ARTICLE

Concentration-Dependent Compatibility and Stability of Dexamethasone and Midazolam

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ABSTRACT

Objective: To study the stability and compatibility of dexamethasone 21 phosphate disodium salt and midazolam at various concentrations at 4°C and 23°C.

Methods: Solutions of dexamethasone (4 and 10 mg/mL) were mixed with midazolam (1 and 5 mg/mL). In addition to visual inspection of the mixtures, the concentrations of dexamethasone and midazolam in the mixtures were determined by a stability-indicating liquid chromatographic method.

Results: Precipitation occurred when equal volumes of the most concentrated solutions were mixed. Some combinations at lower concentrations were compatible on visual inspection and retained 90% of their initial concentrations. Upon dissolution and analysis of the precipitate, the only drug present in the precipitate was midazolam. The stability of a compatible solution of 0.25 mg/mL dexamethasone and 0.25 mg/mL midazolam was tested over a 3-day period at 4°C and 23°C. Physical incompatibility, because of precipitation of midazolam, was observed after 48 h. However, during the first 24 h, both solutions remained clear and free of precipitate and retained 90% of the initial concentration of both dexamethasone and midazolam.

Conclusions: Mixing commercially available formulations of dexamethasone and midazolam in a syringe will generally always result in precipitation, and therapeutically useful mixtures cannot be achieved. Furthermore, although compatible IV additive admixtures of dexamethasone and midazolam in 5% dextrose in water can be maintained for up to 24 h, these solutions (0.25 mg/mL of each compound) are also generally too dilute to be clinically useful. Furthermore, these solutions also developed a precipitate after 48 h of storage.

Key words: stability, compatibility, dexamethasone, midazolam, precipitate

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RÉSUMÉ

Objectif : Étudier la stabilité et la compatibilité des solutions de phosphate de dexaméthasone sodique et de midazolam à diverses concentrations, entreposées à des températures de 4°C et de 23°C.

Méthodes : Les solutions de dexaméthasone (4 et 10 mg/mL) ont été mélangées au midazolam (1 et 5 mg/mL). Outre l'inspection visuelle des mélanges, les concentrations de dexaméthasone et de midazolam dans les mélanges ont été déterminées au moyen de l'épreuve de stabilité par chromatographie liquide à haute pression.

Résultats : Un précipité s'est formé dans les mélanges de solutions les plus concentrées à volumes égaux. Certains mélanges à des concentrations moindres étaient compatibles à l'inspection visuelle et ont conservé 90 % de leur concentration initiale. Après dissolution et analyse du précipité, le seul médicament présent dans le précipité était le midazolam. La stabilité d'une solution compatible de 0,25 mg/mL de dexaméthasone et de 0,25 mg/mL de midazolam a été évaluée sur une période de trois jours, à une température de 4°C et de 23°C. Une incompatibilité physique due à la précipitation du midazolam a été observée après 48 heures. Cependant, durant les 24 premières heures, les deux solutions sont restées claires et sans précipité, et ont conservé 90 % de leur concentration initiale à la fois de midazolam et de dexaméthasone.

Conclusions : Le mélange de formules commerciales de dexaméthasone et de midazolam dans une seringue entraînera généralement toujours la formation d'un précipité, et des mélanges thérapeutiques utiles ne peuvent par conséquent être réalisés. En outre, bien que des mélanges de solutions I.V. compatibles de dexaméthasone et de midazolam dans du dextrose à 5 % dans l'eau peuvent être stables pendant un maximum de 24 heures, ces solutions (0,25 mg/mL de chaque agent) sont généralement trop diluées pour être cliniquement utiles. De plus, ces solutions ont aussi formé un précipité après 48 heures d'entreposage.

Mots clés : stabilité, compatibilité, dexaméthasone, midazolam, précipité

INTRODUCTION

Dexamethasone, an adrenocortical steroid, is frequently prescribed for terminally ill patients.[1] In this population, it is most often used to treat refractory nausea and vomiting and to decrease elevated intracranial pressure. Midazolam, used to manage terminal agitation or opioid-induced myoclonus, is often prescribed to patients receiving dexamethasone.

Terminally ill patients usually have poor venous access and are receiving many drugs. Thus, it is advantageous to minimize the number of IV sites required for drug administration. The mixing of drugs in IV bags is therefore an attractive option but one that necessitates knowledge of the compatibility and stability of these drugs in the IV administration solution.

