data analysis. In our hands, reproducibility of diameter and displacement expressed as coefficient of variation was 4% and 6% for the CCA and 3% and 7% for CFA, respectively. Femoral and carotid pressure waveforms (PWFs) were recorded non-invasively with a Sphygmocor® (AtCor Medical, Sydney, Australia).[24] To obtain local blood pressure at the CCA and CFA, calibration of the recorded PWFs was required. Calibration is based on the validated assumption that DBP and MAP remain constant throughout the large arteries, while SBP and PP (the difference between SBP and DBP) change.[25]

Additionally, isobaric wall properties (expressed as DC_{ISO} and CC_{ISO}) were calculated for each subject. The diameter and pressure waveforms were time-aligned using the peak as reference point. The resulting diameter-time recordings at CCA and CFA were analysed off-line using Matlab®. In each

subject, CC and DC were calculated over the blood pressure interval common in each treatment period (the highest DBP and the lowest SBP). In this way, the direct drug-induced changes in distensibility and compliance could be differentiated from the changes resulting from a change in blood pressure.

Data analysis

The median of 3 measurements was used for data-analysis. Statistics were done using IBM® SPSS® version 18 (SPSS Inc., Chicago, United States). Demographic differences between study groups were analysed using the non-parametric Mann-Whitney U test.

The cardiovascular effects were analysed by the non-parametric Kruskal-Wallis test. If statistically different ($p < 0.1$), a Mann-Whitney U test was run for 2-point comparison.

Results

Demographic data

At study entry, the subgroup of 8 subjects receiving also ritodrine did not differ statistically from the whole group (n=20) (Table 1). All subjects received the total amount of the planned dose, which was 300µg/min for atosiban and 400µg/min as the highest dose for ritodrine. Most of the adverse drug events were seen during ritodrine exposure, no adverse events happened during placebo or atosiban infusion (Table 2).

Hemodynamic data

The effects of the tocolytic drugs compared to placebo on cardiac function, blood pressure, micro- and macrocirculation are shown in Table 3.

CI with ritodrine increased significantly versus placebo (79%). This was due to an increase in heart rate (91%) while stroke index did not change. Administration of atosiban did not change cardiac index, stroke index or heart rate versus placebo, neither did it change blood pressure and total peripheral resistance index. In contrast ritodrine increased systolic blood pressure and heart rate,

decreased diastolic blood pressure while mean arterial pressure did not change statistically. Ritodrine also decreased total peripheral resistance with 48%.

The diameters of the CCA and the CFA were not influenced by either treatment. Ritodrine had significantly increased DC and CC of the CCA (62% and 83%, resp.) and of the more muscular CFA (59% and 33%, resp.). Since changes in blood pressure can passively change arterial wall properties, direct tocolytic drug effects were assessed at isobaric conditions. Except for DC_{ISO} of the CFA, which tended to increase (55%), all isobaric parameters remained significantly increased with ritodrine (DC_{ISO} and CC_{ISO} of the CCA 61% and 83%, respectively, and CC_{ISO} of the CFA 28%). Atosiban had no significant effects on the arterial wall properties of the CCA and CFA. The PWV was not influenced by ritodrine or atosiban but was positively correlated by MAP during ritodrine-infusion. Re-analysis with the adjusted parameter, did not influence the outcome.

Discussion

To the best of our knowledge this is the first placebo-controlled, randomized study investigating the effects of ritodrine and atosiban on cardiac function, micro-and macro-circulation in the same study.[26-29] Ritodrine had large effects while atosiban showed no significant influences on the cardiovascular system.

Like other studies cardiac index increased with ritodrine[30;31] and remained unchanged with atosiban.[32] In the present study the increased cardiac output with ritodrine was predominantly due to a $beta_1$ mediated increase in heart rate, while stroke index (SI) remained unchanged. The latter is not in accordance with other data where an increased stroke volume was found.[30;31] These studies refer to data in pregnant women which had already a decreased stroke volume due to the pregnant uterus.[33] The effect of ritodrine on stroke volume and stroke index was the net result of different effects: 1) The direct betareceptor mediated increased cardiac contractility 2) and the decrease in afterload by the decrease in TPRI would increase SI, while 3) venous dilatation[30] had the opposite effect on SI by a decrease in cardiac filling and cardiac contractility. The decrease in TPRI (almost 50%) with ritodrine

is in line with other data[30;31] and is due to $beta_2$ mediated vasodilation with ritodrine. The "flushing" in some subjects with ritodrine was reflecting this vasodilatation.

