What does the anaesthetist need to know about uterotonics?.

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Abstract

It is not possible to talk about the control of prophylactic uterotonic agents without talking about spontaneous labour at term, because labour includes neuroendocrine mechanisms. Also, immunological and inflammatory factors are part of the of this process - many of them based on synthesis of placental cortisol and prostaglandins.

The thinning of the cervix (effacement), increased cervical dilation, and myometrial contractive activity have molecular and cellular regulations. The combination of elements like leukocytes, (T cells, macrophages, polymorphonuclear leukocytes) points to inflammatory reactions. In fact, at the onset of labour, there is overexposure to inflammatory cytokines. This is not a spontaneous process; an important role is played by two hormones and their receptors (RP): progesterone (PG), corticotropin-releasing hormone (CRH) and one protein associated with progesterone: NF- kB.

Keywords: Uterotonics, Oxytocin, Carbetocine, Labour, anaesthesia, analgesia, obstetric haemorrhage.

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Introduction

Hormonal Factors: Progesterone

For the majority of pregnancy, progesterone promotes myometrial relaxation and its withdrawal initiates parturition; this is confirmed by the decrease in plasmatic levels during delivery. Progesterone, through specific progesterone receptors (PRs) in uterine tissues, is a key player in this process, in women, a functional progesterone withdrawal occurs by changes in PR isoform expression and/or function in myometrial cells. Research in the last 10 to 20 years has shown that progesterone actions are mediated by a variety of receptors (PR) including the classic nuclear PRs, PR-A and PR-B that mediate genomic actions [1].

The A receptor (PR-A) is a truncated form of B receptor (RP-B). This latter receptor has a progesterone-sensitive genomic promotion of action. The RP-A represses the transcriptional activity induced by B. There is an increased proportion of mRNA between the RP-A/RP-B ratio during labour. Furthermore, there has been identification of isoforms RP-B coupled with membrane C protein (mRP) This is involved in the muscular contraction mediated by the myosin phosphorylation. This mRP is increased during labour [2].

The role of the NF- kB

NF-kB is a transcriptional protein observed at cellular level in the stress response. At term, pregnancy progesterone activity decreases not only due to receptor regulation but because this protein has an antagonist activity to PRs, weakening the receptor expression of myometrial muscle, therefore there is a increase of the expression of RP-A . Moreover, the stretching of the foetal membrane needs NF-kB, COX-2 and PGE2.

Role of the Prostaglandins:

Uterine stretch leads to stretch of the foetal membranes, including the amnion, an important source of prostaglandin E2 (PGE2). Chromatin immunoprecipitation studies confirmed that stretch increased binding of NF-kB to the COX-2 promoter in vivo. PGE2 increase mRNA PR- A/PR-B ratio, therefore stretch of the amnion may contribute to increased expression of COX-2 and PGE2 and this prostaglandin activates NF-kB and reduce the synthesis of PR-B in this way the PGE2 contributes to myometrial contractions [3].

Role of CAMP2: endocrine and labour:

CAMP 2nd messenger stimulates protein kinase A enzymes which phosphorylates other proteins through intracellular transducers and recruit and inactivate a transcriptional coactivator. The decrease in transcriptional cofactors of the uterine fundic myometrium can cause a decrease in cAMP, generates a decrease in the transcription of RP-PG and makes the uterus more sensitive to the stimulation of uterine contractions. The fall of the transcriptional cofactor is also due to the inflammatory cascade. Although serum oestrogen levels have been reported to remain stable between the last weeks of gestation and labor, oestrogens receptors increase at delivery and have a stimulating effect on myometrial contractions by promoting the expression of proteins such as the connection of RP to oxytocin [4].

Progesterone withdrawal has been considered a major determinant of labor initiation, since it relaxes the myometrium by repressing the expression of genes that encode factors collectively called contraction-associated proteins, connexin, cyclooxygenase-2 and oxytocin receptor.

Moreover, increased progesterone activity is associated with increased 15- hydroxyprostaglandin dehydrogenase expression, which catalyses the conversion of PGE2 and PGF2α During

spontaneous labor, although no reduction in serum progesterone levels has been observed, a parturition cascade exists, that removes the mechanisms responsible for uterine quiescence and recruits factors that initiate uterine activity, promoting the process of labor.