In emergencies, the usual therapeutic dose of dexamethasone 21 phosphate disodium salt ranges from 4 to 100 mg, and the dose is usually given by injection over several minutes.[1] In the intensive care setting, continuous infusions of dexamethasone (0.125 mg/kg over 24 h) have been used.[1] The usual therapeutic dose of IV midazolam differs depending on the condition being treated. It has been used in managing delirium in terminally ill patients in doses ranging from 25 to 50 mg in 50 mL of 5% dextrose in water (D5W), infused subcutaneously at a rate of 1 mL/h.[2] This generally corresponds to a concentration of 0.5 to 1 mg/mL of midazolam. Midazolam has been administered by infusion in the palliative care setting in dosages up to 2.9 mg/h for restlessness and agitation.[3] A preliminary, unpublished investigation of the compatibility of dexamethasone and midazolam undertaken in our laboratory indicated that combining equal volumes of dexamethasone (10 mg/mL solution) and midazolam (5 mg/mL solution) resulted in precipitation. Although this observation indicated that these drugs could not be mixed at these concentrations, it was possible that the medications were compatible at other concentrations.

The purpose of this investigation was to determine whether dexamethasone and midazolam exhibit a concentration-dependent compatibility similar to that of dexamethasone and diphenhydramine or dexamethasone and hydromorphone.[4] For solutions showing physical compatibility over 24 h, stability over 72 h at 4°C and 23°C was to be evaluated.

METHODS

Assay Validation

Previous experience with dexamethasone had indicated that degradation of this drug could be accelerated by the addition of acid.[4,5] Dexamethasone (dexamethasone 21 phosphate disodium salt, Sigma Chemical Co, Mississauga, Ontario, lot 90HO753) was dissolved in distilled water and acidified with concentrated hydrochloric acid to achieve a final concentration of 0.4 mg/mL with a pH of 1.8. This solution was placed in a 30-mL multidose vial, which was incubated in a water bath at 90°C for 11 h. Samples were drawn just before incubation and at 17 other times over the 11-h period. Chromatograms were inspected for the appearance of additional peaks, and the dexamethasone peaks of the samples were compared to determine changes in concentration, retention time, and peak shape. The ultraviolet spectral purity (200 to 365 nm, 6-nm bandwidth, deuterium lamp [UV3000, Thermo Separation Products, Fremont, California]) of the leading edge, middle, and tail of the dexamethasone peak in a chromatogram of a degraded sample and the sample taken at time zero were compared. The sample taken at 11 h (pH 1.8) was retained to assist in the evaluation of the final chromatographic system.

Previous experience with midazolam had indicated that it could not be degraded with acid or base and heat.[6] However, an opened-ring benzophenone is favoured over midazolam in acidic solution.[7-9] To create this compound, a 5 mg/mL sample of midazolam injectable (Versed®, Hoffmann - La Roche Ltd, Mississauga, Ontario, lot 95182B) was acidified to a pH of 2.0 with concentrated hydrochloric acid. This sample was then injected onto a high-performance liquid chromatography column, and the chromatogram was inspected for the presence of additional peaks. The midazolam peak in the acid-treated sample was compared with an authentic midazolam standard for changes in concentration, retention time, and peak shape. Ultraviolet spectral purity (200 to 365 nm, 6-nm bandwidth, deuterium lamp) of the leading edge, middle, and tail of the midazolam peak in a chromatogram of a degraded sample and the sample taken at time zero were compared.

Chromatographic System and Separation Method

After the creation of degradation products, a chromatographic separation method was developed that allowed analysis of dexamethasone and midazolam simultaneously and ensured the separation of the starting compounds from their degradation products. This chromatographic separation method used a mobile phase similar to that developed by Hagan and colleagues.[7] We had previously modified this mobile phase for the analysis of hydromorphone and midazolam,[6] and for this study the mobile phase was further modified to allow the separation of dexamethasone and midazolam. The initial strength of the mobile phase was weaker than that used by Hagan and colleagues[7] (percentage of organic solvents was 50%, whereas Hagan and colleagues[7] used 60% organic solvents). The chromatographic system consisted of a ternary-gradient solvent delivery pump (System Controller 600E, Waters Ltd, Mississauga, Ontario), which pumped a mixture of acetonitrile (EM Science, Gibbstown, New Jersey), methanol (EM Science), tetrahydrofuran (Fisher Scientific, Toronto,

