STABILITY of 100 mg/mL ERTAPENEM at 4C and 23C.

Shirley Law[1], John Iazzetta[1,2], Bill Perks[1], Scott E. Walker[1,2].

Department of Pharmacy[1] Sunnybrook Health Sciences Centre, and Leslie Dan faculty of Pharmacy
University of Toronto. Toronto, Ontario.

BACKGROUND

Ertapenem's long half-life makes it a potential option for outpatient parenteral antimicrobial therapy. Ertapenem has been used for treatment of infections where once daily parenteral administration is an advantage or where a single 1 g dose has improved patient outcomes, such as for prophylaxis following transrectal biopsy of the prostate. Frequently these 1 g single doses are administered as 100 mg/mL solutions.

Previous studies of ertapenem stability have evaluated concentrations of 10 and 20 mg/mL in normal saline (NS) and have recommended storage at 4C for 5 days or 24 hours at room temperature. However, the degradation rate of ertapenem has been reported to be concentration dependent. Therefore, it is apparent that the stability of 10 and 20 mg/mL solutions of ertapenem should not be extrapolated to 100 mg/mL solutions.

The current Canadian product monograph for ertapenem (Invanz®) states that a reconstituted 100 mg/mL solution should be used within 6 hours following reconstitution. However, a 2014 AJHP paper <Jain et al> reported more than 12% loss of the initial concentration within 1 hour at room temperature. This observation suggests a very different degradation rate and suggests that each dose be freshly reconstituted.

Therefore, the inconsistencies between the recommendations in the product monograph and those of Jain et al <AJHP 2014> need to be reconciled.

OBJECTIVES

The objective of this study was to evaluate the stability of the a 100 mg/mL solution of ertapenem stored in both polypropylene syringes and the manufacturer's original glass vial at both room temperature (23C) and 4C over 18 days. During the 18-day study period, the drug concentration was determined on 8 study days (days 0, 1, 2, 4, 7, 11, 14 and 18).

METHODS

LIQUID CHROMATOGRAPHIC METHOD

A liquid chromatographic stability–indicating method with UV detection at 226 nm was developed and validated.

STABILITY STUDY

On study-day zero, 12 x 1000 mg vials of ertapenem (Invanz®, Merck Canada) were reconstituted according to the manufacturer's instructions with 10 mL of 0.9% sodium chloride to prepare 100 mg/mL solutions. The contents of 6 vials were each drawn into 10-mL polypropylene syringes. Three of the original manufacturer's glass vials and 3 syringes were stored at room temperature (23^0C), unprotected from fluorescent room light, and 3 vials and 3 syringes were stored in the refrigerator (4^0C).

DATA REDUCTION AND STATISTICAL ANALYSIS

Analysis of variance was used to test differences in observed concentration between the storage temperatures and container combinations. A 95% Confidence Interval was constructed around the degradation rate and the Time to Achieve 90% of the initial concentration (T-90) was calculated.

Interested in a copy of this poster
or other Sunnybrook Posters?

Scan the QR code or Go to http://metrodis.org/SB_PPC2015.html

and download the poster from this site.

RESULTS

ACCELERATED DEGRADATION AND ASSAY VALIDATION

Degradation of ertapenem at 80C occurs in an apparent first order fashion with a half-life of 1.9 hours (r= 0.9994). Chromatographic separation of degradation products from ertapenem (Figure 1) and the similarity of the UV spectrum (200-320 nm) between a fresh ertapenem sample and ertapenem in a degraded sample, demonstrated that the analytical method was stability-indicating.

Ertapenem concentrations were measured accurately with a deviation from the expected concentration averaging 2.06% and within day reproducibility averaging 1.32 % for standards and 1.07% for QC samples.

ERTAPENEM STABILITY

The initial concentration and the percent remaining observed on each study day during the study period for each ertapenem storage condition is listed in Table 1.

100 mg/mL ertapenem solutions stored in the manufacturer's vial or polypropylene syringes exhibited a first order degradation rate such that 10% is lost in the first 2.5 days when stored at 4C or within the first 6.75 hours at room temperature.

Analysis of variance was able to detect differences in percent remaining due temperature ($p<0.0015$), study days ($p=0.0055$) but not container ($p = 0.9790$). When a 95% confidence interval for the degradation rate was calculated and used to determine a beyond use date, it was determined that more than 90% of the initial concentration remained for 2.35 days at 4C or approximately 0.23 days (~5 hours and 30 minutes) at room temperature (23C).

