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Review Article

Therapeutic Use of Tocolytic Drugs in Management of Dystocia in Different Species of Animals- A Review

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Abstract

This review article deals with indications and mechanism of action of tocolysis drug used in management of dystocia in different species of animals. Also, brief overview of different tocolytic drug such as beta-mimetics, magnesium sulfate, prostaglandin inhibitors, oxytocin receptor blockers and calcium channel blockers are also discussed here.

Keywords: Atosiban, Clenbuterol, Dystocia, Isoxsprine, Tocolytic Drugs

Introduction

Tocolysis is a Greek derivative (*tokos* = childbirth or labor; *lysis* = dissolution or loosening) that means in practical terms inhibition of labor. It is obtained by the use of substances able to induce a state of myometrial paralysis. Beta-agonist, Isoxuprine was described as a first-line tocolytic (Bishop and Woutersz, 1961). Tocolytic drugs are usually given to prolong gestation during the preterm period in human being and animals. However, they may also be given during term labor, as acute tocolysis, to stop contractions in case of spontaneous or induced tachysystole (i.e. too many contractions). Though tocolytics may not help in prolonging pregnancy to such an extent that fetus may grow and mature further, it may prolong delivery sufficiently to allow the women and animals to be brought to a specialized center that is equipped and staffed to handle preterm deliveries or dystocia. In bovine obstetrics, abdominal straining can be briefly interrupted with epidural anesthesia but uterine contractions cannot (Roberts, S. J., 1971; Arthur, G. H., 1975; Booth, N. H., 1977). Management of dystocia in cattle and buffaloes is sometimes complicated by high uterine tone, which makes manipulation of the fetus for correction of abnormal position or posture difficult. Exteriorization of the uterus during cesarean section is also impaired by high uterine tone. The use of tocolytic drugs is an important intervention in obstetrics for selective blockage of smooth muscle contraction (Zerobin, K. and Kondigh, H., 1980; Zerobin, K., 1980; Bostedt, H. and Rudloff, P.R., 1983; Retzer, R., 1987;). These substances are able to induce a state of myometrial paralysis. Hence, it becomes very easy to handle the hyperactive uterus for further manipulation.

Indications

The main field of application for tocolytics is in threatened premature labor. Premature delivery plays an important part in perinatal mortality. In late pregnancy, labor-like uterine contractions may need to be inhibited during obstetric procedures such as mutation, fetotomy, caesarian section and uterine torsion, to delay, prevent premature parturition under circumstances such as during transportation to another location, and after surgical manipulation of the abdomen or uterus. The ability to induce uterine relaxation may afford an advantage for diagnostic ultrasonography, and by means of ultrasound-guided cardiac puncture in mares that carry many twins.

Sometimes, it has been found that oxytocin or PGF2α is given in pregnant animals at term to induce the parturition or by mistake in dystocia cases in field conditions. These ecbolics will increase the basal tone in the uterus, leading to a decrease in utero-placental perfusion, with the possibility of fetal hypoxia and even fetal death occurs. A second risk from overstimulation is uterine rupture; this may lead to fetal death and substantial maternal blood loss, shock and even maternal death. The use of tocolytic drugs is only method of choice to overcome the stimulatory effects of the oxytocin or PGF2α on the pregnant uterus for well-being of the fetus and the dam.

Xylazine is another drug which is frequently used as a sedative, analgesic and muscle relaxant drug in domestic animals, but its uterine side-effects preclude its use in pregnant females or in conditions where it is important not to alter uterine tone such as surgical embryo transfer. Sometimes, it becomes very necessary to use xylazine in pregnant animals to handle the emergency situations. In such conditions, it becomes very necessary to use tocolytic drugs preceding the ecbolics. Clenbuterol and nifedipine at the dose rate of 4 µg per kg body weight and 80 µg per kg body weight, respectively was found very effective in prevention of uterotonic effects of xylazine in pregnant goats (Ferez, R., et al., 1997). Beside this, clenbuterol at therapeutic dose of 5 µg/ kg body weight intravenously prolonged the parturition for a period of one to two hours in pregnant sheep (Garcia-Villar and Toutain, 1991). Thus, it is possible to propose that tocolytic agents which can be used to inhibit both the spontaneous and drug-induced myometrial contractions irrespective of stage of pregnancy.

