PRODUCT MONOGRAPH

[Pr] DURATOCIN
(Carbetocin Injection)

1 mL ampoule - 100 µg/mL Injection

For Intravenous Use Only

Therapeutic Classification

Uterotonic Agent

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THERAPEUTIC CLASSIFICATION

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ACTIONS AND CLINICAL PHARMACOLOGY

DURATOCINJ (carbetocin injection) is a long-acting synthetic nonapeptide analogue of oxytocin with agonist properties. It can be administered intravenously as a single dose immediately following delivery by cesarean section under epidural or spinal anesthesia, to prevent uterine atony and postpartum hemorrhage.

The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin, another posterior pituitary hormone. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions, and increased uterine tone. The oxytocin receptor content of the uterus is very low in the non-pregnant state, and increases during pregnancy, reaching a peak at the time of delivery. Therefore carbetocin has no effect on the non-pregnant uterus, and has a potent uterotonic effect on the pregnant and immediate postpartum uterus.

The onset of uterine contraction following carbetocin administration by either the intravenous or

intramuscular route is rapid, with a firm contraction being obtained within 2 minutes. The total duration of action of a single intravenous injection of carbetocin on uterine activity is about one hour suggesting that carbetocin may act long enough to prevent postpartum hemorrhage in the immediate postpartum period. In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions.

Carbetocin**,** when administered immediately postpartum as a single intravenous bolus injection of 100 μg to women delivered by cesarean section under epidural or spinal anesthesia, was found to be significantly more effective than placebo in preventing uterine atony and minimizing uterine bleeding.

Carbetocin administration also appears to enhance uterine involution in the early postpartum period.

INDICATIONS AND CLINICAL USE

DURATOCIN (carbetocin injection) is indicated for the prevention of uterine atony and postpartum hemorrhage following elective cesarean section under epidural or spinal anesthesia.

DURATOCIN has not been studied in cases involving emergency cesarean section, classical cesarean section, anesthesia other than epidural or spinal, or in patients presenting significant heart disease, history of hypertension, known coagulopathy or evidence of liver, renal or endocrine disease (excluding gestational diabetes). Appropriate studies have not been undertaken and doses have not been established in women following labour or vaginal delivery.

CONTRAINDICATIONS

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 over dosage, 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.

WARNINGS

Some patients may not have an adequate uterine contraction after a single injection of DURATOCIN (carbetocin injection). In these patients, administration of DURATOCIN should not be repeated and more aggressive treatment with additional doses of other available uterotonic drugs like oxytocin or ergometrine is warranted. In cases of persistent bleeding, the presence of retained placental fragments, coagulopathy, or trauma to the genital tract should be ruled out.

Although no cases of partial retention or trapping of the placenta have been reported, this remains a theoretical possibility if the drug is administered before delivery of the placenta.

PRECAUTIONS

General

DURATOCIN (carbetocin injection) use during pregnancy, prior to the delivery of the infant, is contraindicated (see CONTRAINDICATIONS).

See WARNING section regarding potential requirement for further oxytocin therapy.

DURATOCIN is not recommended for use in elderly patients.

Nursing Mothers

Small amounts of carbetocin have been shown to cross over from plasma into the breast milk of nursing women who were given a 70 μg dose intramuscularly, between 7 and 14 weeks postpartum. The mean peak concentration in breast milk was approximately 50 times lower than in plasma, and the ratio of the milk to plasma area under the concentration versus time curves (M/P_{AUC}) was only 2-3%. The small amount of carbetocin transferred into breast milk or colostrum after a single injection, and subsequently ingested by a breast feeding infant, would not be expected to present a significant safety concern. This is due to the fact that carbetocin would be rapidly degraded by peptidases in the infant gastrointestinal tract.

Oxytocin is known to cause contraction of the myoepithelial cells surrounding the mammary alveoli, thereby stimulating milk let-down. There is no sufficient evidence to determine whether carbetocin can also stimulate milk let-down. However, milk let-down was found to occur normally in 5 nursing women after receiving a 70 μg carbetocin dose by the intramuscular route.

Drug Interactions

No specific drug interactions have been reported with carbetocin. However, since carbetocin is closely related in structure to oxytocin, it is possible that some of the same drug interactions could occur. Severe hypertension has been reported when oxytocin was given 3-4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin=s cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

ADVERSE REACTIONS

The adverse events observed with carbetocin during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin when administered after cesarean section under epidural or spinal anesthesia.

Intravenous carbetocin was frequently (10-40% of patients) associated with nausea, abdominal pain, pruritis, flushing, vomiting, feeling of warmth, hypotension, headache and tremor.

Infrequent adverse events (1-5% of patients) included back pain, dizziness, metallic taste, anaemia, sweating, chest pain, dyspnea, chills, tachycardia and anxiety.

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Over dosage of carbetocin can be expected to produce enhanced pharmacological effects. Therefore, when carbetocin is administered postpartum, over dosage may be associated with uterine hyperactivity and pain. Treatment consists of symptomatic and supportive management.

