Stability and Compatibility of Reconstituted Hydromorphone with Potassium Chloride or Heparin

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ABSTRACT

The stability and compatibility of combinations of hydromorphone (Dilaudid® Sterile Powder) admixed separately with potassium chloride or heparin was tested for 18 days at 4°C and 23°C. In addition to visual inspection and pH, the concentration of hydromorphone in the mixtures was determined by a stability-indicating liquid chromatographic method. The concentration of potassium and the activity of heparin were not measured in this study.

Hydromorphone and potassium chloride were observed to be physically compatible for all concentration combinations tested. The stability of four physically compatible combinations of hydromorphone (2 and 20 mg/mL) admixed with potassium chloride (0.5 and 1 mEq/mL) was tested. These solutions retained more than 90% of the initial hydromorphone concentration over the 18-day period and no change in pH was observed.

Heparin and hydromorphone were observed to be physically incompatible over a wide concentration range. Mixtures prepared with Hep-Rinse® (100 units/mL) or Hepalean-Lok® (10 units/mL) precipitated with hydromorphone concentrations greater than 10 mg/mL unless the final heparin concentration was less than 1 unit/mL. Physically compatible solutions can be prepared with all Hepalean® (25,000 units/mL) containing mixtures if the hydromorphone concentration is less than 12.5 mg/mL. The stability of three physically compatible combinations of hydromorphone and heparin (20 mg/mL with 1 U/mL; 5 mg/mL with 0.5 U/mL; and 5 mg/mL with 8 U/mL) was tested. The hydromorphone concentration in these solutions retained greater than 90% of the initial concentration for 18 days and the pH did not change.

In summary, although this study has determined that hydromorphone retains more than 90% of its initial concentration in compatible solutions, since neither potassium chloride nor heparin concentrations were measured, their stability cannot be assured. Therefore, we recommend that compatible heparin and hydromorphone solutions should be used with caution, being aware of the possibility of reduced heparin activity. However, we recommend an 18-day expiration date for all concentration combinations of hydromorphone and potassium chloride, since we believe that potassium chloride stability and availability will not be affected by hydromorphone. However, expiry dates at each institution must take into account the contamination rate for their IV additive program.

Key Words: *Hydromorphone, heparin, potassium chloride, stability, physical compatibility*

RÉSUMÉ

La stabilité et la compatibilité de l'hydromorphone (poudre stérile Dilaudid®) mélangée séparément au chlorure de potassium ou à l'héparine ont été testés sur une période de 18 jours, à des températures de 4 et 23°C. Outre l'inspection visuelle et la détermination du pH, on a mesuré la concentration d'hydromorphone dans chacune des solutions au moyen d'une épreuve de stabilité par chromatographie liquide. Les concentrations en chlorure de potassium et l'activité de l'héparine n'ont toutefois pas été évaluées au cours de cette étude.

Les résultats montrent que l'hydromorphone et le chlorure de potassium sont physiquement compatibles, et ce à toutes les concentrations testées. On a vérifié la stabilité de quartre concentrations des solutions d'hydromorphone (2 et 20 mg/mL) et de chlorure de potassium (0,5 et 1 mEq/mL) physiquement compatibles. Ces solutions ont conservé plus de 90% de leur concentration initiale d'hydromorphone après 18 jours et leur pH n'a pas changé.

L'hydromorphone et l'héparine se sont toutefois révélées physiquement incompatibles, et ce à diverses concentrations. Les solutions préparées avec Hep-Rinse® (100 unités/mL) ou Hépaléan-Lok® (10 unités/mL) ont formé un précipité lorsque la concentration d'hydromorphone était supérieure à 10 mg/mL, sauf si la concentration finale d'héparine était inférieure à 1 unité/mL. Des solutions physiquement compatibles peuvent cependant être préparées avec tous les mélanges contenant Hépaléan® (25 000 unités/mL), si la concentration d'hydromorphone est inférieure à 12,5 mg/mL. On a testé la stabilité de trois solutions physiquement compatibles d'hydromorphone et d'héparine (20 mg/mL et 1 U/mL; 5mg/mL et 0,5 U/mL; 5 mg/mL et 8 U/mL). Ces solutions ont conservé plus de 90% de leur concentration initiale d'hydromorphone après 18 jour et leur pH n'a pas changé.