Ritodrine had effects on both the arterial wall properties of the CCA as the CFA. These effects were also present under isobaric conditions, indicating a direct (acute) effect of ritodrine on the arterial walls of the CCA and CFA. This effect is at least in part due to smooth muscle relaxation in the arterial wall and is in line with the in vitro observation on the umbilical artery by Dennedy et al..[34] The large effect on the less muscular CCA is somewhat surprising and is correlated with the strong vasodilation, although an ancillary acute mechanism cannot fully be excluded.In contrast, stiffness of the more elastic aorta, measured by pulse wave velocity, did not change with ritodrine. However, a small direct effect hidden by the indirect effects of changes in blood pressure and heart rate could not be expelled.[35] We tested this hypothesis by correlating PWV with its two main confounders MAP and HR. Only the MAP was positively correlated with PWV but did not change the outcome after correction for it (from 6.08 m/sec to 6.07 m/sec).

Clinical implications and study limitations

The present study was carried out in non pregnant women. It is not clear whether the present results in non pregnant women can be fully extrapolated to pregnant women. Physiologic changes during pregnancy like an increase in cardiac output, a decrease in peripheral resistance[33;36] and modulation of oxytocin receptors during pregnancy[37;38] may alter the magnitude of the pharmacodynamic effects. On the other hand, pain and stress during premature labour may also confound the effects of tocolytic drugs. To elucidate these issues, this study would ideally be performed in late pregnant women without signs of premature labour. But this may be difficult because of ethical issues.

Some data-analyses were hampered by the small study population on ritodrine. However, the observed cardiovascular effects observed with ritodrine were large so that the main outcomes are not likely to be influenced by this small sample size.

Ritodrine has important effects on the cardiovascular system. Since heart rate and CI are almost doubled in comparison with placebo, it may not be the preferred drug in patients at risk of cardiac

disorders, as the cardiovascular effects of beta-agonists could exacerbate underlying cardiovascular disease.[30;31] Also very divergent effects of ritodrine have been published like the effects on SBP starting from systolic hypotension and ending with an increased SBP like in the present study.[31;39;40]

Potential beneficial effects of ritodrine may be the higher arterial elasticity and buffering capacity and the lower peripheral resistance. These effects are largely due to a $beta_2$-adrenergic mediated increase in endothelial nitric oxide release[41], which may alleviate the peripheral vasoconstriction due to endothelial dysfunction in cases of gestational hypertension or other vascular complications during pregnancy. However, a potential beneficial effect of ritrodrine may not be overestimated as this drug is only given for a short period of time and as the improved beta-adrenergic mediated endothelial NO release may not be present in subjects with an impaired NO pathway.[41] The latter might be the case in pregnancy since stimulated nitric oxide release was reduced in normal pregnancy and preeclampsia, while vascular smooth muscle sensitivity to nitric oxide was not altered.[42] Moreover, in hypertensive pregnancies, the circulating components of the RAAS (Renin-Angiotensin-Aldosteron system) are decreased and since beta-agonists increase the outflow of the RAAS[31;43;44], this could aggravate endothelial dysfunction and due to lowering the diastolic blood pressure, ritodrine may compromise the flow towards the placenta.[45;46] In addition, the potential beneficial vascular effects of ritodrine appear to be counterbalanced by its cardiac effects, which impels caution for the use of ritodrine in cardiovascular complicated pregnancies.

Atosiban, on the other hand, was shown to have no significant cardiovascular effects which is in agreement with previous findings. Our data add substantial information by using more complex cardiovascular measurements. However, the high cost of atosiban and the similar tocolytic effectiveness compared to ritodrine [5;47], makes it not a cost-effective alternative for widespread use.

In conclusion, the present study shows potentially beneficial vascular effects of ritodrine. These effects appear to be counterbalanced by the cardiac effects. There are no clinically relevant effects of atosiban

on the cardiovascular system. Since the tocolytic effectiveness is the same, atosiban may be a good alternative for ritodrine in pregnant women with cardiovascular complications.

