International Journal of Basic & Clinical Pharmacology
Bhalla A. Int J Basic Clin Pharmacol. 2022 Jul;11(4):352-355
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20221604

New Drug Update

Carbetocin: a therapy advance for prevention of postpartum haemorrhage

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Received: 16 April 2022
Accepted: 20 May 2022

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ABSTRACT

Postpartum haemorrhage (PPH) is the major cause of maternal death. To prevent PPH, the routine administration of a uterus-contracting ('uterotonic') agent is a standard practice across the world. Oxytocin is the standard uterotonic agent recommended for this purpose, and is recommended for all women giving birth. Oxytocin is problematic as it requires cold storage and transport, and in low-resource settings, the cold chain is not commonly available. Heat-stable carbetocin is a promising alternative to oxytocin. Because of its heat stability, it can overcome the persistent problems with oxytocin quality as it does not require cold chain for storage and transport. Considering the totality of the evidence, it appears to have some additional desirable effects compared with oxytocin and a very favourable side effect profile similar to oxytocin. With a standardized dosing of single injection recommendation, it can address the variations in dosing regimen as is with oxytocin. Carbetocin has been added to the World Health Organization (WHO) essential medicines list of uterotonics for the prevention of excessive bleeding after childbirth, we might see a new standard of care in coming months for prevention of uterine atony.

Keywords: Uterine atony, PPH, Uterotonic

INTRODUCTION

Postpartum haemorrhage (PPH) is the major cause of maternal death and morbidity worldwide, commonly due to uterine atony (approximately 70% of cases).[1,2] This type of haemorrhage is defined as blood loss of at least 500 mL after vaginal delivery and blood loss of >1000 ml after caesarean section (C-section).[3] It is a significant contributor to severe maternal morbidity and long-term disability, as well as to a number of other severe maternal conditions, generally associated with more substantial blood loss, including severe anaemia, cardiac failure and sepsis.

Active management of the third stage of labour (AMTSL) as a prophylactic intervention is composed of a package of three components or steps: administration of a uterotonic, preferably oxytocin, immediately after birth of the baby; controlled cord traction (CCT) to deliver the placenta; and massage of the uterine fundus after the placenta is delivered. The administration of a uterotonic to the mother immediately after the birth of the baby is identified as the most important step.[4]

Oxytocin (with or without ergometrine) is the current standard therapy for the prevention of postpartum haemorrhage; it is a peptide hormone secreted by the posterior pituitary gland, which stimulates myometrial contraction in the second and third stages of labour. However, failure of postpartum haemorrhage prophylaxis with oxytocin (as demonstrated by the need for a rescue uterotonic) occurs commonly, necessitating the use of further oxytocin or other treatments to maintain haemodynamic stability.[5] Syntometrine, a mixture of 5 IU oxytocin and 0.5 mg ergometrine, is associated with a significant reduction of PPH compared with intramuscularly administered oxytocin alone. The use of

syntometrine, however, is associated with more adverse effects.[6]

The effectiveness of uterotonics in generating the uterine contractions necessary to prevent haemorrhage can be impaired through exposure to conditions that cause the uterotonic to degrade. In many low- and middle-income countries where access to sustained cold-chain is unavailable, the efficacy of oxytocin cannot be assured because it is susceptible to heat degradation.[7,8] Other uterotonics include ergometrine/methylergometrine, misoprostol and fixed-dose combinations of these uterotonics. Ergometrine degrades when exposed to heat or light. Misoprostol degrades rapidly when exposed to moisture.[9] When degraded, the level of active ingredient is decreased, resulting in reduced effectiveness.