En résumé, bien que cette étude ait déterminé que les solutions compatibles contenant de l'hydromorphone conservent plus de 90% de leurs concentrations initiales d'hydromorphone, on ne peut toutefois être certain de leurs stabilité car ni les

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concentrations de chlorure de potassium ni celles d'héparine n'ont été mesurées. Par conséquent, nous recommandons d'utiliser avec circonspection les solutions compatibles d'héparine et d'hydromorphone, en sachant que l'activité de l'héparine peut être réduite. Par ailleurs, nous recommandons une durée de conservation maximale de 18 jours pour les solutions d'hydromorphone et de chlorure de potassium, à toutes les concentrations, étant donné que nous croyons que ni la stabilité ni la concentration du chlorure de potassium ne seront altérées par l'hydromorphone. Toutefois, chaque établissement devra tenir compte du taux de contamination relatif aux additifs aux solutés dans la détermination des durées de conservation.

Mots clés: *hydromorphone, héparine, chlorure de potassium, stabilité, compatibilité physique*

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INTRODUCTION

Continuous intravenous or subcutaneous infusions of narcotics to control chronic pain in cancer patients has become an acceptable method of treatment,[1] improving pain control while allowing patients to be managed at home[1] at significantly reduced cost. The success of the subcutaneous route has produced a desire for simultaneous administration of other medications with these narcotics. Therefore, questions concerning the compatibility between hydromorphone and other medications within an infusion container or at the site of injection frequently arise.

Hydromorphone stability is well documented [2] and there have been several reports documenting its compatibility with other medications.[3-12] However, the compatibility and stability of hydromorphone combined with potassium chloride or heparin has not been addressed. Therefore, it was the intent of this study to test the compatibility and stability of the combination of hydromorphone with potassium chloride or heparin over an 18-day period. For each combination the concentration of hydromorphone was evaluated by a validated stability-indicating liquid chromatographic method.[9-12] The concentration of potassium chloride and the activity of heparin in these solutions were not determined.

METHODS

Compatibility Studies

Physical compatibility tests were completed first. Sterile hydromorphone powder (Dilaudid® Sterile Powder, 250 mg of hydromorphone per vial; Knoll Pharma Inc., Lot # : 01080012C) was reconstituted with 5 mL of sterile water to prepare a 50 mg/mL solution. One millilitre of this solution was mixed with 1 mL each of either potassium chloride (Potassium Chloride Injection USP, 2 mEq/mL; Astra, Lot # 4B0019); or three different strengths of heparin (Hepalean-Lok® Flush Injection USP, 10 units/mL; Organon Teknika, Lot # 1VMM; Hep-Rinse® Sodium Injection BP, 100 units/mL; Leo Laboratories, lot L31A; and Hepalean® Sodium Injection USP, 25,000 units/mL; Organon Teknika, Lot # 1VFG). After mixing, a visual compatibility test was completed over a 24-hour period. Each solution was observed for the presence of a precipitate, colour change, or evolution of gas. 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 within 24 hours. Since a precipitate was observed with hydromorphone and heparin, concentrations of hydromorphone ranging from 0 to 50 mg/mL and heparin from 0 to 25,000 units/mL (using all three formulations), solutions were prepared to determine the range of incompatible concentrations. A minimum of 20 mixtures were prepared with each strength of heparin to evaluate the relationship. In these studies, sterile water and normal saline were used as diluents.

