

Compatibility and Stability of Hyaluronidase and Hydromorphone

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ABSTRACT

The stability and compatibility of the combination of three different hydromorphone concentrations (2 mg/mL, 10 mg/mL and 40 mg/mL) and hyaluronidase (150 U/mL) was evaluated over a seven day period. In addition to physical inspection and pH, solutions were assayed for hydromorphone content using a validated stability-indicating liquid chromatographic method and hyaluronidase activity using hyaluronic acid as the substrate. Each test was performed at time zero and after 1, 2, 4 and 7 days storage at 4°C, room temperature (23°C), and 37°C.

The solutions were all observed to be physically compatible over the seven day study period and there was no change in the hydromorphone concentration, all concentrations remaining within 10% of the initial concentration. However, hyaluronidase activity was substantially reduced by hydromorphone during storage. The reduction in activity was dependant on the hydromorphone concentration (as the hydromorphone concentration increased there were greater reductions in hyaluronidase activity) and storage temperature (at higher temperatures hyaluronidase activity was lost at a faster rate).

We conclude that although the combination is physically compatible, the chemical incompatibility which results in reduced hyaluronidase activity is such that the practice of mixing these two medications cannot be recommended. Rather, we would support the practice recommended by the manufacturer which involves injecting hyaluronidase subcutaneously into the site prior to the start of hypodermoclysis or priming the intravenous tubing with hyaluronidase.

Key Words: compatibility, hyaluronidase, hydromorphone, stability

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RÉSUMÉ

On a déterminé la stabilité et la compatibilité des mélanges de trois concentrations différentes d'hydromorphone (2 mg/mL, 10 mg/mL et 40 mg/mL) et d'hyaluronidase (150 U/mL) sur une période de sept jours. En plus de procéder à un examen physique et de déterminer le pH des solutions, on a dosé l'hydromorphone au moyen d'une technique de chromatographie en phase liquide éprouvée indiquant la stabilité de la solution et mesuré l'activité de l'hyaluronidase en prenant l'acide hyaluronique comme substrat. Chaque essai a été effectué au temps de départ et après 1, 2, 4 et 7 jours d'entreposage à 4 °C, à température ambiante (23°C) et à 37°C.

Les solutions sont restées physiquement compatibles durant la période de sept jours et on n'a décelé aucune modification de la concentration d'hydromorphone, celle-ci demeurant constamment à 10 % de la concentration initiale. L'hydromorphone a néanmoins réduit de façon appréciable l'activité de l'hyaluronidase au cours de l'entreposage. La baisse d'activité dépend de la concentration d'hydromorphone (à mesure qu'elle augmente, l'activité de l'hyaluronidase diminue) et de la température d'entreposage (l'activité de l'hyaluronidase diminue plus rapidement avec la hausse de la température).

On en conclut que si les deux composés sont physiquement compatibles, l'incompatibilité chimique à l'origine de l'activité réduite de l'hyaluronidase ne permet pas de recommander la pratique qui consiste à mélanger les deux médicaments. On appuierait plutôt la recommandation du fabricant, à savoir injecter l'hyaluronidase sous la peau au site d'inoculation, avant de commencer l'hypodermoclyse, ou amorcer la perfusion avec l'hyaluronidase dans la tubulure.

Mots clés: stabilité, compatibilité, hydromorphone, hyaluronidase

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INTRODUCTION

Pharmacists are often questioned regarding the compatibility of medications. Our interest in compatibility of hydromorphone with other medications stems from recent advances in the management

of chronic pain through the development of portable infusion devices.¹ The success of both the intravenous and subcutaneous routes of administration with narcotics in controlling chronic pain² has produced a desire for simultaneous

administration with other medications. However, the stability of the combination of these agents is often unknown, as is their compatibility. We have often discouraged the mixing of medications in the same infusion container for tech-

nical reasons (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 is important.

