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Initial Experiences with Subcutaneous Recombinant Human Hyaluronidase

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ABSTRACT

We report here our retrospective observations on the use of recombinant human hyaluronidase (rHuPH20) for the facilitation of subcutaneous hydration and drug infusion. Thirty-two patients were treated with rHuPH20 in a hospice setting over a 6-month period. Of these, 26 received this agent to enhance hypodermoclysis with standard hydration fluids for symptom control of delirium, myoclonus and mild to moderate dehydration. Flow rates up to 500 mL/hr were attained without difficulty. Electrolyte replacement in hydration fluid was achieved without incident in 5 patients receiving potassium and in 1 patient receiving both potassium and magnesium. In addition to use for hydration, 6 patients received recombinant human hyaluronidase to enhance subcutaneous infusion of 9 medications, primarily because the medication dosage required subcutaneous flow rates greater than the standard 3 mL/hr. There were no significant adverse events. Induration at the infusion site occurred in 1 patient receiving hydration and higher than expected serum lidocaine concentration was observed in another patient. Based on our positive initial experience with recombinant human hyaluronidase, there is interest in expanding its use in our facility in both the inpatient and outpatient settings.

INTRODUCTION

PHYSICIANS AT San Diego Hospice & Palliative Care began using recombinant human hyaluronidase (rHuPH20)[1] after it became clinically available as Hylenex™ (Baxter, Deerfield, IL) in the summer of 2006. Hyaluronidase, a mucolytic enzyme used as a "spreading factor," hydrolyzes hyaluronan, a megadalton glycosaminoglycan found in connective tissue.[2,3] This hydrolysis reduces the viscosity of the gel-like interstitial matrix, effecting an increase in the diffusion and absorption of subcutaneously administered fluids[4,5] and a decrease in infusion site swelling.[6,7] We present here our initial 6-month experiences using recombinant human hyaluronidase to facilitate hypodermoclysis and the subcutaneous infusion of medications.

METHODS

A retrospective chart review was conducted directly by the authors for the first 6-month period of hospice use of rHuPH20. The following information was retrieved from patient charts via a template spreadsheet: prescribing physician, patient medical record number, age, gender, hospice diagnosis, indications, injection site, recombinant human hyaluronidase dose, repeat frequency, treatment duration, hydration fluid, flow rate, total fluid volume, coadministered drugs and

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dosages, treatment outcome, and adverse events. The method of drug and fluid administration was subcutaneous using a 22- to 24-gauge angiocatheter. Injection sites varied depending on patient and provider preference and included the abdomen, thigh, upper arm, and chest wall. rHuPH20 was injected into the subcutaneous catheter just prior to infusion of fluids or medications into the same site. All infusions were pump-driven. Patient selection for hyaluronidase treatment was at the discretion of the individual physicians; it was not universally administered to all hypodermoclysis and subcutaneous infusion patients. The San Diego Hospice Institutional Review Board approved this project.

RESULTS

A total of 32 patients received a total of 84 separate injections of recombinant human hylauronidase, prescribed by 11 physicians during the initial 6-month review period. The average patient age was 69.7 years, with a median age of 72 and a range of 37–98 years. Patient gender was evenly divided, with 16 men and 16 women. Recombinant human hyaluronidase dosage was the same for all patients, 150 U once every 24 hours. Thirty-one patients were admitted to the 24-bed inpatient hospice facility and 1 patient was treated at home.

Of the 32 patients, 26 were treated with a variety of common electrolyte-containing fluids: 0.9% normal saline (NS); 5% dextrose, 0.9% normal saline (D5NS); and 5% dextrose, 0.45% normal saline (D5 $^1/_2$ NS); as well as 5% dextrose (D5W) (see Table 1 for summary). Initial bolus flow rates of 200 to 500 mL/hr for the first 1 to 2 hours were achieved when immediate rehydration was desired. Maintenance rates of 50 to 100 mL/hr were typical thereafter. For 5 hydration patients, 20 mEq/L potassium was added to the fluid infusion bag. For 1 additional patient, both potassium (20 mEq/L) and magnesium (1g/L) were added to the hydration fluid.

In 6 patients, various medications were infused subcutaneously following recombinant human hyaluronidase administration. These included hydromorphone, lidocaine, dexamethasone, haloperidol, midazolam, sufentanil, glycopyrrolate, ondansetron, and famotidine. Hyaluronidase was prescribed in cases in which the medication dose required a flow rate greater than the nursing norm of 3 mL/hr. One patient with ovarian cancer presenting with dyspnea and severe pain was injected with recombinant human hyaluronidase into separate infusion sites for 3 different drugs because of concerns about drug incompatibility if infused at a single site. A patent with cervical cancer with severe sacral pain syndrome received rHuPH20 daily in combination with pain control medications for a total of 13 days.

Table 1. Hydration Therapy Facilitated by Recombinant Human Hyaluronidase

Hydration fluid	*# Patients*	*Flow rate range*	*Duration*
NS	12	50–250 mL/hr	1–7 days
D5NS	9	75–500 mL/hr	1–3 days
D5 1/2 NS	5	20–100 mL/hr	1–7 days
D5W	1	40 mL/hr	12 hours

No skin reactions at the subcutaneous sites were noted after injection of recombinant human hyaluronidase, despite repeated dosing for up to 13 days. One patient developed an induration at the subcutaneous site after 7 days of therapy with normal saline. Fluids were discontinued in this patient. An unexpected clinical outcome occurred in a patient with lung cancer when serum lidocaine concentration increased to a higher than predicted level after dosing with rHuPH20. The patient had previously been receiving lidocaine by continuous subcutaneous infusion; hyaluronidase was added when the lidocaine dose was increased to an infused volume that exceeded 3 mL/hr.