Stability Studies

Once the range of compatible concentrations had been determined for both hydromorphone-heparin and hydromorphone-KCl, solutions within the compatible range of concentrations were prepared and stored at 4°C and 23°C in PVC minibags containing 20 mL of D5W. These solutions had initial concentrations following mixing of hydromorphone (Dilaudid® Sterile Powder, 250 mg/vial; Knoll Pharma Inc., lot # 01080023E) and potassium chloride (Potassium Chloride Injection USP, 2 mEq/mL; Astra, lot # 4B0019), of 20 mg/mLwith 0.5 mEq/mL; 20 mg/mL with 1 mEq/mL; 2 mg/mL with 0.5 mEq/mL; and 2 mg/mL with 1 mEq/mL; respectively. Similarly, mixtures of hydromorphone (Dilaudid®Sterile Powder, 250 mg/vial; Knoll Pharma Inc., lot # 01080023E) and heparin (Hepalean-Lok® Flush Injection USP, 10 units/mL; Organon Teknika, lot # 1AHB) had initial concentrations following mixing of: 20 mg/mL with 1 U/mL; 5 mg/mL with 0.5 U/mL and 5 mg/mL with 8 U/mL, respectively.

For both the hydromorphone-KCl study and the hydromorphone-heparin combination, study days were day zero, 1, 2, 4, 10, 14, 16, and 18. Physical inspection, pH, and hydromorphone concentration were determined on each of these study days. The validated stability-indicating reverse phase liquid chromatographic method previously reported for hydromorphone in combination with other medications[9-12] was re-validated over a five-day period to ensure assay performance and the separa-

tion of hydromorphone and its degradation products according to stability-indicating procedures.[13,14] Heparin and potassium chloride cannot be detected using this reverse phase chromatographic system with UV detection and so neither interferes with hydromorphone detection. On each study day, six fresh standards of hydromorphone (hydromorphone hydrochloride powder; Knoll Pharma Inc., lot # 50150014), ranging in concentration from 1.1 to 35 mg/mL and a blank, were chromatographed to construct a standard curve. Two additional samples of 15 and 25 mg/mL were prepared each day and used as quality control samples. Each sample, quality control sample and standard was chromatographed in duplicate. The hydromorphone concentration, from the average of three replicates from each solution, was interpolated from the standard curve to the nearest 0.01 mg/mL.

Means (± standard deviation) were calculated for replicated analyses. Reproducibility was assessed by coefficient of variation (CV). Mean concentration results from different days were compared statistically by multiple linear regression (SPSS for windows, release 5.0.1, 1992) to determine if an association existed between the observed concentration and time or storage temperature. The five percent level was used as the *a priori* cut-off for significance. Hydromorphone was considered stable if there was no significant trend for the concentration to decline or any trend to decrease resulted in less than 10% loss of the initial (day-zero) concentration.

RESULTS

Assay Validation

The validated stability-indicating liquid chromatographic method previously reported [9-12] was used without modification after being re-validated using accepted stability indicating procedures.[13,14] Recovery of hydromorphone from quality control samples (15 and 25 mg/mL) determined in duplicate between days, averaged 101.05% (range: 91.33% to 108.13%). The inter-day error of quality control samples, as measured by the coefficient of variation, was 5.46% for the 15 mg/mL sample and 6.42% for the 25 mg/mL sample. Within day recovery for standards averaged 100.77% (range: 95.43% to 105.84%) over a over a five-day period. Within day error, based on duplicate determinations over the study period averaged 1.85% (range: 0.03% to 6.38%) for quality control samples and 1.76% (range: 0.01% to 6.89%) for standards. These analyses indicated that the hydromorphone concentrations were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[15,16]

Compatibility/Stability Studies

Hydromorphone and Potassium Chloride

At room temperature, all solutions of hydromorphone-KCl were observed to be physically compatible over a 24-hour period. Based on these results, three bags each of four different solutions were prepared and stored at both 4°C and 23°C for 18 days. Tests of visual inspection, pH and hydromorphone concentration were completed on each study day. Concentrations of hydromorphone observed during this portion of the study for solutions stored at 4°C and 23°C are found in Table I. All solutions retained more than 90% of the initial hydromorphone concentration over the 18-day study period and there was no significant time dependant change in concentration (p=0.78) or effect of storage temperature (p=0.95). The pH of these solutions remained stable over the study period.

Table I: Mean* Concentration of Hydromorphone (mg/mL) in Solutions Containing Potassium Chloride.

