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**Title: The OTR antagonist, OBE001, inhibits both spontaneous and OT-induced contractions of human pregnant myometrium in vitro.**

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Disclosure Statement:

VT has worked as a consultant to GlaxoSmithKline and ObsEva. PB has worked as a consultant to Boehringer Ingelheim, GlaxoSmithKline, Merck Serono, ObsEva SA, and Tokyo Tanabe Pharmaceuticals, drug companies with an interest in the pharmacological effects of oxytocin and oxytocin antagonists. PB holds shares ObsEva SA. AC and OP are salaried employees of ObsEva SA.

Abstract (311 words):

Currently the only drug licensed in Europe for inhibition of preterm contractions is the intravenous oxytocin (OT)/ arginine vasopressin receptor antagonist Atosiban. OBE001 is a more selective OT receptor antagonist than Atosiban and may be administered orally. Here we compare the effects of Atosiban and OBE001 on spontaneous and OT-induced contractions of human pregnant myometrium in vitro.

Experiments were performed using a DMT Myograph 800MS in oxygenated Krebs's solution, with ADI Powerlab software allowing simultaneous measurements of eight muscle preparations. Once regular contractions had been established for 20+ minutes baseline measurement of contraction frequency, contraction peak, contraction duration, work per contraction (area under curve) and total work (area under all contractions) were made. The inhibitor compound was then added effects upon contractility measured in the next ten minutes. The effect of the inhibitor upon agonist (OT) was then measured by adding increasing concentrations of OT (1, 10, 100nM) at ten minute intervals.

Atosiban was studied at 6, 60 and 600nM. Atosiban had no effect upon spontaneous concentrations (and may have agonist effects upon the rate of contractions at low concentration). Atosiban antagonized the effects of oxytocin upon the rate of contractions and peak tension with a dose dependent effect, although at lowest concentrations the effects were partly agonist.

OBE001 was studied at 6, 60 and 600nM. OBE001 inhibited spontaneous contractions in a dose dependent way, affecting rate, contraction peak tension, and contraction duration and therefore having an overall effect upon total work. OBE001 antagonized the effect of oxytocin in a dose dependent way, affecting all parameters and leading, at high concentrations, to a complete abolishment of contractility.

At equimolar concentrations there was little difference between Atosiban and OBE001 at 6nM, but OBE001 was superior to Atosiban at 60nM and 600nM, and unlike Atosiban, totally inhibited contractility.

OBE001 appear to be a promising candidate tocolytic with a better tocolytic profile than Atosiban.