Stability and Compatibility of Combinations of Hydromorphone and Dimenhydrinate, Lorazepam or Prochlorperazine

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ABSTRACT

The stability and compatibility of combinations of hydromorphone (2, 10 and 40 mg/mL) admixed separately with dimenhydrinate (50 mg/mL), prochlorperazine (5 mg/mL), or lorazepam (4 mg/mL) were tested over a seven-day period at 4°C, 23°C and 37°C. In addition to visual inspection and pH, the concentration of each component in the binary mixture was determined by a stability-indicating liquid chromatographic method. Each test was completed at time zero, one, four, six and seven days after mixing equal volumes of each medication.

The hydromorphone-dimenhydrinate combination was compatible and stable for 24 hours. By 48 hours, 8-chlorotheophylline had precipitated and the degree of precipitate was enhanced by increasing hydromorphone concentration. Lorazepam was physically compatible with hydromorphone. However, lorazepam degraded such that 90% of the initial concentration was maintained for six days at 4°C, four days at 23°C and only 24 hours at 37°C. Prochlorperazine and hydromorphone were physically compatible for seven days, even though prochlorperazine stability was affected by the presence of hydromorphone. However, less than 10% of the prochlorperazine degraded over seven days, even at 37°C.

We recommend a seven-day expiration date for the combination of hydromorphone and prochlorperazine based on the observed physical and chemical stability of the combination at temperatures up to 37°C. However, we cannot recommend admixing hydromorphone and dimenhydrinate due to the precipitation of 8-chlorotheophylline. Admixtures of hydromorphone and lorazepam were physically compatible but the mixture was limited by the stability of lorazepam and so it is recommended that the expiry date not exceed 96 hours (four days) at 4°C. This will allow the solution to be stored at room temperature for up to an additional 24 hours prior to administration.

Key Words: *compatibility, dimenhydrinate, diphenhydramine, 8-chlorotheophylline, hydromorphone, lorazepam, prochlorperazine, stability*

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RÉSUMÉ

On a mélangé diverses solutions d'hydromorphone (2,10 et 40 mg/mL) avec, séparément, un volume égal d'une solution soit de dimenhydrate (50 mg/mL), de prochlorpérazine (5 mg/mL) ou de lorazépam (4 mg/mL), pour vérifier la compatibilité de ces trois médicaments avec l'hydromorphone et déterminer la stabilité du mélange binaire pendant sept jours à 4°C, à 23°C et à 37°C. En plus d'effectuer un examen visuel et de déterminer le pH, on a dosé les composants des mélanges par une méthode de chromatographie en phase liquide indiquant la stabilité. On a analysé les mélanges au moment de leur préparation, puis après un, quatre, six et sept jours.

L'hydromorphone et le dimenhydrate sont compatibles et leur mélange reste stable 24 heures. Cependant, après 48 heures, la 8-chlorothéophylline précipite; la précipitation s'accroît avec la concentration d'hydromorphone. Le lorazépam et l'hydromorphone sont physiquement compatibles. Néanmoins, le lorazépam se dégrade, de sorte que le mélange ne contient plus que 90% de la concentration initiale de ce médicament après six jours à 4°C, quatre jours à 23°C et seulement 24 heures, à 37°C. La prochlorpérazine et l'hydromorphone sont physiquement compatibles pendant sept jours, mais l'hydromorphone altère la stabilité de la prochlorpérazine. La décomposition de cette dernière est toutefois inférieure à 10% après sept jours, même à 37°C.

On recommande de fixer à sept jours la durée de stockage du mélange d'hydromorphone et de prochlorpérazine, étant donné sa stabilité physique et chimique jusqu'à 37°C. Par contre, mélanger des solutions d'hydromorphone et de dimenhydrinate n'est pas indiqué, en raison de la précipitation de la 8-chlorothéophylline. Les solutions d'hydromorphone et de lorazépam sont physiquement compatibles, mais la stabilité du lorazépam dans le mélange étant limitée, on déconseille de le stocker plus de 96 heures (quatre jours) à 4°C. Ceci permettra de stocker la solution à température ambiante jusqu'à 24 heures additionnelles avant l'administration.