Study Day	Storage at 4°C				Storage at 23°C			
	H20: KCl 0.5[a]	H2: KCl 0.5[b]	H20: KCl 1.0[c]	H2: KCl 1.0[d]	H20: KCl 0.5[a]	H2: KCl 0.5[b]	H20: KCl 1.0[c]	H2: KCl 1.0[d]
0	20.76 ± 0.03	2.18 ± 0.02	21.52 ± 0.15	2.27 ± 0.03	20.46 ± 0.08	2.29 ± 0.14	21.23 ± 0.10	2.44 ± 0.09
1	20.06 ± 1.10	2.35 ± 0.01	20.98 ± 0.20	2.43 ± 0.03	20.79 ± 0.22	2.30 ± 0.22	21.22 ± 0.33	2.49 ± 0.10
2	20.44 ± 0.91	2.32 ± 0.03	21.27 ± 0.26	2.45 ± 0.11	20.79 ± 0.55	2.27 ± 0.18	20.53 ± 1.39	2.52 ± 0.11
4	20.58 ± 0.20	2.15 ± 0.04	20.48 ± 1.60	2.37 ± 0.05	20.61 ± 0.55	2.18 ± 0.03	19.31 ± 2.00	2.58 ± 0.19
10	20.33 ± 0.44	2.32 ± 0.02	21.14 ± 0.53	2.48 ± 0.01	20.52 ± 0.83	2.48 ± 0.13	21.30 ± 0.22	2.65 ± 0.10
14	20.33 ± 1.68	2.23 ± 0.06	21.18 ± 0.88	2.47 ± 0.12	21.13 ± 0.23	2.34 ± 0.08	21.80 ± 0.44	2.63 ± 0.05
16	21.37 ± 0.39	2.04 ± 0.09	21.82 ± 1.63	2.36 ± 0.04	21.90 ± 0.11	2.22 ± 0.09	22.68 ± 0.11	2.50 ± 0.06
18	21.09 ± 0.24	2.07 ± 0.03	21.89 ± 0.20	2.24 ± 0.02	21.53 ± 0.06	2.09 ± 0.11	21.84 ± 0.71	2.32 ± 0.05

* Each value represents the average of three samples, each chromatographed in duplicate ± standard deviation
a Symbols represent hydromorphone (20 mg/mL) and potassium chloride (0.5 mEq/mL).
b Symbols represent hydromorphone (2 mg/mL) and potassium chloride (0.5 mEq/mL).
c Symbols represent hydromorphone (20 mg/mL) and potassium chloride (1.0 mEq/mL).
d Symbols represent hydromorphone (2 mg/mL) and potassium chloride (1.0 mEq/mL).

Hydromorphone and Heparin

At room temperature, solutions of hydromorphone and heparin were observed to be physically incompatible over a wide concentration range that was dependant on the concentrations of both hydromorphone and heparin, as well as the proportion and nature of the solvent used for dilution. When mixing a concentration of heparin of 25,000 U/mL (Hepalean® Sodium Injection USP, Organon Teknika) and hydromorphone (50 mg/mL), a white cloudy precipitate was produced immediately in all mixtures in which the final concentration of hydromorphone exceeded 25 mg/mL and the concentration of heparin was 12,500 units/mL or less (Figure 1; Panel III). When less concentrated formulations of heparin (10 units/mL and 100 units/mL) were prepared, incompatibilities were also observed (Figure 1; Panels I and II). This precipitate would not settle even on centrifugation for more than 30 minutes. Dilution of heparin and hydromorphone with either saline or sterile water produced similar ranges for compatible and incompatibles mixtures. The greatest difference occured with heparin concentrations in the range from 10 to 100 units/mL. In this range, mixtures prepared with sterile water were more likely to be incompatible than those prepared with saline. However, at lower (<10 units/mL) and higher (>100 units/mL) heparin concentrations the differences in compatibility were trivial to clinical practice.

