Uterotonic Medications

Oxytocin, Methylergonovine, Carboprost, Misoprostol

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KEYWORDS

• Oxytocin • Methylergonovine • Carboprost • Misoprostol • Uterine atony
• Uterotonic agent • Postpartum hemorrhage

KEY POINTS

- Uterotonic agents are widely used in the prevention and treatment of postpartum hemorrhage, and although oxytocin remains the first-line agent, a standardized guideline for optimal dose and rate of administration has not been clearly defined.
- Methylergonovine is a highly effective second-line agent; however, it is associated with severe vasoconstriction and is contraindicated for hypertensive patients.
- Carboprost is useful for escalation of treatment when oxytocin and uterine massage have been insufficient to restore uterine tone, especially when methylergonovine is contraindicated, but it can cause severe bronchospasm and is thus contraindicated in patients with asthma.
- Misoprostol is characterized by low cost, stability in storage, broad availability, minimal side effects, ease of administration, and multiple medical uses; however, recent studies have called into question its effectiveness as an adjunct uterotonic agent, limiting its role to scenarios in which other, injectable uterotonics are not readily available or easily administered.

OXYTOCIN

Introduction

Oxytocin, the first-line agent in the prevention and treatment of postpartum hemorrhage, is a polypeptide structure that is produced in the paraventricular nucleus of the hypothalamus and released by the posterior pituitary gland. It was first discovered by Sir Henry Dale in 1909 when he discovered that a hormone from the pituitary gland

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caused uterine contractions in a pregnant cat.[1] It was the first polypeptide hormone synthesized in 1953 by the American biochemist, Vincent Du Vigneaud.[2] Oxytocin remains the first-line agent in the management and prevention of uterine atony after vaginal and operative delivery. The clinical roles of oxytocin in the obstetric population include induction and augmentation of labor, and prevention and treatment of postpartum uterine atony.

Structure/Activity

Oxytocin is a short polypeptide consisting of 9 peptides (nonapeptide). Its chemical structure is $C_{46}H_{66}N_{12}O_{12}S_2$, which is structurally similar to vasopressin, and both are secreted by the posterior pituitary gland. A disulfide bridge connects 2 cystines in the primary sequence (Cys1 and Cys 6), forming a ring.[3]

Oxytocin exerts a stimulatory effect on myometrial contractility by increasing the intracellular concentration of calcium. This process is achieved by the release of calcium in the sarcoplasmic reticulum and by enhanced entry of extracellular calcium. Oxytocin binds to a G-protein on the surface of the uterine myocyte, resulting in the generation of diacylglycerol (DAG) and inositol triphosphate (IP3) via phospholipase C on phosphatidyl-inositol bisphosphate.[4] DAG stimulates prostaglandin synthesis, which also contributes to uterine contractions. IP3 stimulates the release of calcium from the sarcoplasmic reticulum and increases the concentration of cytoplasmic calcium.[5] For sufficient activation of myometrial contraction, this increase in intracellular calcium from the sarcoplasmic reticulum alone is not sufficient and entry of extracellular calcium is required. This process is mediated by the oxytocin–G-protein complex, which causes a conformational change in voltage-gated calcium channels allowing the influx of extracellular calcium. Calcium then binds to calmodulin and activates myosin light-chain kinase, which is the fundamental contraction mechanism of uterine smooth muscle.[6]

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.[5] This uneven receptor distribution may explain the less prominent uterine contraction seen in the lower third of the uterus after administration of oxytocin.

Pharmacokinetics

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.[7] The recommended dose for intramuscular injection during cesarean delivery is 10 units after delivery of the placenta. 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,[8] and a maximum concentration is reached in approximately 40 minutes.[9]

Although the mechanism of oxytocin degradation is not clearly elucidated, there are 2 proposed pathways that contribute to oxytocin metabolism, which involve cysteine