Different effects of tocolytic medication on blood pressure and blood pressure amplification.

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Introduction

The importance of tocolysis has been discussed extensively.[1-3] Beta-2 adrenoceptor agonistic drugs like ritodrine have been the reference tocolytic drugs in most countries.[3,4] Their efficacy in prolonging pregnancy compared to placebo is proven although no benefit in neonatal morbidity or mortality has been demonstrated.[5] 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.[5]

Atosiban, a newer tocolytic drug, is a competitive antagonist of oxytocin at uterine oxytocin receptors and has less cardiovascular side effects.[6] The 13th revision (08 July 2009) of the European Public Assessment Report (EPAR) on Tractocile® (atosiban) of the EMEA (European Medicines Agency) states that atosiban has the same effect as beta-mimetics on surrogate endpoints related to tocolysis. A better tolerability was observed, but there was no advantage in improving foetal and maternal outcome in comparison with beta-mimetics. This benefit of safety with atosiban has to be balanced against its cost.[7,8] A study of Ferriols et al.[9] revealed that the cost-effectiveness obtained with a protocol including ritodrine as first-choice drug was three times less than when atosiban was used. In pregnant women with high risk of developing acute pulmonary oedema, or cardiovascular disease (e.g. preeclampsia, cardiomyopathies and cardiovascular syndromes), atosiban may be an appropriate alternative.

Although large studies using atosiban have been performed in both pregnant and non-pregnant groups[5,8,10-12], there is mainly a subjective reporting of adverse reactions during infusion with a focus on peripheral blood pressure data.

Central blood pressure and pulse wave reflections may provide additional information regarding cardiovascular risk beyond peripheral blood pressure.[13-15] The central

hemodynamic effects of tocolytic drugs have never been studied before. In this study, the acute effects of therapeutic doses of ritodrine and atosiban were evaluated on central and peripheral blood pressure, central-to-peripheral blood pressure amplification and pulse wave reflections in healthy non-pregnant female volunteers.

Methods

Subjects

Twenty healthy non-pregnant female volunteers, either non-smokers or smokers (≤10 cigarettes per day) with adequate non-uteral contraception were recruited from the local population. All participants gave written informed consent upon screening, which was organised within two weeks before the planned first drug administration. They were apparently healthy (no cardiovascular diseases – including arrhythmias, obstructive lung diseases, chronic kidney diseases 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.[16]

Design

A double-blind, randomised, crossover 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 in compliance with the Declaration of Helsinki (last amended in 2008 in Seoul).

Twenty female volunteers were given atosiban (Tractocile®, Ferring, Sweden) and placebo (Glucose 5%) intravenously. 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[16]) in a temperature controlled room (22 ± 1 °C).

Medication

Medication and placebo were infused for 120 minutes at the left arm. 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 [3,17-20] and on the manufacturers prescriptions. Each period, a total volume of 48ml was infused.

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) or a SBP above 180 mmHg or less than 90 mmHg and DBP more than 110 mmHg. When the subject suffered intolerable side effects, the infusion was also ended.

Measurements

Sphygmomanometry

Semi-recumbent brachial SBP and DBP and heart rate (HR) were recorded at the right upper arm with a validated semi-automated oscillometric device (OMRON 705IT, OMRON

Healthcare, Hoofddorp, The Netherlands).[21] Blood pressure and HR were recorded predose and at kinetic steady state. Mean arterial pressure (MAP) was calculated by adding 40% of the pulse pressure (PP) to the measured DBP.[22]

Applanation tonometry

Radial (RA) and carotid (CCA) pressure waveforms (PWFs) were recorded non-invasively with a Sphygmocor® applanation tonometry system (AtCor Medical, Sydney, Australia).[23] To obtain local blood pressure at the CCA and RA, calibration of the recorded PWFs is 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.[24] SBP at an arterial site (SBP_X) is $SBP_X=DBP+PP_X$. Using our calibration method, PP at an arterial site (PP_X) can be calculated from PP at the brachial artery (PP_{BA}) as

$PP_X=PP_{BA} \times FF_{BA}/FF_X$[25]

FF_{BA} and FF_X are the form factors (FF) at the brachial artery and the target artery, respectively, and are defined as:[26]

$FF_X=(MAP-DBP)/PP_X$

Brachial FF was calculated as $FF_{BA}=FF_{RA}+0.625(FF_{CCA}–FF_{RA})$. This formula estimates FF_{BA} from carotid (FF_{CCA}) and radial FF (FF_{RA}) assuming the ratio $(FF_{BA}-FF_{RA})/(FF_{CCA}-FF_{RA})$ to be fixed. This ratio was calculated in an age matched population (265 subjects (aged 19-40 years) from the Asklepios database [27] and from unpublished data).

