

DECEMBER 15, 1994

PHARMACY LIBRARY

# AJHP<sup>®</sup>

AMERICAN JOURNAL OF HOSPITAL PHARMACY

now combined with CLINICAL PHARMACY

**Venlafaxine: A heterocyclic antidepressant**

**Clozapine therapy for Parkinson's disease  
and other movement disorders**

**Opportunities for alliances  
between industry and pharmacy**

**Subtleties of managing  
acetaminophen poisoning**

**Annual index**

*Official journal of the  
American Society of Hospital Pharmacists*

*Pharmacists in health systems helping people make the best use of medications*

**Volume 51 Number 24**

**DOCKET  
ALARM**

Find authenticated court documents without watermarks at [docketalarm.com](http://docketalarm.com).

## Official journal of the American Society of Hospital Pharmacists

Joseph A. Oddis

Executive Vice President

Copyright © 1994  
American Society of Hospital Pharmacists, Inc.  
All rights reserved.

AJHP is a federally registered trademark.

Printed on acid-free paper effective with Volume 49, January 1992.

### Commentaries

#### 3061 Opportunities for alliances between industry and pharmacy

Gerald B. Rosenberg

#### 3065 Subtleties of managing acetaminophen poisoning

S. Rutherford Rose

### Reflections

#### 3069 Birthday letter to a brother

C. Richard Talley

### ASHP Report

#### 3070 Acknowledgment to reviewers— November 1, 1993, to October 31, 1994

### At Large

#### 3096 National health care reform, part 2: Response to pharmacists

#### 3072 AJHP Continuing Education

AJHP continuing-education  
instructions and enrollment form

#### 3076 Letters

Infection rates in adult and pediatric  
inpatients when i.v. sets are  
changed every 72 hours  
(Sheri L. Baker, Robert J. Kuhn,  
Sharon Berry)

Paclitaxel diluent and the case of the  
slippery spike (Michael Martin,  
Robert Bepko)

Improved extemporaneous  
formulation of cyclosporine  
ophthalmic drops  
(David W. Mueller)

Unit dose dispensing of chronic  
phosphate P 32 suspension  
(Joseph C. Hung)

Hydralazine injection still available  
(Holly Bowlby)

Validity of originality assessment  
(Mark H. Gross; Robert E. Pearson,  
Elizabeth L. Allan)

#### 3083 Career Opportunities

#### 3088 Current Literature

Journal References  
Self-study Materials: *Clinical Skills  
Program, Patient-Specific  
Pharmacotherapy Series, Module 4:  
Designing and Recommending a  
Pharmacist's Care Plan* (Jones,  
Campbell), Patricia A. Chase

#### 3095 Advertising Index

#### 3097 Annual Index

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.

#### References

1. Stratton CW, Ratner H, Johnston PE et al. Focused microbiological surveillance by specific hospital unit: practical application and clinical utility. *Clin Ther.* 1993; 15(Suppl A):12-20.
2. Bartlett RC. Cost containment in microbiology. *Clin Lab Med.* 1985; 5:761-91.
3. Bartlett RC, Quintiliani RD, Nightingale CH et al. Effect of including recommendations for antimicrobial therapy in microbiology laboratory reports. *Diagn Microbiol Infect Dis.* 1991; 14:157-66.
4. Washington JA II. The clinical microbiology laboratory: utilization and cost effectiveness. *Am J Med.* 1985; 78(Suppl 6B):8-16.
5. Evans RS, Classen DC, Pestotnick SL et al. Improving empiric antibiotic selection using computer decision support. *Arch Intern Med.* 1994; 154:878-84.
6. Marr JJ, Moffet HL, Kunin CM. Guidelines for improving the use of antimicrobial agents in hospitals: a statement by the Infectious Diseases Society of America. *J Infect Dis.* 1988; 157:869-76.

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

QUANYUN XU, LAWRENCE A. TRISSEL, AND  
JUAN F. MARTINEZ

*Am J Hosp Pharm.* 1994; 51:3058-60

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.<sup>1</sup> 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<sup>a</sup> 0.1 and 1 mg/mL were prepared in 5% dextrose injection<sup>b</sup> and in 0.9% sodium chloride injection<sup>c</sup> 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<sup>d</sup> at –70 °C until assayed. (Preliminary studies showed that storage at –70 °C does not adversely affect

QUANYUN XU, PH.D., is Pharmaceutical Chemist, Pharmaceutical Analysis Laboratory; LAWRENCE A. TRISSEL, FASHP, is Director, Drug Delivery and Stability Research; and JUAN F. MARTINEZ is Laboratory Technician II, Pharmaceutical Analysis Laboratory, Division of Pharmacy, The University of Texas M. D. Anderson Cancer Center, Houston.

