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Pharmacokinetics of Tocolytic Agents

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Contents

Abstract

Tocolytic agents are drugs designed to inhibit contractions of myometrial smooth muscle cells. Such an effect has been demonstrated *in vitro* or *in vivo* for several pharmacological agents, including β-adrenergic agonists, calcium channel antagonists, oxytocin antagonists, NSAIDs and magnesium sulfate. However, the aim of tocolysis is not only to stop uterine contractions or to prevent preterm delivery, but to prevent perinatal morbidity and mortality associated with preterm birth. The achievement of this goal has not yet been clearly demonstrated for any of the drugs available, and the use of tocolytic agents may appear controversial. Therefore, it is important to avoid maternal and fetal toxicity when tocolytic agents are used.

During pregnancy, all steps of drug pharmacokinetics are altered. Absorption of drugs administered orally is limited because of delayed stomach emptying and reduced intestinal motility. The volume of distribution of drugs is increased. The metabolic activity of the liver is increased, accelerating the metabolism of lipophilic drugs. Renal filtration is increased, leading to enhanced renal elimination of water-soluble drugs. These modifications are generally responsible for reduced plasma concentration and reduced half-life of most drugs. These specific modifications have to be taken into account when using a drug in pregnant women.

The aim of this review is to provide the reader with pharmacological data about drugs currently used to treat preterm labour. Such data in pregnant women may affect the choice of optimal drug dosage and route of administration.

Preterm birth is the leading cause of neonatal morbidity and mortality in infants without anomalies. Preterm delivery of infants before 37 weeks of gestation complicates 8–10% of births in the US, and the majority of preterm births are secondary to preterm labour (spontaneous preterm deliveries).[1] During the past 40 years, a number of pharmacological agents have been used to treat preterm contractions in order to prevent preterm delivery. These tocolytic drugs are widely used by obstetricians, yet the incidence of preterm delivery remains unchanged. Tocolysis is a purely symptomatic treatment of preterm labour, since the aetiology of the preterm birth (such as infection or cervical incompetence) is often unknown or only discovered after delivery.[1] Moreover, the efficacy of tocolysis remains controversial since a recent systematic review did not provide evidence of a significant improvement in neonatal morbidity or mortality.[2] For several reasons, it is difficult to assess the efficacy of tocolytic agents. Firstly, the criteria used to define preterm labour are heterogeneous in different studies. Secondly, in most placebo-controlled trials, almost 70% of patients receiving placebo are undelivered 48 hours after inclusion. Thus, trying to demonstrate benefits of tocolytic agents on neonatal morbidity requires large numbers of patients in each group. Thirdly, there are wide variations among studies in the outcomes evaluated. Although the final objective should be the prevention of perinatal morbidity and mortality associated with preterm delivery, in most studies the main outcome was prolongation of pregnancy. The result is an excessive use of tocolytic agents in clinical practice, exposing patients and fetuses to inappropriate risks and adverse effects.

The main improvements in neonatal outcome in the last few years have been obtained by the use of corticosteroids for fetal lung maturation[3-5] and by prenatal transfer to centres with neonatal intensive care facilities[3-5] in case of very preterm deliveries. It is believed that tocolytic therapy, by prolonging pregnancy, even for a short period of time, may be useful in allowing these measures to be performed.[6]

The aim of this manuscript is to provide the reader with pharmacological data about drugs currently used to treat preterm labour. Such data in pregnant women may affect the choice of optimal drug dosage and route of administration. During pregnancy, all steps of drug pharmacokinetics are altered.[7] Absorption of drugs administered orally is limited because of delayed stomach emptying and reduced intestinal motility. The volume of distribution of drugs is increased.[8] The metabolic activity of the liver is increased, accelerating metabolism of lipophilic drugs. Renal filtration is increased, leading to enhanced renal elimination of water-soluble drugs. These modifications are generally responsible for reduced plasma concentration and reduced half-life of most drugs.