Augmentation index

Carotid augmentation index (AIx) was calculated from the carotid pressure waveform as the ratio of the amplitude of the pressure wave above its systolic shoulder to the total pulse pressure.[28] Carotid AIx is a surrogate for aortic AIx and is considered to be an index of

pressure wave reflection (PWR).[29] Since the AIx has an inverse, linear relationship with the HR, the AIx was corrected for HR.[30]

Data analysis

The median of 3 measurements was used for data-analysis. Statistics were done using SPSS version 15 (SPSS Inc., Chicago, United States).

A non-parametric Friedman test was run on data of the 8 subjects who also received ritodrine to compare for repeated observations on the same subject. If statistically significant, this was followed by a Wilcoxon signed rank test for 2-point comparison. Comparison between atosiban and placebo was done on all subjects using the Wilcoxon signed rank test. Demographic differences between study groups were analysed using the non-parametric Mann-Whitney U test.

Results

Demographic data

At study entry, the subgroup of 8 subjects also receiving ritodrine did not differ statistically from the whole group (n=20). 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.

Central and peripheral blood pressure, and augmentation index

Data of blood pressure and augmentation index are shown in Table 2. With ritodrine, central SBP (at the CCA) increased with 13% versus placebo ($p = 0.012$) and peripheral SBP (at the BA) increased with 12% ($p = 0.004$). But SBP at the radial artery did not differ statistically from placebo. Compared to placebo, the DBP and MAP in the ritodrine group decreased with 19% ($p = 0.008$) and 8% ($p = 0.044$), respectively. With atosiban, central and peripheral pressures did not differ from placebo.

With atosiban and placebo the systolic pressure rises from the central CCA towards the peripheral RA. Although not statistically significant (p = 0.180) from placebo and atosiban, with ritodrine there was a substantial loss of this systolic pressure amplification.

With ritodrine, the non-corrected AIx decreased (497%; p= 0.005) and the AIx corrected for heart rate (AIx@HR75) tended to decrease (289%; p= 0.225), while AIx did not change with atosiban.

Discussion

To the best of our knowledge this is the first placebo-controlled, randomized study investigating the effects of ritodrine and atosiban on the central blood pressure, pressure wave reflection and central-to-peripheral pressure amplification.[31-34] The results from this study show that ritodrine has important and significant effects on the cardiovascular system, whereas atosiban shows no significant effects on the parameters which we investigated.

Sphygmomanometer blood pressure

Similar effects have previously been reported. In studies with pregnant women, ritodrine caused a decrease in DBP (a drop of 4 and 7 mmHg from beginning to the end of the treatment[3,7,31]). In studies with other beta-receptor agonists, DBP and MAP were reduced because of peripheral vasodilatation.[35-37] For atosiban, no significant fall in DBP occurred, which is consistent with earlier work.[3,32,38,39]

Tonometry data

In a general population the best estimate of the brachial form factor is 0.4.[22] However this form factor can depend on different factors like age.[40] We also observed that medication can change substantially the form factor at different arterial sites (RA: 33.4 during placebo – 28.0 during ritodrine; CCA: 43.4 during placebo – 28.7 during ritodrine). Therefore in the

present study the FF_{BA} of each measurement was estimated using a procedure that expresses the FF_{BA} as a (fixed) ratio of FF_{CCA} and FF_{RA}, circumventing the lack of brachial tonometry recordings.

The SBP_{CCA} during ritodrine was higher and AIx was lower in comparison with those during atosiban and placebo. No other data on the effect of these tocolytic drugs on central SBP or AIx are available in the literature.

AIx has been proposed as an index of early wave reflections at the central arteries. Heart rate is a well-known determinant of AIx. But also after adjustment to a heart rate of 75 beats per minute (bpm) AIx tended to be lower during ritodrine than during atosiban or placebo, suggesting that ritodrine reduces wave reflections. As pulse wave reflections occur at changes in impedance (like at arterial branches), the vasodilation with ritodrine may account for the decrease in arterial impedance and reduction in wave reflections. Studies[35,37,41] investigating effects of salbutamol (another beta-receptor agonist) on arterial stiffness, revealed similar significant effects on AIx due to endothelial nitric oxide synthase (NOS)-dependent vascular relaxation.

In the present study, systolic pressure measured by applanation tonometry at the CCA was used as a non-invasive surrogate for cSBP.[25] The central blood pressure (cBP) may have a higher predictive value for cardiovascular events compared to traditional sphygmomanometer measurements since it is an important determinant of the left ventricular workload and coronary blood flow.[14] In contrast to peripheral blood pressure, early pulse wave reflections (PWR) can boost the cSBP reflected by a positive AIx. Early PWR is being recognized as an important factor that contributes to the increase in central blood pressure.[42] As AIx was negative with ritodrine, early wave reflections cannot contribute to the increase in cSBP during ritodrine, which is due to the beta-agonistic positive inotropic effect witnessed by the increase in heart rate.

