Stability of cisatracurium besylate in vials, syringes, and infusion admixtures

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Abstract: The stability of cisatracurium besylate was studied.

Cisatracurium (as besylate) 2 mg/mL in 5- and 10-mL unopened vials and 10 mg/mL in 20-mL unopened vials, as well as 3 mL of solution from additional 2-mg/mL vials, repackaged in 3-mL sealed plastic syringes, was stored at 4 and 23 °C in the dark and in normal fluorescent room light. Admixtures of cisatracurium (as besylate) 0.1, 2, or 5 mg/mL in polyvinyl chloride (PVC) minibags of 5% dextrose injection or 0.9% sodium chloride injection were stored at 4 and 23 °C in normal fluorescent room light. Triplicate samples for each storage condition were taken initially and at 1, 3, 5, 7, 14, 21, and 30 days; samples from vials were also removed at 45 and 90 days. Solutions were stored in sterile vials at –70 °C and then thawed at room temperature before analysis of chemical stability by high-performance liquid chromatography. Physical stability was assessed as well.

Cisatracurium besylate was physically stable in all samples throughout the study. Cisatracurium (as besylate) 2 mg/mL exhibited drug losses at 23 °C in vials at 45 days and in syringes at 30 days. Cisatracurium (as besylate) 0.1, 2, and 5 mg/mL in 5% dextrose injection and in 0.9% sodium chloride injection was stable for at least 30 days at 4 °C, but substantial drug losses occurred at 23 °C. Admixtures prepared with cisatracurium (as besylate) 0.1 mg/mL and with 5% dextrose injection exhibited the greatest losses.

Cisatracurium besylate was stable in most samples for at least 30 days at 4 and 23 °C; admixtures containing cisatracurium (as besylate) 0.1 or 2 mg/mL exhibited substantial drug loss at 23 °C.

Index terms: Additives; Cisatracurium besylate; Concentration; Containers; Dextrose; Diluents; Incompatibilities; Injections; Photodecomposition; Polyvinyl chloride; Skeletal muscle relaxants; Sodium chloride; Stability; Storage; Syringes; Temperature; Vials

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Cisatracurium besylate (Nimbex, Glaxo Wellcome) is a nondepolarizing skeletal muscle relaxant for intravenous administration. The commercial vials are labeled for storage under refrigeration.[1] The manufacturer recommends that the sealed vials be used within 21 days when stored at room temperature or even if warmed to room temperature and then returned to refrigerated storage. Cisatracurium admixtures diluted in infusion solutions to 0.1 mg/mL (as besylate) are to be used within 24 hours.[1]

The purpose of this study was to determine the physical and chemical stability of cisatracurium (as besylate) 2 and 10 mg/mL in original vials and cisatracurium (as besylate) 2 mg/mL repackaged in plastic syringes, as well as cisatracurium (as besylate) 0.1, 2, and 5 mg/mL in 5% dextrose injection and in 0.9% sodium chloride injection stored at 4 and 23 °C both in the dark and exposed to fluorescent light. The drug's stability in intact vials was evaluated over 90 days; stability in the syringes and admixtures was evaluated over 30 days.

Methods

Materials. Cisatracurium besylate injection[a] and cisatracurium besylate reference standard[b] were supplied by Glaxo Wellcome. The infusion solutions—5% dextrose injection[c] and 0.9% sodium chloride injection[d] in polyvinyl chloride (PVC) bags—and 3-mL plastic syringes[e] and closures[f] were obtained commercially. The reference standard was used without further purification. Acetonitrile[g] and methanol[h] were of a grade suitable for use in high-performance liquid chromatography (HPLC). Water was also HPLC grade[i] and was prepared immediately before use.

Preparation of samples. Cisatracurium (as besylate) 2 mg/mL in 5- and 10-mL unopened vials and cisatracurium (as besylate) 10 mg/mL in 20-mL unopened vials was stored at 4 and 23 °C both in the dark and in normal fluorescent room light. By using aseptic technique in a class 100 biological safety cabinet, solution from additional 2-mg/mL vials was repackaged by placing 3 mL of solution in 3-mL plastic

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syringes and sealing them with Luer-tip closures. The syringes were stored at 4 and 23 °C both in the dark and in normal fluorescent room light. Triplicate vials and syringes for each storage condition were evaluated at each time point.

