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Carbetocin for the Prevention of Postpartum Hemorrhage

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INTRODUCTION

Considering the physical and emotional costs of postpartum hemorrhage (PPH) worldwide, it is not surprising that institutions as diverse as the World Health Organization, the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) all recommend active management of the third stage of labor (AMTSL) even for patients with low risk for PPH[1,2] (see Chapters 14 and 15). Their consensus is understandable given that numerically more women without risk factors for PPH suffer from it than do women with obvious risk factors[2].

The administration of a uterotonic medication soon after the delivery of the fetus is an essential part of the AMTSL[2] that is capable of decreasing the incidence of PPH by 40%[3,4]. However, these medications pose some challenges, in that individually and collectively they have side-effects, contraindications and problems with storage and administration. As such, the search for the ideal uterotonic continues, and today the main uterotonic agents are oxytocin, ergonovine, carboprost, carbetocin and misoprostol. This chapter focuses on carbetocin.

Oxytocin is the most widely available and used uterotonic agent[3,5] (see Chapter 43). It binds to the myometrial oxytocin receptors and stimulates contraction of the uterine muscle by increasing the intracellular concentration of calcium[6,7]. However, its use is not without some limitations. Oxytocin has a short half-life of 3–17 minutes, and a continuous intravenous (IV) infusion is necessary to achieve sustained uterotonic activity[3,5,7]. Moreover, large doses or boluses of oxytocin are associated with adverse effects in the form of hypotension, nausea, vomiting, dysrhythmias, ST-T changes, pulmonary edema and severe water intoxication with convulsions[3,8,9].

In contrast, carbetocin (1-deamino-1-carba-2-tyrosine(O-methyl)-oxytocin) is a synthetic oxytocin analogue that binds to the same oxytocin receptors in the myometrium with an affinity similar to that of oxytocin[6,7]. Its main advantage over oxytocin is a four-fold longer uterotonic activity, a fact which precludes the necessity of a continuous infusion[10,11].

PHARMACOLOGY

As noted above, carbetocin is a synthetic oxytocin analogue that binds to the same myometrium receptors as oxytocin with similar affinity[7,12]. Despite a similar affinity, its potency in animal models is about one-tenth that of oxytocin on a mole per mole basis[13]. At the same time, its plasma half-life is approximately 40 minutes after IV injection, which is 4–10 times longer than that of oxytocin[10]. Similarly to oxytocin, it causes an increase in the intracellular concentration of calcium that promotes uterine contractility, through the generation of inositol phosphates[14].

Oxytocin and vasopressin are neurohypophysial hormones with a short half-life in plasma. By removing the primary amino group from the vasopressin molecule, a prolongation of the half-life was achieved, something which did not happen when the same alteration was made in the oxytocin molecule. A further alteration of the molecule was necessary in order to achieve this same goal. The disulfide bond had been proven not to be important in the mechanism of action of oxytocin[6]. By removing the amino group (1-deamino), and replacing the sulfur atom at position 1 with a carba group (–CH_2–), a prolonged myometrial action was observed[6,7]. Carbetocin is the carba analogue being used clinically in order to prevent and/or treat PPH. The deamination protects carbetocin from aminopeptidase cleavage, and the replacement of the disulfide bond by CH_2S protects the analogue from disulfidase cleavage[15] (Figure 1). This is the suggested explanation for the protracted half-life of carbetocin in plasma. Another suggested explanation for the prolonged activity of carbetocin is its higher lipophilicity that can alter its tissue distribution[7,13]. Atke *et al.* suggested that this increased lipophilicity was responsible for an increased half-life in the receptor compartment[7].

