

A Review on Oxytocin as a Novel Uterine Stimulants

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Summary

The aim of the review is to give complete information about the stimulation of uterine by oxytocin. The action of oxytocin on the uterus, 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin, was studied for the first time in 13 patients with established, uncomplicated premature labour. Intravenous infusion of 10–100 µg/min of the analogue was given for 1–10 h and the effect was monitored by external cardiotoco-graphy. In all women an inhibition of uterine activity was observed, and in the majority of patients infused with 25 µg/min and a total dose of about 5 mg or more of the drug total inhibition of uterine contractions was achieved. There were no effects on the maternal and fetal pulse rates, nor were there any other side-effects. The results of this preliminary study support the concept of an increased concentration of uterine oxytocin receptors being aetiologically important in uncomplicated premature labour.

Keywords: Oxytocin, Uncomplicated premature labour, Receptors, Uterine activity

Introduction

Oxytocin is a naturally occurring hormone used to induce labor. The production and secretion of natural oxytocin is stimulated by the pituitary gland. It is also available in synthetic form under the trade names of Pitocin and Syntocinon. Oxytocin is used in a contraction stress test (CST). A CST is done prior to the onset of labor to evaluate the fetus's ability to withstand the contractions of the uterus. To avoid the possibility of exogenous (introduced) oxytocin putting the woman into labor, she may instead be asked to stimulate her nipples to release her natural oxytocin. A negative, or normal, CST result is three contractions within a 10-minute period with no abnormal slowing of the fetal heart rate (FHR). The CST occasionally produces false positives, however. Oxytocin may be used in the treatment of a miscarriage to assure that all the products of conception (POC) are expelled from the uterus. If the fetus died but was not expelled, a prostaglandin (PGE₂) may be given to ripen the cervix to facilitate a dilatation and evacuation, or to encourage uterine contractions. The prostaglandin may be administered either in gel form or as a vaginal suppository. In a routine delivery, oxytocin may be given to the mother after the placenta has been delivered in order to help the uterus contract and minimize bleeding. It is also used to treat uterine hemorrhage. While hemorrhage occurs in about 4% of vaginal deliveries and 6% of Caesarian deliveries, it accounts for about 35% of maternal deaths due to bleeding during pregnancy. If the bleeding started at the placental detachment site, contractions of the uterus help to close off the blood vessels and thereby stop excessive bleeding. Additional medications may be used, including PGF₂alpha (Hemabate), misoprostol (Cytotec), or the ergot alkaloid methylergonovine (Methergine).

Prostaglandin (PGs) have significant systemic side effects. These include headache, nausea, diarrhea, tachycardia (rapid heartbeat), vomiting, chills, fever, sweating, hypertension, and hypotension (low blood pressure). There is also an increased risk of uterine hyperstimulation and uterine rupture. PGF₂α (carboprost—Prostin 15-M or Hemabate) can cause hypotension, pulmonary edema, and intense bronchospasms in women with asthma. Because carboprost stimulates the production of steroids, it may be contraindicated in women with disorders of the adrenal gland. When used for abortion, it may result in sufficient blood loss to cause anemia, which may make a transfusion necessary. The use of this PG has been reported to increase the fluid pressure in the eyes in women with glaucoma; however, this side effect is fortunately rare.

Physiologic Effects of Oxytocin

Oxytocin is a natural hormone produced in the brain that causes the uterus to contract. Oxytocin can be used when labor needs to be induced or during labor if the contractions are not strong enough to progress normally. It is also used to control bleeding after childbirth. Oxytocin also can help to stimulate contractions if there is an incomplete abortion or miscarriage.