Each of the infusion solutions was passed through a 0.22-µm filter[j] before admixing to reduce the intrinsic particle burden. Triplicate solutions of cisatracurium besylate at each concentration were prepared in 100-mL PVC minibags of 5% dextrose injection and of 0.9% sodium chloride injection. The cisatracurium besylate was also passed through 0.22-µm filters into the infusion solutions, diluting the drug to nominal cisatracurium concentrations of 0.1, 2, and 5 mg/mL. The test solutions were stored under refrigeration (4 °C) and at room temperature (23 °C) in normal fluorescent room light.

Samples of the solutions in intact vials were removed from each container initially and after 1, 3, 5, 7, 14, 21, 30, 45, and 90 days. Solutions in syringes and minibags were sampled initially and after 1, 3, 5, 7, 14, 21, and 30 days. Physical stability was assessed immediately after the samples were removed. In order to assess chemical stability, samples were stored in sterile vials[k] at –70 °C. Preliminary studies showed that storage at –70 °C did not adversely affect the samples. Frozen samples were thawed for analysis by allowing them to stand at room temperature.

Physical evaluation. Physical stability was assessed by visual examination and by measuring turbidity and the size and content of particles. Ten-milliliter samples from each minibag were placed in 15-mL borosilicate glass culture tubes[l] with polypropylene screw caps.[l] Similarly, approximate 1.5-mL portions were taken from each syringe or vial at each test condition and were pooled in the culture tubes for physical evaluation. The tubes had previously been triple-washed in HPLC-grade water and dried. To minimize the effects of scratches and imperfections in the glass, a thin layer of silicone oil was applied to the tube exteriors. Each sample was examined with the unaided eye in normal diffuse fluorescent room light and with a high-intensity monodirectional light source (Tyndall beam)[m] as described elsewhere.[2,3]

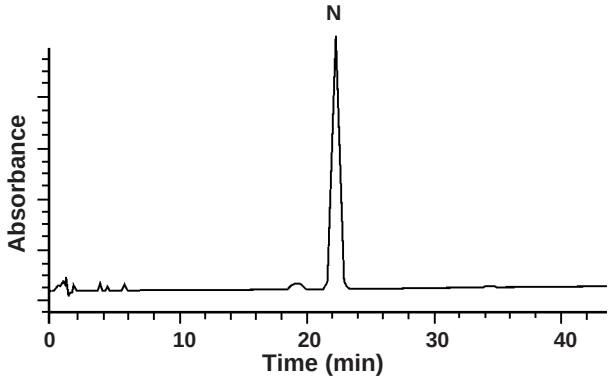
The turbidity of each sample was measured with a formazin-calibrated color-correcting turbidimeter.[n] Triplicate determinations were made on each of the samples. In addition, the particle content of the samples was evaluated by using a light-obscuring particle sizer–counter[o] to determine the content of particles in the diameter range of 1.24–112 µm (the validated detection limits of the particle sizer–counter). Triplicate determinations were made on each sample.

Physical instability was defined as visible particulate matter, haze, or color change or an increase in measured turbidity of 0.5 nephelometric turbidity unit (NTU) or more.

HPLC analysis. Cisatracurium concentrations were determined by using a stability-indicating HPLC assay based on a method provided by Glaxo Wellcome.[4] The liquid chromatograph[p] consisted of a multisolvent delivery pump, an ultraviolet light detector, and an autosampler in one unit with a C_{18} reverse-phase analytical column.[q] The system was controlled and integrated by a personal computer[r] with chromatography-management software.[s] The mobile phase consisted of 600 mL of water, 200 mL of acetonitrile, and 200 mL of methanol with 10 mL of formic acid and 20 g of ammonium formate delivered isocratically. The flow rate was 1.5 mL/min. Detection was performed at a wavelength of 280 nm and a sensitivity of 0.5 absorbance unit full scale. Cisatracurium (as besylate) 0.1 mg/mL was analyzed without dilution. The 2-, 5-, and 10-mg/mL solutions were diluted 20-, 50-, and 100-fold with a solution[t] similar, but not identical, to the mobile phase before injection, as specified by Glaxo Wellcome.[4] The injection volume was 10 µL. Under these conditions, the retention time for cisatracurium besylate was about 22 minutes (Figure 1).