Most of the drugs used to inhibit preterm labour in clinical practice will be discussed in this review: β-adrenergic agonists, calcium channel antagonists, oxytocin antagonists, NSAIDs and magnesium sulfate. However, some of these drugs cannot be considered as first-line therapeutic options, since they are either effective but associated with severe potential adverse effects (NSAIDs) or their effectiveness has not been demonstrated (magnesium sulfate). Treatments used for the prevention of preterm labour will not be considered in this paper.

A literature search of MEDLINE and the Cochrane Library was conducted for the years 1960 to June 2002 with regard to the pharmacokinetics of tocolytic agents. The keywords used were: 'tocolytics', 'pharmacokinetics', 'ritodrine', 'terbutaline', 'salbutamol', 'magnesium sulfate', 'nonsteroidal anti-inflammatory', 'indomethacin', 'nifedipine', 'nicardipine' and 'atosiban'. The reference lists of identified articles were examined to find additional relevant studies.

1. β-Agonists

β-Agonists have been studied extensively and have long been considered acceptable for first-line clinical use. Results from the literature show that β-agonists are more effective than placebo in stopping preterm labour and delaying pregnancy for 48 hours.[9] No benefits have been demonstrated on

perinatal morbidity or on reduction of preterm delivery. Because β-agonists are responsible for frequent maternal adverse effects (such as tachycardia, dyspnoea and maternal anxiety) and rare but potentially life-threatening complications (pulmonary oedema), their use is today becoming more limited.[9-12]

Three types of β-adrenergic receptors have been described – the β_1, β_2 and β_3 subtypes.[13] Subtypes β_1 and β_2 are responsible for the tocolytic action and adverse effects of the drugs. The β_1 adrenergic receptors are localised in the heart, small bowel and adipose tissue.[14] When activated, they are responsible for increased chronotropic and inotropic effects. The β_2 adrenergic receptors are found in smooth muscle of the uterus, blood vessels and bronchioles.[14] When activated they cause uterine relaxation, vasodilation and bronchodilation. The more recently described β_3 adrenoreceptors are linked to smooth muscle relaxation in gastrointestinal, urinary tract, respiratory tract and vascular smooth muscle.[13] β-Adrenergic agonists also have metabolic effects, such as lipolysis through β_1 receptors and glycogenolysis through β_2 receptors.[15-19]

β-Adrenergic receptors are coupled to the enzyme adenylate cyclase. β-Adrenergic drugs increase intracellular levels of cyclic adenosine monophosphate, which inhibits myosin light-chain kinase activity through direct phosphorylation. They also act by lowering intracellular levels of calcium. The result is smooth muscle cell relaxation secondary to disruption of the actin-myosin interaction.[14]

Several β_2-agonists may be used for tocolysis. Ritodrine is the most common, but terbutaline and salbutamol (albuterol) are also used in many countries.

Caritis et al.[11,20,21] performed several studies on the pharmacokinetics of these agents in animals and in humans. Ritodrine pharmacokinetics were compared between four nonpregnant and four pregnant Rhesus monkeys.[22] Significant differences were demonstrated in the distribution phase half-life (0.40 ± 0.08 hours and 0.21 ± 0.03 hours), volume of distribution (1.99 ± 0.94 L/kg and 4.75 ± 0.90 L/kg) and plasma clearance (18.8 ± 7.1 mL/min/kg and 27.2 ± 5.0 mL/min/kg), in the pregnant and nonpregnant animals, respectively. Pregnant animals receiving ritodrine had higher steady-state plasma concentrations than nonpregnant animals (104 vs 53 μg/L, respectively, at an infusion rate of 2 μg/kg/min). The volume of distribution of ritodrine in pregnant animals was less than that in nonpregnant animals. The authors stated that although the reason for this was not clear, these findings suggested that ritodrine binding to extravascular tissue was reduced in pregnancy.[22]