DOSAGE AND ADMINISTRATION

A single intravenous dose of 100 μg (1 mL) of DURATOCIN (carbetocin injection) is administered by bolus injection, slowly over 1 minute, only when delivery of the infant has been completed by cesarean section under epidural or spinal anesthesia. DURATOCIN can be administered either before or after delivery of the placenta.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name

Carbetocin (INN)

Chemical Name

1-desamino-1-monocarba-2-(0-methyl)-tyrosine oxytocin

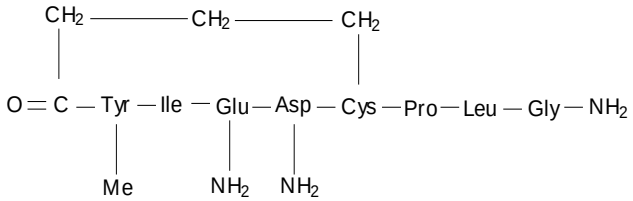
Other Names

[2-0-methyltyrosine]-1-deaminocarba-1-oxytocin

[6,1,B-deaminocystathionine,2-0-methyl-tyrosine-oxytocin]

[tyr(me)^2]-deamino-1-carba-oxytocin

Chemical Structure



Molecular Weight

988.1

Molecular Formula

$C_{45}H_{69}N_{11}O_{12}S$

Description

Carbetocin is a white, fluffy lyophilized powder, soluble in water, ethanol, methanol and acetic acid. Carbetocin is insoluble in ether and petroleum ether. The pH of carbetocin is 3.9.

Composition

Each ampoule contains 100 μg (0.1 mg) of carbetocin, 9 mg sodium chloride, glacial acetic acid (6-14 μg) and water for injection q.s. to 1 mL. Ampoules are clear glass with a white identification ring and a blue dot indicating the cut area.

Stability and Storage Recommendations

DURATOCIN (carbetocin injection) must be stored at refrigerator temperature (2-8°C). DURATOCIN should not be frozen. Once the ampoule has been opened, the product should be used immediately.

AVAILABILITY OF DOSAGE FORMS

DURATOCIN (carbetocin injection) is available in 1 mL ampoules. Each ampoule contains 100 μg carbetocin. Boxes contain 5 ampoules each.

Instructions for Opening Ampoules

1. Hold ampoule with blue dot pointing upwards. Shake or tap ampoule to empty the tip.
2. With blue dot pointing upwards, snap off tip by forcing it downwards.

PHARMACOLOGY

Pharmacodynamics

In vivo studies in rats demonstrated that carbetocin has a uterotonic effect comparable to oxytocin. The maximum intensity is lower but the duration is longer.

An exploratory study in women after normal vaginal delivery was undertaken to determine the intravenous dose of carbetocin required to produce a sustained contraction of the postpartum uterus. Seventeen (17) women received a single intravenous dose of 8-100 μg carbetocin on day 1 to 2 postpartum. In total, 14 women achieved tetanic uterine contraction while no response was observed in 3 women after 10, 12 and 40 μg carbetocin, respectively. Dose levels of 50 μg and 100 μg carbetocin produced a tetanic uterine contraction. Results of the above trial are seen in the following table.

Breakdown of Patients by the Number of Doses Required to Produce Tetany

Increment size (µg)	Case No.	No. of increments administered	Total dose (µg)	Tetantic dose (µg)	Efficacy of a single dose
100	5	1	100	100	1/1 (100%)
50	1	1	50	50	1/1 (100%)
10	2	2	20	20	6/10 (60%)
	3	4	40	No tetany[a]	
	4	4	40	30	
	6	2	20	10	
	7	3	30	10	
	8	1	10	No tetany[b]	
	9	1	10	10	
	10	1	10	10	
	14	1	10	10	
	15	1	10	10	
2	11	5	10	10	0/5 (0%)
	12	5	10	8	
	13	4	8	8	
	16	6	12	No tetany[c]	
	17	5	10	No tetany[d]	

a Record not analyzable. Patient reported cramping starting 2 minutes after first injection which continued for about 5 minutes after injection of last dose.

b Record not analyzable. Patient reported cramping starting 2 minutes after first injection.

c Record not analyzable. Patient reported no cramping.

d Record not analyzable. Patient reported definite contractions starting at 1 min. 40 sec., and lasting for 60 min. after injection.

The onset of uterine activity after intravenous carbetocin is rapid, occurring within 1.2 ∀ 0.5 minutes. Total duration of a single injection of intravenous carbetocin on uterine activity is about one hour.

Pharmacokinetics

The distribution and elimination half-lives of carbetocin in non-pregnant women were found to be 5.5 ∀ 1.6 minutes and 41 ∀ 11.9 minutes respectively after a 400 μg intravenous dose, indicating a lack of dose-dependency for this parameter. The clearance of carbetocin from the body (both total and renal), and the volume of distribution do not appear to be dose dependent, whereas Cmax and AUC_{0-4} show proportional changes with increasing dose.

Approximately 0.7% of the carbetocin dose is eliminated in the unchanged form by the kidney, indicating that carbetocin, like oxytocin, is eliminated primarily by non-renal routes.

The pharmacokinetic parameters of intravenous carbetocin are seen in the following table.