The HPLC analytical method was validated as stability indicating by accelerated cisatracurium besylate decomposition. Exposure of cisatracurium besylate solution to 1 N hydrochloric acid, 1 N sodium hydroxide, 3% hydrogen peroxide, and boiling for two hours resulted in a reduction in the intact cisatracurium peak and the formation of two new peaks, eluting at 4 and 34 minutes, representing decomposition products. The peaks for degradation products did not interfere with the intact cisatracurium peak (Figure 2). For a solution with a nominal cisatracurium (as besylate) concentration of 0.1 mg/mL, the mean ± S.D. precision of the assay, determined from 10 replicate injections, was 103.8 ± 0.49 µg/mL. Precision expressed as percent relative standard deviation was 0.47%. Calibration curves were constructed from a linear plot of cisatracurium peak areas versus concentration of freshly prepared cisatracurium besylate reference standard (0.025–0.150 mg/mL). The correlation coefficient of the standard curve was greater than 0.9997. The intraday and interday coefficients of variation of the assay method were 2.2% and 1.7%, respectively.

Figure 1. Representative chromatogram of cisatracurium besylate (peak N).

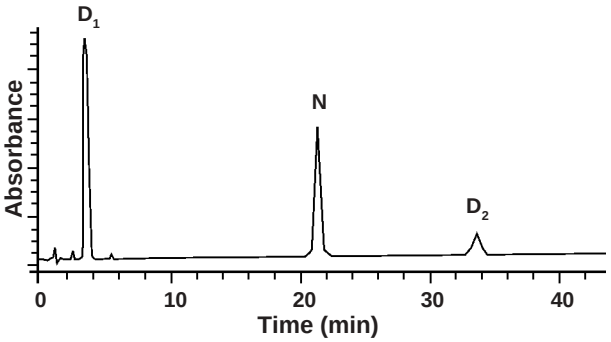


Analysis of data. The initial concentrations of cisatracurium were defined as 100%, and subsequent concentrations were expressed as a percentage of the initial concentration. The drug was defined as stable if more than 90% of the initial concentration remained.

Results and discussion

The drug was physically stable in all test solutions throughout the study. Each solution remained clear and colorless in normal fluorescent room light and when viewed with a Tyndall beam, with no precipitation observed. Particles of 10 µm in diameter or larger were found to be relatively few (generally ≤50 per milliliter). Measured turbidities were low, ranging from about 0.2 to 0.4 NTU.

Figure 2. Chromatogram of cisatracurium besylate (peak N) and decomposition products (peaks D_1 and D_2) after boiling for two hours.



In most of the solutions, the drug was also chemically stable. The results of the HPLC analysis are shown in Tables 1–3. In intact vials, little or no cisatracurium loss occurred with either concentration at 4 °C whether the samples were exposed to light or stored in the dark over 90 days. The 2-mg/mL solution repackaged in plastic syringes exhibited little or no loss under these conditions over 30 days. At 23 °C, cisatracurium losses of about 5–7% occurred in the intact vials within 45 days and in the syringes within 30 days.

Cisatracurium (as besylate) 0.1, 2, and 5 mg/mL in 5% dextrose injection and in 0.9% sodium chloride injection remained stable for at least 30 days when stored at 4 °C, exhibiting losses of 3% or less. However, substantial losses were found in the admixtures stored at 23 °C. The losses appeared to be concentration and solution dependent. The admixture with the lowest concentration (0.1 mg/mL) exhibited the greatest loss; losses of 8% occurred in 7 days in the admixtures prepared with 5% dextrose injection and 14 days in those prepared with 0.9% sodium chloride injection. The 2-mg/mL admixture prepared with 5% dextrose injection exhibited a 10% loss in 14 days; the one prepared with 0.9% sodium chloride injection exhibited only a 6% loss in 30 days. Cisatracurium (as besylate) 5 mg/mL in admixtures prepared with either solution was stable, with a drug loss of about 3–4% over 30 days.

The manufacturer of cisatracurium besylate cites a rate of potency loss in intact vials of about 5% per month when the drug is stored at room temperature.[1] This is consistent with the results of our study, both for vials protected from light and for those exposed to

Table 1.
Stability of Cisatracurium (as Besylate) 2 and 10 mg/mL in Original Vials

