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Commentaries

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tiveness. Drug safety is not a specific component of the scores (although safety is indirectly accounted for in the formulary-restriction and pharmacokinetic-monitoring components). It is possible for unsuitable drugs to have higher point totals than appropriate agents. For example, penicillin G injection might have no activity against methicillin-resistant *Staphylococcus aureus* cultured from blood but might be assigned five points because it has an oral equivalent, has no formulary restrictions, needs no pharmacokinetic monitoring, and is inexpensive. On the other hand, vancomycin injection, even if it were active against the organism, could be assigned a maximum of only four points because it has no bioavailable oral equivalent. The possibility of such inappropriate rankings emphasizes the need for careful review before the system is put in place at an institution. Clearly, drugs without activity against an organism have no place in the rankings for that organism.

Conclusion. A weighted point system can be used to rank injectable antimicrobials in the order of their potential for successful and economical use in empirical therapy.

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Stability of paclitaxel in 5% dextrose injection or 0.9% sodium chloride injection at 4, 22, or 32 °C

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According to the package insert, paclitaxel mixed in 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, to a concentration of 0.3–1.2 mg/mL is stable for 27 hours at 25 °C.[1] This is a brief period, but it is adequate for a single-day infusion. For clinical trials that call for continuous infusions over several days, however, a 27-hour stability limit is problematic. A new container must be made up each day, and the patient must return to the institution each day to have the bag changed. This is inconvenient to patients and staff and increases the cost of therapy. Furthermore, the multiple breaks in the infusion system that are necessary to change bags each day may increase the risk of colonization of the catheter by pathogenic microbes. Clearly, it would be advantageous to establish that paclitaxel is stable in i.v. admixtures for at least several days.

The purpose of this study was to determine the chemical stability and physical compatibility of paclitaxel 0.1 and 1 mg/mL in 5% dextrose injection and in 0.9% sodium chloride injection when stored at 4, 22, or 32 °C for periods up to 31 days.

Methods. *Preparation of admixtures.* Triplicate test solutions of paclitaxel[a] 0.1 and 1 mg/mL were prepared in 5% dextrose injection[b] and in 0.9% sodium chloride injection[c] in 150-mL polyolefin minibags and stored statically at 4, 22, or 32 °C. One 2-mL sample was removed from each bag immediately and after one, three, five, and seven days and stored in 2-mL sterile vials[d] at –70 °C until assayed. (Preliminary studies showed that storage at –70 °C does not adversely affect

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the samples.) Solutions showing gross precipitation were assayed after 31 days of storage.

Analysis by high-performance liquid chromatography. Paclitaxel concentrations were determined by using the stability-indicating high-performance liquid chromatographic (HPLC) assay described by Waugh et al.,[2] modified to achieve satisfactory chromatography in our laboratory. The liquid chromatograph consisted of a multisolvent-delivery pump,[e] a programmable multiple-wavelength ultraviolet light detector,[f] a WISP autosampler,[g] and a C_{18} analytical column.[h] The system was controlled and integrated by a personal computer.[i] The mobile phase consisted of 53% acetonitrile (HPLC grade) in water.[j] The flow rate was 1.5 mL/min, and detection was performed at 254 nm and 0.5 absorbance unit full-scale. The retention time for paclitaxel was 6.09 minutes. Samples were passed through 5-µm filter needles.[k] Samples of paclitaxel 1-mg/mL solution were diluted 10-fold with the respective infusion solution before analysis. Duplicate HPLC determinations were performed on each sample of each test solution.

The HPLC method was validated as stability indicating by accelerating the decomposition of paclitaxel. The pH of freshly prepared paclitaxel 0.1-mg/mL solution was adjusted to 11.1 with 0.1 *N* sodium hydroxide solution. After one hour at room temperature, 78% of the original paclitaxel concentration remained. A major decomposition peak appeared at 9.02 minutes, and several small peaks were observed between 2.00 and 4.18 minutes. The decomposition peaks did not interfere with the parent peak. For a nominal 0.1-mg/mL solution of paclitaxel, the mean ± S.D. precision of the assay, determined from 10 replicate injections, was 0.0993 ± 0.0008 mg/mL. Precision expressed as percent relative standard deviation was 0.76%. Calibration curves were constructed from a linear plot of peak area versus concentration of paclitaxel reference standard[l] (0.025–0.15 mg/mL). The correlation coefficient of the standard curve was greater than 0.9999. The within-day and between-day coefficients of variation were 1.4% and 2.0%, respectively.