Tocolytic effects of clenbuterol have been observed throughout the pregnancy in mare for 2 hours at the therapeutic dose rate of 300 µg without affecting the viability of foals at term and thus also helpful to carry out ultrasound-guided allantocentesis or cardiac puncture in twin pregnancy, obstetric procedures such as mutation, fetotomy, caeserian section or uterine torsion or to delay or prevent premature parturition under circumstances such as during transportation to another location (Claire E. *et al.*,1995). Moreover, clenbuterol was found to be very effective in stopping straining during replacement of prolapsed mass without sacral anasthesia which is given to stop abdominal contractions (Muurling, F. *et al.*, 1981). The use of clenbuterol, albuterol and terbutaline was safe and easy as tocolytic drug for better management of the labor period in cattle and buffaloes (Garg, S. K. *et al.*, 2004).

Mechanisms of Tocolysis

Myometrial contractility is a complex process based on myocytes. It involves the presence of hormonal receptors, ions channels, intercellular gap junctions, and regulatory proteins (Bernal, A. L., 2007; Young, R. C., 2007). The increase of intracellular calcium (Ca) concentration is essential for the uterine smooth muscle contraction (Bernal, A. L., 2007). Phasic contractions of the uterus occur due to spontaneous changes in electrical activity within myometrial cells, the mechanism of which is unknown, but it leads to action potentials and depolarization. The depolarization causes opening of voltage-gated L-type calcium channels, rapid calcium entry and an elevation in intracellular Calcium. The Calcium binds to calmodulin which activates myosin light chain kinase (MLCK), leading to phosphorylation of the myosin regulatory light chains and, enables the interaction of myosin with actin, cross-bridge cycling and force development. Myosin is dephosphorylated by myosin phosphatase (MLCP) and Ca is extruded by Ca-ATPase and Na/Ca exchange. The membrane potential is restored to resting levels by potassium (K) efflux and the myometrium is quiescent until spontaneous depolarization initiates the next contraction. Calcium entry and efflux are the major pathways of myometrial contraction/relaxation.

Types of Tocolytics

There are many different classes of drugs which interfere at various levels in the myometrial contractility process and cause uterine relaxation. They include (1) beta-mimetics; (2) magnesium sulfate; (3) prostaglandin inhibitors; (4) oxytocin receptor blockers and (5) calcium channel blockers

1. Beta-mimetics

The adrenergic system plays an important role in the control of uterine contractility. Currently, beta-mimetics are the most frequently used tocolytics. Ritodrine and salbutamol have been used in clinical practice for preterm labour since the 1980s. Clenbuterol is used successfully for short-term postponement of parturition in the cow and for easier manipulation of both the uterus and fetus. It has been used as a tocolytic agent in veterinary medicine for therapeutic management of parturition. The clinical studies were carried out by different researchers to test its therapeutic usefulness for the correction of abnormal fetal presentations and as a prerequisite to fetotomies, caesarean sections and postponement of parturition in cattle (Wolfe, D.W., 1983; Putnam, M.R., *et al.,* 1982; Greene, H.J., 1981; Arbeitter, K. and Holler, W., 1980; Ballarini, G., 1980; Grunert, E. and Verhoelsdonk, M., 1980; Zerobin, K. and Kondigh, H., 1980; Ballarini G. *et al.*, 1978; Arbeitter, K. and Thurner, M., 1977), sheep (Delaiour, P. and Roizard.D., 1979) and swine (Zerobin, K., 1980). Clenbuterol abolished uterine contractility for eight to ten hours and suspended overnight lambing in 91 per cent of the ewes (Delaiour, P. and Roizard, D., 1979). It also post-poneds the all phases of parturition in the swine even in the case of already born piglets without affecting viability of the piglets born after the subside of the effects of the drug (Zerobin, K., 1980). The duration of tocolysis depends on the position of the fetus at the time of treatment, being longest at the beginning of the labor process (Greene, H.J., 1981; Arbeitter, K. and Holler, W., 1980). There were no adverse effects on vitality of the newborn, expulsion of the placenta or subsequent fertility of the dams. Further, good results have been recorded in cases of dystocia due to fetal oversize, uterine torsion and uterine spasm, fetotomy, caesarean operation and replacement of uterine prolapse (Denooli, P.P., 1984; Renner, J.E., 1982; Albeck, A., 1981; Muurling, F. *et al.*, 1981; Riepe, H., 1981). Two of these, isoxsuprine and clenbuterol, have been used as obstetrical drugs by veterinarians in European countries and possibly others. In veterinary practice isoxsuprine is available as an injectable, aqueous solution containing 11.58 mg isoxsuprine lactate per mL under the trade name of Duphaspasmin. It is used as a tocolytic in large or small domestic animals (0.4-2.0 mg/kg i.m) although practical application is usually reserved to the larger species, particularly ruminants. Tocolysis develops within 10-15 minutes after i.m. application and lasts one to two hours (Poreye, 1978; Horvarih & Bacsfay, 1981).