The pharmacokinetics of intravenous ritodrine have also been studied in 13 pregnant women (table I).[23] With constant infusion of 50 μg/min, steady-state ritodrine concentrations reached 28 ± 11 μg/L (SD) with a range of 15–45 μg/L. The apparent volume of distribution was 6.95 ± 3.54 L/kg, indicating that ritodrine is extensively bound to extravascular tissue. When the ritodrine infusion was stopped, plasma concentrations fell rapidly, initially with a distribution half-life of 5.9 ± 6.0 minutes. After the initial rapid fall over a few minutes, plasma concentrations decreased more slowly, with a mean second half-life of 156 ± 51 minutes.

The pharmacokinetics of terbutaline after subcutaneous administration of a therapeutic dose (250μg) have been studied by Leferink et al.[24] in 14 patients. The drug was rapidly absorbed, with a half-life of 7 minutes. An elimination constant of 0.27 ± 0.07 h^{-1} was observed. The elimination process was biphasic in five patients, with a mean elimination constant of the second phase of 0.10 ± 0.04 h^{-1}. In another study, Lyrenas et al.[25] compared the pharmacokinetics of intravenous terbutaline 250μg during and after pregnancy in eight patients. Mean

Table I. Pharmacokinetics of β-adrenergic agents in pregnant women

Parameter and unit	Ritodrine	Terbutaline
Dose	50 μg/min intravenous	250μg subcutaneous
Peak serum concentration (μg/L)	28 ± 11	0.7
Half-life (min)	5.9 ± 6 (first), 156 ± 51 (second)	7
Plasma clearance (L/h)		0.27 ± 0.07
Volume of distribution (L/kg)	6.95 ± 3.5	

plasma clearance was 30% higher during pregnancy than after delivery. There was a decrease in mean half-life from 5.3 to 3.7 hours and in mean residence time from 5.3 to 3.4 hours. There was no change in volume of distribution. The mean steady-state plasma concentration of terbutaline was about 30% lower during pregnancy than after delivery.

There are two studies on the pharmacokinetics of salbutamol in pregnant women.[26,27] After bolus injection of salbutamol 184μg, mean peak concentration was 8.33 ± 1.9 μg/L.[27] Hutchings et al.[26] found minor differences in salbutamol pharmacokinetics between pregnant and nonpregnant women. During pregnancy, the total clearance of salbutamol was 501 ± 185 mL/min. In the same study, concentrations of salbutamol required to inhibit preterm contractions were 8–33 μg/L.

On the basis of the pharmacokinetic parameters defined previously, Caritis et al.[23] made recommendations for the ritodrine infusion regimen. There is a wide variation in response to a given dose of ritodrine (tocolytic efficacy and adverse effects) among subjects and within individual subjects. The infusion of ritodrine should be started at 50 μg/min and be increased every 20 minutes until uterine quiescence is achieved or unacceptable adverse effects occur. The maximal infusion rate was defined as 350 μg/min. Once labour is inhibited, infusion rate should be maintained for 60 minutes and then decreased by 50 μg/min every 30 minutes until the lowest effective rate is achieved (but not <50 μg/min). The lowest effective infusion rate should be (arbitrarily) maintained for 12 hours.[23]

Maternal adverse effects include tachycardia, nausea, chest pain, shortness of breath, cardiac dysrythmia, hypotension and pulmonary oedema. Caritis et al.[23] also demonstrated that adverse effects were observed most commonly when the infusion rate and concentration of ritodrine were being increased. The maximum infusion rate should be adapted to maternal adverse effects and should not be increased when the maternal heart rate reaches 120 beats/minute, whatever the tocolytic efficacy.