During ritodrine, there was also a rise in SBP at both the levels of the BA and the RA. This is not in accordance with other studies reporting a decrease in sphygmomanometrically taken SBP.[3,7,31] This difference can be explained by the fact that the subjects in those studies were pregnant. Pregnant women in premature labour have an already higher baseline SBP in comparison with the non-pregnant group. It may not be excluded that in those studies with pregnant women, the anxiety for premature birth and the hospital setting artificially boosted SBP at the start of treatment. Finally, an altered effect of ritodrine in pregnant women cannot be fully excluded.[43,44] The effect of atosiban on the SBP, at the levels of the CCA, BA or RA in our study were not significantly different from placebo which is in accordance with other studies.[3,34]

Blood pressure amplification

Mean and diastolic blood pressure hardly change in the large artery tree.[24,25] In contrast, when early wave reflections are absent like in young subjects, a clear amplification of the systolic blood pressure from the heart to the periphery is present. This explains why blood pressure measured at the brachial artery may overestimate the pressure seen by the heart.[45] This pressure amplification is due to a gradual decrease in arterial compliance (C) from central to peripheral arteries[46] and can be influenced by pulse wave reflections.[47] For ritodrine, in contrast with atosiban and placebo, pressure amplification between the CCA and the upper limb is nearly absent (with a difference of only 2 mmHg between the CCA and the RA). This loss of pressure amplification with ritodrine can be explained by an increased arterial compliance, due to $beta_2$ mediated vasodilatation.[48]

Study limitations and clinical implications

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[49,50] and modulation of oxytocin receptors during pregnancy[51,52] 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.

Ritodrine has important but contradictory effects on the cardiovascular system. In the UK, the Royal College of Obstetricians and Gynaecologists' guidelines on beta-mimetics recommend close monitoring of maternal pulse and blood pressure every 15 minutes during the infusion in every patient receiving a β-agonist as tocolyticum.[7] The fall in DBP, MAP and AIx due to the relaxation of the vascular smooth muscle cells, may appear an advantage in cases where the peripheral resistance is raised, like in gestational hypertension or pre-eclampsia. However, in hypertensive pregnancies, the circulating components of the RAAS (Renin-Angiotensin-Aldosteron system) are decreased.[53] On the contrary, beta-agonists like ritodrine may trigger the RAAS with enhanced renal sodium absorption resulting in vascular overfilling with increased risk of pulmonary oedema and acute heart failure.[54,55] In pregnant women with cardiovascular complications like gestational hypertension, preeclampsia and cardiomyopathies or in pregnant women with a history of cardiovascular complications during pregnancy, ritodrine may not be the first-line agent to control premature labour. Atosiban is then one of the alternatives.

In conclusion, the present study shows that the effects of ritodrine on blood pressure, blood pressure amplification and pulse wave reflections are significantly different from atosiban and placebo. The present study clearly demonstrates the absence of those hemodynamic effects during atosiban infusion.

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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; BMI (Body Mass Index); data of SBP (systolic BP), DBP (diastolic BP) and HR (heart rate) are median of tree measurements, bpm (beats per minute); *p-value is based on non-parametric Mann-Whitney U-test. All data are shown as mean ± standard deviation, except for smoking history.

Table 2: Effects on the central and peripheral blood pressures and augmentation indices

Parameter	***Ritodrine (n=8)***	***Atosiban (n=20)***	***Placebo (n=20)***	**p-value[$]**
SBP_{CCA} (mmHg)	115±12[*#]	102±8	102±7	0.012
SBP_{BA} (mmHg)	116±12[*#]	105±8	104±6	0.004
SBP_{RA} (mmHg)	117±14	110±10	110±6	0.180
BP amplification	2.47±8.85	8.07±5.73	8.33±4.07	0.180
DBP_{BA} (mmHg)	55±11[*#]	69±6	68±5	0.008
MAP (mmHg)	78±10[*#]	87 ±9	85±5	0.044
HR (bpm)	111±20[*#]	59±10	58 ±10	0.002
AIx	-19.43±6.75[*#]	4.89±5.04	4.89±5.80	0.005
AIx@HR75	-8.67±12.30	5.58±16.78	4.58±13.33	0.225

SBP (systolic BP), BP-amplification (blood pressure difference from CCA to RA), DBP (diastolic BP), MAP (mean arterial pressure); HR (heart rate), bpm (beats per minute), AIx (augmentation index, not corrected for heart rate), AIx@HR75 (augmentation index at heart rate 75). [$] Friedman-test on 8 subjects receiving all treatments; [*] $p<0.005$ vs. atosiban, [#] $p<0.005$ vs. placebo. All data are shown as mean ± standard deviation.