Mots clés: *compatibilité, dimenhydrinate, diphenhydramine, 8-chlorothéophylline, hydromorphone, lorazépam, prochlorpérazine, stabilité*

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INTRODUCTION

Pharmacists are often asked questions regarding the compatibility of medications. Our interest in the compatibility of hydromorphone with other medications stems from recent advances in the management of chronic pain through the development of reliable portable infusion devices.[1] The use of these devices to deliver continuous intravenous or subcutaneous infusions of narcotics to control chronic pain in cancer patients has become an acceptable method of treatment.[2] In addition to improving the control of chronic pain, the use of portable infusion pumps allows patients to be managed at home[2] with significant cost savings to the health care system. The ease of managing a subcutaneous site has promoted the use of this route for antibiotics, antineoplastic agents, antiemetics and hormonal agents. The success of the subcutaneous route with some of these agents has produced a desire for simultaneous administration of agents and it is, therefore, not surprising that suggestions to simplify therapy include mixing medications in the same infusion container. Thus, questions concerning the compatibility between hydromorphone and other medications within an infusion container or at the site of injection frequently arise.

We have often discouraged the practice of mixing medications in the same infusion container for technical reasons (infusion solution formulation difficulties) or pharmacologic reasons (dose adjustment of one medication results in dosage changes for both medications or wastage of the remaining medication). Nevertheless, situations often arise when knowledge of medication compatibility and stability is important.

Hydromorphone stability is well documented[3] and there have been several reports documenting its compatibility with other medications.[4-11] However, the compatibility and stability of hydromorphone combined with prochlorperazine, lorazepam, or dimenhydrinate has not been addressed.

Therefore, it was the intent of this study to test the compatibility and stability of the combination of hydromorphone with prochlorperazine, lorazepam or dimenhydrinate over a seven-day period. For each combination the concentration of both medications was evaluated by a validated stability-indicating liquid chromatographic method.

METHODS

Assay Validation

The validated stability-indicating liquid chromatographic method previously reported for hydromorphone in combination with other medications[10] was modified for each mixture to ensure the separation of hydromorphone and its degradation products from either prochlorperazine, lorazepam or dimenhydrinate and their degradation products according to accepted stability-indicating procedures.[12-14] Briefly, this involved intentional degradation of each compound using acid or base and heat and inspection of chromatograms for the appearance of additional peaks, changes in retention time, peak shape and UV-VIS spectral purity of each eluted peak using a photodiode array detector (Waters, 990+). Complete UV-VIS spectra (200-800 nm, slit width 0.25 nm, resolution 1.4 nm, deuterium lamp) from the leading edge, middle and tail of each peak of interest in a chromatogram of a degraded sample were compared to UV-VIS spectra observed for the time zero sample. The reverse phase liquid chromatographic system used an acetonitrile/phosphate buffer mobile phase containing 1 mg/mL of heptane sulphonic acid, pumped at 2.0 mL/min through a 25 cm x 4.2 mm C_{18}, 5 μm column (Beckman, Ultrasphere). Hydromorphone, prochlorperazine, lorazepam, diphenhydramine and 8-chlorotheophylline were detected using ultraviolet light at 230 nm (Schoeffel SF770) and chromatograms were recorded on a chromatographic integrator (Spectra Physics, SP4200). Table I lists the specific conditions of the chromatographic system and methods for intentional degradation.

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over a five-day period and system suitability criteria (theoretical plates, tailing and retention time) were also established for each compound of interest to ensure consistency between study days. Each sample was chromatographed in duplicate. Inter- and intra-day reproducibility were assessed using the coefficient of variation of the peak area for samples determined in duplicate.