Address reprint requests to Mr. Trissel at the Division of Pharmacy, Box 90, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

Supported by grant LS93-27 from Bristol-Myers Squibb, Princeton, NJ.

Presented at 51st ASHP Annual Meeting, Reno, NV, June 8, 1994.

Copyright © 1994, American Society of Hospital Pharmacists, Inc. All rights reserved. 0002-9289/94/1202-3058\$00.75.

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.,<sup>2</sup> modified to achieve satisfactory chromatography in our laboratory. The liquid chromatograph consisted of a multisolvent-delivery pump,<sup>e</sup> a programmable multiple-wavelength ultraviolet light detector,<sup>f</sup> a WISP autosampler,<sup>g</sup> and a C<sub>18</sub> analytical column.<sup>h</sup> The system was controlled and integrated by a personal computer.<sup>i</sup> The mobile phase consisted of 53% acetonitrile (HPLC grade) in water.<sup>j</sup> 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- $\mu$ m filter needles.<sup>k</sup> 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  $\pm$  S.D. precision of the assay, determined from 10 replicate injections, was

0.0993  $\pm$  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<sup>l</sup> (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.<sup>3,4</sup> 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).<sup>m</sup> Turbidimetric assessments of the normally hazy paclitaxel solutions were made with a color-correcting turbidimeter.<sup>n</sup> 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 turbidity 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) <sup>a</sup>	% Initial Concentration Remaining <sup>a</sup>			
			1 Day	3 Days	5 Days	7 Days
<i>Paclitaxel 0.1 mg/mL</i>						
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
<i>Paclitaxel 1 mg/mL</i>						
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

<sup>a</sup>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) <sup>a</sup>	% Initial Concentration Remaining <sup>a</sup>			
			1 Day	3 Days	5 Days	7 Days
<i>Paclitaxel 0.1 mg/mL</i>						
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
<i>Paclitaxel 1 mg/mL</i>						
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

<sup>a</sup>Duplicate determinations.

et al.,<sup>5</sup> 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.

<sup>a</sup>Bristol-Myers Squibb, Princeton, NJ 08543, lot E3F32A.

<sup>b</sup>McGaw, Irvine, CA 92714-5895, lot J30960.

<sup>c</sup>McGaw, lot J3E907.

<sup>d</sup>Solopak Laboratories, Franklin Park, IL 60131, lot 930257.

<sup>e</sup>Model 600E, Waters Chromatography, Milford, MA 01757.

<sup>f</sup>Model 490E, Waters.

<sup>g</sup>Model 712, Waters.

<sup>h</sup>Vydac, 5- $\mu$ m particle size, 250  $\times$  4.6 mm, Separations Group, Hesperia, CA 92345, lot 900423-9RE.

<sup>i</sup>NEC Powermate SX/16, NEC Technologies, Boxborough, MA 01719.

<sup>j</sup>Milli-Q Plus, Millipore Corporation, Bedford, MA 01730.

<sup>k</sup>Burron Medical Inc., Bethlehem, PA 18018, lot 585400.

<sup>l</sup>Bristol-Myers Squibb, batch 80617492D.

<sup>m</sup>Dolan-Jenner Industries, Woburn, MA 01801.

<sup>n</sup>Hach Company, Loveland, CO 80539.

## References

1. Mead Johnson Oncology. Taxol package insert. Princeton, NJ; 1992 Dec.
2. Waugh WN, Trissel LA, Stella VJ. Stability, compatibility, and plasticizer extraction of taxol (NSC-125973) injection diluted in infusion solutions and stored in various containers. *Am J Hosp Pharm.* 1991; 48:1520-4.
3. Trissel LA, Bready BB. Turbidimetric assessment of the compatibility of taxol with selected other drugs during simulated Y-site injection. *Am J Hosp Pharm.* 1992; 49:1716-9.
4. Trissel LA, Martinez JF. Turbidimetric assessment of the compatibility of taxol with 42 other drugs during simulated Y-site injection. *Am J Hosp Pharm.* 1993; 50:300-4.
5. Chin A, Ramakrishnan RR, Yoshimura NN et al. Paclitaxel stability and compatibility in polyolefin containers. *Ann Pharmacother.* 1994; 28:35-6.