Some questions about parturition activation have been partially answered after the introduction of the "functional" progesterone withdrawal concept, that consists of myometrial sensitivity loss to progesterone due to the increased expression of the non-functional progesterone receptor PR-A and which results in an increased PR-A to PR-B ratio. This concept explains why, despite high progesterone levels, the myometrium at term loses its refractoriness in humans.

Corticotropin-releasing hormone (CRH) has very rapid rise in late pregnancy associated with an E3 surge and altered P/E3 ratio, this is associated with an estrogenic environment at the onset of labor, it´s clearly implicated in the placental hypothalamic-pituitary-adrenal axis [5]. The main goal of this axis is to induce, before the onset of labor, a shift of progesterone towards estradiol production which in turn will mediate some of the known events leading to or preparing for parturition. During gestation, placental CRH circulates in maternal blood mostly bound to CRH-binding protein (CRH-BP) which is produced by the maternal liver and the placenta. There are two CRH receptors isoforms for CRH: CRH-R1: Very high affinity to protein G and CRH-R2: R2 (urocortin's) possibly involved in increased oestrogen synthesis.

Foetal membranes are an interfacing with paracrine effect, they are the largest source of PGE2 also cytokines, interleukin-1 (IL-1), IL-8 and tumour necrosis factor-alpha (TNF-A) on amniotic fluid in a term pregnancy. Then this E2 disseminated by myometrium and produces inflammation, Oxytocin receptors and uterine contractions.

Distribution of the layers of the fetal membranes: 2 fetal (orange) and maternal (blue) layers, progesterone synthesized in the amnion exerts a direct action on the myometrium and increases estradiol (Figure 1).

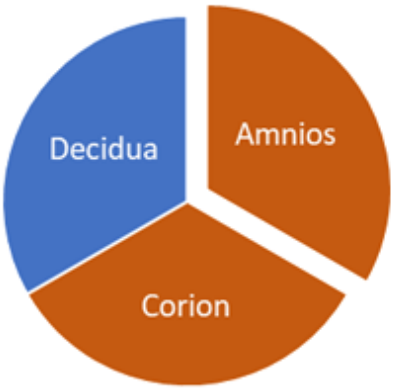

Figure1: *Distribution of the layers of the fetal membranes.*

Once we have reached this point, we will talk about oxytocin and its physiological and molecular characteristics in labor that make it the principal hormone of contraction regulation.

Role of oxytocine in labor

Myometrial Activation is the transformation of the uterine muscle from inactive to contractile, activation prepares the uterus for labor and alters it from a relatively insensitive organ to a sensitive, pro-contractile organ. Once the uterus has become activated, a process termed stimulation initiates the powerful coordinated contractions of labor. It is accepted that hormone oxytocin has a fundamental role in the stimulation process, and there is growing evidence that this hormone might also contribute to the process of activation as well.

Almost half a century of experimental research on many types of smooth muscle provided convincing evidence that contractility of smooth muscle is regulated not only by electromechanical coupling but also by membrane potential independent, pharmacomechanical coupling. In the presence of oxytocin there are a transient increase, and then cytoplasmic Ca2+ returns to its resting level. In vitro, the intraluminal Ca2+ decreases at the beginning of the oxytocin application and remains at a decreased level for as long as the cell is exposed to Ca2+- free extracellular solution, even though the oxytocin has been washed out. After readmission of extracellular Ca2+, the [Ca2+] L returns to its initial level within 2-3 min. However, under physiological conditions (ie, in the presence of extracellular Ca2+), a completely different result is obtained: the cytoplasmic Ca2+ rises to a somewhat higher level and, more importantly, remains at this high level for long period of time. The dynamics of luminal Ca2+ is also different under these conditions. Thus, only a transient fall in the [Ca2+] L level occurs at the beginning of oxytocin application, immediately followed by the increase above resting level, suggesting uptake of Ca2+ into the SR. These data indicate that, under physiological conditions, oxytocin triggers a complex [Ca2+]I response consisting of initial Ca2+ release from the SR followed by Ca2+ entry from outside .