Ontario), 0.1 M aqueous potassium phosphate monobasic (Fisher Scientific), and 0.1 M aqueous potassium phosphate dibasic (Fisher Scientific) through a 100 x 4.6 mm BDS reverse-phase C_{18}, 3-µm column (Hypersil, Alltech Associates Inc, Deerfield, Illinois). The phosphate buffers were mixed to achieve a pH of 6.8 and were then mixed with the organic solvents to achieve a mobile phase that was 24.5% acetonitrile, 24.5% methanol, 1% tetrahydrofuran, and 50% phosphate buffer. The solvent was pumped through the column at 1.0 mL/min. The column effluent was monitored with a variable-wavelength ultraviolet light detector (Spectraflow 783 absorbance detector, Kratos Analytical, Ramsey, New Jersey) at 220 nm. Under these chromatographic conditions, dexamethasone eluted at 3.9 min and midazolam eluted at 26.6 min.

During the stability study, standard curves were prepared daily with dexamethasone (dexamethasone 21 phosphate disodium salt, Sigma Chemical Co, lot 90HO753) and midazolam base (Hoffmann - La Roche, Basel, Switzerland, lot 816072). Five concentrations of dexamethasone and 5 concentrations of midazolam, ranging from 0.05 to 0.35 mg/mL, plus a blank, were used to construct the standard curves. Three quality control samples (0.12, 0.20, and 0.30 mg/mL) were also prepared.

To limit differences due to initial concentrations in the compatibility studies, standards were prepared from the commercially available IV products used in the study. Standard curves for dexamethasone ranged in concentration from 0.04 to 4 mg/mL (prepared with dexamethasone 4 mg/mL, Sabex, Boucherville, Quebec, lot 029511A) or from 0.05 to 10 mg/mL (prepared with dexamethasone 10 mg/mL, Pharmascience, Montreal, Quebec, lot 6B784). Standard curves for midazolam ranged in concentration from 0.01 to 1 mg/mL (prepared with 1 mg/mL Versed®, Hoffmann – La Roche Ltd, Mississauga, Ontario, lot 95182B) and from 0.02 to 5 mg/mL (prepared with Versed®, Hoffmann - La Roche Ltd, Mississauga, Ontario, lot 95108B). The solutions were diluted with D5W and, when combined with a blank, these standards served to construct a standard curve. Four microlitres of each sample was chromatographed in duplicate. The area under the dexamethasone and midazolam peaks in a chromatogram at 220 nm was subjected to least squares linear regression, and the actual concentration in each unknown sample was determined by interpolation from the standard curve. Dexamethasone and midazolam concentrations were recorded to the nearest 0.01 mg/mL.

Physical Stability in Vitro

After preparation, each solution was mixed (Vortex Genie 2, Fisher Scientific) and then visually inspected for colour, clarity, presence of particulate matter, and evolution of gas. Presence of particulate matter was evaluated with the sample in clear glass test tubes against a white and black background under diffuse laboratory light. Microscopic inspection for precipitates was not undertaken. Samples were then centrifuged for 20 min to settle any precipitate, and the supernatant was chromatographed immediately afterward. If a precipitate was observed, the supernatant was decanted and the precipitate redissolved in 1 mL of methanol and chromatographed.

Compatibility in Syringes

To simulate compatibility within a syringe, solutions were prepared using dexamethasone sodium phosphate 4 mg/mL (Sabex, lot 029511A) and 10 mg/mL (Pharmascience, lot 6B784). To each concentration of dexamethasone, midazolam 1 mg/mL (Versed, Hoffmann-La Roche Ltd, Mississauga, Ontario, lot 95182B) or 5 mg/mL (Versed, Hoffmann - La Roche Ltd, Mississauga, Ontario, lot 95108B) was added. The solutions were mixed in a Vortex mixer, and a physical inspection was completed. The solutions were centrifuged for 20 min to settle any precipitate. The supernatant was chromatographed immediately after centrifugation. If a precipitate was seen, additional solutions of various concentrations were prepared to evaluate the range of concentrations at which the drugs were incompatible. A total of 9 solutions were made for each combination of dexamethasone 10 mg/mL with midazolam 1 mg/mL, dexamethasone 10 mg/mL with midazolam 5 mg/mL, and dexamethasone 4 mg/mL with midazolam 5 mg/mL. Seven solutions were made for the dexamethasone 4 mg/mL and midazolam 1 mg/mL mixture. Thirty-six additional solutions were prepared to further test the range of compatibility. Distilled water was used as a diluent to achieve concentrations of dexamethasone and midazolam within and outside the observed compatible range of concentrations.

