Stability and Compatibility of Oxaliplatin and Generic Medical Partners Inc.'s Leucovorin Formulation

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INTRODUCTION

Oxaliplatin and leucovorin are frequently co-administered via Y-site as part of the FOLFOX chemotherapy regimen (folinic acid [leucovorin calcium], 5-fluorouracil, and oxaliplatin) for the treatment of colorectal, hepatobiliary, gastric, esophageal and genitourinary cancers.

The oxaliplatin monograph notes that it should only be diluted with 5% dextrose in water. There are also several incompatibilities listed, including alkaline drugs, alkaline solutions, and chloride-containing solutions, which can adversely affect oxaliplatin's stability. Oxaliplatin may be co-administered with leucovorin via Y-site only if the leucovorin is diluted in 5% dextrose in water and does not contain trometamol, a weak base, as an excipient.

The Generic Medical Partners Inc. (GMP) leucovorin formulation, contains trometamol, which raised concerns over potentially degrading the oxaliplatin when co-administered via Y-site and underdosing patients.

Potential workarounds included ordering leucovorin from an alternate manufacturer or running oxaliplatin and leucovorin sequentially. However, ordering from an alternate manufacturer would have cost the institution an additional $277,000 annually and running the oxaliplatin and leucovorin sequentially instead of concurrently via Y-site would add an estimated 4000 hours of chair time annually.

OBJECTIVES

The objective of the study was to evaluate the stability and compatibility of Sandoz-oxaliplatin and GMP-leucovorin when combined at concentrations frequently given for the FOLFOX regimen and to determine whether these agents could be administered via Y-site.

The concentration of oxaliplatin was evaluated during storage using a validated, stability indicating, liquid chromatographic method using UV detection.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of 5% acetonitrile and 95% 0.05M phosphoric acid which was pumped through a 150mm x 4.6mm reverse-phase C18, 5µm column (Agilent Poroshell 120 EC-C18, Agilent Technologies, Toronto, ON) at 1.0 mL/min. The effluent was monitored with UV detection at 210 nm.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and specificity. The system was shown to be capable of separating oxaliplatin from its degradation products and leucovorin (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 and the standard deviation of regression.

Stability Study

On study day 0, Sandoz-oxaliplatin (DIN: 02436957; lot LW1919, expiry Dec 2023) was prepared according to the manufacturer's instructions in 5% dextrose in water to concentrations of 0.2 and 0.7 mg/mL. GMP-leucovorin (DIN 02496925, lot 11021BA, expiry Sep 2023) was prepared in D5W to concentrations of 0.35 and 1.54 mg/mL.

Equal volumes of each drug and concentration were mixed with each other to produce four concentration combinations to simulate Y-site conditions: oxaliplatin 0.1 mg/mL and leucovorin 0.175 mg/mL; oxaliplatin 0.1 mg/mL and leucovorin 0.77 mg/mL; oxaliplatin 0.35 mg/mL and leucovorin 0.175 mg/mL; and oxaliplatin 0.35 mg/mL and leucovorin 0.77 mg/mL.

Concentration and visual inspection were done at time 0, 30, 60, 90, 120, 150 and 180 minutes. Concentration was determined using a validated, stability indicating liquid chromatographic method with UV detection. Visual inspection was performed by holding the vials against white and black backgrounds to determine if any precipitate formed or if there was evolution of gas.

Data Reduction and Statistical Analysis

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined at time 0) with 95% confidence. Chemical stability was calculated using the lower limit of the observed degradation rate with 95% confidence and the time to achieve 90% of the initial concentration.

RESULTS

Table 1. Percent Remaining[1] of the Initial Oxaliplatin Concentration after Mixing with GMP-Leucovorin and Storage at Room Temperature.

		Combination 1	Combination 2	Combination 3	Combination 4
Initial Drug Concentrations		Oxaliplatin 0.2 mg/mL Leucovorin 0.35 mg/mL	Oxaliplatin 0.2 mg/mL Leucovorin 1.54 mg/mL	Oxaliplatin 0.7 mg/mL Leucovorin 0.35 mg/mL	Oxaliplatin 0.7 mg/mL Leucovorin 1.54 mg/mL
Nominal Initial Oxaliplatin Concentration after mixing		0.1 mg/mL	0.1 mg/mL	0.35 mg/mL	0.35 mg/mL
Actual Initial Oxaliplatin Concentration		0.10 mg/mL ± 0.21	0.10 mg/mL ± 0.14	0.35 mg/mL ± 0.11	0.35 mg/mL ± 0.15
Percent Remaining	0 minutes	100	100	100	100
	30 minutes	99.51 ± 0.32	100 ± 0.52	100.53 ± 1.04	99.94 ± 0.19
	60 minutes	99.76 ± 0.15	99.35 ± 0.95	100.31 ± 0.82	99.76 ± 0.52
	90 minutes	99.78 ± 0.20	100.34 ± 0.52	100.08 ± 0.49	99.23 ± 0.64
	120 minutes	99.88 ± 0.70	100.39 ± 0.51	100.49 ± 0.54	99.63 ± 0.53
	150 minutes	99.66 ± 0.25	99.80 ± 0.10	100.02 ± 0.56	99.88 ± 0.54
	180 minutes	99.79 ± 0.17	99.34 ± 1.07	100.02 ± 0.26	99.44 ± 0.74
Degradation Rate (%/min)		0.000	-0.002	-0.001	-0.002
Intercept		99.791	100.035	100.289	99.903
Sy.x		0.169	0.452	0.244	0.262
Std Error in Slope		0.001063	0.002848	0.001536	0.001649
Confidence interval for slope		0.00273	0.00732	0.00395	0.00424
Fastest Slope 95% Confidence		-0.0030	-0.0089	-0.0049	-0.0065
Shortest T-90[2] (95% CI) for Combination in minutes		**3373.29**	**1119.47**	**2056.37**	**1529.67**