However, IP3-mediated calcium release is not the complete explanation that clarifies the action of oxytocin. It has been found that the use of a calcium release inhibitor at the sarcoplasmic reticulum level, tapsigargine, blocks only partially the action of oxytocin at the myometrial level. Another generally accepted mechanism of the myometrial excitation- contraction coupling is that the action potential-induced rise in [Ca2+]i triggers acto-myosin interaction by Ca2+-calmodulin mediated phosphorylation of the regulatory myosin light chains. In the presence of oxytocin, or indeed any IP3 producing agent, the amplitude of the action potential-induced [Ca2+]I transients can, in principle, be potentiated by sustained elevation of IP3. The possibility of such potentiation stems from the bell-shaped Ca2+ dependence of the IP3 receptor sensitivity.

Regulatory mechanisms of smooth muscle contractility is not only regulate by electromechanics (calcium release, calmoduline binding and Myosin Kinase activation) but also by

a no- dependent membrane potential such a pharmacomechanics coupling. The addition of oxytocin (1 nmol/L) to spontaneously and independently way active myometrium increasing both the duration of the Ca ++ signal and the sensitivity of the contractile machinery to [Ca ++] Intracellular [13] and regulates the duration of the periodic Ca ++ signals and the sensitivity of the contractile machinery to Ca ++. The latter is likely to be mediated by rho kinase, which is essential for the effective coupling of increases in [Ca ++] i to tension

At least three distinct components can be discerned in the effect of oxytocin on human uterine smooth muscle through the release of RS calcium and calcium sensitization.

- increase in frequency of contractions;
- initial transient increase in the base tone (incomplete relaxation)
- long-lasting increase in the amplitude and duration of phasic contractions.

Human myometrial activity during C- section

How is uterine muscle function in a programmed caesarean section without labor?

In labor, there is a slow myometrial depolarization that is produced before actions potentials discharged , however, in C-Section this step skips because inflammatory factors are released from the surgical wound on the uterus wherewith so that mainly the contractile activity is attributed to the action of the cells, considered as cell pacemakers, this kind of cells specialized has been called interstitial cells of Cajal (ICC) has been described also in another types of visceral smooth muscle, for example, gastrointestinal, urogenital and vascular, It is therefore that the multiple components in the effect of oxytocin are due to its action on different cell types within the myometrium. The ICC-like cells might mediate changes in frequency, whereas smooth muscle cells are responsible for the increase in amplitude of contractions, however, in some cases these contractions are insufficient so many obstetricians make an artificial opening of the cervix following birth by planned caesarean section . That is a mechanical dilatation of the cervix at caesarean section, because that dilating the cervix would help the drainage of blood from the uterus, Increased drainage may reduce the risk of intrauterine infection and postpartum haemorrhage to decrease bleeding through increased contractions although this is not proven to be effective. Another measure that both obstetricians and anesthesiologists take is to add synthetic oxytocin to the endogenously released oxytocin.

Oxytocin receptor desensitization

Oxytocin receptor downregulation has been confirmed in an in-vivo study in human myometrial tissue from women exposed to oxytocin during labour. Biomolecular studies have shown that continuous exposure of human myometrial cells to oxytocin results in a significant loss of responsiveness to subsequent oxytocin stimulation, perhaps because of desensitization of the oxytocin receptors is dependent on the preexposed oxytocin concentration and not on the duration of its exposure . Oxytocin receptor concentrations decreased by more than three times, and oxytocin receptor mRNA concentrations decreased by 60 times and 300 times during oxytocin-assisted and oxytocin-induced labour respectively.

Anaesthetic implications

Epidural, Spinal Anesthesia Combined Spinal-Epidural (CSE) Technique

One of the questions that we anaesthesiologists ask ourselves is whether spinal, epidural or combined anaesthesia has any effect on myometrial contractility that in turn influences the doses of uterotonics used. Scientific studies on the interactions between local anaesthetics and uterine contractions are scarse. We need more investigations to better understand the effects of regional analgesia and oxytocin on labor progress and foetal physiology.