Tachyphylaxis is another characteristic of β-adrenergic therapy. Patients treated with β-adrenergic drugs can develop tolerance to the medication. Animal experiments show that continuous infusion of ritodrine for 24 hours is associated with down regulation of β-adrenergic receptors and decrease in adenylate cyclase activity. The result is reduced tocolytic activity.[28]

Ritodrine and terbutaline are known to cross the placenta with a fetomaternal ratio of 0.30.[29,30] They induce β-adrenergic stimulation in the fetus with a marked increase in fetal heart rate.[31] The effects of ritodrine on fetal haemodynamics were recently studied by Gokay et al.[32] using Doppler sonography. Ritodrine infusion caused an increase in the left cardiac output and in the pulsatility index of the middle cerebral artery, whereas the pulsatility index of the umbilical artery was decreased.[32] Metabolic adverse effects have also been described in fetuses after ritodrine administration in pregnant sheep.[15] During the first 6–8 hours of ritodrine infusion, glucose, lactate and insulin increased sharply, whereas glucagon and α-amino acid nitrogen decreased. After this initial increase, these components returned to the normal range in maternal blood during intravenous infusion of ritodrine for 72–96 hours. Only fetal blood lactate levels remained elevated throughout the infusion.[15]

β-Adrenergic agents are effective in prolonging pregnancy, although without evidence of significant improvements in neonatal outcomes. Despite frequent and potentially severe maternal adverse effects, they are still used in first line in some centres because of a long experience in clinical practice.

2. Magnesium Sulfate

Magnesium sulfate has been used for decades in pregnant patients with pre-eclampsia or preterm labour. However, there is no evidence in the literature that magnesium sulfate is able to stop preterm labour or to reduce perinatal morbidity.[6,33-35] Moreover, concern has been raised by some authors for increased perinatal mortality associated with high doses of magnesium sulfate.[36-38] An ongoing study by the Maternal-Fetal Medicine Network is evaluating the fetal and neonatal effects of magnesium sulfate.[39] Although magnesium sulfate is still used

for the treatment of preterm labour, currently available data on neonatal morbidity and mortality associated with its use suggest that it should be abandoned as first-line therapy.[37,40,41]

Myorelaxation by magnesium sulfate has first been demonstrated *in vitro*.[34] Concentrations of magnesium sulfate required to inhibit myometrial activity were similar to serum concentrations associated with maternal toxicity (14–30 mEq/L). The mechanism by which magnesium sulfate inhibits myometrial contractions is still controversial.[34] It is thought to have a direct effect on the uterine smooth muscle by antagonising calcium at the cellular level and in the extracellular space.[34] Elevation of magnesium concentration induces negative feedback on parathyroid hormone secretion and reduces renal reabsorption of calcium. The resulting effect is hypocalcaemia and hypercalciuria.[42,43] Magnesium may also act by a competing effect on calcium channels. Together, these effects reduce intracellular levels of calcium which prevents the activation of the actin and myosin complex.[35]

Magnesium is the second most abundant intracellular cation,[34] mostly localised in the bone and in the blood cells. Only 1% is extracellular. Magnesium is completely excreted from the body by the kidneys by free filtration at the glomerules. A considerable fraction of the filtered magnesium is reabsorbed in the tubules in inverse proportion to the serum concentration.[44]

Pharmacokinetics of magnesium sulfate have first been studied in patients with pre-eclampsia. After intravenous administration (loading dose of 4g over 15–30 minutes and maintenance infusion of 1 g/h), serum concentrations ranged from 0.8 to 2.8 mmol/L (average 1.7 mmol/L).[45] Estimated volume of distribution was 32.3L, with most of the magnesium pool distributed into bone, skeletal muscle and blood cells (but not erythrocytes). After termination of the infusion, magnesium sulfate rapidly decreased with a half-life of 5.2 hours. More than 90% of the magnesium infused was excreted within 24 hours.

A recent study showed that the pharmacokinetics of magnesium sulfate in patients with preterm labour and pre-eclampsia are similar (table II).[46] The volume of distribution of magnesium was 15.6L. After 30 minutes of infusion (4–6g of magnesium sulfate), the mean total magnesium and ionised magnesium concentrations were 5.56 ± 0.30 mg/dL and 2.57 ± 0.17 mg/dL, respectively. The ionised fraction of magnesium was 49% ± 3%. The half-lives for total magnesium and ionised magnesium were 610 ± 137 and 577 ± 110 minutes, respectively. The initial clearance of total magnesium was approximately 60 ± 14 mL/min.