Hydromorphone stability is well documented³ and there have been several reports documenting its compatibility with other medications.⁴⁻¹¹ However, the compatibility and stability of the combination of hydromorphone and hyaluronidase has never been addressed. There are very few reports in the medical literature which describe hyaluronidase stability or compatibility. One brief report indicates that hyaluronidase is physically compatible with morphine over a 24 hour period¹². However, while morphine concentrations are reported to have remained within 10% of the initial concentration over the study period, hyaluronidase activity was not quantified.¹²

It was the intent of this study to test the compatibility and stability of the combination of hydromorphone and hyaluronidase over a seven day period. In addition to quantifying the hydromorphone concentration by a validated stability-indicating liquid chromatographic method, measurement of hyaluronidase activity was also an important endpoint used to determine compatibility and stability of the combination.

METHODS

Assay Validation

A previously validated and reported stability-indicating liquid chromatographic method for hydromorphone^{3,10} was used without modification, following re-validation using accepted stability-indicating procedures¹³⁻¹⁵. Briefly, this reverse phase liquid chroma-

tographic method uses 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 C₁₈, 5 µm column (Beckman; Ultrasphere). Hydromorphone was detected at 230 nm using a UV detector (Schoeffel SF770) and chromatograms were recorded on an integrator (Spectra Physics SP4200).

The method used in this study to evaluate hyaluronidase activity quantifies N-acetyl glucosamine terminal end units released from hyaluronic acid following glycosidic bond cleavage by hyaluronidase. The free N-acetyl glucosamine is reacted with *p*-dimethylamino benzaldehyde to yield a purple colour. In validating this method we evaluated the effect of; (i) the amount of hyaluronidase and sample reaction time; (ii) the effect of borate buffer; and (iii) standing time following derivatization on the reaction sensitivity, reproducibility and standard curve linearity. Once optimum conditions were determined the reproducibility of standard curves and samples was determined on five consecutive days.

The final conditions used to measure hyaluronidase activity required that 0.125 mL of a sample containing hyaluronidase be mixed with a buffered solution containing 625 µg/mL of hyaluronic acid, 0.300 mL of 0.05 M acetate (at pH 4.2), and 0.15 M sodium chloride. This mixture was incubated at 37°C for 120 minutes, during which time free N-acetyl glucosamine was generated. The reaction was terminated by the addition of 250 µL of the borate solution. The borate solution contained 2 volumes of 0.8 M borate (at pH 9.1) and 3 volumes of 0.1 M sodium hydroxide. This mixture was boiled for five minutes, then cooled

before the addition of 2 mL of a 1% solution of *p*-dimethylamino benzaldehyde. The 1% solution of *p*-dimethylamino benzaldehyde was prepared in 87.5% glacial acetic acid and 12.5% 10 N hydrochloric acid. This reagent was kept at 4°C in order to prevent it from changing colour. Derivatization was completed by incubating the mixture at 37°C for 20 minutes and then allowing the solution to stand at room temperature for 45 minutes. The absorbance of the solution at 585 nm was determined and recorded. The amount of N-acetyl glucosamine generated in two hours was determined by interpolation from an N-acetyl glucosamine standard curve and the activity of the hyaluronidase was expressed in terms of µg of N-acetyl glucosamine generated per hour (µg/hr).

Compatibility Study — Hyaluronidase and Hydromorphone

Equal volumes of hydromorphone (2 mg/mL, 10 mg/mL, 40 mg/mL; Knoll Pharmaceuticals) and hyaluronidase (150 units/mL; Wyeth Ltd., Lot number: U811AA) were mixed to prepare study samples. Three additional control samples; [(i) a buffer solution containing 2 mg/mL of citric acid and 2 mg/mL of sodium citrate — to replicate the hydromorphone diluent and; (ii) normal saline and; (iii) five percent dextrose in water;] were also prepared and mixed with equal volumes of hyaluronidase (150 units/mL) to evaluate the effect of solution diluent on hyaluronidase activity. After recording initial physical appearance (colour, clarity, and presence/absence of particles against a black background), pH values, and assay results, the solutions were divided into three lots and stored at 37°C, 23°C and 4°C for the duration of the study period (7 days). On each

subsequent study day (1, 2, 5 and 7) physical inspection, pH, and concentration were determined. On each study day, fresh hydromorphone standards were chromatographed to construct a standard curve. The peak areas were subjected to least squares linear regression and the actual hydromorphone concentration, from the average of four replicates from each sample, was interpolated from these curves and recorded. Concentrations are reported to the nearest 0.01 mg/mL.