Nominal Concentration and Storage Temperature (°C)	% Initial Concentration Remaining[a]					
	1 Day	7 Days	14 Days	30 Days	45 Days	90 Days
Exposed to Fluorescent Light						
2 mg/mL, 5-mL vial[b]						
4	100.8 ± 0.1	101.8 ± 0.4	100.2 ± 0.8	100.6 ± 1.5	100.2 ± 0.5	100.0 ± 0.7
23	99.9 ± 0.2	100.3 ± 0.9	96.9 ± 0.3	95.0 ± 0.2	93.7 ± 0.1	86.5 ± 1.7
2 mg/mL, 10-mL vial[c]						
4	100.8 ± 0.9	99.4 ± 0.8	98.9 ± 0.8	100.3 ± 0.6	100.4 ± 1.0	99.4 ± 0.7
23	99.1 ± 1.0	98.0 ± 0.3	96.4 ± 0.7	95.6 ± 0.3	93.8 ± 0.3	87.7 ± 1.2
10 mg/mL, 20-mL vial[d]						
4	101.2 ± 0.5	99.6 ± 0.7	98.6 ± 0.9	100.9 ± 0.5	101.6 ± 1.4	99.8 ± 1.7
23	99.7 ± 0.9	99.2 ± 0.5	97.3 ± 0.6	97.9 ± 0.9	95.5 ± 0.8	86.7 ± 1.4
Protected from Light						
2 mg/mL, 5-mL vial[b]						
4	100.0 ± 1.0	101.5 ± 0.2	98.7 ± 0.4	100.0 ± 0.3	100.4 ± 0.3	100.0 ± 0.5
23	98.9 ± 0.1	99.5 ± 0.9	97.1 ± 0.0	96.2 ± 0.2	95.8 ± 3.0	89.5 ± 0.6
2 mg/mL, 10-mL vial[c]						
4	100.3 ± 0.5	100.9 ± 0.6	99.4 ± 1.0	99.7 ± 0.3	100.2 ± 0.1	100.0 ± 0.3
23	100.4 ± 0.7	99.4 ± 0.3	97.1 ± 0.3	95.6 ± 0.2	94.2 ± 0.8	89.5 ± 0.5
10 mg/mL, 20-mL vial[d]						
4	99.5 ± 0.4	100.3 ± 0.6	99.4 ± 0.5	101.6 ± 0.4	99.7 ± 1.1	98.6 ± 0.9
23	98.6 ± 0.4	99.3 ± 0.4	98.0 ± 0.2	97.6 ± 0.3	97.3 ± 0.2	91.4 ± 0.1

[a]Mean ± S.D. (n = 6).
[b]Actual initial concentration = 2.02 ± 0.01 mg/mL.
[c]Actual initial concentration = 2.04 ± 0.01 mg/mL.
[d]Actual initial concentration = 10.25 ± 0.06 mg/mL.

Table 2.
Stability of Cisatracurium (as Besylate) 2 mg/mL[a] Repackaged in 3-mL Plastic Syringes

Temperature (°C)	% Initial Concentration Remaining[b]							
	Protected from Light				Exposed to Light			
	1 Day	7 Days	14 Days	30 Days	1 Day	7 Days	14 Days	30 Days
4	99.9 ± 0.9	99.1 ± 0.4	97.9 ± 0.8	97.9 ± 0.3	100.3 ± 0.3	100.1 ± 1.1	99.7 ± 1.2	99.8 ± 1.5
23	98.5 ± 0.1	98.4 ± 0.5	96.6 ± 0.2	93.2 ± 0.2	99.3 ± 0.3	98.9 ± 1.0	96.1 ± 0.2	95.8 ± 0.5

[a]Nominal concentration. Actual initial concentration = 2.04 ± 0.01 mg/mL.
[b]Mean ± S.D. (n = 6).

Table 3.
Stability of Cisatracurium (as Besylate) 0.1, 2, and 5 mg/mL[a] in 5% Dextrose Injection and in 0.9% Sodium Chloride Injection