Magnesium sulfate should be titrated according to maternal toxicity and clinical response.[47] Toxicity appears over 9 mg/dL (10 mEq/L); patellar reflexes disappear between 9 and 13 mg/dL and respiratory depression occurs at 14 mg/mL.[34] The antidote for magnesium adverse effects is 1g of calcium gluconate given intravenously. For *in vivo* tocolytic effect, maternal serum concentrations should be maintained between 4 and 9 mg/dL (5–8 mEq/L).[34] However, it has been shown that magnesium serum concentrations do not correlate with tocolytic effect and, therefore, they should not be used as an endpoint to therapy.[47]

For technical reasons, most obstetric-related studies of magnesium sulfate have measured total magnesium concentrations and not ionised magnesium. Recently, Taber et al.[46] suggested that the measurement of total magnesium may not be appropriate for the titration of therapeutic magnesium infusions because of the lack of correlation between total magnesium and the physiologically active ionised magnesium. However, to date, no well-controlled study has shown benefit of magnesium sulfate as a tocolytic agent.[6,35] Magnesium sulfate is not better than placebo in the treatment of premature labour, and if such therapy is used, it is important to

Table II. Pharmacokinetics of magnesium sulfate in pregnant women

Parameter and unit	Value
Dose	4g intravenous
Peak serum concentration (mg/dL)	5.56 ± 0.30
Half-life (min)	610 ± 137
Plasma clearance (mL/min)	60 ± 14
Volume of distribution (L)	15.6

avoid maternal or fetal toxicity. Use of increasing doses of magnesium sulfate is, therefore, inappropriate.

Magnesium sulfate crosses the placenta. Magnesium readily distributes into the amniotic fluid and the fetal compartment.[48] Some concerns have been raised by recent studies showing that magnesium sulfate treatment could be associated with impaired neonatal outcome, especially mortality.[41] High doses of magnesium sulfate (>48g) are likely to be associated with increased perinatal mortality among fetuses and neonates weighing 700–1250g.[40] Moreover, a dose-response relationship between serum ionised magnesium in the umbilical cord and neonatal death[38] or neonatal intraventricular haemorrhage[36,37] has been reported.

Other neonatal adverse effects have been described after magnesium sulfate therapy, such as lethargy, hypotonia and faecal impaction.[14] Neonatal hypocalcaemia and respiratory depression are possible.[49,50] These adverse effects are rare and are dose-dependent.

3. Calcium Channel Antagonists

All currently available calcium antagonists share the common property of blocking the transmembrane flow of calcium ions through voltage-gated L-type (slowly inactivating) channels.[51] Other calcium channels with different electrophysiological properties have also been identified. These channels, to which the calcium antagonists do not bind, include the N-type channels in neuronal tissue, P-type channels in Purkinje tissues, and T-type (transient potential) channels in cardiac nodal structures and vascular smooth muscle.[52]

The L-type calcium channel has been found in vascular smooth muscle (arteriolar and venous), nonvascular smooth muscle (bronchial, gastrointestinal, genitourinary and uterine) and noncontractile tissues (pancreas, pituitary, adrenal glands, salivary glands, gastric mucosa, white cells, platelets and lacrimal tissue).[53] Blockade of L-type channels in vascular tissues results in the relaxation of vascular smooth muscle and in cardiac tissue results in a negative inotropic effect.[51]

