Stability of Ertapenem 100 mg/mL at Room Temperature

We read with interest the Original Research study regarding stability of high-concentration ertapenem (100 mg/mL) published last year by Walker and others.[1] The investigators studied the degradation of ertapenem 100 mg/mL in glass vials and polypropylene syringes at room temperature (23°C) and under refrigeration (4°C) over 18 days. Using a chemical stability threshold of 90% active ertapenem remaining, they concluded that ertapenem 100 mg/mL would be stable for 48 h under refrigeration followed by 1 h at room temperature. They also concluded that the period of stability was about 5.5 h when the drug was prepared and stored at room temperature (i.e., no refrigeration). These findings differ from our own observations of the stability of ertapenem 100 mg/mL in polypropylene syringes, which was less than 1 h with storage at 25°C and 24 h at 4°C, followed by up to 4 h once removed from the refrigerator.[2]

Both studies employed a validated, stability-indicating assay. Thus, we hypothesize that the reason for the discordant results involves the underlying methodology of experimental sampling times. Walker and others[1] sampled and observed concentrations of ertapenem at 24-h intervals. As a result, they were required to use statistical interpolation to determine the point at which ertapenem concentration dropped below 90% of baseline and were forced to assume zero-order degradation over the initial 24 h. This approach contradicts the earliest studies of ertapenem, which showed that stability was concentration-dependent, with higher concentrations having a more rapid degradation rate than lower concentrations.[3,4] In contrast, our study design involved sampling every hour during the first 24 h, as we anticipated that degradation of a high-concentration solution would be more rapid than currently reported for standard ertapenem concentrations (10 and 20 mg/mL), for which the period of stability is 6 h.[5,6] In room temperature studies, we observed mean ertapenem concentrations below 90% at 1 h, and our use of interpolation was over only a short time interval. Essentially, Walker and others[1] calculated the beyond-use date as 5.5 h, whereas in our study, we actually measured and observed it at less than 1 h. Prescribing information for both the United States and Canada reports the room temperature stability of ertapenem 1000 mg once diluted in 50 mL of 0.9% sodium chloride for treatment of infection (i.e., to a final concentration of 20 mg/mL) as being no longer than 6 h.[5,6] Therefore, it would not be consistent for a solution with 5-fold greater concentration to have the same room temperature stability. Additionally, the prescribing information recommends that the formulation containing 1000 mg in 3.2 mL of 1% lidocaine hydrochloric acid used for intramuscular injection (i.e., a final concentration of 312.5 mg/mL) should be administered within 1 h. Although it involves a different diluent, this recommendation is more in line with our observations.[2]

Ertapenem is a broad-spectrum antibiotic typically reserved for serious infections for both hospital inpatients and outpatients receiving IV antimicrobial therapy. In light of patient safety, the active product at any concentration must be stable at the time of administration; otherwise, there is a risk of underexposure, potential

development of resistance, or even clinical failure. We caution against using ertapenem 100 mg/mL more than 1 h after preparation and storage (in vials or syringes) at room temperature. A safer approach would be storage under refrigeration for up to 24 h followed by administration within 4 h after removal from refrigeration.

References

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[Scott Walker and coauthors reply:]

Kuti and Nicolau hypothesize that the reason for discordant study results is the difference in sampling times. In a previous study, they and other coauthors[1] tested multiple samples over the first 24 h during a room temperature stability study, whereas in our study,[2] sampling during the first 24 h was confined to time zero and 24 h. The implication is that the concentration-dependent stability of ertapenem resulted in a 28% loss of concentration in the first 4 h at 100 mg/mL, which we were unable to observe because we did not draw samples for analysis during this period.

Our paper was under review when the study of Jain and others[1] was published; as a result, during the pre-accept review process we were asked to explain the differences in stability under different storage conditions between the 2 studies. We could not explain the differences in results, but we did note that all of our correlation coefficients were 0.9969 or greater, which indicates that the degradation rate did not dramatically change over the study period, yet the results of Jain and others[1] showed a significant change in rate of loss over their 24-h study period. As a result, we included the following statement in our initial paper[2]: "the reported rate of loss by these authors [Jain and others] was inconsistent between test solutions and over time. More specifically, the rate of loss declined dramatically with time, averaging 1.7% per hour between 4 and 24 h. A rate of loss of 1.7% per hour is consistent with the 6-h recommendation in the product monograph and that observed in the current study" [reference citations omitted].