Table 1. Percent Remaining[1] of Ertapenem during Storage

Study Day	Vial 4C		Syringe 4C		Vial RT		Syringe RT	
Initial Concentration (mg/mL) Day Zero	105.50	±0.97	106.07	±1.03	106.38	±1.12	105.68	±1.37
1	97.16	±0.28	97.31	±0.39	75.63	±1.52	75.92	±2.45
2	92.96	±0.51	93.31	±0.95	51.43	±1.38	52.43	±1.49
4	83.49	±1.01	82.96	±0.93	22.99	±1.92	23.27	±2.17
7	71.36	±2.05	71.36	±0.63	BLOQ		BLOQ	
11	62.42	±0.95	63.03	±1.00	BLOQ		BLOQ	
14	56.54	±1.33	56.16	±1.02	BLOQ		BLOQ	
18	48.21	±0.42	47.27	±2.00	BLOQ		BLOQ	
Slope (Degradation Rate 1/days)[2]	-0.0411		-0.0418		-0.3731		-0.3698	
Correlation (r)[2]	-0.9969		-0.9974		-0.9975		-0.9970	
95% Confidence Interval for slope	±0.0032		±0.0030		±0.0807		±0.0873	
Fastest Degradation[4,5] (1/days) 95% Con. Int. Limit	-0.0443		-0.0449		-0.4538		--0.4571	
Shortest T-90[3,4] (Based on 95% CI) Days	2.38		2.35		0.23		0.23	
Hours					5.57		5.53	

1. Each value is based on duplicate determination of three samples. Percent Remaining is based on 100% found on Day 0.
2. Calculated from log-linear regression of the percent remaining on each study day.
3. T-90 calculated from the intersection of the lower 95% confidence line and the lower limit of acceptance (90%) based on the log-linear degradation rate.
4. Fastest Degradation Rate and T-90 are based on the lower 95% confidence limit of the log-linear regression-determined slope.
5. Calculated from the intersection of the lower 95% confidence limit and the lower limit of acceptance (90%), based on a log-linear degradation rate.

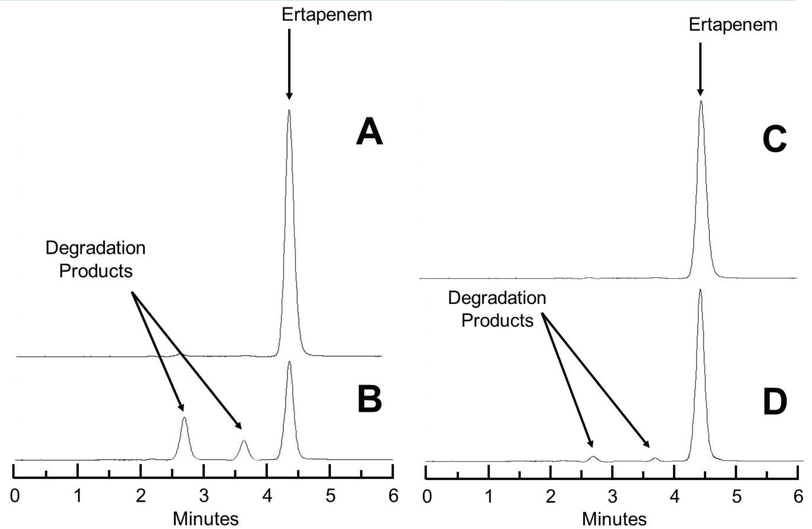

Figure 1. Chromatogram A represents an ertapenem solution at time zero prior to incubation in a water bath at 80C. Chromatogram B shows the same sample after 80 minutes at 80C, when 45.2% of the initial ertapenem concentration remained. Chromatogram C represents a 100 mg/mL solution of ertapenem at time zero and. Chromatogram D shows the same sample after storage at 4C for 48 hours, when 93% of the initial ertapenem concentration remained.

DISCUSSION & CONCLUSION

The current Canadian product monograph for ertapenem (Invanz®) states that 100 mg/mL solutions should be used within 6 hours following preparation. A recently published evaluation of the stability of 100 mg/mL solutions reported 12.2% loss during the first hour. However, the rate of loss reported by Jain et al is inconsistent between test solutions and with time. The rate of loss declines dramatically to 1.7% per hour between 4 and 24 hours. A rate of loss of 1.7% per hour is very consistent with the 6 hour recommendation found in the product monograph and observed in this study.

We have analyzed our results assuming a first order rate of loss based on the rate of loss observed in our accelerated degradation study and the slightly better correlation coefficients observed with our study data (r-values ~ 0.997 for first order compared to ~ 0.987 for zero order rate analysis). This improved the prediction of the degradation rate and reduced the error between 3 and 4.5 fold. The data of Jain et al can also be fit to a first order decline in concentration (r-value of 0.972 for first order compared to 0.930 for the zero order rate analysis at 25C) and reduces the error by more than half; however, the rate of loss continued to change during the study period.

We conclude that reconstituted solutions of 100 mg/mL of ertapenem stored in the manufacturer's original glass vial or polypropylene syringes are chemically stable for up 48 hours at 4C. This may allow for preparation in advance to optimize workload when multiple patients are scheduled for outpatient procedures requiring ertapenem for pre-procedure prophylaxis.