Calcium channel antagonists have been used for tocolysis since 1980.[54] Nifedipine is the calcium antagonist most commonly used in this indication. Such use is, however, not approved by the American or European drug agencies. Several randomised studies have compared calcium channel antagonists with β-adrenergic agonists. Their results suggested that the two drugs had similar tocolytic efficacy, but that calcium channel antagonists caused fewer adverse effects.[55-58] Recent meta-analyses suggest that calcium antagonists are more effective and much better tolerated than β-agonists.[10,59,60] Moreover, nifedipine seems to be associated with lower neonatal morbidity.[10,59,60]

3.1 Nifedipine

Nifedipine is the calcium channel antagonist most commonly used for tocolysis. It is a type 2 calcium channel antagonist of the dihydropyridine family that inhibits the inward flow of calcium across the L-type slow channels of cellular membranes,[61] thus favouring smooth muscle relaxation. According to the target organ, nifedipine causes vascular relaxation (especially on arteries rather than veins), uterine relaxation (tocolytic effect) and bladder smooth muscle relaxation.[62] Interestingly, the vascular relaxation obtained with nifedipine in hypertensive women does not occur significantly in normotensive patients.[62] This explains the absence of severe hypotension induced by high doses of calcium antagonists for tocolysis in normotensive patients.[63] Nifedipine is also characterised by lack of tachyphylaxis and by a reversible effect after discontinuation of the treatment.[62] Unlike type 1 calcium channel antagonists, type 2 calcium channel antagonists have minimal effect on the cardiac conducting system.[61] *In vitro*, nifedipine inhibits myometrial contractions in myometrial muscle strips from pregnant and nonpregnant women.[64,65]

After oral administration, nifedipine is rapidly and nearly completely absorbed from the gastrointestinal tract, but first-pass metabolism results in 40% of the drug being converted into inactive products in the liver. Metabolites are excreted in urine (70–80%) and faeces (20–30%).[66] Maximum se-

rum concentrations of the drug are obtained most quickly when the capsule is bitten before the drug is swallowed. With standard oral administration, the peak concentration occurs slightly later. Ferguson et al.[67] evaluated the pharmacokinetics of nifedipine in pregnant women. Mean peak concentration was 97 μg/L (23.4–197.9 μg/L) during sublingual therapy with nifedipine 10mg. After oral intake of nifedipine 10mg, peak serum concentration was 38.6 ± 18 μg/L at 40 minutes (table III). At 6 hours after the last oral dose, concentrations ranged from 1.5 to 21 μg/L (mean 7.2 μg/L). The mean half-life after initial sublingual administration was 81 minutes. During pregnancy, peak serum concentration and half-life of nifedipine are decreased, and the clearance rate is increased compared with nonpregnant patients. Because of these differences, the duration of action of nifedipine is limited to 6 hours.[68] Long-acting forms of nifedipine have been developed and marketed, but none of them have been studied in pregnancy.

Placental transfer of nifedipine has been documented. Nifedipine is found in umbilical cord blood, fetal blood and amniotic fluid. The ratio of nifedipine concentration in umbilical cord blood compared with maternal serum is 0.93.[61] It has been shown that maternal therapeutic concentrations of nifedipine are not responsible for fetal hypotension.[69,70] No changes in fetal or utero-placental Doppler blood flow have been shown with the maternal use of nifedipine. However, at high concentrations, especially when nifedipine is administered by the sublingual route in hypertensive patients, acute hypotension associated with fetal distress has been reported.[71-73]

Table III. Pharmacokinetics of calcium channel antagonists in pregnant women

Parameter and unit	Nifedipine	Nicardipine
Dose	10mg oral	60mg oral
Peak serum concentration (μg/L)	38.6 ± 18	9.2
Half-life (h)	1.3 ± 0.5	
Plasma clearance (L/h/kg)	2.0 ± 0.8	

3.2 Nicardipine

Nicardipine is another calcium antagonist used for tocolysis in clinical practice. Because the action of each calcium antagonist differs, each agent must be evaluated separately. *In vitro*, nicardipine was found to have more potent smooth cell relaxing effects than nifedipine.[74] This may be due to the associated inhibiting effect of nicardipine on phosphodiesterase and enhanced intracellular calcium sequestration.[74]

The pharmacokinetics of nicardipine in pregnant hypertensive women have been evaluated by Carbonne et al.[75] At 2 hours after oral administration of nicardipine 60mg, the maternal plasma concentration was found to be 9.2 μg/L. Maternal concentration rapidly declined after 2 hours and was below 1 μg/L after 6 hours. Higher maternal concentrations were obtained with intravenous infusion. At steady state, maternal plasma concentrations reached 53.4 μg/L at an infusion rate of 2 mg/h and 62.7 μg/L at 4 mg/h.

