Compatibility of Y-Site Injection of Meropenem Trihydrate With 101 Other Injectable Drugs

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Abstract

Objective: The objective of the study was to establish the compatibility of injectable meropenem with 101 other drugs during Y-site administration. **Methods:** Meropenem (50 mg/mL, 10 mL) was combined with 101 undiluted injectable drugs (10 mL each) at room temperature. Each preparation was performed twice. The first sample underwent a visual evaluation and a particle count test by light obstruction immediately after mixing. These tests were repeated 4 hours after mixing using the second preparation. Incompatibility was defined as precipitation or other visual change (turbidity, crystal formation, gas formation, color change) or failure to meet United States Pharmacopeia (USP) <788> I.B specifications at any time point. **Results:** A total of 83 of the 101 injectable drugs tested with meropenem were found to be compatible both visually and using the USP <788> particle counter. The gross incompatibility of the other 17 drugs was determined by visual observation. One mixture complied with the specifications, but showed an increase of temperature upon mixing and was removed from the study. **Conclusion:** Of the 101 drugs tested, 83 were found to be compatible while the remaining 17 were incompatible. One drug was removed from the study as its compatibility was unclear.

Keywords

Y-site administration, meropenem, and compatibility

Introduction

Meropenem trihydrate is a broad-spectrum carbapenem used in a large range of infections. Its use is primarily restricted to complicated infection. This carbapenem is usually diluted at 50 mg/mL and is usually given by intravenous infusion over approximately 15 to 30 minutes. Sometimes, it is given by intravenous infusion over 3 to 4 hours to maximize its efficacy, or as an intravenous bolus injection (5–20 mL) over approximately 5 minutes if required.¹ The maximum dose is 2 g, typically diluted in 40 mL.

In some cases, it can be administered in combination with other intravenous drug by Y-site injection. The compatibility data with other drugs are not well established in the literature.^{2–4} Generally, there are only data for visual compatibility with other drugs.^{2–4}

The United States Pharmacopeia (USP) establishes specifications regarding the presence of particulate matters in injections, USP <788>. For an injection volume of less than 100 mL, the specifications read as follows:

The preparation complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10 µm and does not exceed 600 per container equal to or greater than 25 µm.⁵

In this study, we simulated a Y-site injection of the meropenem with 101 other drugs. The compatibility data were evaluated by both visual observations and particle count test. Drugs were considered compatible if they complied with both tests initially and after 1 hour and 4 hours.

Methods

Materials

The meropenem (Fresenius Kabi lot MCA1026 and Sandoz lot 0007D6) used in the study was supplied in 1 g/30 mL vials and contained the equivalent of 50 mg/mL (total 20 mL) after dilution with 20 mL of sterile water for injection.

Meropenem was successively mixed with the 101 other injectable drugs shown in Tables 1 and 2. Drugs requiring dissolution were prepared with sterile water for injection,

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Table 1. Mixtures Not Complying With Specifications.

Drug name	Concentration (mg/mL)	Manufacturer	Lot	Comments
Amiodarone hydrochloride	50	Sandoz	GN9954	T = 1 h Opaque liquid
Bupivacaine hydrochloride	5	Hospira	63280DD	T = 0 h Opaque liquid
Calcium gluconate	100	Fresenius Kabi	6011962	T = 4 h Change in the color (turned yellow)
Ciprofloxacin lactate	2	Sandoz	60574	T = 4 h Crystallization
Cyclosporine	50	Novartis	S0085	T = 0 High viscosity, test cannot be made
Diazepam	5	Sandoz	FJ0284	T = 0 Precipitation
Dipyridamole	5	Fresenius Kabi	6112728	T = 0 Opaque liquid
Dobutamine hydrochloride	12.5	Hospira	61123DK	T = 4 h Precipitation
Hydralazine hydrochloride	20	Sterimax	PLNE1620	T = 0 Color change to yellow-brown
Hydroxyzine hydrochloride	50	Sandoz	GB3916	T = 0 Precipitation
Ketamine hydrochloride	50	Sandoz	GH6414	T = 0 Precipitation
Midazolam	1	Sandoz	GF8221	T = 0 Precipitation
Nitroglycerin	5	Omega	5G044	Formation of opaque liquid at T = 0
Ondansetron hydrochloride dihydrate	2	Mylan	7008090	T = 0 Precipitation
Phenytoin sodium	50	Sterimax	152079.1	T = 0 Formation of opaque liquid
Sodium phosphate dibasic	3 mmol/mL	Sandoz	GL7535	T = 1 h Degassing (visible bubbles)
Vancomycin hydrochloride	50	Sandoz	GC4605	T = 0 Precipitation

