

DURATOCIN

Carbetocin Injection

Presentation

Each ampoule contains 100µg of carbetocin, 9mg sodium chloride, acetic acid - glacial to pH 3.8 and water for injections to 1mL.

DURATOCIN is a ready-for-use clear, colourless solution for injection containing 100µg carbetocin in a 1mL clear glass ampoule with a white identification ring and a blue dot indicating the cut area.

Uses

Actions

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

The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin, another posterior pituitary hormone. In *in vitro* studies, carbetocin was shown to bind to the oxytocin receptor with similar affinity as the natural peptide. Carbetocin elicited similar uteronic and galactogogic effects to oxytocin in animals and *in vitro*. Carbetocin was less potent than oxytocin, but its action was more prolonged. 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 in around 90% of patients. 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 haemorrhage 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 100µg to women delivered by caesarean section under epidural or spinal anaesthesia, was found to be significantly more effective than placebo, as evidenced by the need for additional oxytocin therapy in the operating room.

Carbetocin administration also appears to enhance uterine involution in the early postpartum period, as evidenced by the repeated measurement of the uterine fundus.

Pharmacokinetics

The distribution and elimination half-lives of carbetocin in 25 non-pregnant women were found to be 5.5 ± 1.6 minutes and 41 ± 11.9 minutes respectively after a 400µg 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 C_{max} and $AUC_{0-\infty}$ 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.

Indications

DURATOCIN is indicated for the prevention of uterine atony and excessive bleeding following delivery of the infant by elective caesarean section under epidural or spinal anaesthesia.

DURATOCIN is an oxytocic that reduces the need for additional oxytocics.

DURATOCIN has not been studied in women at high risk of postpartum haemorrhage, for example with parity greater than 4, with hypertension, following labour especially prolonged labour, or with general anaesthesia.

Dosage and Administration

Withdraw 1mL of DURATOCIN containing 100 micrograms carbetocin and administer by bolus intravenous injection slowly over 1 minute, under adequate medical supervision in a hospital.

A single dose of DURATOCIN must be administered only after delivery of the infant by Caesarean section under epidural or spinal anaesthesia. It should be given as soon as possible after delivery, preferably before removal of the placenta. DURATOCIN is to be used as a single dose only.

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 overdosage, including hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions, tumultuous labour, uterine rupture, cervical and vaginal lacerations, postpartum haemorrhage, utero-placental hypoperfusion and variable deceleration of foetal heart, foetal 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 serious cardiovascular disorders, especially coronary artery disease.

Carbetocin is not intended for use in children.

Warnings and Precautions

Precautions

Carbetocin is intended for use only at well equipped specialist obstetrics units with experienced and qualified staff available at all times.

The use of carbetocin at any stage before delivery of the infant is not appropriate because its uterotonic activity persists for several hours after a single bolus injection. This is in marked contrast to the rapid reduction of effect observed after discontinuation of an oxytocin infusion. 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. DURATOCIN is currently not indicated in emergency caesarean section or after vaginal delivery. DURATOCIN is not recommended for use in elderly patients.

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. Significant antidiuretic effect is not anticipated and has not been demonstrated at the recommended dose, but as carbetocin is closely related in structure to oxytocin, hyponatraemia and water intoxication should be considered in relevant clinical situations.

In general, carbetocin should be used cautiously in the presence of epilepsy, migraine, asthma and cardiovascular disease or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. The decision of administering carbetocin can be made by the physician after carefully weighing the potential benefit carbetocin may provide in these particular cases.

Patients with eclampsia and pre-eclampsia should be monitored for changes in blood pressure for up to 8 hours.

Specific studies have not been undertaken in gestational diabetes mellitus.

Appropriate studies have not yet been undertaken and doses established in women following vaginal delivery.

Carcinogenicity/Mutagenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of carbetocin.

Carbetocin was not genotoxic in assays for gene mutation (*in vitro* bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes *in vitro* and mouse micronucleus test *in vivo*).

Use in pregnancy

Category C. Carbetocin induces uterine contraction and may cause premature or hypertonic labour. Therefore, DURATOCIN (carbetocin injection) use during pregnancy is contraindicated (see **Contraindications**).

Use in Lactation

Small amounts of carbetocin have been shown to cross over from plasma into the breast milk of nursing women who were given a 70µg 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 70µg carbetocin dose by the intramuscular route.

In a pilot postnatal development study, administration of IV dose ≥ 0.01 mg/kg/day (similar to the clinical dose based on body surface area) to lactating rats was associated with impaired pup growth. A no-effect-dose was not determined.

