The compatibility of a low concentration of hydrocortisone sodium succinate with selected drugs during a simulated Y-site administration

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ABSTRACT

Objectives: Bolus dose concentrations of hydrocortisone (50 mg/mL) are reported to be incompatible with midazolam and ciprofloxacin in Y-site mixing studies. We evaluated the physical and chemical compatibility of low concentrations of hydrocortisone sodium succinate (1 mg/mL) with midazolam (1 mg/mL and 2 mg/mL) and ciprofloxacin (2 mg/mL) solutions during a simulated Y-site administration study.

Methods: The midazolam 1 mg/mL, midazolam 2 mg/mL and ciprofloxacin 2 mg/mL solutions were individually combined with hydrocortisone sodium succinate 1 mg/mL solution in a 1:1 ratio and tested in triplicate. Physical compatibility was evaluated using a previously described method immediately on mixing, after 60 minutes and after 120 minutes. Chemical compatibility was determined by measuring the hydrocortisone sodium succinate concentration of the test solutions 120 minutes after mixing compared with that of a reference sample of hydrocortisone sodium succinate solution.

Results: At all time points, when hydrocortisone was mixed with midazolam (1 mg/mL and 2 mg/mL) and ciprofloxacin (2 mg/mL), the solutions remained clear, with no haziness, colour change, gas or precipitate formation, thus showing total physical compatibility. There were pharmacologically significant reductions (> 10%) in measured hydrocortisone concentration (18.6% with midazolam 2 mg/mL, $P = 0.06$; and 21.3% with ciprofloxacin, $P = 0.01$) in all of the test samples, as compared with the reference sample.

Conclusions: According to currently recommended criteria, combining hydrocortisone sodium succinate at a concentration of 1 mg/mL with a 1 mg/mL solution of midazolam appears to be both chemically and physically compatible. However, mixing 1 mg/mL hydrocortisone sodium succinate with 2 mg/mL midazolam or with 2 mg/mL ciprofloxacin cannot be recommended.

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Hydrocortisone improves vasopressor responsiveness in patients with septic shock[1,2] but has not been consistently shown to improve mortality.[1-4] The recommended dose is 200 mg/day administered either as a 50 mg intermittent bolus or as an infusion at a concentration of 1 mg/mL.[5] Guidelines recommend administration as an infusion, based on immunological and pharmacokinetic equivalence data.[5]

Administering hydrocortisone as an infusion in critically ill patients poses practical problems. These patients require multiple intravenous medications administered by continuous infusion, necessitating multiple venous access sites. Venous access can be associated with significant morbidity.[6-8] In an effort to reduce the number of access sites, infusions are sometimes administered through a Y-site connector, creating the potential for drug incompatibilities.

Although hydrocortisone sodium succinate is compatible with many commonly used intensive care unit medications such as propofol, fentanyl, vecuronium and vasopressors, current guidelines state that 50 mg/mL of hydrocortisone is incompatible with midazolam and ciprofloxacin (both frequently prescribed medications in critically ill patients) and should not be used in the same giving set or Y-site connector.[9,10] However, similar data are not available for hydrocortisone when used as an infusion at concentrations of 1 mg/mL. In the absence of data, pharmacists recommend avoiding Y-site mixing even at low concentrations of hydrocortisone, often necessitating dedicated venous access. This has significant practical implications as venous access may be limited.

We devised an in-vitro study to clarify the physical and chemical compatibility of two concentrations of midazolam (1 mg/mL and 2 mg/mL) and ciprofloxacin (2 mg/mL) with a 1 mg/mL solution of hydrocortisone sodium succinate. Physical and chemical compatibility was evaluated in accordance with published recommendations.[11]

Methods

Physical and chemical compatibility testing was conducted in the ICU laboratory of the Royal Brisbane and Women's Hospital (RBWH) and the Department of Chemical Pathol-

Table 1. Changes in pH of test solutions after mixing with 1 mg/mL hydrocortisone sodium succinate solution

Drug and concentration	pH of test solutions	
	Before mixing	120 minutes after mixing
1 mg/mL midazolam	4.46	5.54
2 mg/mL midazolam	3.63	4.56
2 mg/mL ciprofloxacin	3.36	4.53

ogy at Pathology Queensland, RBWH, respectively. Commercially available midazolam (Steriluer 50 mg/mL, 10 mL vial, Pfizer), ciprofloxacin (Aspen Ciprofloxacin 200 mg/100 mL, Aspen) and hydrocortisone (Solu-Cortef 100 mg vial, Pfizer) were used.