Another recently registered uterotonic agent is carbetocin. Carbetocin is a synthetic long-lasting oxytocin agonistic analog. Its prolonged uterine activity may theoretically offer advantages over oxytocin in the management of the third stage of labor. The side-effect profile of carbetocin, in comparison with that of syntometrine, may prove to be advantageous. Heat-stable carbetocin does not require cold-chain transport and storage; it has been shown to maintain stability over a period of 36 months at 30°C and 75% relative humidity.[10]

PHARMACOLOGICAL PROPERTIES OF CARBETOCIN

Carbetocin is a long-acting structural analog of the natural human hormone oxytocin, which has uterotonic activity resulting from its binding to oxytocin receptors on the myometrial plasma membranes. A major disadvantage of naturally occurring oxytocin is its short half-life (3–17 minutes).[11] By modifying the oxytocin molecule, its half-life has been prolonged and its enzymatic degradation reduced. The modified molecule is named carbetocin. Because of these alterations carbetocin has more pronounced pharmacological effects.[12]

Mechanisms of action

Carbetocin binds selectively to oxytocin receptors in the smooth muscle of the uterus. It stimulates rhythmic contractions of the uterus, increasing the frequency of existing contractions and raises the tone of the uterine muscle by releasing Ca^{2+}. Uteri of nonpregnant women have very low oxytocin receptor content, but during pregnancy the number of oxytocin receptors increases, peaking at the time of delivery. Therefore, carbetocin affects only the pregnant and puerperal uterus. Oxytocin receptors are also located in the myoepithelial cells surrounding the alveoli of the lactating breast. Binding of oxytocin to these receptors stimulates the let-down of milk in breast-feeding mothers. Oxytocin also has moderate antidiuretic effects because of its structural similarity to vasopressin. Therefore, when used in high dosages, oxytocin can result in hyponatremia if not administered as an isotonic solution. As oxytocin can influence the cardiac and vascular tissues, oxytocin may occasionally induce hypotension and tachycardia.

Pharmacokinetics

Intramuscular use

Carbetocin enters the circulation rapidly, with a peak concentration within 30 minutes. The absolute bioavailability is approximately 80%. The C_{max} is 6.35±1.39 µg/l at an administered dose of 400 µg.

Intravenous use

The distribution and elimination half-lives of a 400-µg dose are 5.54±1.6 minutes and 41.0±11.9 minutes, respectively.

Drug interaction

As carbetocin is in similar chemical structure to oxytocin, the same interactions as with oxytocin may be expected. During clinical studies carbetocin was administered together with analgesics, spasmolytics and anesthetic agents used for spinal or epidural anesthesia, and so far, no specific drug interactions have been reported.

Adverse reactions

The adverse reactions of carbetocin were the same as those that occur during the use of oxytocin when administered after cesarean section under epidural or spinal anesthesia. Intravenous carbetocin was frequently associated with nausea (21%–27%), abdominal pain (40%), pruritus (10%), flushing (26%), vomiting (7–9%), feeling of warmth (20%), headache (3–14%), and tremor (11%).[13]

Carbetocin versus oxytocin to prevent hemorrhage after vaginal birth

Carbetocin haemorrhage prevention (CHAMPION) trial. Widmer et al enrolled women across 23 sites in 10 countries in a randomized, double-blind, noninferiority trial comparing intramuscular injections of heat-stable carbetocin (at a dose of 100 µg) with oxytocin (at a dose of 10 IU) administered immediately after vaginal birth.[14] Both drugs were kept in cold storage (2 to 8°C) to maintain double-blinding. There were two primary outcomes: the proportion of women with blood loss of at least 500 ml or the use of additional uterotonic agents, and the proportion of women with blood loss of at least 1000 ml. The noninferiority margins for the relative risks of these outcomes were 1.16 and 1.23, respectively. A total of 29,645 women underwent randomization. The frequency of blood loss of at least 500 ml or the use of additional uterotonic agents was 14.5% in the carbetocin group and 14.4% in the oxytocin group (relative risk, 1.01; 95% confidence interval [CI], 0.95 to 1.06), a finding that was consistent with noninferiority. The frequency of blood loss

of at least 1000 ml was 1.51% in the carbetocin group and 1.45% in the oxytocin group (relative risk, 1.04; 95% CI, 0.87 to 1.25), with the confidence interval crossing the margin of noninferiority. The use of additional uterotonic agents, interventions to stop bleeding, and adverse effects did not differ significantly between the two groups. The authors concluded that heat-stable carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 ml or the use of additional uterotonic agents.