Stability was defined as at least 90% of the initial paclitaxel concentration remaining.

Analysis by visual examination and turbidimetry. Physical compatibility was evaluated by using previously described techniques of visual examination and turbidimetry.[3,4] Visual examination of the samples was performed with the unaided eye in normal laboratory fluorescent light and by using a high-intensity monodirectional light source (Tyndall beam).[m] Turbidimetric assessments of the normally hazy paclitaxel solutions were made with a color-correcting turbidimeter.[n] Visual inspections and turbidimetric assessments were performed immediately after the solutions were prepared and after 1, 3, 5, 7, 14, and 31 days of storage at each temperature protected from light.

Compatibility was defined as the absence of particulates under visual examination and no change in turbitidy exceeding 0.5 nephelometric turbidity unit under turbidimetric examination.

Results and discussion. Paclitaxel 0.1 and 1 mg/mL was stable throughout the study as long as the drug remained dispersed in the infusion solutions (Tables 1 and 2). All concentrations remained above 90% of the initial value, and most were near 100%. No evidence of decomposition products appeared in the chromatograms. These findings are consistent with those of Chin

Table 1.
Stability of Paclitaxel 0.1 and 1 mg/mL in 5% Dextrose Injection

Temperature (°C)	Sample	Actual Initial Concentration (mg/mL)[a]	% Initial Concentration Remaining[a]			
			1 Day	3 Days	5 Days	7 Days
Paclitaxel 0.1 mg/mL						
4	1	0.102, 0.101	99.6, 100.6	100.1, 100.6	100.0, 101.7	100.0, 100.3
	2	0.101, 0.102	99.6, 100.8	100.2, 100.4	99.8, 100.3	99.9, 100.0
	3	0.101, 0.101	100.3, 101.4	100.0, 101.1	99.6, 101.4	100.5, 101.4
22	4	0.100, 0.101	99.8, 100.4	99.3, 99.1	99.1, 99.8	100.1, 101.1
	5	0.100, 0.099	100.6, 100.5	100.8, 101.7	101.1, 100.9	99.6, 100.6
	6	0.100, 0.102	99.1, 99.1	99.1, 100.4	99.4, 99.2	99.3, 99.9
32	7	0.107, 0.107	98.9, 100.9	98.9, 99.3	98.7, 99.2	100.4, 99.7
	8	0.104, 0.106	100.6, 100.7	100.2, 100.5	100.3, 100.1	99.4, 101.2
	9	0.106, 0.105	98.4, 99.5	99.1, 100.4	99.8, 99.7	99.5, 100.0
Paclitaxel 1 mg/mL						
4	1	0.955, 0.960	98.6, 99.7	98.9, 99.1	99.1, 99.2	99.3, 99.0
	2	0.942, 0.944	101.4, 100.4	99.9, 99.9	99.0, 99.0	99.9, 100.0
	3	0.959, 0.959	100.6, 101.2	100.3, 101.0	100.1, 100.2	99.7, 99.7
22	4	0.960, 0.962	99.2, 99.3	100.3, 100.3	99.8, 99.8	99.2, 98.4
	5	0.983, 0.986	97.8, 98.4	100.1, 99.4	98.1, 98.2	100.1, 100.3
	6	1.009, 1.009	98.3, 99.3	99.1, 100.0	99.2, 99.8	99.7, 99.1
32	7	1.013, 1.010	98.9, 99.6	99.7, 98.8	100.0, 99.5	100.8, 100.7
	8	0.997, 0.994	100.4, 100.2	100.0, 100.4	100.1, 101.2	99.4, 98.6
	9	0.985, 0.993	100.6, 100.3	99.4, 100.1	100.3, 100.5	100.0, 100.6

[a] Duplicate determinations.