The structural differences between the molecules of oxytocin and carbetocin could also explain the decreased potency of the latter when compared with the former. The current recommended dose of carbetocin for the prevention of PPH is 100 μg, which is roughly equivalent to 10 μg (5 IU) of oxytocin[13]. However, it is important to highlight that these figures are derived from animal data. Human myometrium

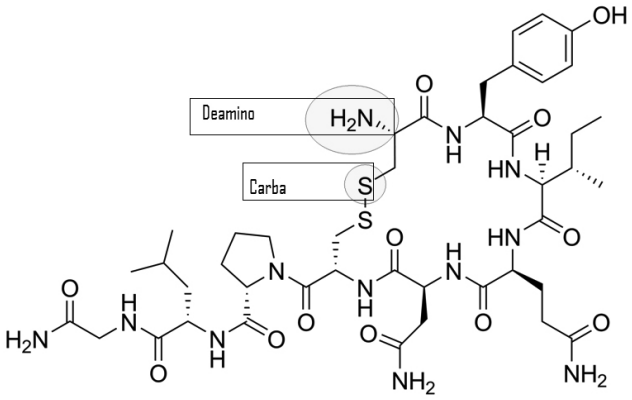

Figure 1 Oxytocin molecule. The amino group and the disulfide bond, which were altered in order to create carbetocin, are indicated. The amino group was removed and the sulfur atom was replaced by a carba group

receptors might have higher affinity to carbetocin than rat receptors; therefore, it is not clear if the decreased potency found in animal models can be extrapolated to humans[7,13].

In a study, performed on 40 women, carbetocin was administered either IV in doses varying from 8 to 30 μg or intramuscularly (IM) in doses varying from 10 to 70 μg, 24–48 h postpartum. After IV administration, tetanic contraction was achieved in a mean time (± SD) of 1.2 ± 0.5 min. Uterine tetany lasted for 6.9 ± 2.1 min followed by rhythmic contraction for 60 ± 18 min. After IM administration, the onset was 1.9 ± 0.6 min, with tetanic contractions lasting for 11.3 ± 3 min, followed by rhythmic contractions that lasted for 119 ± 69 min[13]. According to these findings, the onset is not affected by the route of administration, but the uterotonic activity is significant longer (two-fold) after IM injection when compared with IV. After IM injection, carbetocin reaches peak plasma levels in 30 min and its bioavailability is 80%[5,10,16,17].

Small amounts of carbetocin can cross over from plasma to breast milk, with a mean peak concentration in breast milk that is 50 times lower than in plasma[11]. This small amount is not of clinical concern, as carbetocin would be rapidly degraded by peptidases in the infant's gastrointestinal tract.

CARBETOCIN AT CESAREAN DELIVERY

To the best of our knowledge, only nine studies have used carbetocin for prevention of PPH after cesarean delivery. These are presented in Table 1 in chronological order.

The first study was published in abstract form. It was a dose-finding study with a total of 18 patients who underwent elective cesarean section under epidural anesthesia. This study established the recommended dose of 100 μg. There was a 0% response in terms of uterine contractility with doses below 60 μg, and 83% (5 out of 6) response with a dose of 100 μg[18].

Barton *et al.* published in abstract form their findings comparing carbetocin 100 μg versus placebo[19]. Although carbetocin is in fact more efficient than placebo, 28% of the women in the placebo group did not require any uterotonic therapy.

Boucher *et al.* conducted a double-blind randomized control trial to compare carbetocin 100 μg IV bolus after placental delivery with oxytocin 2.5 IU IV bolus followed by a 16 h infusion of oxytocin for a total of 30 IU[20]. Their primary outcome was blood loss as calculated by means of aspiration from the surgical field from the time the study drug was administered until skin closure. Although not statistically significant, women in the carbetocin group bled 29 ml less ($p = 0.3$). More important, significantly fewer women had blood loss greater than 200 ml with carbetocin ($p = 0.0041$). In addition, the three study participants that required additional uterotonic intervention were all in the oxytocin group.

Similarly, Dansereau *et al.* also compared carbetocin as a single 100 μg bolus IV with oxytocin IV bolus followed by 8 h infusion of oxytocin after cesarean delivery for women with low risk for PPH[9]. This Canadian multicenter double-blind randomized controlled trial is the largest study to date, with 694 participants. The major finding was a 50% decrease in the necessity of additional uterotonic therapy in patients treated with carbetocin when compared with oxytocin.

Del Angel-Garcia *et al.* published in abstract form their findings comparing carbetocin 100 μg IV with oxytocin 5 IU IV after elective cesarean delivery in patients with at least one risk factor for PPH[21]. Uterine atony was reported in 8% of the patients in the carbetocin group versus 19% in the oxytocin arm. This Mexican study included a cost analysis. According to the authors, allocation of patients to carbetocin therapy resulted in lower cost than those treated with oxytocin (US dollars 3525 vs. US dollars 4054).