Carbetocin versus oxytocin to prevent hemorrhage after caesarean section

This retrospective cohort study included women at increased risk of postpartum haemorrhage after C-section for various indications in a public hospital.[15] Women who received carbetocin infusion and women who received oxytocin infusion were compared, stratified by C-section timing (elective or emergency). The primary outcome was the requirement for additional uterotonic agents or procedures. Secondary outcomes included total blood loss, operating time, rate of postpartum haemorrhage, need for blood transfusion, and need for hysterectomy. Of 1236 women included in the study, 752 received oxytocin first and 484 received carbetocin first. The two groups had comparable blood loss, operating time, rate of postpartum haemorrhage, requirement for additional uterotonics or procedures, need for blood transfusion, and need for hysterectomy. There was a reduction in the requirement for additional uterotonics or procedures, and in the rate of postpartum haemorrhage for women with major placenta praevia or with multiple pregnancies, following receipt of carbetocin first. Compared with oxytocin, carbetocin can reduce the requirement for additional uterotonics or procedures in selected high-risk patient groups.

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis

The objective of the uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis is to assess the clinical effectiveness and side-effect profile of uterotonic drugs to prevent PPH and to generate a clinically useful ranking of available uterotonics according to their effectiveness and side-effects. A scientifically rigorous ranking could reduce uncertainty about which is the most effective drug for preventing PPH. All uterotonic drugs used for prevention of PPH have been compared with each other including oxytocin, misoprostol, ergometrine, carbetocin, oxytocin plus misoprostol, oxytocin plus ergometrine and placebo or no-treatment. The study included all randomised controlled individual or cluster trials evaluating effectiveness or side effects of uterotonic drugs for preventing PPH identified from the Cochrane's pregnancy and childbirth group (PCG) trials register. The interventions considered were uterotonics administered by healthcare providers during the third stage of labour for preventing PPH compared with a control uterotonic or with placebo or no treatment. The targeted population was women having a vaginal birth or a caesarean section in hospitals or community settings. The study found that, based on published studies, ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination were most effective in preventing PPH ≥500 ml. Carbetocin had the most favourable side-effect profile amongst the top three options.[16]

The World Health Organization (WHO) did not include a recommendation for carbetocin in its 2012 guideline regarding postpartum hemorrhage.[17] The 2018 update to the WHO's recommendations on uterotonics for the prevention of PPH has included heat-stable carbetocin to the essential medicines list.[18] The guidelines recommend heat-stable carbetocin for the prevention of excessive bleeding after all births in settings where oxytocin is unavailable or its quality cannot be guaranteed, and where its cost is comparable to other effective uterotonics. The CHAMPION trial, the largest clinical trial in PPH prevention, showed that heat-stable carbetocin is non-inferior to current standard of care oxytocin, for the primary outcome of ≥500 ml blood loss or additional uterotonic use, after vaginal birth. Heat-stable carbetocin remains effective at high temperatures, addressing a significant limitation of oxytocin, which must be stored and transported at 2–8°C.[19]

CONCLUSION

Efforts to reduce maternal mortality from PPH include research studies seeking to identify safe, stable, effective uterotonics. Heat stable carbetocin is the subject of much interest for its effectiveness in preventing PPH following vaginal deliveries, and caesarean section backed by emerging evidence across multiple studies. The new information could expand its application for prevention of PPH, especially in low-resource settings, where the cold chain is not commonly available. Considering the totality of the evidence, it appears to have some additional desirable effects compared with oxytocin and a very favourable side effect profile similar to oxytocin.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Bhalla A. Carbetocin: a therapy advance for prevention of postpartum haemorrhage. Int J Basic Clin Pharmacol 2022;11:352-5.