On each study day, fresh N-acetyl glucosamine standards were prepared and the mean absorbance from four replicates of each standard was subjected to least squares linear regression and a standard curve constructed. The mean concentration of N-acetyl-glucosamine determined from four replicates of a sample containing hyaluronidase and incubated with hyaluronic acid was interpolated from these curves and recorded. The hyaluronidase activity in each sample is reported to the nearest 0.01 μg of N-acetyl-glucosamine produced per hour.

Data Reduction and Statistical Analysis.

Reproducibility of each method was assessed by coefficient of variation. Mean results from different times of an identical test were compared statistically by least squares linear regression to determine whether an association existed between the observed result and time. Analysis of Variance and Fisher's Protected least significant difference multiple range test were used to compare the differences between observed hyaluronidase activity at different times and different hydromorphone concentrations. The 5% level was used as the *a priori* cut-off for significance. Hydromor-

phone concentrations and hyaluronidase activity were considered "acceptable" or "within acceptable limits" if the concentration at any time of analysis was not less than 90% of the initial concentration or activity. A solution was judged to be physically incompatible when there was a visible change in colour, clarity or particulate matter or precipitate appeared in the mixture.

RESULTS:

Assay Validation: Hyaluronidase Activity Assay

The effects of borate buffer, pH, incubation time, and wavelength of absorbance on the sensitivity and specificity of the dimethylamino benzaldehyde reaction with N-acetyl amino sugars were thoroughly investigated and reported by Reissig et al.¹⁸ We also investigated most of these variables in the validation of the method. The amount of N-acetyl glucosamine produced during a two minute incubation period was directly and linearly related to the hyaluronidase concentration between 0 and 2500 units/mL. However, under these conditions, at least 200 units/mL of hyaluronidase are necessary to observe sufficient N-acetyl glucosamine product. Since the concentrations of hyaluronidase used by Doak and Zahler¹⁹ were approximately 30 fold higher than those used in our studies, in order to increase the amount of N-acetyl glucosamine produced, we increased the incubation time that hyaluronidase had to act on hyaluronic acid. As incubation at 37°C continues the reaction proceeds until the hyaluronidase has cleaved all terminal N-acetyl glucosamine. After 120 minutes of incubation no further N-acetyl glucosamine was produced and, therefore, we chose 120 minutes as the sample reaction time.

The borate buffer, while necessary to halt the enzymatic cleavage of hyaluronic acid also enhances the development of colour in the reaction between *p*-dimethylamino benzaldehyde and N-acetyl glucosamine and increases the sensitivity of the method. Standard curves were prepared on five consecutive days, five with borate added, four without. The addition of borate buffer in the preparation of the N-acetyl-glucosamine standards, increased absorbance approximately 15 fold. The slope of the N-acetyl-glucosamine standard curve, which was linear, increased from 0.6191 to 14.672 with the addition of borate buffer. The y-axis intercept did not change as the result of the addition of borate buffer.

After 20 minutes of incubation of N-acetyl glucosamine with *p*-dimethylamino benzaldehyde at 37°C, it was observed that there was further development of the purple colour on standing. In an evaluation of this stage of colour development, the test sample was allowed to stand and the absorbance continually monitored. It was observed that the absorbance reading stabilized after 35 to 45 minutes. This standing time was also observed to improve the reproducibility with which N-acetyl glucosamine concentrations were estimated.

Five standard curves of N-acetyl-glucosamine (with borate buffer added) were prepared on five consecutive days. The standard curve was linear in the range of 0 - 40 $\mu\text{g/hr}$ and the limit of sensitivity was 0.50 $\mu\text{g/hr}$. The average slope of the standard curves was found to be 14.672 with a coefficient of variation of 0.547%. This coefficient of variation represents an estimate of the inter-day reproducibility of the N-acetyl glucosamine assay. The coefficient

of variation of samples run in duplicate within a day was less than 5% for all samples and averaged 2.41%. Samples containing hyaluronidase and incubated with hyaluronic acid showed similar in-traday reproducibility (mean CV(%) = 3.39). To further improve the confidence with which hyaluronidase activity is reported each study sample was assayed in quadruplicate.