Baziian et al realized in 2013 an experiment 26 pregnant rabbit females induced in labor by oxytocin on the 30th day of pregnancy was conducted. The effects of bupivacaine (0, 5% - 1 ml) epidural anaesthesia (EA) on the contractile activity of the uterus, the functional state of the females and their foetuses were studied. It was shown that under standard conditions EA didn't induce changes in uterine activity parameters of the female located in its natural position, and didn't affect on the foetal heart rate. 10 minutes after EA, the momentary acceleration of female heart rate (9%) was recorded in relation to the reference level, which may be associated with transient hypotension. Thus, in conditions of our experience the bupivacaine (0,5% -1,0 ml) EA in induced labor of female rabbit has no significant effect on the uterus contractile activity and the functional state of the foetus.

However, clinical observation is another matter. In our practice, epidural or more frequently spinal epidural analgesia with the addition of opioids is associated with elevated uterine basal tone and foetal heart rate abnormalities within the first 15 minutes of analgesia Effective and rapid pain relief using intrathecal fentanyl significantly decreased circulating catecholamine level, especially epinephrine, but not norepinephrine, which may be responsible for increased uterine tone, that is why the rapid onset of analgesia could be associated with uterine hyperactivity. Uterine hypertonus could not alleviated spontaneously after suspending oxytocin infusion and CSE analgesia. We considered that the loss of the tocolytic effect of epinephrine after CSE analgesia and continuous oxytocin infusion worked together to form a totally synergistic function, finally leading to inevitable uterine hypertonus and foetal bradycardia. In based on comments submitted that both obstetrical provider and anaesthesiologist should carefully monitor all patients in the first 15 minutes after CSE analgesia induction.

Volatile anaesthetics and uterine contractions

It has been shown that large concentrations of halogenates can cause deep relaxation and is best avoided during caesarean

section, in fact, halogenates are very useful in facilitating some cases where hypertonicity complicates labour. When compared anaesthetics sevoflurane, desflurane, isoflurane, and halothane produced a dose-dependent depression of contractility

The mechanism of decreased uterine contractility is not well elucidated, it is known that volatile anaesthetics modulate K+ channel activity. Sevoflurane inhibited the amplitude and frequency of spontaneous myometrial contractions in a concentration-dependent manner TEA (Ca2+-activated K+ channel blocker) caused a significant reduction in sevoflurane-induced inhibitor responses, but glibenclamide (ATP-sensitive K+ channel) did not. i.e., sevoflurane inhibits contractility through activation of calcium channel activators of potassium channel BKca which slows down the contractions. It has been shown that the potency in inhibiting uterine contractility of desflurane and sevoflurane is comparable to that of halothane and is dose dependent.

However, the findings regarding isoflurane are contradictory because it has been seen in some works that there is a depressing effect of the myometrial activity of isoflurane compared to enfluorane and halothane. while in others the myometrial depressing activity is lower compared to the other halogenates probably mediated by the activated K+ATP channels these authors explain that the difference lies in the different methodologies used

The differences with respect to the old halogenates lies in the low blood gas partition coefficient which allows in the sevoflurane and desflurane a very fast start and end of the pharmacological action with respect to the others. It has been shown that at 0.5 CAM of sevoflurane and 1 CMA of desflurane can be safely used in the presence of oxytocin without the fear of atony or haemorrhage, beyond this, both agents inhibited the duration, amplitude and frequency of oxytocin-induced contractions Modern anaesthetics are indeed similar in structure and similar effects could be expected in all K+ channels however, much remains to be seen in this respect.

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Postpartum haemorrhage

Postpartum haemorrhage (PPH) is generally defined as blood loss greater than 500 ml after vaginal delivery or 1000 ml after caesarean delivery. It is an emergency that occupies not only obstetrics but also obstetric anaesthesiology and intensive care medicine, which are primarily responsible for the hemodynamic management and resuscitation of these patients. PPH is associated with significant morbidity and is one of the 2 most common reasons for peripartum admission to the intensive care unit.

Changes in recent years have been an increase in the numbers of PPH which may be due to the changing demographics of the obstetric patient as well as obstetric and gynaecological

Practice; this has resulted in an increase in the rate of caesarean sections, a higher proportion of multiple gestations, and more older pregnant women.