Additive Stability in IV Minibags

Dexamethasone 4 mg/mL and midazolam 5 mg/mL were diluted in 50-mL polyvinyl chloride minibags of D5W to make a compatible solution of dexamethasone 0.25 mg/mL and midazolam 0.25 mg/mL. Three replicates of this solution were stored at 4°C, and a second set of 3 containers was stored at 23°C. Samples were inspected physically and chromatographed immediately after preparation and on each of 3 other study days (days 1, 2, and 3). Four microlitres of each sample was chromatographed in duplicate.

Data Reduction and Statistical Analysis

Means were calculated for analyses completed in duplicate. Error was assessed by the coefficient of variation (CV: standard deviation divided by the mean). Log–linear and linear–linear fits for the data from the

accelerated degradation study (at 90°C) were compared for goodness of fit by the maximum likelihood method of Box and Cox[10] and Sclove.[11] Drugs were considered stable and acceptable if the concentration was within 90% of the initial concentration on any given day. On each study day or at each evaluation period, a visual inspection for colour, clarity, presence of particles, and evolution of gas was also completed. In the event that there was no change in the colour or clarity of a solution and no precipitate was evident, the solution was considered physically and visually compatible. The 5% level was used as the *a priori* cut-off for significance, and all references to significance refer to this level.

RESULTS

Assay Validation

When dissolved in water, adjusted to a pH of 1.8, and heated at 90°C, dexamethasone degraded to less than 30% of the initial concentration over the 11-h period. Dexamethasone degraded in an apparent first-order fashion (r^2 = 0.9924) with a half-life of about 6 h. The major degradation product eluted at 12.8 min, and 2 other minor degradation products could be detected in the chromatograms of the degraded dexamethasone. None of these products (Figure 1, chromatogram D) interfered with the quantification of the parent compound, dexamethasone (Figure 1, chromatograms B and C).

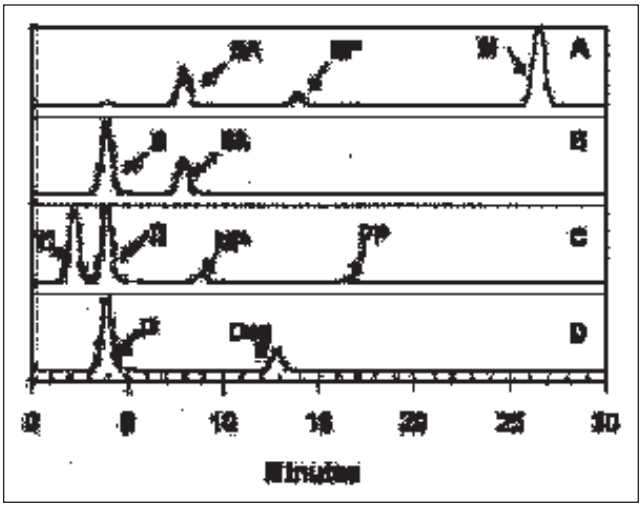

Figure 1. Representative chromatograms of midazolam and dexamethasone. Chromatogram A shows midazolam injectable (Versed) (M; eluted at 26.6 min) following acidification with hydrochloric acid to create the opened-ring benzophenone (BP; eluted at 13.9 min). BA = benzyl alcohol. Chromatogram B shows dexamethasone (D; eluted at 3.9 min) in a formulation (from Pharmascience) containing benzyl alcohol (BA; eluted at 7.8 min). Chromatogram C shows dexamethasone (D) in a formulation (from Sabex) containing creatinine (C; eluted at 2.2 min), methylparaben (MP; eluted at 8.9 min), and propylparaben (PP; eluted at 16.5 min). Chromatogram D shows dexamethasone (D) in a sample that was degraded by heat and acid. The major degradation product (Deg) eluted at 12.8 min, and a second product (not visible at this scale) eluted at 7.2 min. Chromatogram D is shown at 3 times its original scale.

The addition of acid to midazolam resulted in the appearance of a peak ahead of the midazolam peak. At a pH of less than 3.3, midazolam has been reported to form an opened-ring structure (benzophenone).[7-9] Midazolam is in equilibrium with this compound, which is favoured in acidic media.[7-9] At a pH of 7.4 or greater, the opened-ring structure can completely revert to the closed-ring midazolam,[7-9] so it is not a true degradation product of midazolam.