Concentration and Storage Temperature (°C)	Actual Initial Concentration (mg/mL)	% Initial Concentration Remaining[b]			
		1 Day	7 Days	14 Days	30 Days
5% Dextrose Injection					
0.1 mg/mL					
4	0.102 ± 0.001	100.1 ± 0.7	98.6 ± 0.3	98.2 ± 0.3	96.8 ± 0.2
23	0.101 ± 0.000	99.1 ± 0.3	92.1 ± 0.3	85.4 ± 0.5	71.9 ± 0.2
2 mg/mL					
4	2.05 ± 0.13	99.9 ± 1.5	99.1 ± 0.7	96.3 ± 1.3	98.4 ± 0.9
23	2.04 ± 0.03	98.4 ± 0.6	95.4 ± 0.3	90.0 ± 0.7	86.4 ± 1.7
5 mg/mL					
4	5.09 ± 0.05	98.5 ± 1.3	98.7 ± 1.3	99.1 ± 1.2	99.9 ± 1.5
23	5.04 ± 0.03	100.5 ± 0.9	98.2 ± 0.8	98.7 ± 0.9	96.3 ± 0.6
0.9% Sodium Chloride Injection					
0.1 mg/mL					
4	0.104 ± 0.001	100.3 ± 1.2	98.9 ± 0.8	99.7 ± 2.5	98.1 ± 0.9
23	0.104 ± 0.000	99.9 ± 0.8	95.5 ± 1.3	92.3 ± 1.2	85.7 ± 0.8
2 mg/mL					
4	2.07 ± 0.01	99.8 ± 1.7	98.2 ± 0.7	98.2 ± 0.4	99.6 ± 0.7
23	2.05 ± 0.03	99.3 ± 1.0	97.1 ± 1.3	96.2 ± 1.2	94.4 ± 1.6
5 mg/mL					
4	5.04 ± 0.04	99.8 ± 2.6	100.3 ± 0.2	101.5 ± 0.6	100.7 ± 1.4
23	5.08 ± 0.07	99.6 ± 2.3	98.1 ± 2.3	98.1 ± 2.8	97.3 ± 2.7

[a]Nominal concentration.
[b]Mean ± S.D. (n = 6).

normal fluorescent room light. Transferring the undiluted injection to plastic syringes resulted in a rate of loss similar to that observed in intact vials. Although the drug is chemically and physically stable, only the 10-mL vial contains an antibacterial preservative (0.9% benzyl alcohol). The 5- and 20-mL vials are unpreserved and for single use only; their stoppers should not be punctured multiple times.

Our results indicate that cisatracurium besylate in admixtures is stable for longer than the 24-hour limit stated by the manufacturer,[1] particularly under refrigeration—at 4 °C, little loss occurred within 30 days.

Conclusion

Cisatracurium (as besylate) 2 and 10 mg/mL in the original vials was physically and chemically stable for 90 days at 4 °C and for 45 days at 23 °C exposed to fluorescent light or in the dark. Similarly, cisatracurium (as besylate) 2 mg/mL was stable for 30 days repackaged in 3-mL plastic syringes. Cisatracurium (as besylate) 0.1, 2, and 5 mg/mL in 5% dextrose injection and 0.9% sodium chloride injection was stable for 30 days at 4 °C. Cisatracurium (as besylate) 5 mg/mL was stable for 30 days in admixtures stored at 23 °C. However, the 0.1- and 2-mg/mL admixtures exhibited drug loss.

[a]Nimbex, Glaxo Wellcome Co., Research Triangle Park, NC 27709; 2 mg/mL, 5-mL vial, lot 5YH3024; 2 mg/mL, 10-mL vial, lot 5Y1298; 10 mg/mL, 20-mL vial, lot 602454.
[b]Glaxo Wellcome, lot AWS626.
[c]Baxter Healthcare Corp., Deerfield, IL 60015, lots PS044636 and ZP083410.
[d]Baxter, lots PS045989 and ZP084427.
[e]Becton-Dickinson & Co., Franklin Lakes, NJ 07417.
[f]Red Cap, Burron Medical Inc., Bethlehem, PA 18018.
[g]EM Science, Gibbstown, NJ 08027, lot 36151.
[h]EM Science, lot 36145.
[i]Milli-Q Plus, Millipore Corporation, Bedford, MA 01730.
[j]Millex-GS, Millipore.
[k]Solopak Laboratories, Franklin Park, IL 60131.

[l]Kimble, Division of Owens-Illinois, Toledo, OH 43666.
[m]Dolan-Jenner Industries, Woburn, MA 01801.
[n]Ratio X/R, Hach Company, Loveland, CO 80539.
[o]Model 8003, Hiac-Royco, Division of Pacific Scientific Company, Silver Spring, MD 20910.
[p]LC Module 1, Waters Corporation, Milford, MA 01757.
[q]Kromasil 5µ C18 100A, 250 × 4.6-mm inner diameter, Series 149752, Phenomenex, Torrance, CA 90501.
[r]Digital Venturis 575, Austin, TX 78720.
[s]Millenium 2010 Chromatography Manager, Waters.
[t]Water 600 mL, acetonitrile 200 mL, methanol 200 mL, and formic acid 0.4 mL.

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2. Trissel LA, Martinez JF. Physical compatibility of melphalan with selected drugs during simulated Y-site administration. *Am J Hosp Pharm*. 1993; 50:2359-63.
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