Compatibility Study

For each study hydromorphone 2mg/mL injection (Dilaudid, Knoll Pharmaceuticals, lot #00500109), or 10 mg/mL and 40 mg/mL solutions prepared from hydromorphone powder (Dilaudid, Knoll Pharmaceuticals: lot #L51050269) were used. Each solution also contained 2 mg/mL each of citric acid and sodium citrate. In a glass tube a 1 mL sample of a hydromorphone solution was mixed with 1 mL of each of the following drugs: dimenhydrinate 50 mg/mL (Dimenhydrinate Injection, USP, Squibb, lot #ON1311); lorazepam 4 mg/mL (Ativan, Wyeth, lot #T807XA); or prochlorperazine 5 mg/mL (Stemetil, Rhone Poulenc, lot #AM80). After mixing each solution was observed for a precipitate, colour change or evolution of gas. Solutions were stored

Table I: Assay Validation Data

Compound	Accelerated Degradation Study Conditions[1]					Compatibility/Stability Study					
						Chromotographic Conditions		Relative Error (CV%)			
								Hydro-morphone		Second Drug	
	Initial Conc. mg/mL	Solvent	Initial pH	Study Duration	Percent Remaining (%)	Acetonitrile Initial Percentage	Acetronitrile Final Percentage	Inter-Day	Intra-Day	Inter-Day	Intra Day
Dimenhydrinate	10	water	1.4 2.6 6.6	83 min 368 min 45 hr	3.7 73.1 >95	13% (G-14)[2]	40%	0.87	0.65	1.97	0.40
Lorazepam	4	MOS[3]	5.3	1164 min	42	19% (G-15)	50%	2.22	1.40	2.71	1.53
Prochlorperazine	5	water	4.9	194 hr	95	16% (G-14)	46%	2.03	1.88	4.22	0.76
Hydromorphone	10	water	8.2	68 hr	70						

1. All accelerated studies were completed in a water bath at 90°C.
2. In parenthesis 'G' indicates that a gradient was used to elute each drug of interest and the number indicates the total chromatographic run time in minutes.
3. MOS indicates Manufacturer's Original Solution.

at 37°C, 23°C and 4°C and a physical inspection, pH and concentration were determined on days one, four, six and seven.

The pH was measured and recorded to the nearest 0.05 of a pH unit. The pH meter (Fisher Accumet model 925) was fitted with a microprobe glass body electrode (Fisher cat #13-639-280) and was standardized each day with two commercially available buffer solutions (ph 7: Fisher cat #S108-500 and pH 4: fisher cat #S0-B-98).

The concentration of each compound of interest was determined on each study day by liquid chromatography. The dimenhydrinate concentration was not determined, rather the concentration of 8-chlorotheophylline and diphenhydramine were determined and reported separately. On each study day, fresh standards of hydromorphone (Knoll Pharmaceuticals, lot #L51050269), diphenhydramine (Sigma, lot #48F0546), 8-chlorotheophylline (Sigma, lot #116C-005), lorazepam (Altech Applied Science, lot #NDC-0079) and prochlorperazine edisylate (Sigma, lot #18F0266, 66.29% w/w of prochlorperazine base) were prepared and chromatographed to construct a standard curve. The peak areas were subjected to least squares linear regression and the actual concentration, from the average of four replicates from each sample, was interpolated from these curves and recorded. Concentrations were recorded to the nearest 0.01 mg/mL.

Data Reduction and Statistical Analysis

Means (+/- standard deviation) were calculated for replicated analyses. Reproducibility was assessed by coefficient of variation (CV). Mean results from different days of an identical test were compared statistically by least squares linear regression to determine if an association existed between the observed result and time. Log-linear and linear-linear fits for the data from the accelerated degradation study (90°C) were compared for goodness of fit by the Maximum Likelihood Method of Box and Cox.[15,16] Analysis of variance and the least significant difference multiple range test or Student's t test (where appropriate) were used to compare differences between temperature, and/or solutions for similar analytical tests. The 5% level was used as the *a priori* cut-off for significance.