Previous reports have indicated that the opened-ring structure could not be separated from midazolam;[7-9] however, the chromatographic system used in this study could separate midazolam from benzophenone (Figure 1, chromatogram A). This method can also separate dexamethasone degradation products and benzophenone from dexamethasone and midazolam (Figure 1). Furthermore, other compounds in the dexamethasone and midazolam formulations were separated from the drugs of primary interest. For example, dexamethasone 21 phosphate disodium injection (Sabex) contains methylparaben, propylparaben, and creatinine in addition to dexamethasone (Figure 1, chromatogram C), whereas dexamethasone 21 phosphate disodium injection (Pharmascience; Figure 1, chromatogram B) and midazolam (Versed; Figure 1, chromatogram A) contain benzyl alcohol as a preservative. The ability of the method to separate all of these components demonstrates its stability-indicating properties.[12,13]

The reproducibility and accuracy of the measurement of dexamethasone and midazolam concentrations was assessed by standard curves and quality-control samples. This evaluation indicated that for dexamethasone, concentrations above 0.3 mg/mL were measured reproducibly (CV averaged 3%) within and between days as well as accurately (deviations less than 4%). Similarly, for midazolam, concentrations above 0.05 mg/mL were measured reproducibly (CV averaged 4%) within and between days as well as accurately (deviations less than 6%).

Compatibility

At room temperature (23°C), the mixing of equal volumes of dexamethasone 21 phosphate disodium salt 10 mg/mL and midazolam 5 mg/mL immediately produced a cloudy mixture. Upon vigorous agitation, the solution became clear, with the formation of a clear, stringy, water-immiscible, crystalline precipitate, which adhered to the walls of the test tube. The same observations were noted in the combination of equal volumes of dexamethasone 4 mg/mL and midazolam 1 mg/mL, dexamethasone 4 mg/mL and midazolam 5 mg/mL, and dexamethasone 10 mg/mL and midazolam 1 mg/mL.

Table 1. Summary of Dexamethasone and Midazolam Compatibility Study

Solution	Concentration of Dexamethasone			Concentration of Midazolam			Physical Inspection§
	Expected* (mg/mL)	Observed† (mg/mL)	% Diff.‡	Expected* (mg/mL)	Observed† (mg/mL)	% Diff.‡	
Dexamethasone 10 mg/mL and midazolam 5 mg/mL							
	9.80	10.39	6.0	0.10	0.07	-25.9	no ppt
	9.09	9.47	4.2	0.45	0.08	-83.1	ppt
	8.33	8.72	4.6	0.83	0.04	-94.7	ppt
	6.67	7.11	6.7	1.67	0.16	-90.2	ppt
	5.00	5.12	2.4	2.50	0.21	-91.6	ppt
	3.33	3.03	-9.0	3.33	0.22	-93.3	ppt
	1.67	0.80	-52.0	4.17	0.69	-83.5	ppt
	0.91	0.25	-72.5	4.55	2.48	-45.4	ppt
	0.10	0.06	-38.2	4.95	5.44	10.0	no ppt
	0.04			4.99			no ppt
Dexamethasone 10 mg/mL and midazolam 1 mg/mL							
	8.33	8.86	6.3	0.17	0.14	-14.6	no ppt
	7.89			0.11			no ppt
	6.67	7.08	6.2	0.33	0.17	-48.3	ppt
	5.56	5.90	6.1	0.44	0.20	-55.6	ppt
	5.00			0.10			ppt
	5.00	5.24	4.7	0.50	0.19	-61.4	ppt
	3.33	3.44	3.3	0.67	0.20	-69.7	ppt
	1.67	1.72	3.0	0.83	0.22	-73.8	ppt
	0.91	0.66	-27.7	0.91	0.41	-54.6	ppt
	0.70	0.45	-34.9	0.93	0.59	-36.5	ppt
	0.10	0.07	-27.2	0.99	1.06	7.0	no ppt
Dexamethasone 4 mg/mL and midazolam 5 mg/mL							
	3.96	3.91	-1.2	0.05	0.00	-96.6	no ppt
	3.64	3.50	-3.7	0.45	0.06	-86.7	ppt
	3.33	3.18	-4.6	0.83	0.10	-87.5	ppt
	2.67	2.75	3.1	1.67	0.02	-99.1	ppt
	2.00	1.95	-2.7	2.50	0.22	-91.2	ppt
	1.33	1.03	-22.6	3.33	0.42	-87.3	ppt
	0.67	0.29	-55.9	4.17	1.58	-62.2	ppt
	0.36	0.14	-62.2	4.55	3.10	-31.9	ppt
	0.19	0.10	-47.1	4.76	4.81	1.1	ppt
	0.05			2.50			no ppt
	0.05			1.00			ppt
	0.04			2.00			no ppt
Dexamethasone 4 mg/mL and midazolam 1 mg/mL							
	3.64	3.56	-2.2	0.09	0.04	-58.9	ppt
	3.08	3.10	0.8	0.23	0.03	-85.1	ppt
	2.67	2.60	-2.6	0.33	0.07	-77.6	ppt
	2.50			0.25			ppt
	2.50			0.10			no ppt
	2.00	1.99	-0.4	0.50	0.13	-73.2	ppt
	2.00			0.38			ppt
	2.00			0.26			ppt
	1.50			0.25			ppt
	1.43			0.07			no ppt
	1.33	1.27	-4.8	0.67	0.14	-78.9	ppt
	1.00			0.50			ppt
	1.00			0.38			ppt
	1.00			0.26			ppt
	1.00			0.25			ppt
	1.00			0.10			ppt
	0.67	0.62	-7.2	0.83	0.18	-78.6	ppt
	0.50			0.50			no ppt
	0.36	0.29	-21.3	0.91	0.24	-73.9	ppt
	0.25			0.50			no ppt
	0.25			0.25			no ppt