Summary of Pharmacokinetic Parameters

		Intravenous Injection	
Parameter		**400 µg IV**	**800 µg IV**
AUC (0 to 4) (µg*min/L)	Mean Range	749.2∀ 131.0 539.5-916.9	1,370.4∀ 214.9 1,148-1,733
Clt (L/min)	Mean Range	0.549∀0.105 0.436-0.741	0.595∀0.089 0.462-0.696
Clr (L/min)	Mean Range	0.004∀0.002 0.002-0.007	0.004∀0.002 0.002-0.007
Clnr (L/min)	Mean Range	0.545∀0.103 0.433-0.735	0.591∀0.089 0.458-0.692
Vc (L)	Mean Range	9.27∀2.98 5.2-13.6	8.38∀1.78 6.4-11.3
Alpha HL (min)	Mean Range	5.54∀1.6 3.3-7.8	6.05∀1.15 5.1-8.2
Beta HL (min)	Mean Range	41.0∀11.9 28.7-59.2	42.7∀10.6 39.3-49.4
Cmax (µg/L)	Mean Range	-	-
Tmax (min)	Mean Range	-	-
F (%)	Mean Range	-	-
Ae (%)	Mean Range	0.70∀0.30 0.36-1.13	0.68∀0.30 0.42-1.20

AUC = area under the curve; Clt = total body clearance; Clr = renal clearance; Clnr = nonrenal clearance; Vc = volume of the central compartment; alpha-HL = distribution half-life; beta-HL = elimination half-life; Cmax = peak concentration; Tmax = time to peak concentration; F= percent bioavailability of intramuscular carbetocin; Ae =percent carbetocin.

CLINICAL TRIALS

Two large double blind trials were conducted using carbetocin. The first trial evaluated the safety and efficacy of carbetocin versus placebo for control of bleeding after cesarean section. This multicentre trial included 122 patients. Efficacy was determined as the requirement for intervention with additional oxytocic therapy following test drug administration.

When given as a single bolus intravenous dose of 100 μg after delivery of the infant at elective cesarean section done under epidural, carbetocin was found to be significantly more effective than placebo in preventing uterine atony and excessive bleeding with only 13% of patients requiring intervention with further oxytocic therapy compared to 72% of patients in the placebo group (p=0.001).

The second double-blind trial compared a single intravenous dose of 100 μg carbetocin to an 8-hour oxytocin infusion after elective cesarean section done under epidural or spinal anesthesia. The primary objective was to compare the safety and efficacy of the two treatments in maintaining adequate uterine contraction after cesarean section. The primary efficacy variable was the incidence rate of the need for further oxytocic therapy for 48 hours after delivery. Carbetocin was associated with lower incidence of "need for additional oxytocic intervention" when compared to oxytocin: such intervention occurred in 5% of patients receiving carbetocin compared to 10% of patients administered oxytocin. Carbetocin was associated with a significantly longer time to intervention when compared to oxytocin: 2.03 versus 0.18 hours respectively (medians).

The dose-response relationship of carbetocin and uterine contraction was evaluated in a clinical trial involving 18 patients. Here the intravenous dose of carbetocin required to produce sustained tetanic contraction after cesarean section was determined. "Minimally effectiveness dose" was determined, and was defined as the dose that produces adequate uterine contraction

in 100% of patients. A single 100 μg intravenous injection was capable of maintaining contraction after cesarean section.

In another trial carbetocin was compared to oxytocin for their ability to reduce intraoperative blood loss during cesarean section. A single 100 μg injection of carbetocin was compared to oxytocin (total dose 32.5 IU).

It was found that a single intravenous bolus injection of carbetocin was at least as effective as 16 hours of continuous oxytocin infusion, in terms of efficacy in maintaining uterine contraction after cesarean section, and in preventing excessive intraoperative blood loss following cesarean delivery. This study confirmed the ability of a 100 μg intravenous dose of carbetocin to maintain adequate uterine tone after cesarean section.

Carbetocin also appeared to accelerate the initial stages of uterine involution, associated with the return of the uterus to the non-pregnant size and position.

TOXICOLOGY

In acute toxicology studies, the LD_{50} was estimated at 10 mg/kg in an intravenous rat study. Marked clinical signs (lethargy, hunched posture, piloerection, rapid breathing and uncoordinated movement) were noted for all animals. Using this LD_{50}, the corresponding dose for a 100 g rat would be 1,000 μg, which is ten times the dose used in humans.

Four groups of 20 rats were given carbetocin intravenous at doses of up to 1.0 mg/kg/day for 28 days. There were no deaths or clinical signs attributable to treatment.

Sixteen female beagles were given carbetocin by intravenous injection daily for 28 days at doses of up to 1.0 mg/kg/day. There were no deaths or clinical signs attributable to treatment. No treatment related changes in hematology, clinical chemistry or urinalysis occurred.

Carbetocin was found to be devoid of mutagenic activity in a battery of mutagenicity tests. Carcinogenicity studies have not been performed.

Reproduction and teratology studies have not been performed since the drug is intended for a single administration immediately after delivery.

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