Based on the results observed for mixtures prepared with heparin 10 units/mL, three bags each of three solutions, that were observed to be physically compatible over a 24-hour period, were prepared and the bags were stored at 4°C and 23°C for 18 days. Tests of visual inspection, pH and hydromorphone concentration were completed on each of the three bags on each study day. Concentrations of hydromorphone observed during this portion of the study for solutions stored at 4°C and 23°C are found in Table II. Solutions stored at both 4°C and 23°C retained more than 90% of the initial concentration throughout the 18-day study period. There was no significant time dependant change in concentration ($p=0.62$) or effect of storage temperature ($p=0.93$). The variance in observed concentration between-days appears larger than the variance in concentration observed in the hydromorphone-KCl concentration results. The ratio of residual variability between the two studies (F ratio for variance) is 1.52, which is significantly different ($p<0.025$). There is no apparent explanation for this and random error is unlikely ($p<0.025$), although the replicate design of the study is capable of detecting small, clinically unimportant changes in concentration of 3%. The pH of all solutions remained stable throughout the duration of the study.

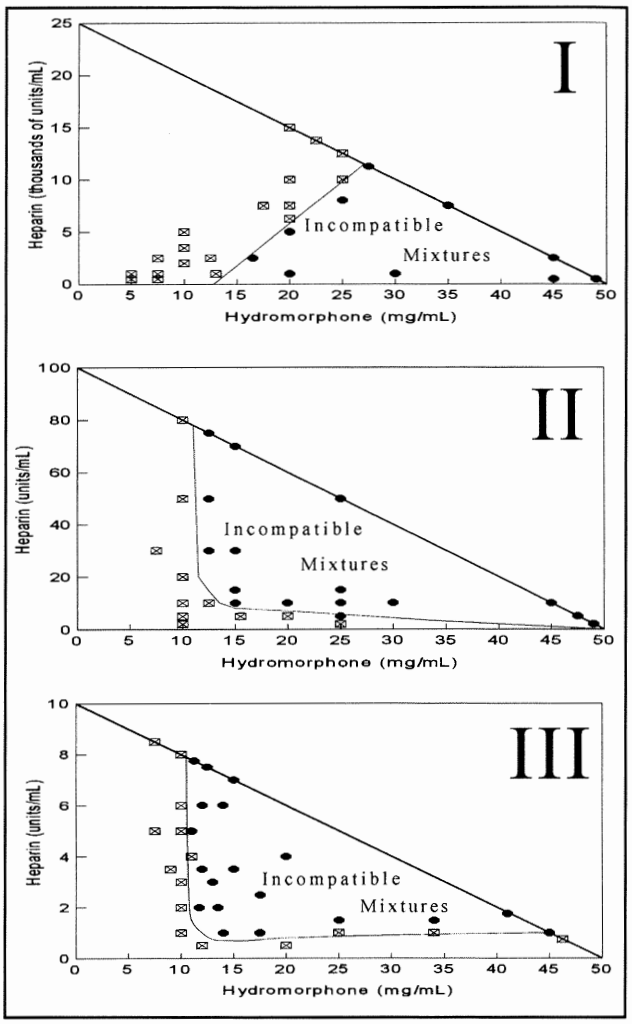

Figure 1. Compatibility Profile of Hydromorphone and Heparin; Panel I: Hepalean Sodium Injection -25,000 units/mL; Panel II: Hep-Rinse Sodium Injection -100 units/mL; Panel III: Hepalean-Lok Flush Injection -10 units/mL. The solid line separates compatible and incompatible mixtures where saline was used as a diluent. Mixtures prepared with final concentrations within the areas identified as "Incompatible Mixtures" will develop a precipitate upon mixing. In preparing these mixtures sterile hydromorphone powder was reconstituted with sterile water for injection.

DISCUSSION

A number of reports have been published concerning hydromorphone compatibility with various drugs.[3-12] Physical incompatibilities have been observed with dexamethasone,[9] phenytoin,[10] phenobar-

Table II: Mean* Concentration of Hydromorphone (mg/mL) in Solutions Containing Heparin.