Table 1. Summary of Dexamethasone and Midazolam Compatibility Study — continued

Solution	Concentration of Dexamethasone			Concentration of Midazolam			Physical Inspection§
	Expected* (mg/mL)	Observed† (mg/mL)	% Diff.‡	Expected* (mg/mL)	Observed† (mg/mL)	% Diff.‡	
Dexamethasone 4 mg/mL and midazolam 1 mg/mL (continued)							
	0.25			0.10			no ppt
	0.16			0.80			ppt
	0.14			0.60			ppt
	0.13			0.17			no ppt
	0.12			0.80			ppt
	0.10			0.25			no ppt
	0.10			0.16			no ppt
	0.08			0.21			no ppt
	0.07			0.60			ppt
	0.06			0.80			ppt
	0.055			0.89			ppt
	0.05			0.50			no ppt
	0.05			0.25			no ppt
	0.05			0.50			no ppt
	0.04			0.20			no ppt
	0.03			0.25			no ppt

***** Expected concentrations are calculated on basis of the volumes of dexamethasone and midazolam added to each sample with a syringe. In general, on the basis of the volumes used, actual concentrations should be prepared within about 5% of the expected concentrations.
† Observed concentrations are concentrations determined by liquid chromatography.
‡ % difference = [(observed – expected)/expected] x 100. A negative value indicates that the observed concentration was less than the expected concentration. The expected and observed values have been rounded for presentation here.
§ Observation of precipitate (ppt).

Table 2. Observed Mean Concentrations of Dexamethasone and Midazolam in Study of Stability*

Study Day	Refrigerated (4°C)		Room Temperature (23°C)	
	Dexamethasone (mg/mL)	Midazolam (mg/mL)	Dexamethasone (mg/mL)	Midazolam (mg/mL)
0	0.28 ± 0.00	0.26 ± 0.01	0.27 ± 0.00	0.27 ± 0.01
1	0.26 ± 0.00	0.27 ± 0.02	0.26 ± 0.00	0.26 ± 0.02
2†	0.26 ± 0.00	0.27 ± 0.02†	0.26 ± 0.00	0.20 ± 0.10†
3†	0.27 ± 0.00	0.26 ± 0.02†	0.27 ± 0.00	0.22 ± 0.16†
% remaining ([day 3/day 0] x 100)	95.7	96.6	98.1	80.3

* All solutions were prepared as 0.25 mg/mL (see text for method). Concentrations presented are the means and standard deviation of duplicate analysis from samples prepared in triplicate. Values have been rounded for presentation here.
† Particulate matter was observed in 2 of 3 samples at 48 h (on day 2) and in all samples by 72 h (day 3).