The assay validation investigations of the hyaluronidase method indicated that the activity of hyaluronidase could be reproducibly and accurately determined by quantifying N-acetyl glucosamine concentrations following incubation of the hyaluronidase sample with a solution containing hyaluronic acid.

Assay Validation:

Hydromorphone Assay

The validation of the hydromorphone assay confirmed that hydromorphone could be quantified without interference from hydromorphone degradation products or hyaluronidase. The coefficient of variation for replicate samples determined on the same day was less than 2% and the coefficient of variation of replicates determined of different days averaged less than 4%.

Compatibility/Stability Study

All samples were initially clear and colourless and all samples at all concentrations and temperatures remained clear and colourless throughout the study period. The pH was observed to gradually increase, although only slightly, over the seven-day study period. The initial pH of all samples was approximately 4.44 (range: 4.38 to 4.51) and did not increase by more than 0.21 of a pH unit throughout the seven day study period. These changes are not significant.

Activity: Hyaluronidase

Dilution of hyaluronidase in citrate buffer, normal saline or 5% dextrose in water had no effect on the initial activity of hyaluronidase. However, the addition of hydromorphone to citrate buffer reduced the initial activity of hyaluronidase by 17-28%. Further reductions in hyaluronidase activity were observed with storage. (Table I) The time related reduction in activity was also dependant on temperature and hydromorphone concentration. By day seven, the hyaluronidase activity had been eliminated (no N-acetyl-glucosamine was produced after two hours of incubation with hyaluronic acid) in

solutions containing any hydromorphone. The reduction in hyaluronidase activity was more rapid with higher hydromorphone concentrations; 20 mg/mL of hydromorphone more rapidly reduced the hyaluronidase activity than concentrations of 1 mg/mL and 5 mg/mL. Similarly, higher temperatures were associated with a more rapid decline in hyaluronidase activity.

Hydromorphone Concentrations:

When stored at 4°C, 23°C or 37°C, the hydromorphone concentration in all samples remained greater than 90% percent of the initial concentration for seven days

Table I: Amount of N-acetyl-D-glucosamine produced in µg per hour*

| SAMPLE | Temperature (°C) | DAY 0 | DAY 1 | DAY 2 | DAY 4 | DAY 7 |
|----------------------------------------------------|------------------|--------------------|-----------------|-----------------|-----------------|-----------------|
| 150 U/mL Hyaluronidase plus Citrate Buffer | 4 | 10.18 (100.00) | 9.46 (92.85) | 7.64 (74.98) | 6.19 (60.82) | 5.00 (49.08) |
| 150 U/mL Hyaluronidase plus Citrate Buffer | 23 | 10.18 (100.00) | 9.36 (91.95) | 6.87 (67.43) | 5.34 (52.44) | 3.90 (38.32) |
| 150 U/mL Hyaluronidase plus Citrate Buffer | 37 | 10.18 (100.00) | 8.80 (86.27) | 5.70 (56.01) | 3.90 (38.32) | 2.90 (28.52) |
| 150 U/mL Hyaluronidase plus 2 mg/mL Hydromorphone | 4 | 7.32 (100.00) | 4.17 (56.95) | 2.54 (34.68) | 0.83 (11.29) | 0 |
| 150 U/mL Hyaluronidase plus 2 mg/mL Hydromorphone | 23 | 7.32 (100.00) | 3.23 (44.11) | 2.17 (29.60) | 0 | 0 |
| 150 U/mL Hyaluronidase plus 2 mg/mL Hydromorphone | 37 | 7.3160 (100.00) | 3.02 (41.19) | 1.18 (16.18) | 0 | 0 |
| 150 U/mL Hyaluronidase plus 10 mg/mL Hydromorphone | 4 | 8.5183 (100.00) | 2.40 (28.11) | 1.27 (14.91) | 0 | 0 |
| 150 U/mL Hyaluronidase plus 10 mg/mL Hydromorphone | 23 | 8.5183 (100.00) | 2.38 (27.99) | 1.03 (12.14) | 0 | 0 |
| 150 U/mL Hyaluronidase plus 10 mg/mL Hydromorphone | 37 | 8.5183 (100.00) | 2.34 (27.49) | 0.83 (9.73) | 0 | 0 |
| 150 U/mL Hyaluronidase plus 40 mg/mL Hydromorphone | 4 | 7.5375 (100.00) | 2.27 (30.16) | 0 | 0 | 0 |
| 150 U/mL Hyaluronidase plus 40 mg/mL Hydromorphone | 23 | 7.5375 (100.00) | 1.37 (18.14) | 0 | 0 | 0 |
| 150 U/mL Hyaluronidase plus 40 mg/mL Hydromorphone | 37 | 7.5375 (100.00) | 1.20 (15.94) | 0 | 0 | 0 |

