Stability of esmolol hydrochloride in intravenous solutions

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Abstract: The stability of esmolol hydrochloride in a variety of i.v. solutions was studied.

Solutions of esmolol hydrochloride 10 mg/mL were prepared separately in 0.45% sodium chloride injection, 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.45% sodium chloride injection, 5% dextrose and 0.9% sodium chloride injection, 5% dextrose with lactated Ringer's injection, lactated Ringer's injection, 5% sodium bicarbonate injection, and 5% dextrose injection with potassium chloride 40 meq/L. One glass and one polyvinyl chloride container of each solution (except glass only in the case of the solution in 5% sodium bicarbonate injection) were stored in the dark at 5 °C, under ambient room light at 23–27 °C, in the dark at 40 °C, and under intense light at 25–30 °C. At storage intervals up to 168 hours, samples were tested for esmolol hydrochloride concentration by high-performance liquid chromatography. Optical density and pH were also measured.

Esmolol hydrochloride was stable in the various i.v. fluids for at least 168 hours when stored at 5 °C or 23–27 °C, for at least 24 hours when stored under intense light, and, with one exception, for at least 48 hours when stored at 40 °C. When mixed with 5% sodium bicarbonate injection, the drug was stable for only about 24 hours at 40 °C. There were no substantial changes in optical density or pH. The type of container had no effect on stability.

With one exception, esmolol hydrochloride was stable in all the i.v. solutions under all the conditions tested.

Index terms: Additives; Cardiac drugs; Containers; Esmolol hydrochloride; Glass; Incompatibilities; Polyvinyl chloride; Sodium bicarbonate; Stability; Storage; Temperature; Vehicles

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Esmolol hydrochloride injection has been reported to be visually compatible[1-4] and chemically stable[5-7] when mixed with various drugs, but data on the stability of esmolol hydrochloride in i.v. solutions have not appeared in the scientific literature. We describe here a series of studies that provide those data. These studies are the basis of information included in the package insert for esmolol hydrochloride.[8]

Methods

Preparation and storage of solutions. A disposable syringe[a] and needle[b] were used to withdraw 20 mL of solution from 500-mL containers of the following i.v. fluids: 0.45% sodium chloride injection,[c] 0.9% sodium chloride injection,[d] 5% dextrose injection,[e] 5% dextrose and 0.45% sodium chloride injection,[f] 5% dextrose and 0.9% sodium chloride injection,[g] 5% dextrose with lactated Ringer's injection,[h] lactated Ringer's injection,[i] and 5% sodium bicarbonate injection.[j] Twenty milliliters of esmolol hydrochloride injection[k] 250 mg/mL (from ampuls) was then injected into the containers to produce solutions with an esmolol hydrochloride concentration of approximately 10 mg/mL.

A slightly different procedure was used to prepare another solution. Twenty milliliters of fluid was withdrawn from 500-mL containers of 5% dextrose injection,[e] and 10 mL of potassium chloride injection[l] 2 meq/mL was added and mixed in. Twenty milliliters of esmolol hydrochloride injection[k] 250 mg/mL was then injected into the containers to produce solutions with an esmolol hydrochloride concentration of approximately 10 mg/mL and a potassium chloride concentration of approximately 40 meq/L.

With one exception, eight admixtures of each solution were prepared—four in glass containers and four in polyvinyl chloride (PVC) containers. Four admixtures of esmolol hydrochloride in 5% sodium bicarbonate injection were prepared in glass containers.

All the solutions were mixed thoroughly and checked immediately for visual changes. Samples were taken from each container for initial testing. One glass

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container and one PVC container (if available) of each solution were stored under each of the following conditions: (1) in the dark at 5 °C, (2) under ambient room light at 23–27 °C, (3) in the dark at 40 °C, and (4) under intense light (1400–2000 foot-candles) at an uncontrolled temperature (normally 25–30 °C).