A range of dexamethasone and midazolam concentrations were prepared to evaluate the range of incompatibilities. Most samples became cloudy immediately on mixing. A summary of the concentrations of dexamethasone and midazolam before (expected) and after (observed) precipitation is shown in Table 1. Samples that precipitated had midazolam concentrations that were less than the expected concentrations (Figures 2 to 5) whereas the dexamethasone concentrations showed little change after mixing. At least 2 samples had a large change in concentration but no visible precipitate. In both cases (dexamethasone 9.80 mg/mL and midazolam 0.1 mg/mL; dexamethasone 3.96 mg/mL and midazolam 0.05 mg/mL) the observed change in midazolam concentration was less than 0.05 mg/mL, and it was assumed that the change in concentration was due to a precipitate that was not evident visually. It was presumed that the observed concentration in the supernatant (shown as solid triangles in Figures 2 to 5) represented a saturated solution of midazolam and dexamethasone. To test this presumption, an additional 35 dexamethasone and midazolam concentrations were prepared, using saline as a diluent. Twenty-nine of these samples were prepared to fall within and outside the compatible concentration range (shaded area) of Figure 4 (mixing of 4 mg/mL dexamethasone and 1 mg/mL midazolam). Most mixtures prepared with an initial concentration within the shaded area precipitated immediately (solid squares in Figure 4), whereas a precipitate was not visible in samples with an initial concentration outside this range (open squares in Figure 4). Upon redissolution of the precipitate, midazolam was found in every sample, which agrees with the finding that the midazolam concentrations decreased substantially with precipitation. However, dexamethasone concentrations also decreased in some samples, and these tended to be samples with a smaller proportion of dexamethasone relative to midazolam.

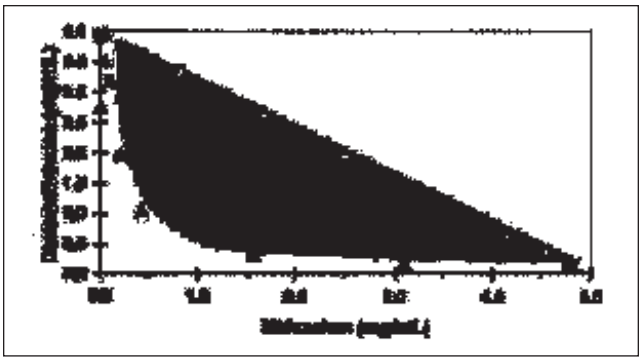

Figure 2. Compatibility profile of dexamethasone 4 mg/mL (Sabex) and midazolam 5 mg/mL (Hoffmann – La Roche). The shaded area represents a region of incompatibility. All study solutions tested in the shaded area were incompatible. The open triangles represent the concentrations that were prepared, and the solid triangles represent the concentrations that were observed after mixing.

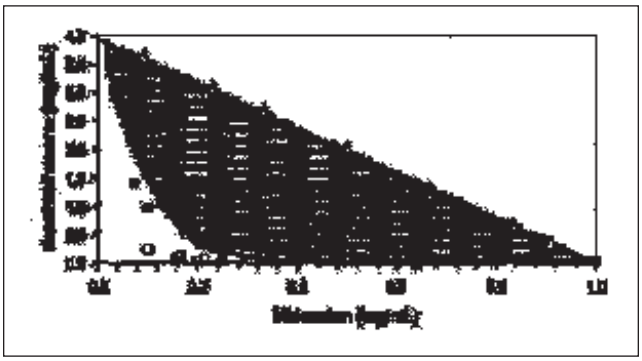

Figure 4. Compatibility profile of dexamethasone 4 mg/mL (Sabex) and midazolam 1 mg/mL (Hoffmann – La Roche). The shaded area represents a region of incompatibility. All study solutions tested in the shaded area were incompatible. The open triangles represent the concentrations that were prepared, and the solid triangles show the concentrations that were observed after mixing. Additional mixtures were prepared and observed visually. The solid squares represent the concentrations that were prepared and that were observed to have a precipitate. The open squares represent the concentrations that were prepared and that remained clear and colourless and without visible precipitate.

The results indicate that virtually every combination of the commercially available formulations of dexamethasone and midazolam yielding a midazolam concentration exceeding 0.05 mg/mL (most readily apparent in Figures 4 and 5) will result in either a visible precipitate or a change in the concentration of one of the compounds by more than 10%.