unless the monograph required 0.9% sodium chloride or dextrose 5%. All drugs, including meropenem, were tested at their maximum, initial, or original concentration to simulate the worst case scenario and detect any potential clinical problems. The only 2 exceptions were imipenem/cilastatin that was diluted at the infusion concentration as it is a suspension and not a solution like the other tested drugs, and cyclosporine that was diluted because the original concentration is too viscous to perform the test. Concerning drugs in glass ampoules, a 5- μ m filter was used for the collection to remove any potential glass debris from the solution.

Test Solutions

All tests were carried out under fluorescent and natural light at controlled room temperature ($21 \pm 2^\circ\text{C}$). Manipulations were carried out under a laminar flow hood in a sterile room to limit the risks of contamination, as proposed by the USP <788>.⁵ All mixtures were made in duplicate using 30 mL

sterile polypropylene syringes (BD). A volume of 10 mL of meropenem was manually mixed by inversion with 10 mL of each tested drug. Immediately after mixing meropenem and the tested drug, a visual evaluation with the naked eye against a white and black background was performed to detect any visual incompatibilities (discoloration, haziness, degassing, precipitation, or lack of miscibility).⁶⁻⁸ In the absence of these signs, 1 of the 2 samples was tested with the particle counter. Mixtures with any visually detectable incompatibility were not tested with the particle counter to avoid unnecessary contamination or damage of the instrument. One hour later, another visual test was performed with the second sample. Four hours later, the second sample underwent the same initial procedure, which is a visual test and a particle count test.

The time interval of 4 hours simulated the contact time of 2 simultaneous Y-site injections in a worst case scenario conditions, ie, very low flow rates, as used for premature infants. Typically, the maximum length of stay in the tubing of 2 drugs administered in Y-site injection is about 3 hours.^{7,8}

Table 2. Mixtures Complying With Specifications.

Drug name	Concentration (mg/mL)	Manufacturer	Lot
Acetylcysteine	200	Alveda Pharma	60086
Adrenaline hydrochloride	1	ERFA	F5J017
Albumin, human (Alburex-25)	250	CSL Behring	4309900012
Amikacine sulfate	250	Sandoz	FP9767
Amphotericin B (liposomal)	2	Astellas—Gilead	006315
Ampicillin sodium	250	Novopham	Fw6817
Atropine sulfate	0.4	Alveda Pharma	30153
Azithromycin monohydrate	100	Sterimax	7603015
Aztreonam	100	Squibb	4G79396R
Benzotropine mésylate	1	Omega	4B543
Bretylum	50	Sandoz	EF9361
Caffeine citrate	20	Sagent Pharmaceuticals	MR11552
Calcium chloride	100	Lifeshield	65469DK
Caspofungin acetate	0.5	Fab Ste-Justine	F20170119034
Cefazolin sodium	100	Hospira	118G002
Cefotaxime sodium	100	Fabrication Ste-Justine	F20170118027
Cefoxitin sodium	100	Novopham	0001D6
Ceftazidime	100	Fresenius Kabi	105935c
Ceftriaxone sodium	100	Sterimax	4CN1652CA
Cefuroxime sodium	100	Sterimax	157043.1
Clindamycin phosphate	150	Sandoz	GH7982
Cloxacillin sodium	250	Sterimax	2CL1548CA
Colistimethate sodium	75	Sterimax	00200B16
Cyclosporine	5	Novartis	S0085
Dexamethasone sodium phosphate	4	Sandoz	FW2103
Dexmedetomidine Hydrochloride	0.1	Hospira	67294DK
Dextrose	50	Baxter	W6127BO
Digoxin	0.25	Sandoz	FG7843
Dimenhydrinate	10	Sandoz	FU4820
Diphenhydramine hydrochloride	50	Fresenius Kabi	6112728
Dopamine hydrochloride—Dextrose	32 - 50	Hospira	P347740
Ertapenem	100	Merck	M009484
Erythromycin Lactobionate	50	Amdipharma pharmaceuticals	44906TB24
Esmolol hydrochloride	10	Baxter	115376Z
Fentanyl citrate	0.05	Sandoz	GF5993
Fluconazole	2	Sandoz	GA8831
Foscarnet	24	Clinigen	16KA3285
Furosemide	10	Omega	6C286
Gentamicin sulfate	40	Sandoz	GB3917
Granisetron hydrochloride	1	Omega	5GO45
Heparin sodium	1000 units/mL	Sandoz	GB3923
Hydrocortisone sodium succinate	125	Pfizer	R78226
Hydromorphone hydrochloride	10	Sandoz	FM5398, FA1043
Imipenem/cilastatin	50	Hospira	615F002
Insulin (Humulin R®)	100 units/mL	Lilly	C517669c
Isoproterenol hydrochloride	0.2	Sandoz	FM8982
Labetalol hydrochloride	5	Sandoz	GE8284
Levocarnitine	200	sigma-tau pharmaceuticals	140250
Lidocaine hydrochloride	10	Alveda Pharma	0121AF01
Linezolid	2	Teva	170115023