* Numbers in parenthesis indicate percent of initial (Day zero Activity) activity remaining.

(Table II). No hydromorphone degradation products, observed during the accelerated assay validation procedures were observed in chromatograms during the study period.

DISCUSSION:

Hyaluronic acid is an endogenous constituent of connective tissue consisting of alternating units of N-acetyl-glucosamine and D-glucuronic acid joined by beta-1-3-glucuronidic and beta-1-4-glucosaminidic bonds. Hyaluronidase (hyaluronate 3-glycanohydrolase; EC 3.2.1.35) is an enzyme capable of cleaving these bonds, and to a variable degree other mucopoly-

saccharides of connective tissue, to yield N-acetyl glucosamine. The USP test for hyaluronidase is based on the tyrosine content of hyaluronidase which is not greater than 0.25 µg of tyrosine per unit of hyaluronidase. In developing the protocol for this study we considered this method, but reasoned that the tyrosine content of the mixture would likely reflect the amount of hyaluronidase enzyme present, but would not accurately indicate the activity of this enzyme. Therefore, the USP test was unlikely to be activity-indicating. However, when hyaluronidase cleaves the glycosidic bonds of terminal N-acetyl glucosamine,

free N-acetyl glucosamine is produced and can be quantified by reacting this product with *p*-dimethylamino benzaldehyde. This reaction was first described by Muller in 1901.¹⁶ Successive investigators¹⁷⁻¹⁹ have improved the specificity and sensitivity of this reaction over the years. The method described by Doak and Zahler¹⁹ involves initial incubation of hyaluronidase with hyaluronic acid in a buffered solution at 37°C. During this reaction N-acetyl glucosamine is generated. The reaction is stopped by a basic borate buffer solution and the N-acetyl glucosamine is reacted with *p*-dimethylamino benzaldehyde at 37°C to yield a purple colour. The absorbance of this colour is proportional to the N-acetyl glucosamine concentration in the sample and can be equated to hyaluronidase activity expressed as the quantity of N-acetyl glucosamine generated per hour. The effects of borate buffer, pH, incubation time, and wavelength of absorbance on the sensitivity and specificity of the *p*-dimethylamino benzaldehyde reaction with N-acetyl amino sugars has been thoroughly investigated and reported by Reissig et al.¹⁸ In our study of the stability of hyaluronidase activity, it was necessary to increase the sensitivity of assay by increasing the period of time hyaluronidase has to act on hyaluronic acid. This increased the amount of N-acetyl glucosamine produced which was necessary, since, the hyaluronidase activity in each sample in this study was one thirtieth that of previous reports.¹⁹ These modifications were validated prior to initiating our study and are briefly reported.