Borruto *et al.* also compared carbetocin as a single IV bolus with oxytocin infusion. Their study included both elective and emergency cesarean delivery among patients who had at least one risk factor for PPH[22]. Similar to the previous studies, the odds ratio (OR) for uterotonic intervention was 1.83 (95% CI 0.9–2.6) times higher in the oxytocin group compared with the carbetocin group.

Attilakos *et al.*, in a double-blind randomized controlled trial compared carbetocin 100 μg single IV bolus with oxytocin 5 IU single IV bolus after low risk cesarean deliveries[23]. Additional uterotonics were necessary in 33.5% of patients in the carbetocin group patients compared with 45.5% in the oxytocin group ($p = 0.023$). This study included 377 patients. Although the need for additional uterotonics was decreased, not dissimilar to other studies mentioned above, this study did not demonstrate a decrease in blood loss or in the incidence of PPH. Of interest, both arms of the study had a high failure rate.

Triopon *et al.*, in a French two-phase observational study[24], compared the outcomes of a cohort of 155 patients who received oxytocin with the outcomes of a subsequent cohort of 155 patients who received carbetocin after cesarean delivery (after the

Table 1 Studies with carbetocin after cesarean delivery

Author	*Year*	*Type of study*	*Population*	*Intervention*	*Outcomes*
Boucher *et al.*[18]	1991	Dose-ranging	Low-risk, elective C/S under epidural (n = 18)	Carbetocin IV ranging from 10 to 100 μg after delivery of placenta	0% response with doses ≤60 μg 83% (5/6) with tetanic contraction with 100 μg
Barton *et al.*[19] (abstract)	1996	Double-blind RCT	Low-risk elective C/S under regional anesthesia (n = 119)	100 μg carbetocin (n = 62) vs. saline (n = 57)	Uterine tone significantly increased in carbetocin treated women (p <0.05) Use of additional uterotonic therapy 8/62 vs. 41/57, RR 0.18 (CI 95% 0.09–0.35)
Boucher *et al.*[20]	1998	Double-blind RCT	Low-risk, elective C/S under epidural (n = 57)	Carbetocin 100 μg IV (n = 29) vs. oxytocin 2.5 IU IV bolus + 16 h infusion of 30 IU after delivery of placenta	Mean intraoperative blood loss was 159 vs. 188 ml (p = 0.3) Significantly fewer women had blood loss ≥200 ml with carbetocin (33%) vs. oxytocin (79%) (p = 0.0041) Comparable vital signs and hematologic values
Dansereau *et al.*[9]	1999	Canadian multicenter double-blind RCT	Low-risk elective C/S under regional anesthesia (n = 694)	Carbetocin 100 μg IV (n = 317) vs. oxytocin 5 IU IV bolus 8 h infusion of 20 IU (n = 318)	Additional oxytocic intervention was 4.7% vs. 10.1% (p <0.05) OR for treatment failure was 2.03 times higher with oxytocin vs. carbetocin (95% CI 1.1–2.8) Similar safety profile
Del Angel-Garcia *et al.*[21] (abstract)	2006	Randomized pragmatic clinical trial	At least 1 risk factor for PPH, elective C/S (n = 152)	Carbetocin 100 μg IV (n = 77) vs. oxytocin 5 IU IV (n = 75)	Uterine atony in 8% vs. 19 % (p <0.0001) Blood loss ≥500 ml only observed with oxytocin Cheaper mean cost per patient treated with carbetocin (USD 3525 vs. USD 4054)
Borruto *et al.*[22]	2009	Randomized controlled clinical trial	Singleton, at least 1 risk factor for PPH, elective or emergency C/S (n = 104)	Carbetocin 100 μg (n = 52) vs. oxytocin 2 h infusion of 10 IU (n = 52) after placental delivery	Uterotonic intervention in 3.8% vs. 9.6% (p <0.01) OR for treatment failure was 1.83 (95% CI 0.9–2.6) Mean blood loss 30 ml less with carbetocin (p = 0.05)
Attilakos *et al.*[23]	2010	Double-blind RCT	Low-risk, elective or emergency C/S (n = 377)	Carbetocin 100 μg IV (n = 188) vs. oxytocin 5 IU IV (n = 189)	Additional oxytocic 33.5% vs. 45.5% (RR 0.74, 95% CI 0.57–0.95, p = 0.023) No difference in estimated blood loss, side-effects, or hematologic values
Triopon *et al.*[24]	2010	Two-phase observational study	Elective or emergency C/S (n = 310)	Use of carbetocin as a sentinel event separating the 2 groups. Data from 155 who received oxytocin 5 IU compared with 155 women who received carbetocin 100 μg after fetal delivery	Significant decrease in postoperative IV iron administration in the carbetocin group (6.5% vs. 14.5%, p = 0.03) Fewer compression sutures (although not significant) in the carbetocin group (0.6% vs. 4.5%, p = 0.06) No difference in the incidence of vascular sutures, necessity of additional uterotonic, and blood transfusion
Cordovani *et al.*[25]	2012	Double-blind, randomized dose-finding study	Low-risk, elective C/S under spinal anesthesia (n = 80)	Carbetocin 80, 90, 100, 110 or 120 μg IV after fetal delivery	Similar failure rate among all dose groups. Not possible to calculate ED95 Similar incidence of side-effects and blood loss in all groups Overall, uterus was boggy at 2 min in 10/80 (12.5%) Additional uterotonic given to 9/80 (11.25%) 6/10 (60%) with boggy uterus at 2 min 3/70 (4.3%) with firm uterus at 2 min