None of the arguments presented by Kuti and Nicolau has caused us to change our conclusion. Although there was a fundamental difference between the study results, differences in sampling time cannot explain the fact that Jain and others[1] observed a 28% loss within 4 h and our study reported a 25% loss only after 24 h. The fact that there were changes in the rate of loss observed by Jain and others[1] leads us to believe that multiple factors, in addition to concentration-dependent stability, could be affecting the results. Although concentration-dependent stability is acknowledged as a factor, we believe that temperature has a greater effect on the degradation rate; we might also remind readers that binding of drugs to the rubber gasket in BD syringes (Becton-Dickinson) was reported to cause issues with a few drugs across North America last year,[3] and this could also be a contributing factor. However, it is important to note that Jain and others[1] used Monoject syringes (Covidien Ltd). The only other fundamental methodologic difference between the studies is that Jain and others[1] froze samples at –80°C, thawing them later for analysis, whereas we analyzed our samples immediately after they were drawn.

In an attempt to evaluate the effect of temperature, concentration, and sampling frequency on the results, we have now completed additional ertapenem stability studies, with more frequent sampling. The results of these additional analyses are presented here.

On each of 5 study days, a single 1000-mg vial of ertapenem (Invanz, Merck Canada, Kirkland, Quebec; lot 2204890, expiry November 2017) was reconstituted with 0.9% sodium chloride (normal saline) to prepare a 100 mg/mL solution. The reconstituted vial was placed in a water bath at 20°C, 25°C, 30°C, 35°C, or 40°C (depending on the study day) and at least 6 samples were drawn from the vial over the first 24 h. For studies at 20°C, 25°C, and 30°C, additional samples were drawn up to 50 h. Additional studies were also conducted at 20°C for concentrations of 50 mg/mL and 25 mg/mL. Solutions at various concentrations were analyzed using the same liquid chromatographic method with UV detection that was described in our 2015 publication.[2] As was the case for that previous study, the current results were analyzed on the basis of a first-order rate of loss because of improved prediction of the degradation rate ($r > 0.980$) compared with a zero-order rate of loss, for which correlation coefficients are slightly lower.

The results are shown in Figure 1 and summarized in Table 1. As concentration increased from 25 mg/mL to 100 mg/mL, the degradation rate increased by more than 80%, reducing the time to achieve 90% of the initial concentration (with 95% confidence) from 14.45 h to 7.94 h. A change in temperature from 20°C to 40°C had a more dramatic effect, increasing the degradation rate more than 7-fold and resulting in a reduction in the time to achieve 90% of the initial concentration from 7.94 h to 0.92 h (with 95% confidence). Therefore, although concentration does affect the

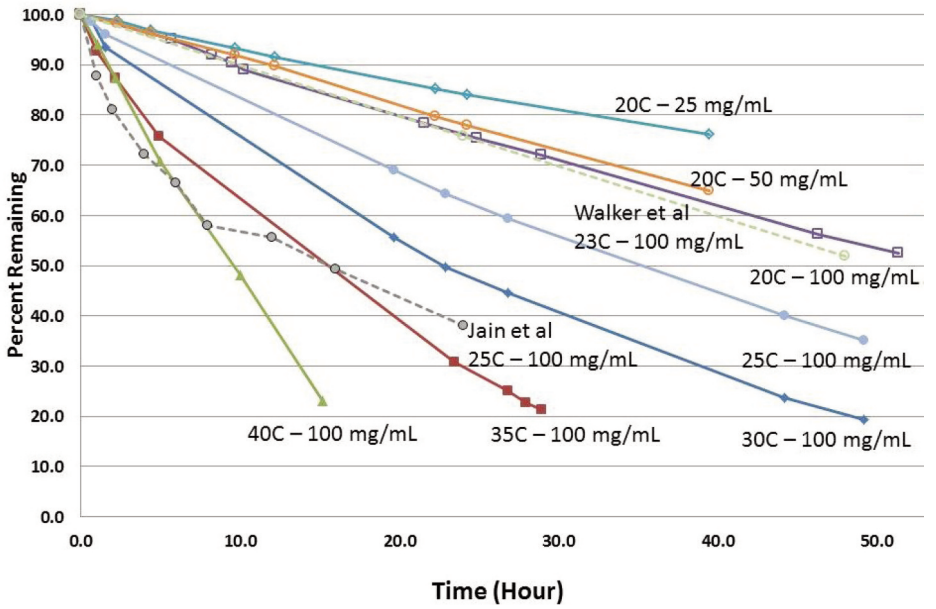

Figure 1. Observed concentration–time profiles for ertapenem solutions at various temperatures and concentrations. Dashed lines indicate the previously published studies of Jain and others[1] (grey circles) and Walker and others[2] (open circles). Solid lines represent the results of the study reported here: the solid lines with open symbols (toward top right of the graph) represent the effect of concentration, and the solid lines with solid symbols represent the effect of temperature (see also Table 1).