Methods and Materials

Uterotonics:

In the physiology of childbirth, postpartum haemorrhage is prevented by myometrial contractions that begin with the separation of the placenta and the involvement of hormones. For this reason, the promotion of myometrial contractions has become the main goal of treatments for postpartum haemorrhage

They are drugs used for active management of uterine contractility, in the third stage of labour or after uterine raffia in case of caesarean sections. They can be administered prophylactically or therapeutically. Prophylaxis correlates with a shorter third stage, less risk of bleeding and less need for additional uterotonics there are currently four drugs or groups of drugs with uterotonic activity: Oxytocin, Carbetocine, ergot alkaloids and Prostaglandins

Oxytocin

Structure: It´s a short Neuropeptide (nonapeptide) synthetized in 1953 by Vincent du Vigneaud It is known that du Vigneaud's work on OXT was a result of his original interest in insulin. Its chemical structure is C46H66N12O12S2, structurally it is similar to vasopressin, and both are naturally secreted by the posterior pituitary gland. A disulphide bridge connects 2 cystines in the primary sequence (Cys1 and Cyst 6), forming a ring.

Although it was already described in the section on labor physiology the rate-limiting step for the action of oxytocin is the concentration of oxytocin receptors on the myometrium. Of note, the oxytocin receptor is absent in a nonpregnant uterus. Once a woman becomes pregnant, oxytocin receptors appear in myometrial cells at approximately 13 weeks' gestation and increase in concentration until term. The distribution of oxytocin receptors in the uterus is not uniform throughout. There is a higher concentration of receptors in the fundus of the uterus, and the concentration decreases closer to the lower uterine segment and cervix. This uneven receptor distribution may explain the less prominent uterine contraction seen in the lower third of the uterus after administration of oxytocin.

Pharmacokinetics/Pharmacodynamics

Oxytocin is absorbed via intravenous, intramuscular, buccal, or nasal mucosal routes, but it is most commonly administered intravenously to allow for precise dosing and rapid

discontinuation if adverse reactions occur. Intravenous injection has an immediate onset of action compared with intramuscular injection, which takes approximately 3 to 7 minutes. Once absorbed, oxytocin redistributes to the extracellular space and does not bind to plasma proteins. The half-life of oxytocin is 10 to 12 minutes. There is a linear increase in plasma concentration of oxytocin after a continuous infusion. It takes approximately 20 to 30 minutes to reach a steady-state in plasma, and a maximum concentration is reached in approximately 40 minutes.

Although the mechanism of oxytocin degradation is not clearly elucidated, there are 2 proposed pathways that contribute to oxytocin metabolism, which involve cysteine aminopeptidase and postproline endopeptidase. Aminopeptidase splits the ring structure of oxytocin by cleaving tyrosine and destroys the conformational active state. Postproline endopeptidase cleaves oxytocin between proline and leucine, splitting the molecule into 2 inactive moieties. There are other minor enzymes involved in inactivating oxytocin, which include carboxypeptidase and leucine aminopeptidase

There are different protocols in order to avoid oxytocin´s sides effects. According the British National Formulary Oxytocin 5 IU by slow intravenous injection should be used at caesarean section (CS) to encourage contraction of the uterus and to decrease blood loss while in US for long time they employed the same dose depended by endogenous 10-40 IU in perfusion , intramuscular 10 IU or bolus 5-10 IU but since 2000 decade they calculated effective dose in 90% of parturient (ED90) for oxytocin using an up-down sequential allocation dose-response study. They found that the minimum effective dose of oxytocin required to produce adequate uterine response in 90% of women (ED90) was estimated to be 2.99 IU (95% confidence interval 2.32-3.67). This is during caesarean delivery in labouring compared with nonlaboring women when the ED90 is lower ED90= 0,35 IU This could be explained either by the use of oxytocin in stages prior to the epidural, which causes receptor desensitization, by a decrease in the sensitivity of the receptors or by a decrease in the release of calcium due to the decrease in inflammatory factors such as prostaglandins.

Oxytocin is often overdosed without taking into account that it has a narrow therapeutic range and causes a number of particularly haemodynamic side effects these include cardiovascular instability (hypotension, tachycardia, myocardial ischaemia and arrhythmias), nausea, vomiting, headache and flushing. Rarely, as a result of structural similarities with vasopressin, large doses of oxytocin may cause water retention. Although oxytocin causes fewer emetic effects compared with other uterotonics, the incidences of nausea and vomiting are 29 and 9% respectively after a bolus of 5 IU of oxytocin. The most common side effects are hypotension and tachycardia and are related to the dose and rate of administration.