Preparation of drug dilutions

Solution precision for the chemical compatibility study was obtained by using calibrated volumetric borosilicate flasks with a 0.1% error at 20°C and Eppendorf manual pipettes. All samples were agitated for 30 seconds. For logistic reasons physical and chemical compatibility testing was performed on freshly prepared solutions on separate days.

Hydrocortisone sodium succinate dilution: Hydrocortisone sodium succinate 100 mg was reconstituted to a 1 mg/mL concentration with 0.9% sodium chloride.

Midazolam dilution: Midazolam was diluted to a 1 mg/mL and a 2 mg/mL solution with 0.9% sodium chloride.

Ciprofloxacin dilution: Ciprofloxacin is available as a 2 mg/mL solution in 100 mL 5% dextrose.

Physical stability testing

All the solutions were coded to enable blinded observation and evaluated in triplicate. The 1 mg/mL midazolam, 2 mg/mL midazolam and 2 mg/mL ciprofloxacin dilutions were individually combined with the 1 mg/mL hydrocortisone sodium succinate solution in borosilicate glass test tubes in a 1:1 ratio. These solutions were mixed in front of two independent observers and the ICU pharmacist.

Before the physical compatibility testing, the observers were shown a panel of controls, both positive (forms a precipitate on mixing) and negative (stays as a clear solution on mixing). A mixture of 50 mg/mL hydrocortisone and 5 mg/mL of midazolam, a combination known to immediately precipitate, was prepared as a positive control. A 0.9% sodium chloride solution was used as a negative control.

The independent observers commented on change in colour, clarity or haziness and on any precipitate formation or gas evolution. Observations were taken immediately on mixing and at 60 and 120 minutes after mixing. The test tubes were kept at room temperature (range, 22.6–23.4°C) under constant laboratory fluorescent light.

Physical incompatibility was defined as either a change in the colour or clarity, or the presence of any haziness, precipitate or gas evolution in the test solutions. The pH of the hydrocortisone sodium succinate solution was measured after the initial preparation and at 120 minutes. The pH of the midazolam and ciprofloxacin solutions was measured on initial dilution and at 120 minutes after mixing with the hydrocortisone sodium succinate.

Chemical compatibility testing

Compatibility was determined by measuring hydrocortisone sodium succinate concentrations in the mixed solutions at 120 minutes. These levels were compared with a reference hydrocortisone sodium succinate concentration, obtained by diluting the original 1 mg/mL hydrocortisone sodium succinate solution to a 500 μg/mL solution with 0.9% sodium chloride.

Hydrocortisone sodium succinate concentrations were measured using an Acquity Ultra Performance Liquid Chromatography System coupled with a Micromass Quattro Premier XE Mass Spectrometer (Waters) with electron spray ionisation in positive ion detection mode. As no quantifier standards existed for the hydrocortisone sodium succinate, the transitions and mass spectrometer settings for hydrocortisone sodium succinate were established by infusing a 100 ng/mL solution into the system and generating a calibration curve over a series of dilutions of hydrocortisone sodium succinate. The variability with the mass spectrometry for cortisol assays is < 5%.[12]

Statistical analysis

Summary measures included calculations of means and SDs. Unpaired *t* tests assuming unequal variances were used to compare the means of the various test solutions with the reference solution. Solutions were deemed chemically compatible if the concentration of the hydrocortisone sodium succinate levels within the test samples was within 10% of the reference sample.[13]

Results

Physical testing

The pH of the 1 mg/mL hydrocortisone solution at the time of dilution and at 120 minutes was 6.44 and 6.54, respectively. Table 1 shows the pH of the test samples on constitution (before mixing) and 120 minutes after mixing with the 1 mg/mL solution of hydrocortisone sodium succinate. At all time points, when hydrocortisone was mixed with midazolam (1 mg/mL and 2 mg/mL) and ciprofloxacin,