Table 1. Results of Ertapenem Degradation Studies at Various Concentrations and Temperatures

	Current Study								
	← Effect of Conc'n →								
Variable or Result			← Effect of Temperature →					Jain et al.[1]	Walker et al.[2]
Temperature (°C)	20	20	20	25	30	35	40	25	23
Concentration (mg/mL)	25	50	100	100	100	100	100	100	100
Slope* (h^{-1})	–0.007	–0.011	–0.013	–0.021	–0.033	–0.052	–0.094	–0.079	–0.015
Correlation coefficient	–0.999	–0.998	–0.998	–0.998	–0.998	–0.999	–0.987	–0.980	–0.997
No. of samples	8	8	10	8	8	8	6	4	4
Estimated T-90 (h)	15.00	9.57	8.30	5.03	3.20	2.03	1.12	1.34	6.78
Shortest T-90† (h)	14.45	9.00	7.94	4.76	3.01	1.95	0.92	0.82	5.53

Conc'n = concentration, T-90 = time until 90% of original concentration remains.
*Degradation rate.
†Based on 95% confidence interval.

degradation rate, as demonstrated by a comparison of the profiles for 25 mg/mL, 50 mg/mL, and 100 mg/mL in Figure 1, inspection of individual concentration–time profiles shows no change in the rate of loss until the concentration is below 75 mg/mL. Therefore, the estimated time to achieve 90% of the initial concentration did not change as the result of more frequent sampling and cannot explain the differences between the study of Jain and others[1] and our 2015 publication in this journal.[2]

The effect of concentration on the first-order degradation rate is evaluated in greater detail and illustrated in Figure 2. On the basis of published data, we also determined the first-order rate constant for concentrations reported in previous publications by McQuade and others[4] and Jain and others[1] for comparison with our results.[2] Because of a changing degradation rate, Jain and others[1] determined a first-order rate constant only during for the first 4 h. In this current analysis, the results of Jain and others[1] demonstrate a 4-fold faster degradation rate than has been observed in any other study, even after the effect of concentration is considered (Figure 2). Furthermore, as observed in Figure 1, the change in degradation rate in the study by Jain and others[1] was unusual, relative to our results in the current study and our previous publication.[2] Although there is some similarity in the rate of loss between the study of Jain and others[1]

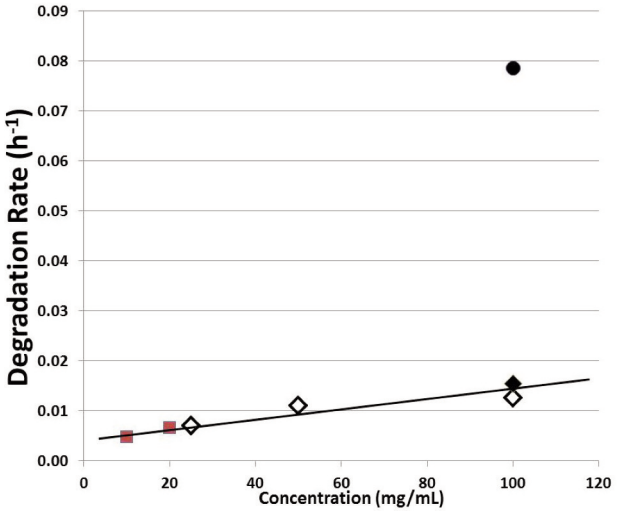

Figure 2. Degradation rate as a function of concentration. The open diamond symbols represent the first-order degradation rate observed at 25, 50, and 100 mg/mL in the current study. The solid symbols represent the first-order degradation constants calculated for the previously published studies of McQuade and others[4] (solid squares), Walker and others[2] (solid diamond), and Jain and others[1] (solid circle). A linear relationship ($r > 0.95$) between degradation rate and concentration is apparent when the results of Jain and others[1] are excluded (solid black line).

(once the concentration is less than 60 mg/mL) and our current investigation at 50 mg/mL, the rate of loss in the first 4 h reported by Jain and others[1] exceeds that reported in all other studies, except for our study conducted at 40°C. We cannot explain the basis of these discrepancies. However, the rather rapid loss of almost 20% of the concentration in the first 2 h in the study by Jain and others[1] creates the differences in results, and we believe that the data provided here conclusively demonstrate that sampling time is not responsible for the differences.

We agree with Nicolau and Kuti that the active product at any concentration must be stable at the time of administration; otherwise, there will be a risk of underexposure. However, we have confidence in our results, in that they are reproducible and appear to be in agreement with the results of McQuade and others.[4] We would point out that although ertapenem does demonstrate concentration-dependent stability, this drug is very sensitive to temperature, and an increase in storage temperature of 5°C can reduce its stability by 60%.

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