Table 2.
Stability of Paclitaxel 0.1 and 1 mg/mL in 0.9% Sodium Chloride Injection

Temperature (°C)	Sample	Actual Initial Concentration (mg/mL)[a]	% Initial Concentration Remaining[a]			
			1 Day	3 Days	5 Days	7 Days
Paclitaxel 0.1 mg/mL						
4	1	0.101, 0.101	99.5, 99.5	100.0, 99.5	99.8, 99.8	98.7, 99.6
	2	0.100, 0.100	99.2, 100.7	100.6, 101.8	100.0, 100.3	99.9, 101.1
	3	0.100, 0.100	99.6, 99.4	100.2, 98.9	99.7, 98.5	100.1, 100.1
22	4	0.101, 0.100	100.2, 99.8	100.3, 100.7	100.6, 100.6	99.9, 100.6
	5	0.102, 0.103	99.6, 100.6	99.3, 99.8	99.1, 99.5	99.6, 100.1
	6	0.103, 0.103	100.1, 100.0	100.0, 100.6	98.9, 99.6	99.4, 99.8
32	7	0.102, 0.102	101.0, 100.4	100.9, 101.3	100.1, 101.7	101.5, 99.5
	8	0.104, 0.105	100.1, 100.7	100.7, 100.1	99.4, 100.1	100.2, 100.0
	9	0.102, 0.102	99.5, 100.8	99.8, 98.2	99.5, 98.2	98.0, 99.0
Paclitaxel 1 mg/mL						
4	1	0.997, 1.002	101.3, 101.3	99.8, 99.6	99.1, 97.9	98.7, 98.2
	2	0.995, 0.995	97.5, 96.7	98.8, 98.7	98.4, 96.4	97.1, 94.7
	3	0.985, 0.982	97.8, 97.9	99.0, 98.6	96.0, 95.8	97.3, 96.2
22	4	0.955, 0.948	97.9, 100.0	99.2, 98.8	101.3, 98.2	100.6, 98.0
	5	0.971, 0.970	97.5, 97.8	97.1, 99.0	98.7, 97.4	98.7, 98.8
	6	0.961, 0.963	99.5, 98.1	99.0, 98.6	99.4, 98.4	98.8, 98.4
32	7	0.973, 0.970	99.9, 100.3	100.4, 101.0	99.2, 99.3	99.9, 100.3
	8	0.982, 0.975	99.7, 99.3	99.8, 99.4	100.1, 100.2	100.1, 100.4
	9	0.980, 0.977	100.3, 99.7	100.2, 100.4	100.6, 101.1	100.9, 100.5

[a] Duplicate determinations.

et al.,[5] who found that paclitaxel admixtures were stable for 48 hours. However, there were paclitaxel losses of 30–50% in our solutions that had gross precipitation.

When viewed with the Tyndall beam, all samples were initially free of particulate matter but had the normal haze of paclitaxel solutions. Turbidity did not change during the study except for solutions with noticeable precipitation. Large amounts of white, flocculent precipitate appeared in many of the solutions after 31 days of storage and in a few solutions after 14 days. Crystalline and needle-like precipitation, visible only with the Tyndall beam, began much earlier. Two solutions (one with 5% dextrose injection and one with 0.9% sodium chloride injection) had small amounts of crystalline precipitate within five days of storage. Most solutions had crystalline precipitate within a week. Compatibility was maintained for at least three days at all three temperatures in these static solutions. It is possible that agitation or other factors could reduce the time to precipitation.

Conclusion. Paclitaxel 0.1 and 1 mg/mL in 5% dextrose injection or 0.9% sodium chloride injection was stable and compatible for at least three days at 4, 22, or 32 °C. Precipitation may occur after three days and is the primary factor limiting storage time.

[a]Bristol-Myers Squibb, Princeton, NJ 08543, lot E3F32A.
[b]McGaw, Irvine, CA 92714-5895, lot J30960.
[c]McGaw, lot J3E907.
[d]Solopak Laboratories, Franklin Park, IL 60131, lot 930257.
[e]Model 600E, Waters Chromatography, Milford, MA 01757.
[f]Model 490E, Waters.
[g]Model 712, Waters.
[h]Vydac, 5-µm particle size, 250 × 4.6 mm, Separations Group, Hesperia, CA 92345, lot 900423-9RE.
[i]NEC Powermate SX/16, NEC Technologies, Boxborough, MA 01719.
[j]Milli-Q Plus, Millipore Corporation, Bedford, MA 01730.
[k]Burron Medical Inc., Bethlehem, PA 18018, lot 585400.
[l]Bristol-Myers Squibb, batch 80617492D.
[m]Dolan-Jenner Industries, Woburn, MA 01801.
[n]Hach Company, Loveland, CO 80539.

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