DISCUSSION

In 6 months of clinical use, 32 patients were treated with recombinant human hyaluronidase, primarily to facilitate parenteral hydration. Although it was challenging to determine clinician intent from the medical record in some cases, indications for hydration with this agent included control of symptoms such as nausea, delirium, myoclonus, and rehydration of patients with poor oral intake. Rapid hydration with flow rates of up to 500 mL/hr for bolus dosing and repeated dosing of up to 7 days were noted. Composition of infusion fluids was typical of parenteral fluids administered intravenously. Successful supplementation of both potassium and magnesium for up to 2 days without skin irritation is also noteworthy.

There has been vigorous debate about the role of parenteral hydration in patients near the end of life. Concerns about the contributions of intravenous administration to fluid overload and patient burden have limited the use of hydration in palliative care.[8] However, several authors have advocated that, in selected patients, hydration by hypodermoclysis is effective for control of symptoms caused or aggravated by mild to

moderate dehydration, such as delirium, myoclonus, and renal failure.[9,10] An important barrier to subcutaneous administration of parenteral fluids can be tissue swelling at the site of infusion.[6] Although Bruera et al.[11] have achieved 500 mL/hr flow rates without the aid of hyaluronidase, they admit that hyaluronidase may still be useful for patients "who are not able to tolerate infusion well due to swelling or pain." Of 28 patients in their study, 4 patients had to withdraw due to swelling: 3 of these patients were in the group that did not receive bovine hyaluronidase while only 1 withdrew from the bovine hyaluronidase group. The introduction of rHuPH20 potentially reduces physicians' concerns regarding patient comfort, and may make hypodermoclysis a more appealing option.[1] Although the hydration infusions, which demonstrated flow rates up to 500 mL/hr, were pump-driven for these patients, with the aid of recombinant human hyaluronidase, a pump may not be essential to achieve adequate subcutaneous flow rates. A recent study used the same dosage of (150 U) as an aid to hypodermoclysis by gravity, attaining a mean flow rate of 383 mL/hr without a pump.[12]

The facilitation of drug delivery was a less frequent indication for prescription of recombinant human hyaluronidase, occurring in only 6 of 32 patients, or 19%. The subcutaneous route is a common and preferred route of medication administration in this inpatient unit. Because the nursing standard of care is not to exceed 3 mL/hr in any subcutaneous site, it is routine for medications to be reformulated to increase their concentration and/or to start an additional subcutaneous site rather than to exceed this flow rate. The use of hyaluronidase makes these measures unnecessary by allowing for higher subcutaneous infusion volumes.

rHuPH20 is shown to increase the bioavailability of macromolecular compounds in animals.[1] However, there is little information about its effect on the pharmacokinetics of drugs administered via the subcutaneous route in humans. A study of the effects on subcutaneous morphine pharmacokinetics is currently underway at this institution.[13] As recombinant human hyaluronidase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs[14] physicians used the opportunity to obtain clinical experience with this agent for the infusion of a variety of drugs (Table 2).

Induration at the subcutaneous infusion site was observed in 1 patient after 7 days of fluid therapy. As this patient was very close to death and showing signs of fluid overload, all hydration was discontinued. The clinicians thought it unlikely that this induration was related to the use of recombinant human hyaluronidase. Previously described problems with bovine hyaluronidase, including anaphylaxis,[15] local allergic reactions and skin irritation[16] were not seen over the course of 84 injections. The only unexpected event was related to the administration of parenteral lidocaine as an analgesic.[17,18] Serum concentrations of lidocaine reached levels beyond those expected from a linear increase in dosage, probably due to better absorption from the subcutaneous space. Further study is required to determine optimal dosages of lidocaine or other drugs for which systemic levels require monitoring.

Table 2. Drug Therapy Facilitated by Recombinant Human Hyaluronidase

Electrolytes and medications
Magnesium
Potassium
Hydromorphone
Lidocaine
Dexamethasone
Haloperidol
Midazolam
Ondansetron
Famotidine
Sufentanil
Glycopyrrolate

CONCLUSIONS

We conclude that rHuPH20 has been used successfully by a variety of physicians in an inpatient hospice unit for the administration of parenteral fluids and medications subcutaneously. With the exception of a higher than expected lidocaine level in one patient, there were no significant adverse effects and infusion rates approaching intravenous flow rates were attained without causing local swelling or discomfort. The subcutaneous route for hydration and administration of medications for pain control is frequently used in the hospice and palliative care setting. For patients requiring parenteral hydration, this modality potentially decreases both patient burden and staff time and skill level. Bovine hyaluronidase was shown to increase absorption of fluids infused subcutaneously and decrease associated tissue swelling by the early 1950s.[4,6] The ability of hyaluronidase to enzymatically facilitate subcutaneous infusion was confirmed in the 1990s,[5,7] however, problems with patient allergic and skin irritation reactions to bovine hyaluronidase preparations[15,16] limited its usefulness. After the discontinuation of the sale of bovine hyaluronidase, no

hyaluronidase products were available for clinical use until the recent introduction of recombinant human hyaluronidase.

There are obvious limitations to a retrospective study, however, the dissemination of these findings is intended to raise physician awareness of the safe and effective use of rHuPH20 to enhance subcutaneous infusion rates. Future prospective studies will be conducted at this institution to address such questions as, which patients are the best candidates for treatment with rHuPH20, and how it effects the pharmacokinetics of different drugs with which it is coadministered. rHuPH20 may have the potential to prevent inpatient admissions and to reduce total cost, especially with regard to skilled staff time and the ability to hydrate without a pump. Based on these positive initial experiences and our ongoing research, we are interested in expanding the use of recombinant human hyaluronidase into home hospice care, including skilled nursing facilities.

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