Stability of Juno-Carbetocin 100 mcg/mL Prefilled Syringes at Room Temperature with Protection from Light for 31 Days

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INTRODUCTION

Carbetocin is a long-acting oxytocin analogue used to prevent post partum hemorrhage. Currently, there are two carbetocin products available on the Canadian market: Ferring Inc.'s Duratocin®, available as a 100 mcg / 1 mL vial, and Juno Pharmaceutical's carbetocin available as a 100 mcg / 1 mL prefilled syringe.

Duratocin® was developed to withstand International Council for Harmonisation climate IV conditions (30°C with 65% relative humidity) without the equipment or capital to maintain cold chain. It contains sodium succinate buffer, mannitol and methionine to stabilize carbetocin. Since Juno Pharmaceutical's formulation does not contain the same heat stabilizing excipients, it requires storage under refrigerated conditions. The ability to store Juno-Carbetocin prefilled syringes at room temperature would allow stock to be located at the point of care without the need for a refrigerator.

OBJECTIVES

The objective of the study was to evaluate the chemical stability of Juno-Carbetocin 100 mcg/1 mL prefilled syringes at room temperature (25°C) for 31 days.

METHODS

Liquid Chromatographic Method

The liquid chromatographic (LC) methods were adapted and revalidated using a previously published protocol. The LC system was composed of a solvent delivery pump and autoinjector system (Waters Alliance 2695 Separations Module, Waters Scientific, Toronto ON) which pumped the mobile phase through a 150 mm x 4.6 mm reverse-phase C18, 3 µm column (YMC-Pack ODS AQ, VWR, Mississauga ON). The effluent was monitored with UV detection (Waters 998 photodiode array detector, Waters Scientific, Toronto ON) at 220 nm.

The mobile phase consisted of 25% acetonitrile and 75% buffer (2.34 g/L potassium phosphate monobasic with pH adjusted to 6.5 with concentrated NaOH) and was pumped through the column at a rate of 1 mL/min and held at a temperature of 40°C.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to separate carbetocin from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter- and intra-day errors of reproducibility were assessed by the coefficients of variation (CV) and the standard deviation of regression.

Stability Study

On study day 0, 21x syringes of Juno-Carbetocin (lot: 240092, exp: 2028-02) were removed from the refrigerator and stored at room temperature (25°C) with protection from light. Physical inspection and concentration analysis were completed on study days 0, 1, 3, 7, 14, 28, and 31. On each study day, the standard curve was prepared with carbetocin USP reference standard (Sigma Aldrich).

Data Reduction and Statistical Analysis

The concentration of the carbetocin in the prefilled syringe was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence, was also greater than 90% of the initial concentration.

DISCLOSURES

Authors of this poster have the following to disclose concerning possible personal or financial relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Shirley Law – Nothing to disclose