2. Magnesium Sulphate

Magnesium Sulphate inhibits uterine contractions however it is not very effective tocolytic drug (Crowther, C.A., 2002). As the drug is crossing the placenta and thus increases the risk of perinatal death and neonatal adverse effects including neurological and metabolic disorders at high dosage (Crowther, C. A. *et al*., 2002; Caritis, S. *et al.*, 2005). However, recently it has been shown that magnesium sulphate acts as a neuroprotective agent when administered prophylactically at low dose during preterm labor. There is no evidence available to recommend this drug as a first-line tocolytic agent (Crowther, C. A. *et al*., 2002; Caritis, S. *et al.*, 2005).

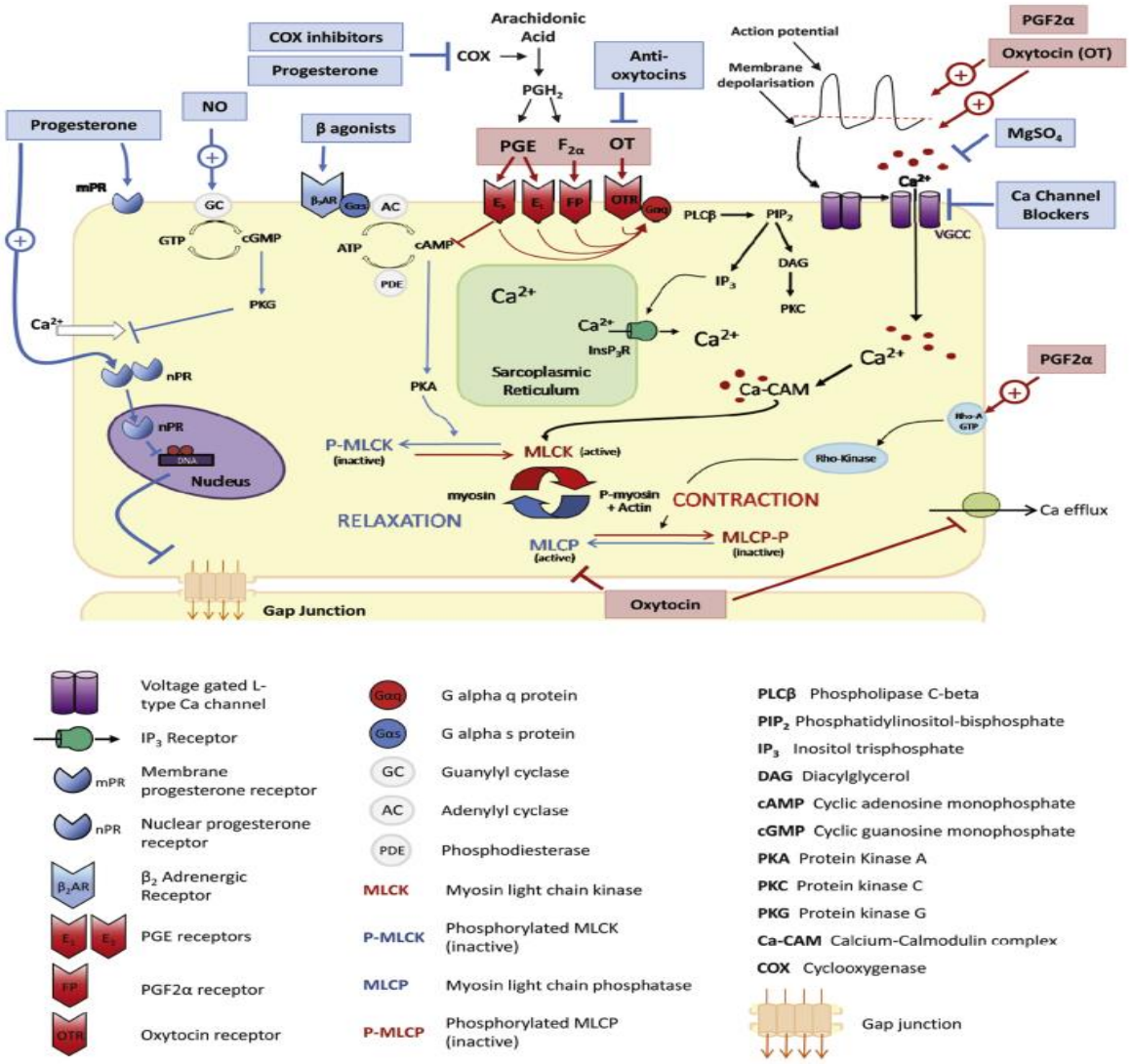

Figure 1: Schematic diagram show the major mechanisms of action by the different uterotonics and tocolytics used to modulate myometrial contractions (Arrowsmith *et al*., 2010)

3. Prostaglandin Inhibitors

Prostaglandins affect uterine muscle contraction by enhancing formation of myometrial gap junctions, causing an increase in free intracellular calcium levels and amplifying activation of myosin light chain kinase (Tsatsaris, V. *et al.*, 2004; Bernal, A. L., 2007; Smith, V. *et al.*, 2009;). Indomethacin is the prostaglandin inhibitor most frequently used for tocolysis and achieves its effect by reversibly binding to cyclooxygenase. Cyclooxygenase is an essential enzyme which converts arachidonic acid to prostaglandins. Thus, it is an efficient tocolytic drug with no serious adverse drug reaction and is indicated for short term effect during the second trimester of pregnancy.

4. Oxytocin Receptor Blockers

The only drug used in clinical practice is atosiban. It is a new intravenously used compound registered for tocolysis. Global availability, however, is limited due to cost. Atosiban competes with oxytocin for binding to oxytocin receptors in the myometrium, thus preventing the increase of free calcium in the cell (Wing, D.A. and Gaffaney, C.A., 2006). Atosiban is considered a safe drug in comparison with calcium antagonists and beta-mimetics. Adverse drug reactions were significantly lower as compared to beta-mimetics or calcium-channel blocking agents. Thus, atosiban seems to be an adequate therapeutic choice for effective tocolysis with a low maternal and fetal adverse effects profile.

5. Calcium-Channel Blockers

Uterine contractile activity is regulated by the increase in intracellular calcium ion concentration in the myometrial cells. Calcium channel blockers interfere with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration (Tsatsaris, V. *et al.*, 2004; Romero, *et al.*, 2006; Simhan. H. N. and Caritis, S. N., 2007;). Reduced intracellular calcium concentrations prevent activation of myosin light chain kinase, and thereby myometrium contraction. Nifedipine is a drug that is used more frequently in obstetrics and gynecology. It is an efficient tocolytic agent, with an easy oral route of administration, few side effects, and a low neonatal complications rate. In obstetrics and gynecology, calcium channel blockers can be used in control of pregnancy-induced hypertension, prevention of premature uterine contractions and dysmenorrhea. However, it should be used with caution in patients with compromised cardiovascular condition as they may be at risk of pulmonary oedema and cardiac failure (Smith, V. *et al.*, 2009).

Conclusion

Pharmaceutical research has provided many tocolytic agents for use in human obstetrical applications. Two of these, isoxsuprine and clenbuterol, are presently being used as obstetrical drugs by some veterinarians in India. On a purely theoretical basis, the newest of these substances, clenbuterol, appears to be a superior tocolytic for animal use although comparative studies have not yet been reported.

Conflict of Interests

There is no conflict of interest.

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