RCT, randomized controlled trial; C/S, cesarean section; USD, US dollars

department's drug of choice for prevention of PPH was converted from oxytocin to carbetocin). In contrast to the previous studies, there was no significant decrease in the need for additional uterotonics. On the other hand, there was a significant decrease in postoperative IV iron administration in the carbetocin group (6.5% vs. 14.5%, $p = 0.03$) and fewer compression sutures were necessary (although not significant) in the carbetocin group (0.6% vs. 4.5%, $p = 0.06$).

A recent dose-finding study performed by Cordovani *et al.* attempted to calculate the ED95 of carbetocin for elective cesarean delivery in low-risk patients for PPH[25]. The authors were unable to calculate the ED95 of carbetocin, as the failure rate was evenly distributed across all dose groups (80, 90, 100, 110 and 120 μg). Overall, 12.5% of patients failed to present a firm uterus after 2 min of drug administration, and 11.25% of women required additional uterotonic therapy within 4 h. It is important to point out that, three of the women requiring additional uterotonics in fact had a firm uterus after 2 min of carbetocin administration.

In general, the studies on cesarean deliveries have shown a decrease in the necessity of additional uterotonic intervention, although none demonstrated a decrease in either the incidence of PPH or the mean blood volume loss, as the study design practically eliminated such end points. At the same time, fewer patients in the carbetocin arms of the studies lost larger amounts of blood[21,22]. The optimal dose of carbetocin is yet to be determined, but recent data suggest that doses as low as 80 μg are as effective as the current recommended dose of 100 μg[25].

CARBETOCIN IN VAGINAL DELIVERY

Six studies on carbetocin therapy used in vaginal deliveries are presented in Table 2 in chronological order.

Van Dongen *et al.* performed an ascending dose-tolerance study with IM carbetocin administered after low risk vaginal deliveries[10]. Their findings revealed a maximum tolerated dose of 200 μg due to the presence of limiting side-effects, namely retained placenta, blood loss of 1000 ml or more and blood transfusion. Optimal results were within the 75–125 μg dose range in keeping with the 100 μg dose determined in the original dose-finding study[19].

Boucher *et al.*, in a double-blind randomized controlled trial involving 160 patients with at least one risk factor for PPH, compared carbetocin 100 μg IM with oxytocin 10 IU IV infusion over a 2 h period[26]. Their findings showed no difference in the requirement of additional uterotonics or in the presence of PPH. However, significantly fewer women in the carbetocin arm required uterine massage compared with in the oxytocin arm.