The hydromorphone assay used in this study has been used in other hydromorphone stability studies^{3,10} and was re-validated, according to

Table II: Concentration of Hydromorphone in mg/mL*

| SAMPLE | Temperature (°C) | DAY 0 | DAY 1 | DAY 2 | DAY 4 | DAY 7 |
|----------------------------------------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| 150 U/mL Hyaluronidase plus Citrate Buffer | 4 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 150 U/mL Hyaluronidase plus Citrate Buffer | 23 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 150 U/mL Hyaluronidase plus Citrate Buffer | 37 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 150 U/mL Hyaluronidase plus 2 mg/mL Hydromorphone | 4 | 0.92 (100.00) | 0.95 (103.26) | 0.89 (96.74) | 0.93 (101.09) | 0.95 (103.26) |
| 150 U/mL Hyaluronidase plus 2 mg/mL Hydromorphone | 23 | 0.95 (100.00) | 0.97 (102.11) | 1.04 (109.74) | 1.04 (109.47) | 0.93 (97.89) |
| 150 U/mL Hyaluronidase plus 2 mg/mL Hydromorphone | 37 | 0.97 (100.00) | 0.97 (100.00) | 1.03 (106.19) | 1.03 (106.19) | 0.97 (100.00) |
| 150 U/mL Hyaluronidase plus 10 mg/mL Hydromorphone | 4 | 5.13 (100.00) | 5.07 (98.83) | 5.18 (100.97) | 5.01 (97.66) | 5.14 (100.19) |
| 150 U/mL Hyaluronidase plus 10 mg/mL Hydromorphone | 23 | 5.12 (100.00) | 5.24 (102.73) | 5.35 (104.49) | 5.57 (108.79) | 5.53 (108.00) |
| 150 U/mL Hyaluronidase plus 10 mg/mL Hydromorphone | 37 | 5.15 (100.00) | 5.24 (101.75) | 4.97 (96.50) | 5.17 (100.39) | 5.36 (104.08) |
| 150 U/mL Hyaluronidase plus 40 mg/mL Hydromorphone | 4 | 19.45 (100.00) | 19.94 (102.52) | 19.77 (101.65) | 20.03 (102.98) | 20.10 (103.34) |
| 150 U/mL Hyaluronidase plus 40 mg/mL Hydromorphone | 23 | 19.33 (100.00) | 20.84 (107.81) | 21.07 (109.00) | 20.99 (108.58) | 21.21 (109.72) |
| 150 U/mL Hyaluronidase plus 40 mg/mL Hydromorphone | 37 | 19.54 (100.00) | 20.09 (102.81) | 20.54 (105.21) | 21.29 (108.96) | 20.29 (103.84) |

* Numbers in parenthesis indicate percent of initial (Day zero) concentration remaining.

accepted standards¹³⁻¹⁵, prior to use in this study.

A number of reports have been published concerning hydromorphone compatibility with various drugs⁴⁻¹¹. 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 this study, hydromorphone and hyaluronidase were noted to be physically compatible. However, this study also demonstrated that hyaluronidase activity is profoundly affected by hydromorphone. Greater losses in hyaluronidase activity were observed with increasing concentrations of hydromorphone and increasing temperature, such that 40 mg/mL of hydromorphone can reduce hyaluronidase activity to 16% of its initial activity within 24 hours when stored at 37°C. However, even hyaluronidase diluted in a citrate buffer solution maintained only 90% of its initial activity for 24 hours. These results bring into question the stability of hyaluronidase diluted in almost any IV solution. Since no reports of hyaluronidase stability in IV solutions have ever been published, the effectiveness of solutions stored for any length of time is questionable. However, many institutions using hyaluronidase for hypodermoclysis have indicated apparent continued clinical effect of hyaluronidase even in solutions containing hydromorphone. While this would appear to be contrary to the observations of this study, it is possible that although activity is reduced, sufficient activity remains to maintain a site that still enhances dispersion and absorption drugs and solutions.

Although there may be some residual activity remaining in solutions of hyaluronidase, even though more than 10% of the initial activity has been lost, we cannot recommend the use of solutions of hydromorphone and hyaluronidase for more than 24 hours. In fact, because of the effect of hydromorphone on hyaluronidase activity, the practice recommended by the manufacturer of injecting hyaluronidase subcutaneously into the site prior to the start of clisis or priming the intravenous tubing with hyaluronidase is probably a preferable procedure. ☒

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