Hypotension predominantly caused by transient relaxation of vascular smooth muscle through calcium-dependent stimulation of the nitric oxide pathway, leading to peripheral vasodilation, hypotension, and a compensatory increase in heart rate, stroke volume, and cardiac output.

Review

Carbetocine

Chemical estructure: The natural hormone oxytocin is not receptor-selective and may cause hyponatremia via V2 receptor mediated antidiuresis. Carbetocine is a potent oxytocin analogue. The main difference between carbetocin and oxytocin is the protracted uterotonic activity of the analogue. It can be administered as a single dose injection, either intravenously or intramuscularly. Carbetocine acts as an agonist of peripheral oxytocin receptors, particularly in the myometrium, with less affinity for myoepithelial cells.

Carbetocin selectively binds to oxytocin receptors on the smooth muscle of the uterus. It stimulates the rhythmic contractions of the uterus, increasing the frequency of existing contractions and increases the tone of the uterine muscle in the other hand mimics the mechanism of action of oxytocin by coupling to receptors that mediate the G protein and its mechanism of action involves the action of second messengers and the production of inositol

phosphates by releasing Ca ++. Binding for Carbetocin and other Oxytocin agonists has been shown to be non-selective in the extracellular N-terminal and E2 and E3 circuits The uteri of non-pregnant women have a very low content of oxytocin receptor, but during pregnancy the number of oxytocin receptors increases, reaching its peak at the time of delivery. Therefore, carbetocin affects only the pregnant and puerperal uterus.

This oxytocin analogue has a half-life of approximately 40 min, around 4-10 times longer than that reported for oxytocin the distribution and elimination half-lives of a 400 µg of intravenous dose are 5.54 ± 1.6 minutes and 41.0 ± 11.9 minutes, respectively. Similarly, the half-lives (distribution and clearance) of a 0.8 mg intravenous dose were 6.1 ± 1.2 minutes and 42.7 ±

10.6 minutes. Approximately 0.7% of the carbetocin dose was eliminated unchanged by the kidney, indicating that like oxytocin, is eliminated primarily by non-renal routes. Carbetocin administered intramuscularly (IM) was found to have a peak concentration time of less than 30 minutes. The absolute of IM bioavailability was approximately 80%.

The minimum effective intravenous dose of carbetocin required to produce adequate uterine contractions in 95% of women (effective dose [ED] 95) is 100 µg. The justification for the 100-µg dose seems to be based on the fact that most clinical trials to date have used almost exclusively this dose, following the manufacturer's recommendation. Unpublished data provided by the pharmaceutical company show the results of a study involving 18 women undergoing elective CS wherein none of the women had effective uterine contractions with doses of carbetocin below 60 µg, and 83% (five out of six) developed adequate uterine tone after receiving a dose of

100 lg. The number of patients in this study was small and probably insufficient to establish the recommended dose of 100 µg as a routine practice.

Cordovani in 2012 carried out a study where he stated that the 100 µg dose is adequate. However, the study had some design limitations, so two studies are conducted in this regard

The first was a double-blind study in patients undergoing scheduled caesarean sections in the absence of labouring with successive ascending doses of carbetocin. They determined that the ED90 of carbetocin is 14.8 µg (95% CI: 13.7 to 15.8 µg), which represents a dose almost 8 times less than recommended. In 2015 they carried out the study of successive ascending doses with the difference that this time in women who have received oxytocin infusions before caesarean section, that is, caesarean sections in labor, they concluded that for women with increased oxytocin, the ED90 for carbetocin is 121 µg; (95% CI: 111 - 130) which is even higher than the 100 µg dose. Carbetocin has a minimal antidiuretic action (vasopressin activity

<0.025) EV administration of carbetocin is associated with nausea (21-27%), abdominal pain (40%), pruritus (10%), facial flushing (26%), vomiting (7% -9%), feeling hyperthermic (20%), headache (3% -14%), and tremor (11%) Contraindications to the use of carbetocin are hypersensitivity, kidney or liver disease, pre-eclampsia or eclampsia, severe heart disease and epilepsy.