Leung *et al.* compared carbetocin 100 μg IM ($n = 165$) with Syntometrine®, a combination of oxytocin and ergometrine, IM ($n = 164$) given after low risk vaginal deliveries[17]. No significant difference was observed in hemoglobin drop or use of additional uterotonics, but women treated with Syntometrine had a significantly higher incidence of nausea, vomiting and hypertension.

Ngan *et al.*, in a retrospective study involving 118 low risk patients, found that carbetocin was associated with less blood loss compared with a combination of oxytocin and ergometrine[27].

Nirmala *et al.* studied 120 women at high risk for PPH who delivered vaginally in another randomized controlled trial which compared carbetocin 100 μg IM with Syntometrine IM[16]. In contrast to the findings observed in a low risk population[17], these authors found a significant decrease in the mean blood loss as well as a significant smaller decrease in hemoglobin drop in the carbetocin group. However, there was no difference in the necessity of additional uterotonic agents or blood transfusion. Interestingly, also in contrast to the findings of Leung *et al.*[17], there was no difference in the incidence of side-effects.

Su *et al.* performed yet another comparison of carbetocin with Syntometrine[28] evaluating 370 women with low risk for PPH. Similar to previous findings[17], no differences were found in the requirements for additional uterotonic agents, in blood loss or in the incidence of PPH. On the other hand, side-effects were noticeably more prevalent in the Syntometrine group.

In general, studies of vaginal deliveries found no difference in the requirement for additional uterotonic medication when compared with oxytocin or with a combination of oxytocin and ergometrine. However, when compared with oxytocin alone, carbetocin-treated patients with at least one risk factor for PPH required less uterine massage. The findings regarding decrease in blood loss are conflicting. The most consistent finding was a decrease in the incidence of nausea and vomiting when compared with a combination of oxytocin and ergometrine.

SIDE-EFFECTS AND CONTRAINDICATIONS

Oxytocin and carbetocin are without differences regarding either the types of side-effects or their frequency[9,20,22,23]. The incidence of side-effects in three reports is presented in Table 3[9,20,22]. Although not shown in the table, Borruto *et al.* described 28.8% of arrhythmias after oxytocin injection, but none for carbetocin[22]. Similarly, Boucher *et al.* found a 3.6% incidence of premature ventricular contraction after oxytocin administration, but none after carbetocin[20]. The safety of carbetocin in patients with severe cardiovascular disease has not yet been determined.

As carbetocin should not be administered prior to fetal delivery, under no circumstances should it be used for induction of labor or labor augmentation. It should be administered as an IM injection or slow IV bolus over 1 min after fetal or placental delivery[1,11]. The following is an extract from the product leaflet provided by its manufacturer:

Table 2 Studies with carbetocin after vaginal delivery

Author	*Year*	*Type of study*	*Population*	*Intervention*	*Outcomes*
Van Dongen *et al.*[10]	1998	Ascending dose tolerance	Low-risk, vaginal delivery ($n = 45$)	Carbetocin IM (15, 30, 50, 75, 100, 125, 150, 175, 200 μg) immediately after birth of infant	Maximum blood loss at the upper and lower dose levels. Lowest in the 70–125 μg range Maximum tolerated dose calculated to be 200 μg (4/18 retained placenta, 3/18 blood transfusion, 4/18 additional oxytocics)
Boucher *et al.*[26]	2004	Double-blind RCT	At least 1 risk factor for PPH ($n = 160$)	Carbetocin 100 μg IM + IV placebo ($n = 83$) vs. placebo IM + oxytocin 10 IU 2 h IV infusion ($n = 77$) after delivery of placenta	No difference in requirement for additional uterotonic medication, nor in laboratory PPH indicators Uterine massage required in 43.4% vs. 62.3% ($p < 0.025$)
Leung *et al.*[17]	2006	Double-blind RCT	Low-risk, vaginal delivery ($n = 329$)	Carbetocin 100 μg IM ($n = 165$) vs. Syntometrine IM ($n = 164$) after delivery of infant	No difference in drop of hemoglobin (1.4 vs. 1.5 g/dl), or additional uterotonic agents (8.7% vs. 6.7%) Significant lower incidence of nausea (RR 0.18, 95% CI 0.04–0.78), vomiting (RR 0.1, 95% CI 0.01–0.74), hypertension at 30 min ($p < 0.01$) and 60 min ($p < 0.05$) Higher incidence of tachycardia (RR 1.68, 95% CI 1.03–3.57)
Ngan *et al.*[27]	2007	Retrospective study	Low-risk, vaginal delivery ($n = 118$)	Carbetocin 100 μg IM vs. IM combination of oxytocin 5 IU and ergometrine 0.2 mg immediately after infant delivery	Mean blood loss 388 vs. 551 ($p = 0.01$) Blood loss ≥500 ml was 21.4% vs. 43.5% ($p = 0.01$) and blood loss ≥1000 ml was 1.8 % vs. 14.5% ($p = 0.02$)
Nirmala *et al.*[16]	2009	Randomized controlled study	High-risk for PPH, vaginal delivery ($n = 120$)	Carbetocin 100 μg IM ($n = 60$) vs. Syntometrine IM ($n = 60$) immediately after infant delivery	No difference in requirement for additional oxytocic agent, time interval to well contracted uterus, blood transfusion, adverse effect or complications Significantly lower mean blood loss in carbetocin group (244 ± 114 ml vs. 343 ± 143 ml, 95% CI 52–146 ml) Significant reduced drop in hemoglobin in carbetocin group (0.3 ± 0.2g/dl vs. 0.4 ± 0.2 g/dl, 95% CI 0.1–0.2)
Su *et al.*[+28]	2009	Double-blind RCT	Low-risk, vaginal delivery ($n = 370$)	Carbetocin 100 μg IM ($n = 185$) vs. Syntometrine IM ($n = 185$) immediately after infant delivery	No difference in requirement for additional oxytocic agent, blood loss or incidence of PPH Women who had Syntometrine were four times more likely to experience nausea (RR 4.2, 95% CI 2.2–7.8) and vomiting (RR 4.3, 95% CI 1.9–9.5). Tremor, sweating, retching and uterine pain were also more likely in the Syntometrine group ($p < 0.05$)

RCT, randomized controlled trial

Table 3 Side-effects associated with carbetocin and frequency of occurence

>20%	*<20% and >10%*	*<10% and >5%*	*<5%*
Abdominal pain	Feeling of warmth	Pruritus	Back pain
Nausea	Headache	Shortness of breath	Sweating
Flushing	Tremors	Vomiting	Dizziness
		Metalic taste	

'Because of its long duration of action relative to oxytocin, uterine contractions produced by carbetocin cannot be stopped by simply discontinuing the medication. Therefore, carbetocin should not be administered prior to delivery of the infant for any reason, including elective or medical induction of labour. Inappropriate use of carbetocin during pregnancy could theoretically mimic the symptoms of oxytocin overdosage, including hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions, tumultuous labour, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, utero-placental hypoperfusion and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, or death. Carbetocin should not be used in patients with a history of hypersensitivity to oxytocin or carbetocin. Carbetocin should not be used in patients with vascular disease, especially coronary artery disease, except with extreme caution. Carbetocin is not intended for use in children.'

CARBETOCIN TODAY

In email correspondence with Ferring Pharmaceuticals in July 2011, the authors were informed that carbetocin has been available for clinical use since the year of 2000. Today, carbetocin is approved in 23 countries for the prevention or treatment of uterine atony[5]. Of these, Canada has undertaken a leading role in carbetocin research, including the largest randomized controlled trial executed to date[9]. As a consequence, the Society of Obstetricians and Gynaecologists of Canada (SOGC) in their 2009 guidelines on the active management of the third stage of labor[1], released the following recommendations:

'6. Carbetocin, 100 μg given as an IV bolus over 1 minute, should be used instead of continuous oxytocin infusion in elective Caesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics. (I-B)
7. For women delivering vaginally with 1 risk factor for PPH, carbetocin 100 μg IM decreases the need for uterine massage to prevent PPH when compared with continuous infusion of oxytocin. (I-B)'

This means that, for cesarean delivery performed in Canada under regional anesthesia, carbetocin is the first choice as a uterotonic agent. It is also recommended for vaginal deliveries with increased risk for PPH. How frequent these recommendations are being followed is yet to be assessed, as it is recognized that the practice varies across the country.