1. Concentrations are shown as mean ± coefficient of variation (CV), expressed as a percentage
2. Time to achieve 90% of initial concentration

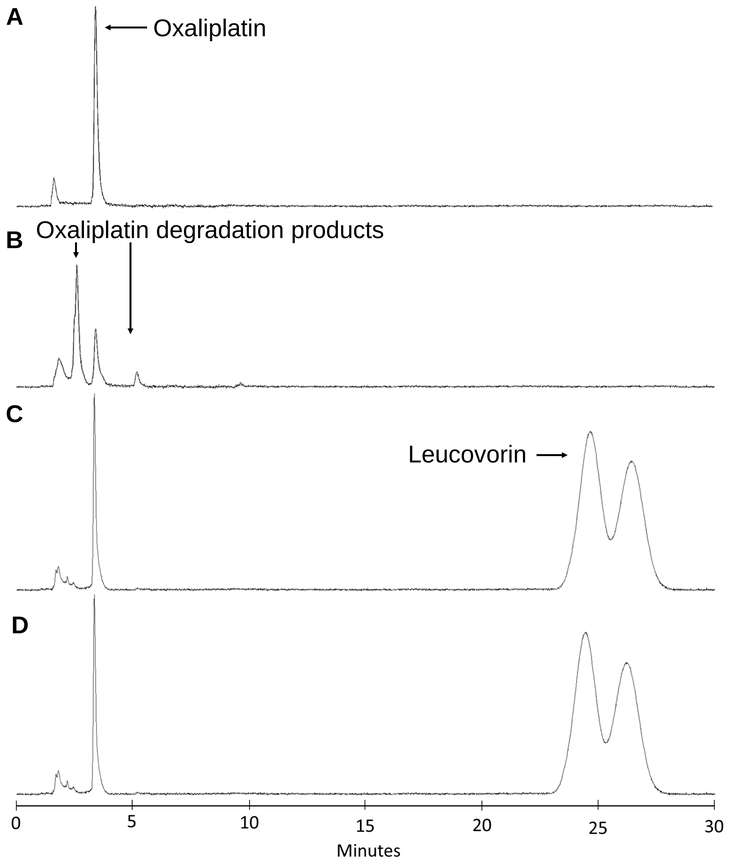

Figure 1. Representative Chromatograms

Chromatogram A represents a 0.7 mg/mL solution of oxaliplatin. Chromatogram B shows a 0.7 mg/mL solution of oxaliplatin after degradation with NaOH (pH 10.4) at 90°C for 14.5 hours with 18% of the initial concentration remaining. Oxaliplatin eluted at 3.4 minutes and the degradation products eluted at 2.6 and 5.2 minutes.

Chromatogram C represent a 1:1 mixture of 0.7 mg/mL oxaliplatin and 1.54 mg/mL GMP-leucovorin at time 0 and Chromatogram D represents the same mixture at 180 minutes. Leucovorin eluted at 24.5 and 26.5 minutes.

Assay Validation

Assay validation demonstrated that the oxaliplatin degradation products and leucovorin are separated from oxaliplatin (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 1.20% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.30% within a day, 0.59% between days and the standard deviation of regression averaged 0.29.

Concentration Results

The percent remaining of the initial oxaliplatin concentration at each study time are reported in Table 1. Oxaliplatin retained >99% of its initial concentration after mixing with GMP-leucovorin at all time points for all concentration combinations. The time to achieve 90% of the initial concentration, with 95% confidence, exceeded the 180 minute study period for all solutions.

No precipitation or evolution of gas was noted at any time for any combination.

CONCLUSIONS

Sandoz-oxaliplatin is stable and compatible for 180 minutes when mixed with GMP-leucovorin at 25°C.

The results of the study support the practice of administering Sandoz-oxaliplatin and GMP-leucovorin via Y-site.

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