Additive Stability in IV Minibags

Over the 72-h study period there was less than a 10% change in the dexamethasone and midazolam concentrations at 4°C (Table 2). Similarly, at 23°C the dexamethasone concentration remained unchanged at

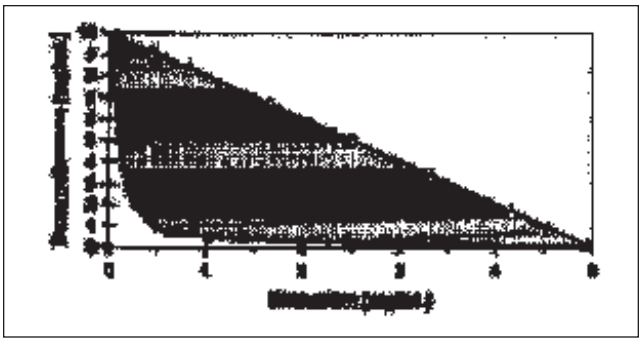

Figure 3. Compatibility profile of dexamethasone 10 mg/mL (Pharmascience) and midazolam 5 mg/mL (Hoffmann – La Roche). The shaded area represents a region of incompatibility. All study solutions tested in the shaded area were incompatible. The open triangles represent the concentrations that were prepared, and the solid triangles represent the concentrations that were observed after mixing.

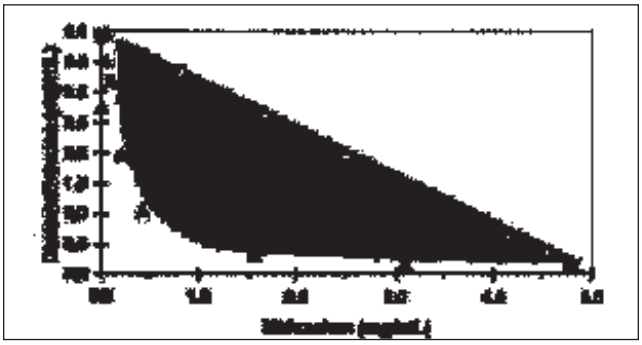

Figure 5. Compatibility profile of dexamethasone 10 mg/mL (Pharmascience) and midazolam 1 mg/mL (Hoffman - La Roche). The shaded area represents a region of incompatibility. All study solutions tested in the shaded area were incompatible. The open triangles represent the concentrations that were prepared, and the solid triangles represent the concentrations that were observed after mixing.

98.1% of the initial concentration, whereas the midazolam concentration declined to approximately 80% of the initial value (Table 2). However, although the concentration of midazolam remained greater than 90% after 48 h at 4°C, white, flaky particles appeared in 2 of 3 samples at both temperatures. A precipitate was found in all samples by 72 h. The precipitate was redissolved in methanol and was found to contain midazolam but no dexamethasone. No degradation products were observed in the chromatograms, a further indication that the drugs did not degrade throughout the study.

DISCUSSION

There are no known studies to date that have examined the compatibility of dexamethasone and midazolam. It was shown in a previous study that dexamethasone is compatible with diphenhydramine and hydromorphone but only within specific concentration ranges.[4]

Studies of midazolam have shown that it retains over 90% of the initial concentration in normal saline or D5W solutions for up to 30 days at 4°C or 23°C,[7] in parental nutrition solutions for 5 h,[14] in flavoured gelatin for 28 days,[15] in polypropylene syringes for 13 days,[16] and in an oral formulation for 102 days.[17] Compatibility and stability of midazolam with morphine for 14 days[18] and with hydromorphone[6] have been reported.

Dexamethasone and midazolam showed a concentration-dependent compatibility profile. The concentrations in the compatible range were very low (0.25 mg/mL for each compound) and may not be applicable to the clinical setting, where higher concentrations are commonly required for adequate therapeutic response. These solutions also developed a precipitate after 48 h of storage. It should be noted that the precipitate was difficult to detect visually, and solutions must be examined carefully before use. Mixture of the commercially available formulations of dexamethasone and midazolam in a syringe will generally always result in precipitation, and therapeutically useful mixtures cannot be obtained.

Commercial formulations of dexamethasone and midazolam were physically incompatible and cannot be used to prepare clinically useful solutions for delivery in a syringe. A compatible mixture containing 0.25 mg/mL of dexamethasone and 0.25 mg/mL of midazolam diluted in D5W can be prepared. This concentration is approximately equivalent to 12.5 mg of dexamethasone and 12.5 mg of midazolam added to a 50-mL minibag of IV solution. However, this solution is compatible for only 24 h at 4°C or 23°C, and a precipitate was observed in some solutions at 48 h. The physical incompatibility of dexamethasone and midazolam is due to the precipitation of midazolam. During the first 24 h of storage, both drugs remained clear and free of precipitate and retained 90% of their initial concentration, 0.25 mg/mL.

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