Transplacental passage of nicardipine was confirmed. The ratio between maternal plasma and fetal plasma concentrations ranged from 0.2 to 0.5. There was no linear correlation between maternal and fetal plasma concentrations, and the ratio was lowest with intravenous therapy.

4. Oxytocin Antagonists

Several types of oxytocin antagonists have recently been developed and others are currently under development, including non-peptidic agents. The only currently used oxytocin antagonist in clinical practice is atosiban, a peptidic agent.[76]

A recent multicentre randomised trial demonstrated that atosiban is as effective as ritodrine for stopping preterm labour, but with fewer maternal adverse effects.[77] Compared with placebo, no difference in maternal or fetal adverse effects was observed with the use of atosiban.[78] The use of atosiban as a tocolytic is approved by most European drug agencies, but not by the US FDA. Because of the absence of maternal adverse effects, the use of atosiban as a first-line tocolytic agent is being considered in Europe.

Peptidic oxytocin antagonists act by competition with oxytocin at its receptors on the myometrial plasma membrane, inhibiting the second messenger process that normally leads to an increase in intracellular free calcium and to contraction. Atosiban is a nonapeptide desamino oxytocin analogue that has greater affinity for oxytocin binding sites than for vasopressin binding sites of the myometrial membranes.[79] Atosiban has also been shown to be a competitive vasopressin antagonist.[80]

Contrary to other drugs previously mentioned, atosiban has been specifically developed for tocolysis, providing adequate pharmacokinetic data in pregnant patients. The pharmacokinetics of atosiban in 11 healthy nonpregnant subjects were studied by Lundin et al.[81] Atosiban was administered intravenously as bolus injection (10 nmol/kg body weight). The total body clearance amounted to 0.623 ± 0.099 L/h/kg (SEM) and the half-life to 16.2 ± 2.4 minutes. Peak concentrations in plasma appeared 2–8 minutes after intravenous administration. It was concluded that the half-life allowed treatment of patients in premature labour with intravenous infusion at 50 μg/min. Blood pressure and pulse rate were not significantly affected by the drug and no other adverse effects were observed. Similar studies[82,83] showed a 97% bioavailability and significant binding to proteins (33%) and erythrocytes (13%). The volume of distribution of the drug in nonpregnant patients was 13.1 ± 3.8L. In a randomised placebo-controlled study, Kahn[84] showed that atosiban had no adverse effects at infusion rates from 10 to 300 μg/min. In this study it was also demonstrated that half-life and volume of distribution of the drug were not dose-dependent. Inhibition of uterine contractility was first demonstrated in nonpregnant women.[85] Bolus intravenous injections of atosiban 0.2–1.25mg decreased uterine tone and frequency of contractions induced by vasopressin for 10–20 minutes.

The pharmacokinetics of atosiban in pregnant women with preterm uterine contractions have been studied by Goodwin et al.[86] (table IV). Eight patients were included in the study. Atosiban was administered by continuous intravenous infusion at a rate of 300 μg/min until uterine contractions stopped for 6 hours or up to a maximum infusion length of 12 hours. Plasma atosiban concentrations reached steady state (442 ± 73 μg/L, mean ± SD) within 1 hour after the start of the infusion. After completion of the infusion, plasma atosiban concentrations declined rapidly in a biexponential manner (initial half-life 13 ± 3 minutes; terminal half-life 102 ± 18 minutes). The effective half-life was 18 ± 3 minutes. Clearance and volume of distribution were found to be 41.8 ± 8.2 L/h and 18.3 ± 6.8L, respectively.

