DURATOCIN®
(Carbetocin Injection)

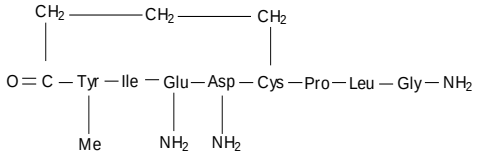
NAME OF THE MEDICINE

Carbetocin

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-deaminocarba-1-oxytocin
(6,1-β deaminocystathionine, 2-0-methyl-tyrosine)-oxytocin
[Tyr(Me)^2]-desamino-1-carba-oxytocin

CAS: 37025-55-1

Structure:



Molecular Formula: $C_{45}H_{69}N_{11}O_{12}S$ **Molecular Weight:** 988.1

DESCRIPTION

Carbetocin is a white, fluffy lyophilized powder, soluble in water, ethanol, methanol and acetic acid. Carbetocin is insoluble in ether and petroleum ether.
Each vial contains 100 micrograms of carbetocin, 1 mg methionine, 1.19 mg succinic acid, 47.0 mg mannitol, sodium hydroxide 2 M to pH 5.5 and water for injections to 1 mL.

PHARMACOLOGY

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 100 micrograms 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 400 micrograms 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 $AUC_{0-\infty}$ 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.

CLINICAL TRIALS

Two large double blind trials were conducted using carbetocin.

A randomised parallel group, double-blind, placebo-controlled multicentre clinical trial to evaluate the safety and efficacy of a single dose of carbetocin to control uterine bleeding after elective caesarean section.

Inclusion Criteria:

Women undergoing elective caesarean section under epidural anaesthesia, without a history of heart disease, hypertension, cardiac arrhythmia or evidence of liver, renal or endocrine disease, who gave informed consent.

Primary Efficacy variable:

The incidence of further oxytocic therapy following test drug administration.

Treatment Group	No. Patients Randomised (Evaluable)	Efficacy Results	Safety Results
		Patients requiring further oxytocic therapy	Serious Adverse Events
Carbetocin 100 micrograms (single IV injection)	64 (62)	8	0
Placebo (IV injection)	58 (57)	41	0

Summary:

When given as a single bolus intravenous dose of 100 micrograms after delivery of the infant by elective caesarean section under epidural, carbetocin was found to be significantly more effective than placebo in preventing the clinician assessed need for additional oxytocin therapy with only 13% of patients requiring intervention with further oxytocic therapy compared to 72% of patients in the placebo group ($p = 0.001$). There were no serious or unexpected adverse events and no patient dropped out of the study due to safety concerns. There was an increased incidence of the following adverse events in the carbetocin group vs the placebo group; Flushing (34% vs 10%, $p = 0.002$), abdominal pain (27% vs 10%, $p = 0.02$), pruritus (48% vs 31%, $p = 0.05$). The overall incidence of nausea during the study was not significantly different between the groups but was higher in the carbetocin group whilst the patient was in the operating room (36% vs 17%, $p < 0.05$). There was no significant difference between the groups for other adverse events reported.

A randomised parallel group, double-blind, double-dummy, multicentre clinical trial to evaluate the safety and efficacy of a single dose of carbetocin vs 8 hours oxytocin infusion after caesarean section in maintaining adequate uterine contraction after caesarean section.

Inclusion Criteria:

Healthy women undergoing elective caesarean section under epidural anaesthesia, who gave written informed consent.

Primary Efficacy variable:

The incidence of further oxytocic therapy following test drug administration.

Treatment Group	No. Patients Randomised (Evaluable)	Efficacy Results: Patients requiring further oxytocic therapy	Safety Results: Serious Adverse Events
Carbetocin 100 micrograms (single IV injection)	348 (317)	15	4
Oxytocin: 5IU bolus + 8 hours 20IU IV infusion	346 (318)	32	4

Summary:

When given as a single intravenous dose of 100 micrograms, carbetocin was associated with lower incidence of "need for additional oxytocic intervention" when compared to an 8 hour oxytocin infusion: such intervention occurred in 15 (5%) of patients receiving carbetocin compared to 32 (10%) of patients administered oxytocin. Odds of intervention were 2.0 times lower for carbetocin vs oxytocin ($p = 0.031$).

There were no significant differences in the frequency of adverse events between treatment groups. Four serious or unexpected adverse events occurred in each group.

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 30-90 micrograms carbetocin, none was considered to have adequate response to a starting dose less than 60 micrograms. All 6 women given 100 micrograms had an adequate uterine contraction although one did not satisfy the response criteria of the study. A single 100 micrograms 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 100 micrograms injection of carbetocin was compared to oxytocin (total dose 32.5IU).

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 100 micrograms 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.

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.

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 vascular disease, especially coronary artery disease, except with extreme caution.
Carbetocin is not intended for use in children.

PRECAUTIONS

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.
Carbetocin should be used cautiously in the presence of epilepsy, migraine, asthma or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system.
Patients with eclampsia and pre-eclampsia should be monitored for changes in blood pressure.

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 70 micrograms 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 not 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 micrograms carbetocin dose by the intramuscular route.

In a pilot postnatal development study, administration of IV doses ≥ 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.

Carcinogenicity

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

Genotoxicity

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).

INTERACTION WITH OTHER MEDICINES

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.

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.
Intravenous carbetocin was frequently (10-40% of patients) associated with nausea, abdominal pain, pruritus, 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.

In a 122 patient placebo controlled study, the adverse events occurring in >5% of women are presented in Table 1, below.

Table.1

Adverse Event	Carbetocin (n = 64)	Placebo (n = 58)	Statistical Significance
	%	%	
Nausea	61	57	NS
Pruritus	48	31	*
Hypotension	45	38	NS
Vomiting	41	36	NS
Flushing	34	10	*
Abdominal pain	27	10	*
Feeling of warmth	19	10	NS
Anaemia	17	21	NS
Tremors	16	17	NS
Back Pain	13	7	NS
Dizziness	13	7	NS
Incisional abnormality	11	12	NS
Headache	9	16	NS
Sweating	8	0	NS
Fever	6	5	NS
Tachycardia	5	5	NS
Insomnia	3	7	NS
Chills	3	5	NS
Metallic Taste	2	5	NS
Paraesthesia	0	5	NS

NS = Not Significant, * $p \leq 0.05$

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

DOSAGE AND ADMINISTRATION

A single intravenous dose of 100 micrograms (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 caesarean section under epidural or spinal anaesthesia. DURATOCIN can be administered either before or after delivery of the placenta. DURATOCIN is to be used as a single dose only.

OVERDOSAGE

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

PRESENTATION AND STORAGE CONDITIONS

DURATOCIN is a ready-for-use solution containing 100 micrograms carbetocin in a 1 mL clear glass vial with a bromobutyl rubber stopper and an aluminium crimp cap with a tear-off over cap. Each pack contains 5 vials.

Storage conditions: Store below 30°C. Once the vial has been opened, the product should be used immediately.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

(S4) Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

17 April 2015

DATE OF MOST RECENT AMENDMENT

N/A