(continued)

Table 2. (continued)

Drug name	Concentration (mg/mL)	Manufacturer	Lot
Lorazepam (this mixture was excluded from the study as it showed an exothermic reaction upon mixing)	4	Hospira	58232EV
Magnesium sulfate	500	Fresenius Kabi	6011287
Mannitol	250	Hospira	61171DK
Methylprednisolone sodium succinate	62.5	Novopham	4460915
Metoclopramide hydrochloride	5	Sandoz	F63415
Metoprolol tartrate	1	Sandoz	ED2734
Metronidazole	5	Hospira	66002JT
Milrinone lactate	1	Fresenius Kabi	6012487
Morphine sulfate	50	Sandoz	FV4894
Multi-12® (multivitamins)	complex (original vial)	Sandoz	GA9314
Multi-12/K pediatric® (multivitamins)	complex (original vial)	Sandoz	GD1106
Naloxone hydrochloride	0.4	Alveda Pharma	60308
Nitroprusside sodium	25	Hospira	643103A
Norepinephrine bitartrate	1 mg base	Sandoz	6K1258
Oxytocin	10 IU/mL	Hospira	676448-E01
Pantoprazole sodium	4	Sandoz	GP6390
Penicillin G sodium	500 000 IU/mL	Fresenius Kabi	30246
Piperacillin sodium	200	Hospira	1P301MC6
Piperacillin/tazobactam	200	Sterimax	2PT15139CA
Potassium chloride	2 mEq/mL	Hospira	50151DK
Potassium phosphate dibasic	3 mmol P/mL	Baxter	FR0446
Procainamide	100	Sandoz	GL9766
Propranolol hydrochloride	1	Sandoz	FX4815
Ranitidine hydrochloride	25	Sandoz	GL9766
Rocuronium bromide	10	Sandoz	FV7482
Salbutamol sulfate	1	GlaxoSmithKline	J393
Sodium bicarbonate	1 mEq/mL	Hospira	62051EV
Sufentanil citrate	0.05	Sandoz	FT3523
Tobramycin sulfate	40	Fresenius Kabi	6011081
Trimethoprim /sulfaméthoxazole	16/80	Aspri Pharma	5M406, 5M392
Valproate sodium	100	Abbvie	56020DD
Voriconazole	10	Sandoz	GB1800

Control Solution

Every day, a control test was performed using 20 mL of sterile water for injection to ensure system suitability.

Two lots of meropenem were used and both of them were tested with sterile water, with a ratio of 1:1, using the particle counter to ensure the initial quality of the product.

Compatibility Definition

A mixture was considered compatible when no visual change was observed, discoloration, haziness, degassing, precipitation, or lack of miscibility initially, after 1 hour and after 4 hours and also complied with USP <788> specifications by light obscuration for injection volumes of less than 100 mL initially and after 4 hours.