Minimal placental passage of atosiban has been shown by Valenzuela et al.[87] The average ratio for the fetal to maternal compartment was 0.124 ± 0.025. Drug concentrations in fetal circulation did not increase with higher infusion rates.

5. NSAIDs

NSAIDs inhibit prostaglandin synthesis.[34] Because of the importance of prostaglandins in the initiation of parturition, NSAIDs have been widely used as tocolytic agents. Placebo-controlled studies support the use of indometacin (indomethacin) as a tocolytic.[88,89] However, because of severe fetal and neonatal adverse effects, the use of NSAIDs is now restricted.[90,91]

The most commonly used NSAID for tocolysis is indometacin, probably because of the historic study by Zuckerman et al.[92] reporting a delay in delivery by more than 1 week in 80% of women treated. Indometacin is a nonselective cyclo-oxygenase (COX) antagonist, in which it is similar to ibuprofen, ketoprofen or diclofenac.

The complete pharmacokinetics of indometacin in nonpregnant women are available (table V).[93,94] Following oral administration, the absorption of the

Table IV. Pharmacokinetics of atosiban in pregnant women

Parameter and unit	Value
Dose	300 μg/min intravenous
Peak serum concentration (μg/L)	442 ± 73
Half-life (min)	16.2 ± 2.4
Plasma clearance (L/h)	41.8 ± 8.2
Volume of distribution (L)	18.3 ± 6.8

Table V. Pharmacokinetics of indometacin in nonpregnant women

Parameter and unit	Value
Dose	50mg oral
Peak serum concentration (mg/L)	2–3
Half-life (h)	2.2
Plasma clearance (L/h/kg)	0.044–0.109
Volume of distribution (L/kg)	0.34–1.57

drug is rapid and complete, but with large inter- and intraindividual variations. Peak plasma concentrations of 2–3 mg/L are achieved with 1–2 hours. In plasma, 90% of indometacin is bound to albumin at therapeutic plasma concentrations.[93] After a 50mg oral dose, indometacin has a biological half-life of 2.6–11.2 hours, a plasma clearance of 0.044–0.109 L/kg/h and a volume of distribution of 0.34–1.57 L/kg.[94]

In pregnant women, indometacin can be given either orally or rectally, with a usual dose of 150–300 mg/day. Many authors propose an initial loading dose (100–200mg rectally, 50–100mg orally) and then 25–50mg every 4–6 hours.[95] After an oral loading dose, peak concentrations are achieved within 2 hours.[96] The rectal route offers faster absorption.[96] Maternal half-life has been reported to be 2.2 hours.[97] Metabolism in the liver into inactive products accounts for 90% of the disposition of indometacin,[97] and 10% is excreted unchanged in the urine.

Indometacin and other NSAIDs cross the placenta. For indometacin, the fetomaternal ratio reaches 100% by 6 hours after administration.[97] Moreover, the half-life of the drug is much longer in the fetal circulation (14.7 hours) than in the maternal circulation (2.2 hours). Such pharmacokinetics, together with the mode of action of NSAIDs, may play a role in the high rate of fetal adverse effects (oligohydramnios, premature closure of the ductus arteriosus).

6. Conclusions

Pharmacokinetic data on drugs used for tocolysis are rather limited in pregnant women and in the neonate. β-Agonists have been studied quite extensively, as they have been the main registered tocolytic drug in many countries for many years. Oxytocin antagonists have been designed for tocolysis and have thus been studied as part of the assessment required for registration of the drug. Other drugs, such as calcium channel antagonists, are tending to become more widely used as tocolytic therapy, but are not yet registered for this indication. More thorough assessment of the pharmacokinetics of these drugs in mother and fetus will be required if they are to be used more extensively in the future.

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