The ergot alkaloid group

Methylergometrine (methylergonovine) is the semisynthetic derivative of ergonovine that, like other ergot derivatives, markedly increases the motor activity of the uterus. With small doses, contractions increase in strength, frequency, or both, but are followed by a normal degree of relaxation. As the dose is increased, the contractions become more powerful and prolonged, the basal tone rises sharply, and a sustained contraction may occur. This characteristic prevents its use for the induction or facilitation of labor; however, it is very useful in late pregnancy and during the puerperal stage, when the contraction of the uterine wall around the blood vessels at the placental sites produces haemostasis.

Its molecular structure, structurally, and biochemically very similar to that of ergoline, is similar to that of some brain neurotransmitters. It is a natural substance with biological activity that is identified according to the CAS chemical nomenclature with the code 113-15-5 and whose IUPAC formula is (6aR, 7R) -7-methyl-4,6,6a, 7,9- hexahydride quinelline-9-methanoic acid ((2R, 5S, 10bS) -5-benzylene-10b-hydroxy-2-methyl-3,6-dioxoctahydrooxazolo pyrrolo pyrazine -2-yl) amine. Its molecular mass is 581.66 g / mol.

It is claimed to directly stimulate smooth muscle; however, it has also been reported to exert its effects by acting as a partial agonist or antagonist at the level of alpha 1 adrenergic, dopaminergic, and serotonergic receptors. Orally, its contractile effect begins in 5 to 10 minutes and persists for approximately 3 hours. Orally, its contractile effect begins in 5 to 10 minutes and persists for approximately 3 hours. Intramuscularly, it begins in 2-5 minutes and lasts 3 hours; intravenously, its effect is immediate and persists for 45 min. It is rapidly absorbed after oral administration and from intramuscular deposits. It is widely distributed in the body and is metabolized in the liver. Its elimination is mainly renal. When administered intravenously, its half-life is biphasic, the initial 2 to 3 min and the final 20 to 30 min.

Dosage ED50-95 the ED 50 of methylergonovine is not reported, but the doses described vary depending on the routes: intravenous 0.2 mg, repeat every 2 hours; oral or sublingual: 0.2-0.4 mg 3-4 times a day for a week, IM 0.4 mg almost never repeat

Side effects Contraindicated in cases of hypersensitivity to ergotamine alkaloids, coronary disease, myocardial infarction, cerebrovascular accident, cardiovascular disease, arterial hypertension, Raynaud's syndrome, eclampsia, pre-eclampsia, peripheral vascular occlusive disease and during pregnancy. The risk-benefit ratio should be carefully assessed in cases of liver or kidney dysfunction, electroencephalographic abnormalities, hypocalcaemia. Its administration must be discontinued if manifestations of ergotism appear. Its use is not recommended during the delivery of the placenta, as it can become trapped; neither for induction of labor nor for incomplete abortion. Its vasoconstrictor effect increases with the simultaneous use of adrenergic drugs and the uterotonic one decreases with halothane.

Intravenous application usually produces more frequent and more intense adverse reactions.

Conclusion:

Obstetric haemorrhage is one of the top two causes of maternal death worldwide

It is necessary for the anaesthesiologist working in obstetrics to know the mechanisms that trigger labor in order to recognize which are the most effective approaches when dealing with hypotonia and uterine bleeding.

Anaesthesia and aesthetic agents themselves have the ability to directly or indirectly influence myometrial contractility. The drugs used to improve uterine tone are still oxytocin and carbetocine the most referenced without there being a clear limit that indicates when to use one or the other.

The anaesthesiologist is as involved as the obstetrician in the process of caesarean section or childbirth as well as maternal resuscitation, thus knowing the mechanisms of action, side effects, and the administered doses of each of the drugs used to improve uterine contractility must be managed with criteria of excellence and timeliness. Much remains to be done in this regard, but we are well on our way to determining what are the mechanisms of action of halogenates, uterine hypertonia secondary to analgesia, epidural and spinal anaesthesia and administering the most effective doses with fewer side effects than uterotonics.

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