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Research Article

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Physical compatibility and stability of norepinephrine bitartrate with selected antibiotics for Y-Site administration

Abstract

This study aimed to determine the physical stability of norepinephrine bitartrate (Levophed®) with various antibiotics such as ampicillin-sulbactam, ceftolozane/tazobactam (Zerbaxa®), levofloxacin, azithromycin, cefepime and isavuconazonium sulfate (Cresemba®) when infused simultaneously with Levophed® during simulated intravenous Y-site administration. Simulation of Y-compatibility of intravenous fluids beaches has been experimentally demonstrated by mixing equal volumes of two drugs of interest. Therefore, we prepared a 1:1 mixture of Levophed® by mixing 32 µg/mL or 64 µg/mL of Levophed® individually with clinically relevant concentrations of ampicillin-sulbactam, Zerbaxa®, azithromycin, cefepime, levofloxacin, and Cresemba® when infused simultaneously with Levophed®. Physical compatibility of the mixtures was determined by visual and turbidimetric assessments performed immediately after mixing and at both 2 and 4 hours. The visual assessment and turbidity measurements showed that Levophed® is compatible with ampicillin-sulbactam, Zerbaxa®, azithromycin, cefepime, levofloxacin, and Cresemba®.

Volume 11 Issue 3 - 2023

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Received: July 19, 2023 | **Published:** July 28, 2023

Introduction

Sepsis is a clinical manifestation of severe infection characterized by systemic inflammation.[1] Hence patients with sepsis routinely require treatment with intravenous (IV) antibiotics and vasopressors to avoid septic shock. Intravenous administration of appropriate antibiotics and a vasopressor is recommended to prevent septic shock. The International Guidelines for Management of Severe Sepsis and Septic Shock suggests an immediate antibiotic treatment with vasopressor therapy to target a mean arterial pressure (MAP) of 65 mm Hg.[1] Norepinephrine is used as the first choice vasopressor, and epinephrine is added or potentially substituted when an additional agent is needed to maintain a MAP of 65 mm Hg. Dopamine is an alternative vasopressor agent to norepinephrine reserved only for highly selected patients, such as patients with cardiac arrhythmias.[2] Dopamine is also associated with more adverse effects and mortality. Therefore, Y-site compatibility information/data between norepinephrine and some common antibiotics that help treat sepsis is necessary in many patients. Unfortunately, compatibility data is lacking for various antibiotics such as ampicillin-sulbactam, Zerbaxa®, azithromycin, cefepime, levofloxacin, and Cresemba® when infused simultaneously with Levophed®. This study aimed to determine the compatibility of Levophed® with the antibiotics above using simulated Y-site techniques.

For a drug to be considered compatible, it must be physically compatible, meaning there is no precipitation, change in color, or cloudiness. Drug incompatibility implies that the two drugs that run simultaneously do not dissolve or dilute, causing a decrease in therapeutic efficacy. If drugs are incompatible, this can jeopardize with the patient's safety. Drugs can be identified as inconsistent based on the color of the solution, the formation of particles, and the cloudiness when they interact at the Y–site of the IV line.

Based on the molecular structure of some drugs, we can assume or deny that they would be compatible. For some medicines, ionization and water solubility play a significant role in their dissolution. Levophed® is a water-soluble drug that is acidic and soluble in acids. Each medicine is either acidic or has a weak base. When testing the Y site, it is best to have a 1:1 ratio of the medication to have an equal amount of each drug so that one drug does not mess up the concentration skewing the results. Medications are mixed using syringes and the results are recorded based on precipitation, color, and cloudiness.[3-5]

Materials and methods

All medications used for the test are included in Table 1. Levophed®, as supplied, was further diluted using dextrose 5% in water (Lot No: P347286). Other medications were reconstituted using normal saline (Lot No: 54002JT).

Levophed® (Hospira, lot RL2341) was supplied as a 4 mg/4 mL solution per vial and further diluted to a concentration of 32 µg/mL or 64 µg/mL using 5% dextrose in water. A total of 6 secondary medications, listed in Table 1, were tested with Levophed®. The secondary drugs requiring reconstitution were prepared using sterile water and further recommended diluent per package insert.