Study Days	Storage at 4°C			Storage at 23°C		
	H20: Hep 1.0[a]	H5: Hep 0.5[b]	H5: Hep 8.0[c]	H20: Hep 1.0[a]	H5: Hep 0.5[b]	H5: Hep 8.0[c]
0	20.59 ± 0.32	5.24 ± 0.04	5.29 ± 0.08	20.46 ± 0.19	5.06 ± 0.03	5.34 ± 0.11
1	20.72 ± 0.50	5.12 ± 0.43	5.28 ± 0.39	20.69 ± 0.29	5.32 ± 0.20	5.59 ± 0.09
2	20.58 ± 0.23	5.30 ± 0.23	5.30 ± 0.36	20.18 ± 0.50	5.42 ± 0.11	5.47 ± 0.13
4	21.13 ± 0.28	5.67 ± 0.11	5.35 ± 0.19	19.24 ± 0.62	5.15 ± 0.33	5.41 ± 0.09
10	20.88 ± 0.28	5.48 ± 0.11	5.42 ± 0.08	21.14 ± 0.57	5.45 ± 0.01	5.68 ± 0.27
14	21.55 ± 0.39	5.45 ± 0.04	5.46 ± 0.05	21.63 ± 0.36	5.36 ± 0.04	5.50 ± 0.03
16	21.70 ± 0.70	5.39 ± 0.02	5.43 ± 0.23	22.05 ± 0.05	5.29 ± 0.26	5.30 ± 0.34
18	20.97 ± 0.46	5.19 ± 0.10	5.28 ± 0.17	21.34 ± 0.23	5.18 ± 0.06	5.23 ± 0.11

* Each value represents the average of three samples, each chromatographed in duplicate ± standard deviation
a Symbols represent hydromorphone (20 mg/mL) and heparin (1.0 unit/mL).
b Symbols represent hydromorphone (5 mg/mL) and heparin (0.5 unit/mL).
c Symbols represent hydromorphone (5 mg/mL) and heparin (8.0 unit/mL).

bital,[10] diazepam,[10] cloxacillin in D5W,[10] high concentrations of cefazolin,[8,10] and dimenhydrinate.[12] Hydromorphone has also been observed to inactivate hyaluronidase.[11] The combination of hydromorphone and lorazepam, although physically compatible, is limited by the stability of lorazepam.[12]

In this study only potassium chloride was found to be physically compatible and chemically stable with hydromorphone over the 18-day study period. Solutions stored at either 4°C or 23°C for 18 days will retain more than 90% of the original hydromorphone concentration.

Heparin was not physically compatible with hydromorphone over a wide range of concentrations. When heparin formulations of 100 U/mL or less were prepared, precipitation occurred in all mixtures where the final hydromorphone concentration was greater than 15 mg/mL, unless the final heparin concentration was less than 1 units/mL (Figure 1; Panel I and II). However, when using heparin formulations of 25,000 units/mL, a white cloudy precipitate was produced immediately in all mixtures in which the final concentration of hydromorphone exceeded 25 mg/mL and the concentration of heparin was 12,500 units/mL *or less* (Figure 1; Panel III). The range of compatible concentrations was similar for mixtures diluted in both saline or sterile water. Hydromorphone and heparin solutions that did not show signs of physical incompatibility after mixing retained more than 90% of the hydromorphone concentration over an 18-day period when stored at either 4°C and 23°C.

In summary, although this study has determined that hydromorphone retains more than 90% of its initial concentration in compatible solutions, since neither potassium or heparin concentrations were measured, their stability cannot be assured. While the instability of potassium is unlikely, the activity of heparin could be affected in compatible solutions, similar to the loss in activity seen with hyaluronidase[11] in physically compatible solutions. Therefore, we recommend that heparin concentrations greater than 1 units/mL not be mixed with hydromorphone, unless (i) compatibility is predicted from Figure 1 and then (ii) compatible solutions should be used with caution, being aware of the possibility of reduced heparin activity. Furthermore, we recommend an 18-day expiration date for all concentration combinations of hydromorphone and potassium chloride. Although we have not monitored potassium chloride concentrations in this study and a similar caution should technically be placed on hydromorphone and potassium chloride solutions, we believe that potassium chloride stability and availability will not be affected by hydromorphone. We also suggest that expiry dates on these solutions at each institution should be established after appropriate consideration of the contamination rate within the IV additive program. Industry standard for bacterial contamination of sterile solutions is less than 0.2%. Even when chemical stability and physical compatibility can be assured, the expiry date may and should be limited by concern for sterility.

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