

Potentialiation of the uterus relaxing effects of magnesium-sulfate with terbutaline and nifedipine: studies on the pregnant rat myometrium

Tamara Barna¹, Judit Hajagos-Tóth¹, Kálmán Szűcs¹, Róbert Gáspár¹

¹ Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary
Tamara Barna 5th year pharmacy student

Corresponding author: Judit Hajagos-Tóth, hajagos-toth.judit@med.u-szeged.hu

Keywords: pregnancy, magnesium-sulfate, combination, uterine contractility, rat

Introduction: Tocolysis is one of the greatest challenges in obstetrical practice. Magnesium-sulfate is an extensively used tocolytic agent, as it has better side-effect profile compared to other agents. However the efficacy of this drug has been questioned. Therefore our aim was to investigate the uterus-relaxing effect of magnesium-sulfate in combination with other tocolytic drugs *in vitro* and *in vivo*.

Methods: Contractions of uterine rings from 22-day-pregnant Sprague-Dawley rats were measured in an organ bath. The contractions were stimulated with 25 mM KCl and cumulative-dose response curves were elicited in the presence of magnesium-sulfate (10^{-8} – 10^{-1} M), nifedipine (10^{-10} – 10^{-6} M) or terbutaline (10^{-9} – 10^{-5} M). The uterus relaxing effects of nifedipine and terbutaline were also investigated in the presence of magnesium-sulfate (10^{-7} M).

In the *in vivo* studies an electromyographic method with subcutaneous electrode was carried out during ketamine (36 mg/kg) and xylazine (4 mg/kg) induced anesthesia. The rats were treated with 50 mg/kg MgSO₄ intravenously, then 100 µg/kg terbutaline or 100 µg/kg nifedipine were given in repeated bolus injections.

Results: Both terbutaline and nifedipine caused myometrial relaxation *in vitro*, which was further enhanced by administration of magnesium-sulfate. Magnesium-sulfate increased the maximal relaxing effect of terbutaline ($p \leq 0.001$), while it shifted the dose-response curve of nifedipine to the left ($p \leq 0.5$). In the *in vivo* studies magnesium-sulfate increased the uterus-relaxing effect of terbutaline, however it could not enhance the uterus-relaxing effect of nifedipine.

Discussion: As magnesium-sulfate closes the voltage-gated calcium channels, the uterus relaxing effect of the calcium channel antagonist nifedipine cannot be enhanced further.

Conclusion: The combination of magnesium-sulfate and terbutaline can have important clinical significance, which remains to be validated in clinical trials. In addition, it is supported by the fact that the pharmacodynamic and pharmacokinetic parameters and risks of these two agents are well-known.

Ethical Committee or Institutional Animal Care and Use Committee Approval: Ethical Committee or Institutional Animal Care and Use Committee Approval: All experiments involving animal subjects were carried out with the approval of National Scientific Ethical Committee on Animal Experimentation (permission number: IV/198/2013).

Grants and financial support: Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT is acknowledged.

Acknowledgements: The study was supported by Cedars-Sinai Medical Center's International Research and Innovation in Medicine Program, the Association for Regional Cooperation in the Fields of Health, Science and Technology (RECOOP HST Association) and the participating Cedars – Sinai Medical Center - RECOOP Research Centers (CRRC).