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Table 1 Study medications for physical compatibility

Drug	Manufacture	Lot No.	Test Concentration (mg/mL)
Levofloxacin	Sandoz	20057	5000
Ampicillin-Sulbactam	Auromedics	AF0116026A	30000
Azithromycin	APP	6104527	2000
Cefepime	APP	320620	20000
Zerbaxa®	Merk & Co, Inc.	SP1339	15000
Cresemba®	Astellas	928452	1500

The solution's pH analysis was measured using the Fisher Benchmeter pH 501 (Fisher Scientific). The turbidity of each sample was measured by a color-correcting turbidity meter (Hach TL2360 LED; Hach Corp, Loveland, Colorado). Triple determinations of pH, temperature, and turbidity were made of each sample.

Preparation of standard solution

Intravenous fluids in a Y-site administration are mixed in a 1:1 ratio. This ratio was used for each technique during this study (turbidity and pH analysis). Luer-lock syringe (BD, Franklin Lakes, New Jersey), 15 mL of Levophed® (32µg/mL, 64µg/mL) and 15 ml of ampicillin-sulbactam (30000µg/mL) or Zerbaxa® (15000µg/mL) or azithromycin (2000µg/mL) or cefepime (20000µg/mL) or levofloxacin (5000µg/mL) or Cresemba® (1500µg/mL) were combined and mixed gently in a glass vial. Each medication was passed through a 0.22-micron syringe filter before introducing it into the glass vials. Control samples (30 mL) of Levophed®, ampicillin-sulbactam, Zerbaxa®, azithromycin, cefepime, levofloxacin, and Cresemba® were also filtered and prepared as above.

Turbidity and visual inspection

Physical incompatibility is the presence of particulate matter, haziness, or color change during mixing. Samples are deemed incompatible if there is any visible evidence or a change in turbidity of more than 0.5 nephelometric turbidity units (NTU).[3,4,6] Turbidity of each sample was measured by a color-correcting turbidity meter (Hach TL2360 LED; Hach Corp, Loveland, Colorado). Triplicate determinations were made on each of the samples. Using a standard luer-lock syringe (BD, Franklin Lakes, NJ), 15mL of Levophed® and 15mL of ampicillin-sulbactam, Zerbaxa® azithromycin, cefepime, levofloxacin, or Cresemba® were combined into a single syringe and mixed gently. The combined solution was passed through a 0.22-micron syringe filter and introduced into glass vials for use with the Hach TL2360 LED turbidimeter. Control samples (30mL) of Levophed® 64 µg/mL or 32 µg/mL and the antibiotics of interest were also prepared and filtered as above. Each sample was visually inspected (haziness, particulates, or gas generation) under fluorescent light and using a high-intensity light source immediately after preparation, at 2 and 4 hours. At these time points, triplicate turbidity measurements were done using a color-correcting turbidity meter (Hach TL2360 LED; Hach Corp, Loveland, Colorado), and the pH of the solution was analyzed. Samples were assumed incompatible if the change in turbidity measurement was more than 0.5 NTU or if any observance of precipitates, haziness, or gas was observed as reported previously.[6-9] The pH of the solution was measured using a pH meter (Fisher Benchmeter pH 510). PH, temperature, and turbidity measurements were taken immediately after mixing at 2 and 4 hours. The incompatibility in pH is defined as ±1 pH deviation from the initial recorded pH. All samples were stored at room temperature under constant fluorescent light for the duration of the experiment.

Results and discussion

Physical stability

Fifteen mL of Levophed® and 15 mL of various antibiotics were combined into a single syringe, and the integrated solution passed through a 0.22-micron syringe filter. The control samples of each pair were also prepared and filtered the same way as above. Each sample was visually inspected under fluorescent light, and all samples were colorless except levofloxacin which was light pale yellow. However, there was no color change after mixing samples with Levophed®. After using triplicate turbidity measurements, the difference in turbidity was minimal from baseline at 2 and 4 hours for each Levophed® and various antibiotics pair tested. The pH measure was taken immediately after mixing and then at both 2 and 4 hours, which was minimal. In addition, throughout the test period, the temperature remained stable with no changes.

Conclusion

Levophed® is physically compatible with ampicillin-sulbactam, Zerbaxa®, azithromycin, cefepime, levofloxacin, and Cresemba® after simulated Y-site co-administration at relevant drug concentrations for at least 4 hours.

Acknowledgments

The authors thank South University SOP and PCOM for their financial support and laboratory space used in this study.

Conflicts of interest

Authors declare that there is no conflict of interest.

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Citation: Najafabadi IK, Ethredge H, Samuel E, et al. Physical compatibility and stability of norepinephrine bitartrate with selected antibiotics for Y-Site administration. *Pharm Pharmacol Int J*. 2023;11(3):96–97. DOI: 10.15406/ppij.2023.11.00407