Oxytocin is one of the two major hormones secreted from the posterior lobe of the pituitary gland, the other being vasopressin, the antidiuretic hormone. The posterior pituitary itself largely comprises endings of nerves whose cell bodies lie in the brain in the hypothalamus. Its hormones are extruded from the nerve endings directly into blood capillaries and thence into the general circulation. Oxytocin is a relatively small peptide hormone, composed of only 9 amino acids. It is synthesized in nerve cells in the hypothalamus in the form of a larger, precursor molecule, which is transported down the nerve fibres through the pituitary stalk to the posterior lobe. The active hormone is cleaved from the precursor during this process. Oxytocin was the first hormone to have its structure identified and to be synthesized in the laboratory. The hormone plays an important role in birth and in feeding the infant. It has two major actions, the first being to promote contractions of the uterus, an action which is used in obstetric practice when the hormone is infused if labour is protracted. The second action is to cause contraction of the muscular elements surrounding the alveoli and milk ducts in the breasts, thereby helping to expel the milk (milk let-down). Oxytocin is also found in men, but its role is not clear, although it has been suggested that it aids sperm transport during mating. Thus it is released during vaginal stimulation, so that during the process of birth, as the infant enters the birth canal, oxytocin is released and in turn causes increased uterine activity, allowing the process to proceed more rapidly. The oxytocin released at this time may also cause milk ejection, a response known as Ferguson's reflex. Oxytocin is also released in response to suckling and many other stimuli associated with breast feeding, such as the sight and sound of the infant. If the mother is not relaxed, this may act via the hypothalamus to inhibit oxytocin release so that problems with breast feeding may arise. Oxytocin in a species ranging from mice to humans has revealed a number of effects on social behavior. Nevertheless, it has been best studied in females.

Stimulation of uterine smooth muscle contraction at birth

At the end of gestation, the uterus must contract vigorously and for a prolonged period of time in order to deliver the fetus. During the later stages of gestation, there is an increase in abundance of oxytocin receptors on uterine smooth muscle cells, which is associated with increased "irritability" of the uterus (and sometimes the mother as well). Oxytocin is released during labor when the fetus stimulates the cervix and vagina, and it enhances contraction of uterine smooth muscle to facilitate parturition or birth. In cases where uterine contractions are not sufficient to complete delivery, physicians and veterinarians sometimes administer oxytocin ("pitocin") to further stimulate uterine contractions - great care must be exercised in such situations to assure that the fetus can indeed be delivered and to avoid rupture of the uterus. Oxytocin takes effect rapidly when it is given intravenously. Individual responses to oxytocin vary considerably; for this reason, the drug dosage is usually increased slowly and incrementally. Oxytocin can cause hyperstimulation of the uterus, which in turn can place the fetus at risk for asphyxia uterine rupture has also been linked to oxytocin administration. Oxytocin has a mild antidiuretic effect that is usually dose-related; it can lead to water intoxication (hyponatremia). Onset occurs gradually and may go unnoticed. Signs of water intoxication may include reduced urine output, confusion, nausea, convulsions, and coma. Expectant mothers receiving oxytocin should have their blood pressure monitored closely, as both hypotension and hypertension can occur. Although the subject remains controversial, some evidence suggests oxytocin increases the incidence of neonatal jaundice. Although oxytocin may increase the risk of uterine rupture in women who were delivered by Caesarian section in a previous pregnancy, contraindications to the use of the drug are virtually the same as contraindications for labor. Other side effects of oxytocin include nausea, vomiting, cardiac arrhythmias, and fetal bradycardia (slowing of the heartbeat).

Uterine Stimulants

Uterine stimulants are used to induce, or begin, labor in certain circumstances when the mother's labor has not started naturally. These circumstances may include the mother's being past her due date; that is, the pregnancy has lasted longer than 40 weeks. Labor is especially likely to be induced if tests indicate a decrease in the volume of amniotic fluid. Uterine stimulants may also be used in cases of premature rupture of the membranes; preeclampsia (elevated blood pressure in the later stages of pregnancy); diabetes; and intrauterine growth retardation (IUGR), if these conditions require delivery before labor has begun. These medications may be recommended if the expectant mother lives a great distance from the healthcare facility and there is concern for either her or her baby's safety if she were unable to reach the facility once labor begins. Uterine stimulants are also used in the augmentation of existing contractions, to increase their strength and frequency when labor is not progressing