Optical density measurements and pH testing. The optical density of the solutions was measured at 400 and 600 nm with a double-beam spectrophotometer[m] or a single-beam photodiode array.[n] These wavelengths were chosen to detect yellowing (400 nm) and cloudiness or opalescence (600 nm). Readings were compared with those for deionized water. Solution pH was determined with a pH meter[o] that had been calibrated with two standards. Optical density and pH were measured immediately after the admixtures were prepared and after 168 hours for the solutions stored at 5 °C and 23–27 °C, after 48 hours for the solutions stored at 40 °C, and after 24 hours for the solutions stored under intense light.

Esmolol assay. A high-pressure liquid chromatographic procedure[9] was adapted to measure the esmolol hydrochloride concentration. The system consisted of a liquid chromatograph,[p] an ultraviolet light-absorption photometer[q] set at 214 nm, and a 10-mV recorder.[r] A 3.9-mm × 30-cm column[s] was operated at a constant flow rate of 2.0 mL/min, which produced a head pressure of 2000 psi.

The mobile phase consisted of 0.005 M monobasic potassium phosphate[t] in water (65%), methanol[u] (20%), and acetonitrile[u] (15%). An autosampler[v] injected 100-µL samples into the system.

The following stock solutions were prepared: esmolol hydrochloride[w] 200 µg/mL, 3-[4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl]propionic acid (the free-acid degradation product of esmolol[9]) 20 µg/mL, and *o*-chlorobenzyl alcohol[x] (the internal standard) 200 µg/mL. The free-acid degradation product was made from esmolol by base hydrolysis, acidification, extraction into chloroform, and reduction to dryness.

Five-milliliter samples of admixture solutions were diluted to 25 mL with distilled water, and, after thorough mixing, 5-mL portions were further diluted to 50 mL. Then, 10-mL portions of each diluted sample, the esmolol hydrochloride standard, the free-acid degradation product, and the internal standard were diluted separately to 50 mL with distilled water to obtain working concentrations. Esmolol hydrochloride concentrations in the admixtures were determined from peak height ratios; the single-point standard was esmolol hydrochloride 40 µg/mL. All determinations were done in duplicate.

Chromatography, as described above, was performed for each of the infusion solutions without esmolol hydrochloride; there were no interfering peaks. The stability-indicating nature of the assay has been demonstrated.[9]

Samples were tested immediately after the admixtures were prepared and after 24, 48, 72, and 168 hours for the solutions stored at 5 °C and 23–27 °C; after 24 and 48 hours for the solutions stored at 40 °C; and after 24 hours for the solutions stored under intense light. Stability was defined as the retention of at least 90% of the mean initial concentration of esmolol hydrochloride.

Results

No changes were visible in any of the admixtures throughout the storage periods. All optical density readings were negligible (absorbance, ≤0.01). The pH remained within 0.3 unit of the initial value for the sodium bicarbonate solutions and within 0.1 unit for all the other solutions.

Esmolol hydrochloride was stable in the various i.v. fluids for at least 168 hours when stored at 5 °C or 23–27 °C, for at least 24 hours when stored under intense light, and with one exception, for at least 48 hours when stored at 40 °C (Table 1). When mixed with 5% sodium bicarbonate injection, the drug was stable for only about 24 hours at 40 °C.

The type of container used had no effect on stability.

Discussion

Esmolol hydrochloride was stable in all the solutions tested for at least 168 hours when kept at typical storage temperatures (5 °C or 23–27 °C). The drug was also stable after 24 hours under intense light, a condition chosen to simulate short-term storage directly in indoor or window light. At 40 °C—a high but conceivable storage temperature—all the admixtures were stable for at least 48 hours except for the one prepared with 5% sodium bicarbonate injection, which was stable for only about half that time.