Hydromorphone, prochlorperazine, lorazepam, diphenhydramine and 8-chlorotheophylline concentrations were considered "acceptable" or "within acceptable limits" if the concentration on any day of analysis was not less than 90% of the initial (day-zero) concentration. A solution was judged to be physically compatible if there was no visual change in the colour or clarity of the mixture and no precipitate or other particulate formation was visually apparent.

RESULTS

Assay Validations

The validation of each assay confirmed that hydromorphone, prochlorperazine, lorazepam, diphenhydramine and 8-chlorotheophylline could be quantified without interference from their own degradation products, the degradation products of the other compound, or the other compound itself. The coefficients of variation for replicate samples determined on the same day (intra-day) and on five consecutive days (inter-day) are listed in Table I. In general these values are less than 5%;

therefore, with duplicate determinations these methods have the power to detect 10% differences or changes in concentration.[17,18]

Compatibility/Stability Study

Hydromorphone: When stored at 4°C, 23°C or 37°C, the hydromorphone concentration in all samples of each combination remained at or greater than 90% of the initial concentration for seven days. No hydromorphone degradation products were observed during the study period.

Dimenhydrinate: Dimenhydrinate is the 8-chlorotheophylline salt of diphenhydramine. Quantification of 8-chlorotheophylline and diphenhydramine separately in a solution containing 25 mg/mL of dimenhydrinate yields an initial theoretical diphenhydramine concentration of 13.6 mg/mL. The combination of dimenhydrinate and hydromorphone was physically compatible and chemically stable for a period of 24 hours at 4°C, 23°C and 37°C. However, on standing for longer than 24 hours, 8-chlorotheophylline begins to precipitate. The amount of precipitate is enhanced by increasing concentrations of hydromorphone. Degradation products of hydromorphone, diphenhydramine and 8-chlorotheophylline were not observed, and the concentrations for both remained within 10% of the initial concentration (Table II). There was no change in pH.

Prochlorperazine: Prochlorperazine concentrations were measured using a prochlorperazine edisylate standard. Prochlorperazine edisylate concentrations were converted to concentrations of prochlorperazine base using known molecular weights (prochlorperazine MW: 373.94; prochlorperazine edisylate MW: 564.10; edisylate salt is 66.29% prochlorperazine base). Prochlorperazine and hydromorphone were physically compatible for a seven day period. Both hydromorphone and prochlorperazine were extremely stable and retain more than 90% of the initial concentration for the entire seven-day study period (Table II). However, an additional peak was observed on chromatography. This peak represented a prochlorperazine degradation product. Prochlorperazine degradation was enhanced by the presence of hydromorphone. However, even at 37°C only about 5% of the prochlorperazine was lost during the seven-day study period and there was no change in pH at any temperature.

Lorazepam: Lorazepam and hydromorphone were physically compatible, such that neither component precipitated nor was there any change in colour over a seven-day period. During this period hydromorphone also retained more than 90% of its initial concentration. However, lorazepam degraded and this degradation is temperature dependent such that at 4°C more than 90% of the initial lorazepam concentration is retained for six days (Table II), while at 23°C 10% is lost after four days and at 37°C 90% of the initial concentration remains for only up to 24 hours. There was no change in pH during the study period.

DISCUSSION

A number of reports have been published concerning hydromorphone compatibility with various drugs.[4-11] Physical incompatibilities have been observed only with dexamethasone,[10] phenytoin,[11] phenobarbital,[11] diazepam,[11] cloxacillin in D5W,[11] and high concentrations of cefazolin.[9,11] In a recent study, hydromorphone was observed to inactivate hyaluronidase