- a. Oxytocin can be used on either an inpatient or an outpatient basis. On an inpatient basis, the drug is used to induce labor and/or to aid in controlling postpartum hemorrhage. For these uses, the physician can use either the injection or the buccal tablet dosage form. The dosage of either dosage form is adjusted

based on the uterine response of the patient. On an outpatient basis, oxytocin is used to aid in breast milk ejection. the physician uses the nasal spray.

b. Stimulation of uterine smooth muscle : At the end of gestation, the uterus must contract vigorously and for a prolonged period of time in order to deliver the fetus. During the later stages of gestation, there is an increase in abundance of oxytocin receptors on uterine smooth muscle cells, which is associated with increased "irritability" of the uterus (and sometimes the mother as well). Oxytocin is released during labor when the fetus stimulates the cervix and vagina, and it enhances contraction of uterine smooth muscle to facilitate parturition or birth. In cases where uterine contractions are not sufficient to complete delivery, physicians and veterinarians sometimes administer oxytocin ("pitocin") to further stimulate uterine contractions.

THERAPEUTIC USE.

Antepartum: Induction or stimulation of labor at term.
Oxytocin is indicated:

1. For uterine inertia.
2. For induction of labor in cases of erythroblastosis fetalis, maternal diabetes mellitus, preeclampsia, and eclampsia, and for induction of labor after premature rupture of membranes in last month of pregnancy when labor fails to develop spontaneously within 12 hr.
3. For routine control of postpartum hemorrhage and uterine atony, and to hasten uterine involution.
4. To complete inevitable abortions after the 20th week of pregnancy.
5. Intranasally for initial letdown of milk.

a. **Induce Labor at Term.** If the physician believes it is required, oxytocin may be administered intravenously to the pregnant woman at term in order to induce contractions of the uterus.

b. **Control Postpartum Hemorrhage.** Oxytocin can also be used to reduce uterine bleeding after the infant has been born. Remember, oxytocin causes contractions of the uterus.

c. **Relieve Postpartum Breast Engorgement.** Oxytocin is used to relieve postpartum breast engorgement in women who are going to breastfeed their infants in that it causes "milk let-down." "Milk let-down" is a situation in which the milk in the breasts travels from alveoli to the nipples where it can be suckled by the infant. If the milk does not travel from the alveoli to the nipples, the breasts can become swollen and sore. In addition to relieving postpartum breast engorgement, oxytocin can also aid in milk ejection from the breasts by having the milk move toward the nipples.

d. **Prevent Uterine Atony.** After delivery, the uterus must return to its normal size and position. Oxytocin can help in this process by causing the uterine muscle to contract back to its original position. Thus, oxytocin can prevent uterine atony (i.e., when the uterus loses its proper muscle tone).

e. **Aid in Placental Transfer.** Placental expulsion can be aided by the administration of oxytocin.

Advers Effects

CV: Cardiac arrhythmias; fetal reactions include bradycardia, premature ventricular contractions, death, jaundice, low Apgar scores, retinal hemorrhage and other arrhythmias.

CNS: Neurologic damage; convulsions.

GI: Nausea; vomiting.

GU: Postpartum hemorrhage; cervical/vaginal lacerations; uterine hypertoxicity; uterine rupture; tetanic contractions; decreased uterine blood flow; pelvic hematoma.

RESP: Hypoxia.

OTHER: Maternal reactions include anaphylaxis; death; increased blood loss.

Premature ventricular contractions and other arrhythmias, Permanent CNS or brain damage, Fetal death, Neonatal seizures have been reported with the use of Pitocin.