Effects on Ability to Drive and Use Machines

Not applicable.

Adverse Effects

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 caesarean section under epidural or spinal anaesthesia.

Frequency	MedDRA System Organ Class	Adverse Events
Very common (≥10%)	General signs and symptoms	Feeling of warmth
	Reproductive system and breast disorders	Abdominal pain, including pain
	Gastrointestinal disorders	Nausea
	Vascular disorders	Hypotension, flushing
	Skin and subcutaneous tissue disorders	Pruritus
Common (≥1% & <10%)	Nervous system disorders	Headache, dizziness, tremor
	Gastrointestinal disorders	Vomiting, metallic taste
Rare (≥0.01% & <1%)	Cardiac Disorders	Tachycardia

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

As most of these reactions also occurred in patients treated with placebo, it is likely that many were associated with caesarean section, spinal or epidural anaesthesia or drugs used during the procedure.

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 anaesthesia.

Overdosage

Overdosage of carbetocin may produce uterine hyperactivity whether or not due to hypersensitivity to this agent. At single doses up to 800 micrograms tachycardia was observed. Overdosage of oxytocin may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake. As carbetocin is an analogue of oxytocin, the possibility of a similar event cannot be excluded.

Signs of overdose may be the symptoms arising from water intoxication and uterine hyperactivity. Treatment of overdosage of carbetocin consists of symptomatic and supportive therapy.

Pharmaceutical Precautions

Storage

DURATOCIN is stable for 2 years from date of manufacture when stored at 2-8°C (Refrigerate. Do not freeze) and protected from light. Once the ampoule has been opened, the product should be used immediately.

Incompatibilities

Carbetocin should be given by IV bolus and should not be mixed with other infusion fluids.

Instructions for use and handling

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The product should not be used if particulate matter or discoloration is observed.

Medicine Classification

Prescription Medicine.

Package Quantities

Packs containing 5 x 1mL ampoules.

Further Information

Synonyms

2,1-Desamino-4, 1-desthio-O4, 2-Methyl 1 [1-homocysteine] oxytocin 1-desamino-1-monocarba-2-(0-methyl)-tyrosine-oxytocin (2-0-methyltyrosine)-1-deaminocarpa-1-oxytocin (6,1-β deaminocystathionine, 2-0-methyl-tyrosine)-oxytocin [Tyr(me)²]-desamino-1-carba-oxytocin CAS 37025-55-1.

Molecular Formula

C₄₅H₆₉N₁₁O₁₂S

Molecular Weight

988.1

Clinical Trials

Two large double-blind trials were conducted using carbetocin. The first trial (study CLN 6.3.10) evaluated the safety and efficacy of carbetocin versus placebo for control of bleeding after caesarean section. This multicentre trial included 122 patients. Efficacy was determined as the requirement for intervention with additional oxytocic therapy following test medicine administration.

When given as a single bolus intravenous dose of 100µg after delivery of the infant at elective caesarean 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 (study CLN 6.3.9) compared a single intravenous dose of 100µg carbetocin to an 8-hour oxytocin infusion after elective caesarean section done under epidural or spinal anaesthesia. The primary objective was to compare the safety and efficacy of the two treatments in maintaining adequate uterine contraction after caesarean section. The primary efficacy variable was the incidence rate of the need for further oxytocic therapy for 48 hours after delivery. A single dose of carbetocin was associated with lower incidence of "need for additional oxytocic intervention" when compared to an 8 hour oxytocin infusion: such intervention occurred in 5% of patients receiving carbetocin compared to 10% of patients administered oxytocin. Odds of intervention were 2.0 times lower for carbetocin vs oxytocin (p=0.031).

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 caesarean section was determined. Although 11 of 12 women responded with adequate uterine contraction to total doses of 30-90µg carbetocin, none was considered to have adequate response to a starting dose less than 60µg. All 6 women given 100µg had an adequate uterine contraction although one did not satisfy the response criteria of the study. A single 100µg intravenous injection was therefore selected for clinical use. In a trial in 57 women undergoing elective caesarean section under epidural anaesthesia, carbetocin was compared to oxytocin for its ability to reduce intraoperative blood loss. A single 100µg 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 caesarean section, and in preventing excessive intraoperative blood loss following caesarean delivery. This study confirmed the ability of a 100µg intravenous dose of carbetocin to maintain adequate uterine tone after caesarean 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. DURATOCIN has not been studied in cases involving emergency caesarean section, classical caesarean section, anaesthesia 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 established in women following labour or vaginal delivery.

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Date of Preparation

23 June 2008

(PI dated 22 Oct 2007)