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Trial Number

EudractNr: 2008-000845-76

Table 1: Subjects' characteristics at study entry

Parameters	**Characteristics**		
	Double-blinded study part (n=20)	Single-blinded study part (n=8)	p-value*
Age (years)	25±7	25±11	0.862
BMI (kg.m^{-2})	21±3	22±4	0.980
Height (m)	1.69±0.07	1.68±0.06	0.901
Smoking n (%)	4 (20)	1 (12.5)	0.784
SBP (mmHg)	101±7	101±9	0.826
DBP (mmHg)	65±5	67±6	0.748
HR (bpm)	58±8	58±9	0.901

Twenty non-pregnant, healthy female volunteers received atosiban and placebo in a double-blinded way whereas eight of them also received ritodrine in a single-blinded way. All data are expressed as mean ± standard deviation, except for smoking history. BMI (Body Mass Index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HR (heart rate); bpm (beats per minute)

Table 2: Adverse events during drug exposure.

Adverse event	Ritodrine (n=8)	Atosiban (n=20)	Placebo (n=20)
None	2	20	20
Tremor	3	0	0
Palpitations	6	0	0
Flushing	2	0	0

Table 3: Cardiovascular effects of ritodrine and atosiban in healthy non-pregnant women.

Parameters	*Ritodrine (n=8)*	*Atosiban (n=20)*	*Placebo (n=20)*	*p-value*[$]
CI ($l.min^{-1}.m^{-2}$)	3.15±0.92[*#]	1.85±0.58	1.76±0.47	0.001
SI ($mL.m^{-2}$)	28±6	31±6	30±7	0.802
HR (bpm)	111±20[*#]	59±10	58 ±10	< 0.001
TPRI ($kPa.l^{-1}.min^{-1}.m^{-2}$)	1.63±0.58[*#]	3.03±1.01	3.12±0.84	< 0.001
CCA diameter (mm)	6.52±0.93	6.25±0.63	6.23±0.66	0.400
DC_{CCA} ($10^{-3}kPa^{-1}$)	76.67±25.40[*#]	53.01±20.46	47.26±13.46	0.006
DC_{CCA_ISO} ($10^{-3}kPa^{-1}$)	72.49±25.17[*#]	52.39±20.55	44.98±12.40	0.007
CC_{CCA} ($mm^2.kPa^{-1}$)	2.55±0.90[*#]	1.58±0.49	1.39±0.35	0.003
CC_{CCA_ISO} ($mm^2.kPa^{-1}$)	2.45±0.91[*#]	1.56±0.48	1.34±0.34	0.003
CFA diameter (mm)	7.77±1.13	8.18±1.07	8.27±0.81	0.615
DC_{CFA} ($10^{-3}kPa^{-1}$)	32.47±16.16[*#]	19.40±9.19	20.43±9.30	0.057
DC_{CFA_ISO} ($10^{-3}kPa^{-1}$)	30.69±15.09	19.17±9.22	19.83±9.12	0.112
CC_{CFA} ($mm^2.kPa^{-1}$)	1.45±0.53[*#]	0.94±0.37	1.09±0.56	0.057
CC_{CFA_ISO} ($mm^2.kPa^{-1}$)	1.36±0.50[*#]	0.93±0.37	1.06±0.55	0.075
PWV ($m.s^{-1}$)	6.08±0.84	5.82±0.78	5.96±0.95	0.730
SBP (mmHg)	116±12[*#]	105±8	104±6	0.067
DBP (mmHg)	55±11[*#]	69±6	68±5	0.004
MAP (mmHg)	78±10	87±9	85±5	0.226

CI (cardiac index), SI (stroke index), HR (heart rate), TPRI (total peripheral resistance index), CCA (common carotid artery), CFA (common femoral artery), DC_{CCA} (distensibility coefficient of the CCA); DC_{CCA_ISO}

(isobaric DC of the CCA); CC_{CCA} (compliance coefficient of the CCA); CC_{CCA_ISO} (isobaric CC of the CCA); DC_{CFA}(distensibility coefficient of the CFA); DC_{CFA_ISO} (isobaric DC of the CFA); CC_{CFA} (compliance coefficient of the CFA); CC_{CFA_ISO} (isobaric CC of the CFA), SBP (systolic blood pressure), DBP (diastolic BP), MAP (mean arterial pressure), PWV (pulse wave velocity); [$]Kruskal-Wallis test on all subjects, comparing three groups :[*] significant versus atosiban; [#] significant versus placebo. All data are shown as mean ± standard deviation.

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