Due to use of oxytocin in the mother:

Low Apgar scores at five minutes, Neonatal jaundice, Neonatal retinal hemorrhage

Side Effects

Nausea, vomiting, cramping, and stomach pain may occur. Irregular heartbeat, dizziness, lightheadedness, swelling, severe bleeding (after childbirth), seizures, headache, blurred vision, one-sided weakness. Side effects occur in the newborn: irregular heartbeat, yellowing eyes or skin, bleeding in the eyes, seizures. An allergic reaction to this drug is unlikely, but seek immediate medical attention if it occur. An allergic reaction (shortness of breath, closing of the throat, hives, swelling of the lips, face, or tongue, rash, or fainting), difficulty urinating, chest pain or irregular heartbeat, difficulty breathing, confusion, sudden weight gain or excessive swelling, excessive vaginal bleeding, itching, dizziness. Side effects, like vomiting and high temperature (fever). To avoid such side effects and any further complications, it is advisable to give counter medicines like antibody and anti-vomiting pill/injection etc. Apart from these two types of side effects--vomiting and high temperature in less than 2% patients, not any other symptoms like headache, nausea, diarrhea, tachycardia, chills, sweating, hypertension, hypotension, increased incidence of uterine hyper stimulation and potential for uterine rupture etc. are observed. Therefore the proposed uterine stimulant stick is much more safe, side effect free and normal contraction initiating medicine as compare to other conventionally available such stimulants. Mother: Tetanic uterine contractions, *anaphylaxis* cardiac arrhythmia, fatal afibrinogenemia N&V, PVCs, increased blood loss, pelvic hematoma, hypertension, tachycardia, and ECG changes. Also, rarely, anxiety, dyspnea, precordial pain, edema, cyanosis or reddening of the skin, and CV spasm. Water intoxication from prolonged IV infusion, death due to hypertensive episodes, SAH, postpartum hemorrhage, or uterine rupture. Excessive dosage may cause uterine hypertonicity, spasm, tetanic contraction, or uterine rupture. Fetus: Death PVCs, bradycardia, tachycardia, arrhythmias, hypoxia, intracranial hemorrhage due to overstimulation of the

uterus during labor leads to uterine tetany with marked impairment of uteroplacental blood flow. Hypertensive episodes, Premature ventricular contractions, Subarachnoid hemorrhage, Rupture of the uterus.

The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug. Severe water intoxication with convulsions and coma has occurred, associated with slow oxytocin infusion over a 24-hour period. Maternal death due to oxytocin-induced water intoxication has been reported.

Overdose

Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H₂O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, perinatal hepatic necrosis or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

Complications

The effect of IV oxytocin is rapid following administration. The individual response to oxytocin can vary considerably, and administration is usually increased slowly and incrementally. Hyperstimulation of the uterus, which can result from oxytocin augmentation, can place the fetus at risk for asphyxia. Hyperstimulation is defined as more than five contractions in 10 minutes, contractions lasting longer than 60 seconds, and increased uterine tonus either with or without significant decrease in FHR. Uterine rupture has also been linked to oxytocin administration, particularly for periods longer than four hours. Oxytocin has a small antidiuretic effect that is usually dose related and that can lead to water intoxication (hyponatremia). Onset occurs gradually and may go unnoticed. Signs may include reduced urine output, confusion, nausea, convulsions, and **coma**. Mothers receiving oxytocin need to have their blood pressure monitored closely, as both hypotension and hypertension can occur, and—although the subject remains controversial—evidence suggests oxytocin increases the incidence of **neonatal jaundice**. Although oxytocin may put women with a classical cesarian section scar from a prior delivery at increased risk of uterine rupture, contraindications to the use of the drug are virtually the same as contraindications for labor. Other side effects of oxytocin include nausea, vomiting, cardiac arrhythmias, and fetal bradycardia. When used judiciously, oxytocin is a very effective medication for the progression of labor.

Contraindications

Significant cephalopelvic disproportion; inadequate, undeliverable fetal position, cases of fetal distress in which delivery is not imminent, prolonged use in uterine inertia or severe toxemia, Hypersensitivity to drug. Undeliverable without conversion prior to delivery.