Basic solutions tend to promote ester hydrolysis. Thus, the stability of esmolol hydrochloride, an ester, is influenced by both pH and temperature. The initial pH (at room temperature) of the esmolol hydrochloride–sodium bicarbonate admixtures was 8.1–8.2, but USP specifications allow the pH of sodium bicarbonate injection to be as high as 8.5,[10] and storage temperatures for admixtures could easily approach 40 °C. Thus, it would be difficult to predict the stability of esmolol hydrochloride in 5% sodium bicarbonate injection under all likely storage conditions. The package insert for esmolol hydrochloride takes the conservative position that the drug is not compatible with 5% sodium bicarbonate injection.[8] Our data suggest that if an admixture of esmolol hydrochloride in 5% sodium bicarbonate injection is required, it should be used within 24 hours or, if possible, immediately.

Esmolol hydrochloride is available in ampuls (2.5 g/10 mL), which were used in these studies, and vials (100 mg/10 mL).[8] The ampuls contain propylene glycol and alcohol, which the vials do not. We do not

Table 1.
Stability of Esmolol Hydrochloride in Various I.V. Solutions

Solution and Container Type	Storage Condition[a]	Initial Esmolol Hydrochloride Concentration (mg/mL)[b,c]	% Mean Initial Concentration Remaining[c]			
			24 hr	48 hr	72 hr	168 hr
0.45% Sodium chloride injection						
Glass	5 °C	9.99, 9.83	102.6, 99.2	100.8, 100.7	100.8, 100.1	100.9, 100.8
	23–27 °C	10.07, 10.10	98.4, 97.4	99.7, 97.1	99.2, 98.4	98.3, 98.4
	40 °C	9.82, 9.79	99.1, 98.3	98.2, 98.8	...	...
	Intense light	9.82, 9.93	100.4, 100.1	...	...	...
PVC[d]	5 °C	9.61, 9.58	98.8, 97.3	99.5, 98.4	100.3, 98.6	99.9, 99.9
	23–27 °C	9.71, 9.49	97.6, 98.3	96.8, 96.7	100.2, 97.2	98.8, 98.8
	40 °C	9.58, 9.58	99.5, 99.1	98.9, 96.8	...	...
	Intense light	9.93, 9.88	98.2, 98.3	...	...	...
0.9% Sodium chloride injection						
Glass	5 °C	9.89[e]	100.2, 100.0	98.6, 98.5	99.3, 98.2	98.4, 98.4
	23–27 °C	10.23, 10.19	97.9, 98.8	97.7, 96.7	97.6, 97.5	97.2, 97.2
	40 °C	10.73, 10.85	100.9, 101.3	99.5, 98.3	...	...
	Intense light	10.25, 10.21	99.9, 99.9	...	...	...
PVC	5 °C	9.89, 9.94	100.1, 100.4	98.9, 97.6	98.6, 98.3	98.5, 98.5
	23–27 °C	9.92, 9.83	99.4, 99.1	98.1, 98.4	99.8, 97.9	98.4, 98.4
	40 °C	9.91, 9.96	98.8, 98.1	97.2, 96.8	...	...
	Intense light	9.91, 9.80	97.3, 99.9	...	...	...
5% Dextrose injection						
Glass	5 °C	10.05, 9.96	99.7, 99.9	99.6, 98.8	99.9, 99.5	100.0, 99.0
	23–27 °C	10.33, 10.25	100.1, 100.0	99.8, 98.8	99.6, 100.3	98.6, 99.3
	40 °C	10.09, 10.20	101.0, 100.7	99.7, 100.0	...	...
	Intense light	10.24, 10.25	100.0, 100.4	...	...	...