Andrew Wyllie – Nothing to disclose

Nathan H Ma – Nothing to disclose

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RESULTS

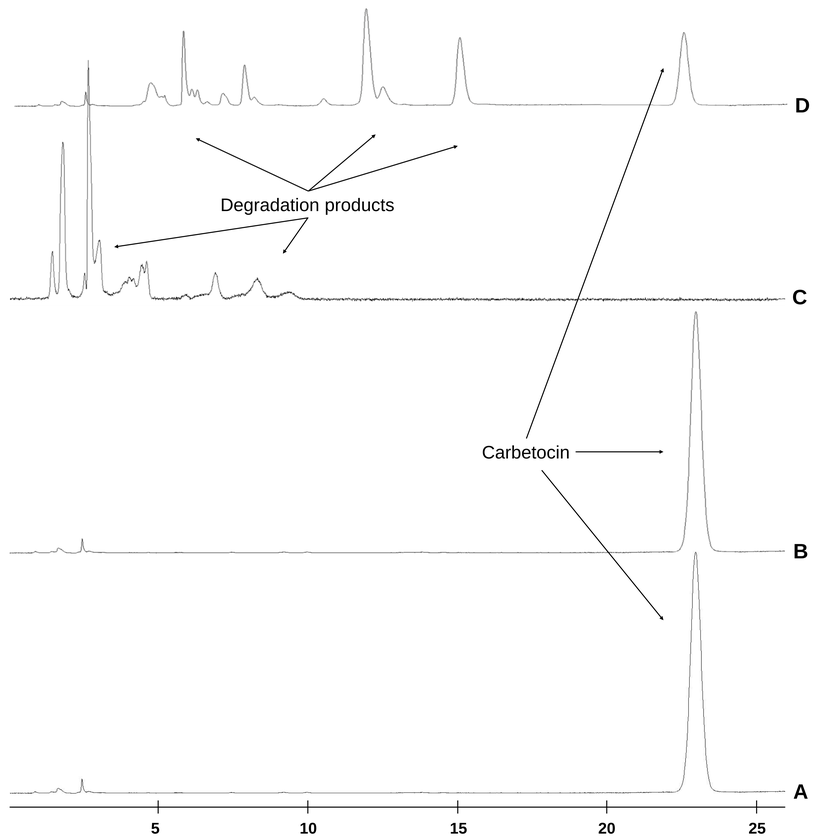

Figure 1: Representative chromatograms.

Chromatogram A represents a carbetocin 100 mcg/mL prefilled syringe on study day 0. Chromatogram B shows the carbetocin 100 mcg/mL prefilled syringe after 31 days of storage at 25°C with protection from light with 100% of the initial concentration remaining. Carbetocin eluted at approximately 23 minutes.

Chromatogram C shows a 1 mL sample of 50 mcg/mL sample of carbetocin USP standard after the addition of 0.7 mL of 0.5% sodium hypochlorite. 0% of carbetocin remained. Degradation products were noted to elute from 2-10 min.

Chromatogram D shows a 50 µL sample of carbetocin 100 mcg/mL USP standard adjusted to a pH of 2.0 with HCl and heated at 85°C for 356 minutes with 28.6% of the initial concentration remained. Degradation products were noted to elute from 2-15 min.

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Table 1. Percent Remaining of Initial Carbetocin Concentration[1]

Initial nominal concentration		**100 mcg/mL**
Initial actual concentration		97.03 mcg/mL
Study Day	0	100.00
	1	101.14 ± 0.46
	3	101.77 ± 0.23
	7	104.65 ± 0.73
	14	105.86 ± 0.59
	28	102.53 ± 0.35
	31	100.56 ± 0.16
Rate of change of concentration (%/day)		0.011
Intercept		102.23
Correlation (r)		0.066
Standard Deviation of Slope (Sy.x)		2.369
Confidence Interval for slope		0.1933
Fastest Slope 95% Confidence		-0.1823
Upper Limit 95% Confidence		0.2044
Shortest T-90 (95% CI) days		54.86

[1]: Concentrations expressed as percent remaining ± coefficient of variation.

Assay Validation

The results of assay validation demonstrated that carbetocin was separated from its degradation products (Figure 1).

Carbetocin was measured specifically, accurately (deviations from known averaged 1.32%), and reproducibly (within day variation averaged 0.44% and between day variation averaged 1.11%). The standard deviation of the study samples, a second estimate of between day reproducibility, averaged 2.37%. Therefore, the assay was determined to be stability indicating.

Concentration Results

The carbetocin percent remaining on each study day are reported in Table 1. Carbetocin retained its initial concentration for the 31 day study duration. Inspection of the chromatograms did not identify any degradation products on any of the study days. There was no precipitation, evolution of gas, or changes in colour noted. The calculated time to achieve 90% of the initial concentration with 95% confidence exceeded the 31 study day duration.

CONCLUSIONS

Juno-Carbetocin 100 mcg/1 mL was stable for at least 31 days when stored at room temperature with protection from light.