Table 2. Concentrations of hydrocortisone sodium succinate 120 minutes after mixing with test solutions

Test solution	Concentration of hydrocortisone sodium succinate (mean ± SD)	Change from reference sample (%)
Hydrocortisone sodium succinate 500 μg/mL*	473 ± 24 μg/mL	0
Midazolam 1 mg/mL	430 ± 45 μg/mL†	9.1%
Midazolam 2 mg/mL	385 ± 35 μg/mL‡	18.6%
Ciprofloxacin 2 mg/mL	372 ± 35 μg/mL§	21.3%

* Reference sample. † $P = 0.26$, when compared with reference solution. ‡ $P = 0.06$, when compared with reference solution. § $P = 0.01$, when compared with reference solution.

the solutions remained clear, with no haziness, colour change, gas or precipitate formation.

Chemical compatibility data

A statistically and pharmacologically significant reduction in hydrocortisone sodium succinate concentration was noted when compared with the reference sample in two of the test samples (ciprofloxacin 2 mg/mL and midazolam 2 mg/mL), as shown in Table 2.

Discussion

Hydrocortisone at a concentration of 1 mg/mL showed both physical and chemical compatibility with midazolam at concentrations of 1 mg/mL. At higher concentrations of midazolam, despite physical compatibility, there was a significant reduction in the amount of available hydrocortisone sodium succinate. Similar observations were noted with ciprofloxacin 2 mg/mL, suggesting that the administration of 1 mg/mL of hydrocortisone sodium succinate with either 2 mg/mL of midazolam or 2 mg/mL of ciprofloxacin is incompatible.

Potential causes for the incompatibility include alterations in pH, reaction temperature and a chemical reaction. Previous studies have documented that 25 mg/mL of midazolam precipitates at a pH around 5.[9] In this study, both the test samples containing midazolam (1 mg/mL and 2 mg/mL) failed to demonstrate any macroscopic precipitation, despite pH readings of 5.54 and 4.56. This shows that precipitation is only partly predicted by the pH; other determinants include drug concentration and temperature.[14] It is likely that the reduction in the measured hydrocortisone concentrations at the higher concentrations of midazolam and ciprofloxacin was caused by a chemical reaction, which did not produce a macroscopic precipitation. These findings are consistent with recent work by Foinard et al.[15] The temperature over the 2-hour observation period differed by only 0.8°C, and was therefore unlikely to influence drug compatibilities.[11] Assay variability may potentially explain some of the observed discrepancy between the reference and test sample values, although the coefficient of variation with mass spectrometry for the cortisol assay is < 5%.[12]

Data from ICU medication compatibility studies are limited, and surveys have reported that 8.4% of patients are exposed to drug incompatibilities.[11,16] Incompatibilities may have serious consequences, with some case reports of precipitant-related pulmonary embolism,[17,18] occlusion of venous access lumens, venous thrombophlebitis and the possibility of a chemical alteration to a medication resulting in therapeutic failure.[11,15]

Strengths of the study

The study followed recommended guidelines for compatibility testing,[11] including blinded observation. Most published studies on Y-site compatibility have only tested for physical compatibility. We also used the direct visual inspection method, which is considered superior to the turbidimetric method.[19] The 2-hour period over which the physical compatibility study was performed is in keeping with published recommendations for Y-site compatibility testing.[11] Moreover, the transit time for drugs in a Y-site mixing unit rarely exceeds 2 hours. The results of this study strongly reinforce the need for both physical and chemical compatibility testing in Y-site compatibility studies.

In conclusion, during a simulated Y-site administration, combining hydrocortisone sodium succinate at a concentration of 1 mg/mL with a 1 mg/mL solution of midazolam appears to be both chemically and physically compatible. The 9.1% reduction noted is within the limits of acceptability.[13] However, we do not recommend co-administration of hydrocortisone sodium succinate with 2 mg/mL midazolam or ciprofloxacin through a Y-site connector.

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Competing interests

None declared.

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