Table II: Concentration of Second Drug at 4°C

Second Drug[1]	Concentration of Second Drug (mg/mL)					Comments
	Time (days)					
	0	1	4	6	7	
Dimenhydrinate						8-chlorotheophylline precipitates such that between 66% and 75% remains on day seven at 4°C, 23°C, and 37°C.
DMH 25/HYD 1	15.02	15.12	14.82	NSA[2]	14.82	
DMH 25/HYD 5	14.67	14.82	14.54	NSA	14.37	
DMN 25/HYD 20	14.73	14.68	15.49	NSA	14.56	
Prochlorperazine						Prochlorperazine and hydromorphone are physically and chemically compatible over a seven-day period at 4°C, 23°C and 37°C.
PCP 2.5/HYD 1	2.51	2.20	2.29	2.49	2.49	
PCP 2.5/HYD 5	2.53	2.43	2.53	2.74	2.75	
PCP 2.5/HYD 20	2.47	2.45	2.57	2.68	2.65	
Lorazepam						Lorazepam degrades and degradation increases with increasing temperature. After seven days only 83% remains at 23°C and 63% remains at 37°C.
LOR 2/HYD 1	2.10	2.12	2.00	2.00	1.94	
LOR 2/HYD 5	2.13	2.09	1.97	2.06	1.90	
LOR 2/HYD 20	2.13	2.05	1.94	2.09	1.88	

1. Theoretical concentrations of the second drug are given after their abbreviations; DMH indicates dimenhydrinate, PCP indicates prochlorperazine and LOR indicates lorazepam. Dimenhydrinate is the 8-chlorotheophylline salt of diphenhydramine. Diphenhydramine concentrations are reported. Since diphenhydramine represents only 54.33% of the mass in dimenhydrinate, the theoretical initial concentration of diphenhydramine is 13.58 mg/mL. Theoretical Hydromorphone (abbreviated HYD) concentrations are also shown.
2. NSA indicates that no sample was analyzed.

and, while the combination was judged to be physically compatible, hyaluronidase and hydromorphone were judged to be chemically unstable.[19]

In this study, only prochlorperazine was found to be physically compatible and chemically stable with hydromorphone over the seven day study period. However, Cutie[6] has previously reported that prochlorperazine edisylate 5 mg/mL (Compazine, SKF) and hydromorphone 2 mg/mL (Dilaudid, Knoll) were incompatible when mixed in equal volumes. Since we did not observe a precipitate, we can only assume that the incompatibility observed by Cutie[6] was due to a formulation difference between the SKF and Rhone-Poulenc brands. The most obvious difference between the products is the salt, edisylate vs mesylate, but precipitation may also have been due to differences in the buffers or solvent systems.

Lorazepam was also observed to be physically compatible. However, using a stability-indicating assay in addition to standard visual inspection techniques, lorazepam was observed to degrade rapidly, and there was a tendency for lorazepam degradation to be enhanced by increasing hydromorphone concentration. As a result, solutions of lorazepam and hydromorphone lose approximately 10% of their initial concentration within six days when stored at 4°C. Therefore, solutions should not be stored for more than four days at 4°C. Storage for this length of time allows the solution to be held for an additional 24 hours at room temperature or an additional 12 hours at 37°C.

Only dimenhydrinate was observed to be physically incompatible. However, since it is the 8-chlorotheophylline salt of diphenhydramine that precipitated and no degradation products of diphenhydramine or hydromorphone were observed over the seven-day study period, the data suggest that the combination of diphenhydramine and hydromorphone are physically compatible and chemically stable at 4°C, 23°C and 37°C for seven days. This prediction may appear to be supported by the physical observations of Cutie[6] who reported the combination of hydromorphone and diphenhydramine to be compatible over a 30 minute period. However, Cutie's[6] 30-minute study period is considerably shorter than the study period used in this study and even dimenhydrinate and hydromorphone were physically compatible for as long as 24 hours.

In summary, we recommend a seven-day expiration date for the combination of hydromorphone and prochlorperazine based on the observed physical and chemical stability of the combination at temperatures up to 37°C. However, we cannot recommend admixing hydromorphone and dimenhydrinate due to the precipitation of 8-chlorotheophylline after 24 hours storage at 4°C, 23°C or 37°C. Admixtures of hydromorphone and lorazepam are physically compatible but the mixture is limited by the stability of lorazepam and so it is recommended that an expiry date not exceeding 96 hours at 4°C be used. This will allow the solution to be brought to room temperature and stored at 23°C for up to 24 hours prior to drug administration.

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