COST-EFFECTIVENESS

British data from 2010 states that one ampoule of carbetocin 100 μg costs £17.64, whereas one ampoule of oxytocin 10 IU costs £0.86[23]. Although it is significantly more expensive, other factors must be considered. Among these, only one ampoule of carbetocin would be used in a successfully treated patient, whereas an average of 2–4 ampoules of oxytocin would be necessary to supply a continuous infusion.

A Mexican study from 2006 analysed the overall cost to treat women with carbetocin compared with oxytocin[21]. The use of resources was obtained from a clinical trial involving 152 women with high risk for PPH who underwent cesarean delivery. The cost was calculated using the financial information provided by the Mexican Institute of Social Security, which is the third party payer. Their finding was that women treated with carbetocin cost less to the health care system than those treated with oxytocin (US dollars 3525 vs. US dollars 4054)[21]. One could infer that this is due to a decrease in the necessity for additional uterotonic, blood products and faster hospital discharge. However, at this point this inference cannot be confirmed. These data were accurate for Mexico at the time of the study, but a similar benefit with carbetocin in other settings could be expected.

The ease of administration and the potentially lower overall cost with a greater efficacy could become the basis of a wider use of carbetocin for the prevention of PPH, especially in low-resource areas. However, because the manufacturer recommends carbetocin to be stored at temperatures of 2–8°C, this requirement may preclude its more widespread use in poorly resourced areas where 24 h access to reliable sources of electricity is problematic. Carbetocin in a room temperature formulation would potentially increase its usefulness in such countries. To date, no data have been published on drug stability at room temperature

REMAINING QUESTIONS

Although current data suggest that carbetocin can be more effective than oxytocin in the prevention of PPH, studies to date have not focused on the hemodynamic effects of this agent. The practice of administering oxytocin as a bolus has been discouraged due to its hemodynamic effects[3,8,9]. At the same time, current recommendations of carbetocin, which is an oxytocin analogue with agonistic properties at the same receptors, state that this drug should be given as a single IV bolus. The only caveat is that the recommendation is for a slow IV bolus administered over a 1 min duration. This is not based on clinical data, but presumably on extrapolation from findings with oxytocin[29,30].

The safety of carbetocin for use in patients with vascular disease as well as coronary disease has not been tested. Similarly, no studies were performed on patients under general anesthesia. Although there is no clear reason that would preclude the use of carbetocin in women under a general anesthetic, the lack of clinical trials accounts for the manufacturer's

recommendation of using this drug only in women who are not anesthetized or who are only under regional or local anesthesia[11].

Further analysis is warranted to assess the cost-effectiveness of carbetocin. Should the Mexican study findings[21] be replicated in different settings, this will further justify the use of carbetocin as a first choice of uterotonic agent. In addition, the drug stability at room temperature remains unclear.

Finally, the optimal dose of carbetocin is still to be determined. In the case of oxytocin, initial IV doses as low as 0.5 IU are effective in providing adequate uterine contractility at elective cesarean delivery[31]. Extrapolating the findings for carbetocin, it is reasonable to assume that 100 μg, which is equivalent to 5 IU of oxytocin according to animal data[13], is considerably more than the minimum necessary. This is especially true if the suggestions that the human uterus is more sensitive to carbetocin than the rat myometrium are accurate[7,13]. In addition, similarly to oxytocin, carbetocin will have to be evaluated in different clinical scenarios, namely non-laboring elective cesarean section, urgent/emergent cesarean section on laboring women and vaginal delivery. Its usefulness in the area of medical interruptions of pregnancy remains to be investigated.

CONCLUSIONS

Carbetocin is a synthetic oxytocin analogue. It combines the quick onset of oxytocin with the long-acting effect of ergometrine. Compared with oxytocin, it reduces the necessity of uterotonic intervention with similar incidence of side-effects; compared with a combination of oxytocin and ergometrine, it is as effective with fewer side-effects, namely nausea, vomiting and hypertension. According to the Society of Obstetricians and Gynaecologists of Canada, it should be the first choice of uterotonic agent to prevent PPH at elective cesarean delivery under regional anesthesia. It is also suggested that it should be used in women at risk for PPH after vaginal delivery.

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