In obstetric emergencies where the benefit-to-risk ratio for either the mother or fetus favors surgical intervention. Fetal distress where delivery is not imminent, prolonged use in uterine inertia or severe toxemia, hypertonic or hyperactive uterine patterns, when adequate uterine activity does not achieve satisfactory progress. Induction or augmentation of labor where vaginal delivery is contraindicated(eg, prolapse), pregnancy (nasal product only), including invasive cervical cancer, cord presentation or prolapse, total placenta previa and vasa previa, active herpes genitalis. Use of oxytocin citrate in severe toxemia, cv or renal diseases. Use of intranasal oxytocin during pregnancy. Also, predisposition to thromboplastin and amniotic fluid embolism (dead fetus, abruptio placentae), history of previous traumatic deliveries, or women with four or more deliveries. Never give oxytocin IV undiluted or in high concentrations.

Antepartum Use of Pitocin is contraindicated:

1. Where there is significant cephalopelvic disproportion, In unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery;
2. In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention, In fetal distress where delivery is not imminent;
3. Where adequate uterine activity fails to achieve satisfactory progress, Where the uterus is already hyperactive or hypertonic;
4. In cases where vaginal delivery is contraindicated, such as invasive cervicalcarcinoma, active herpes genitalis, total placenta previa, vasa previa, and cord presentation or prolapse of the cord, In patients with hypersensitivity to the drug.

Precautions

It is important to establish a clear baseline of vital signs before a woman is given any medication to induce labor. Consistent reevaluation and documentation of vital signs allow for faster recognition of an abnormal change in a woman's condition. Also, a clear labor and delivery record will assist the postpartum nurse in monitoring for changes as well. Documentation includes time and dosage of any medications given, as well as any side effects that might occur. Proper documentation will help avoid the chance of medication doses being given too close together. An increasing pulse and a decreasing blood pressure signal a potential hemorrhage. When oxytocin is given by IV, it must be diluted in IV fluid and never given as a straight IV. PGs should not be given if there is any question about fetal well-being, for example, an abnormal FHR tracing. The ergot Methergine should never be given via IV and never to a woman with hypertension.

Pregnancy: No indication for use in first trimester unless related to spontaneous or induced abortion.

Lactation: Excreted in breast milk. If used postpartum to control bleeding, patient should not nurse for 24 hr after last dose.

Children: Contraindicated in children.

Special risk patients: Not recommended in prematurity, borderline cephalopelvic disproportion, previous major surgery on cervix or uterus (including cesarean section), uterine over-distention, grand multiparity, history of uterine sepsis, traumatic delivery, fetal distress, partial placenta previa or invasive cervical carcinoma, except in unusual circumstances.

Mortality: Hypertensive episodes, subarachnoid hemorrhage and rupture of uterus have resulted in maternal deaths. Fetal deaths and infant brain damage have been reported with IV use during first and second stages of labor.

Over stimulation of uterus: Can occur and can be hazardous to mother and fetus.

Water intoxication: Consider possibility when patient is receiving oxytocin by IV infusion and fluids by mouth.

1. All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and are qualified to identify complications. Electronic fetal monitoring provides the best means for early detection. A fetal scalp electrode provides a more dependable recording of the fetal heart rate than any external monitoring system.
2. oxytocin should stimulate uterine contractions comparable to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.
3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and any condition in which there is a predisposition for uterine rupture, such as previous major surgery on the cervix or uterus including cesarean section, overdistention of the uterus, grand multiparity, or past history of uterine sepsis or of traumatic delivery.
4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.
5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.
6. When oxytocin is used for induction or reinforcement of already existent labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before use of the drug

Conclusion

Anticipated outcomes for uterine stimulants are either to prepare the cervix for childbirth, induce or stimulate uterine contractions to produce a safe delivery of a newborn,

encourage a complete spontaneous or induced abortion, eliminate blood clots or other POC debris from the uterus, and decrease or stop hemorrhage following childbirth or abortion. Normal results would meet these outcomes without significant side effects—either for the mother or, in the case of childbirth, the infant.

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