PVC	5 °C	9.90, 9.74	100.6, 100.5	100.3, 99.8	101.0, 100.7	98.8, 100.2
	23–27 °C	9.83, 9.79	99.2, 99.6	99.3, 99.2	99.6, 100.2	98.8, 98.7
	40 °C	9.88, 9.86	100.6, 101.0	99.3, 99.5	...	...
	Intense light	9.94, 9.85	100.1, 99.8	...	...	...
5% Dextrose and 0.45% sodium chloride injection						
Glass	5 °C	10.30, 10.29	100.3, 99.3	99.8, 100.0	100.2, 100.2	98.8, 98.5
	23–27 °C	10.12, 10.17	99.8, 100.4	100.0, 100.7	100.5, 99.9	99.4, 99.3
	40 °C	10.09, 10.03	100.1, 101.1	100.3, 99.8	...	...
	Intense light	9.96, 9.96	100.7, 100.6	...	...	...
PVC	5 °C	9.96, 9.96	99.8, 100.9	100.3, 98.2	100.4, 100.6	99.2, 99.1
	23–27 °C	10.11, 10.16	100.4, 100.6	99.7, 99.8	98.5, 99.4	98.6, 98.6
	40 °C	9.97, 10.00	100.9[e]	101.2, 100.6	...	...
	Intense light	10.00, 9.94	100.9, 100.5	...	...	...
5% Dextrose and 0.9% sodium chloride injection						
Glass	5 °C	10.47, 10.44	100.4, 101.1	100.1, 100.4	100.7, 100.0	99.7, 99.6
	23–27 °C	10.43, 10.45	100.5, 100.0	100.7, 95.8	100.2, 100.0	99.0, 98.9
	40 °C	10.32, 10.39	99.8, 100.0	101.2, 99.4	...	...
	Intense light	10.30, 10.35	100.7, 100.2	...	...	...
PVC	5 °C	9.91, 9.92	101.9, 99.5	100.3, 100.3	100.6, 100.3	99.7, 99.7
	23–27 °C	9.87, 9.95	100.4, 99.9	100.5, 99.6	99.7, 98.4	98.9, 98.9
	40 °C	9.80, 9.79	101.4, 100.3	100.2, 100.8	...	...
	Intense light	10.05, 9.93	99.7, 99.7	...	...	...
5% Dextrose and lactated Ringer's injection						
Glass	5 °C	10.11, 10.11	99.4, 100.3	100.5, 99.9	99.1, 98.1	99.1, 98.9
	23–27 °C	10.15, 10.18	99.9, 99.6	100.3, 100.0	97.6, 99.5	97.8, 99.1
	40 °C	10.17, 9.98	100.0, 101.1	101.0, 101.4	...	...
	Intense light	10.34, 10.33	99.9, 98.2	...	...	...
PVC	5 °C	9.93, 9.94	100.6, 99.6	99.6, 99.5	99.2, 98.9	98.8, 98.7
	23–27 °C	9.87, 9.90	99.9, 98.9	98.8, 98.8	99.0, 98.6	99.3, 98.7
	40 °C	9.89, 9.95	101.8, 102.0	101.9, 101.4	...	...
	Intense light	10.14, 9.98	99.9[e]	...	...	...
Lactated Ringer's injection						
Glass	5 °C	9.84, 9.54	106.2, 103.4	102.5, 102.0	103.1, 103.8	102.5, 102.2
	23–27 °C	10.33, 10.28	96.5, 99.3	99.7, 98.7	100.4, 99.8	98.7, 98.4
	40 °C	10.25, 10.20	96.9, 99.3	99.1, 99.1	...	...
	Intense light	9.97, 9.99	96.9[e]	...	...	...
PVC	5 °C	9.92, 9.78	101.1, 99.9	100.9, 101.1	102.0, 102.0	100.6, 100.6
	23–27 °C	9.84, 9.84	98.8, 99.9	99.5, 99.7	100.9, 101.0	99.4, 100.3
	40 °C	9.51, 9.50	101.6, 100.2	95.8, 99.2	...	...
	Intense light	9.93, 9.96	100.9, 98.1	...	...	...
5% Sodium bicarbonate injection						
Glass	5 °C	10.12, 9.93	99.7, 99.0	101.1, 100.0	100.9, 100.4	94.3, 95.1
	23–27 °C	10.34, 10.27	98.4, 98.8	98.0, 98.3	95.2, 96.6	92.3, 92.4
	40 °C	10.02, 10.19	91.5, 91.7	81.3, 84.5	...	...
	Intense light	10.38, 10.42	96.3, 96.5	...	...	...

Continued on next page

Table 1 (*continued*)

Solution and Container Type	Storage Condition[a]	Initial Esmolol Hydrochloride Concentration (mg/mL)[b,c]	% Mean Initial Concentration Remaining[c]			
			24 hr	48 hr	72 hr	168 hr
5% Dextrose injection with potassium chloride 40 meq/L						
Glass	5 °C	10.04, 10.01	100.1, 100.1	101.9, 100.3	98.1, 99.6	98.9, 97.8
	23–27 °C	10.15, 10.13	100.5, 101.3	100.6, 101.1	98.8, 100.4	97.7, 100.1
	40 °C	9.95, 9.97	101.5, 101.4	101.4, 101.4	...	...
	Intense light	10.32, 10.35	99.9, 100.6	...	...	...
PVC	5 °C	9.91, 9.97	97.3, 98.7	99.2, 98.2	99.0, 98.7	103.4, 97.6
	23–27 °C	9.79, 9.81	99.7, 100.1	101.1, 99.5	96.8, 97.6	98.8, 100.0
	40 °C	9.86, 9.79	101.2, 100.7	101.8, 101.6	...	...
	Intense light	9.71, 9.73	99.4, 97.5	...	...	...

[a] Solutions stored at 5 °C and 40 °C were protected from light. Solutions stored at 23–27 °C were kept under ambient room light. Intense light = 1400–2000 foot-candles, normally 25–30 °C.
[b] Theoretical concentration = 10 mg/mL.
[c] Duplicate values.
[d] PVC = polyvinyl chloride.
[e] Duplicate value not obtained because of instrument failure.

know whether using the vials in our studies would have produced different results, but the ampuls are intended for use in preparing solutions for infusion, whereas the vials are intended for direct i.v. injection. Thus, we used the more appropriate formulation for our investigations.

Conclusion

With one exception, esmolol hydrochloride was stable in a variety of i.v. solutions under a broad range of conditions. In 5% sodium bicarbonate injection, the drug was stable for only about 24 hours at 40 °C.

[a]B-D Plastipak, Becton-Dickinson and Co., Franklin Lakes, NJ.
[b]18 gauge, Becton-Dickinson.
[c]McGaw Laboratories, Inc., Irvine, CA, lot B2N134B (glass), and Travenol Laboratories, Inc., Deerfield, IL, lot 4C931110 (polyvinyl chloride [PVC]).
[d]McGaw, lot B3A098B (glass), and Travenol, lot 4C916H5 (PVC).
[e]McGaw, lot B3D111A (glass), and Travenol, lot 8C90755 (PVC).
[f]McGaw, lot B3D081B (glass), and Travenol, lot 4C925F5 (PVC).
[g]McGaw, lot J9P083B (glass), and Travenol, lot 9C925L3 (PVC).
[h]McGaw, lot B2N096C (glass), and Travenol, lot 6C928L6 (PVC).
[i]McGaw, lot B2P053A (glass), and Travenol, lot 7C864W2 (PVC).
[j]McGaw, lot 66680W7A (glass).
[k]Brevibloc, American Critical Care, Aguadilla, PR, lots 767-49, 803-31, and 5DA101.
[l]Elkins-Sinn Inc., Cherry Hill, NJ, lot 082131.
[m]Acta CIII, Beckman Instruments, Inc., Irvine, CA.
[n]Model 8450A, Hewlett-Packard Co., Avondale, PA.
[o]Model 130 or 145, Corning Glass Works, Inc., Corning, NY.
[p]System 2/2, Perkin-Elmer Corp., Norwalk, CT.
[q]LC-55A, Perkin-Elmer, or LC-160, Beckman.
[r]Model 285/mm, Scientific Products, McGaw Park, IL.
[s]μBondapak C_{18}, Waters Associates, Milford, MA.
[t]Fisher Scientific, Pittsburgh, PA.
[u]Burdick and Jackson, Muskegon, MI; or J. T. Baker, Inc., Phillipsburg, NJ.
[v]WISP, Waters.
[w]Gaines Chemicals, Inc., Carlstadt, NJ, lot 907-32.
[x]Aldrich Chemical Co., Milwaukee, WI.

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