The particle counting was carried out using the LS-20 Liquid Particle Counter (Lighthouse Worldwide Solutions, Medford, Oregon), according to USP <788> 1.B.^{5,6,9} To test small volumes, it is recommended to analyze 4 portions greater than 5 mL each and eliminate the first reading.⁹ In our case, the sample volume was 20 mL, the first 4 mL were used to prime the instrument. An analysis was then carried out on three 5-mL samples. After this procedure, 1 mL remained in the vial and prevented the aspiration of air during the analysis of the last fraction. This procedure facilitated manipulation and reduced the total amount of drugs used.^{8,10}

Results

Of the 101 drugs tested, 83 were considered compatible based on the acceptance criteria. The incompatible drugs are

listed in Table 1 while the compatible drugs are listed in Table 2. The numbers of particles per mL with a size equal or greater than 10 μm were between 0.21 and 486 for the compatible drugs. The numbers of particles with a size equal or greater than 25 μm were between 0 and 310.2 throughout the overall test for the compatible drugs. All mixtures that were visually compatible also conformed to the USP criteria for the particle count test.

Of the 101 drugs tested, 17 were incompatible based on the acceptance criteria. Incompatible drugs were identified with the visual test only as gross incompatibility was observed. For this reason, there are no data available for the particle counter test for the incompatible drugs as they were not tested using this instrument. Among the incompatible drugs, 6 drugs precipitated immediately, 4 became turbid immediately, 1 changed color immediately, 1 was too viscous to be analyzed, 1 became turbid at 1 hour, 1 formed bubbles at 1 hour, 2 had visible crystals at 4 hours, and 1 changed color at 4 hours.

When the 2 lots of meropenem diluted alone in water were analyzed, the numbers of particle with a size equal or greater than 10 μm was between 10.4 and 89.6 and the number of particle with a size equal or greater than 25 μm was between 1 and 6.

The mixture of lorazepam with meropenem showed an increase in temperature upon mixing; although it complied to the specifications, there was a doubt regarding the compatibility of this mixture. We preferred to remove this mixture from the study.

Discussion

The simulated Y-injection site model used in this study is similar to those used in the previous compatibility studies.^{6-8,10} The 1:1 ratio of the 2 drugs tested simulated the amount of drug that can be mixed in a Y-site administration and this method is widely used in the literature.^{6-8,10} Because drugs were tested at their highest concentration, it would be unlikely to get different results at less concentrated level. The mean number of particles was higher right after the mixing but always within the specifications. It is probably caused by the presence of air bubbles introduced during mixing.

In this study, only physical incompatibility was evaluated. This type of incompatibility refers to a visual change or physical aspect of the drug (discoloration, haziness, degassing, precipitation, or lack of miscibility) and informs us about the safety of mixing those drugs for administration. There are 2 other types of incompatibilities: pharmacological and chemical incompatibilities, both informing us about its safety. Pharmacological incompatibility refers to a change in the pharmacologic response and can only be measured by a clinical trial, while chemical incompatibility refers to a change in the chemical structure of 1 or both of the drugs and can be measured by analytical chemistry method like high-performance liquid chromatography. These 2 types of incompatibility were out of the scope of this study.

In our study, there was one occurrence of a possible chemical incompatibility and that happened with lorazepam. When lorazepam was mixed with meropenem, the experimenter reported an increase in the temperature after the mixture. It was not validated objectively with a thermometer, but this could be caused by an exothermic reaction. However, lorazepam showed to be physically compatible with meropenem based on the study criteria. In doubt, we have chosen to remove this compound from the study. No other event of the same kind was reported during the study.

Our results are similar to those found in the literature,²⁻⁴ but there are a few differences.²⁻⁴ Diazepam, ondansetron, and calcium gluconate were found to be incompatible with meropenem, as reported in the literature.²⁻⁴

Atropine sulfate, caspofungin acetate, cyclosporine, dexamethasone sodium phosphate, digoxin, diphenhydramine HCl, fluconazole, furosemide, gentamicin sulfate, heparin sodium, insulin regular, linezolid, metoclopramide HCl, milrinone lactate, morphine sulfate, norepinephrine bitartrate, and potassium chloride were found to be compatible with meropenem, as reported in the literature.²⁻⁴

Some drugs were found compatible in our study were reported to be incompatible in the literature. Pantoprazole was reported incompatible, using the ethylenediaminetetraacetic acid (EDTA)-free formulation of pantoprazole.² Mannitol, sodium bicarbonate, and multivitamin are also reported incompatible in an admixture compatibility test because of meropenem loss and darkening of the solution.² For Y-site compatibility test specifically, Amphotericin B precipitated in literature, but it was tested at a higher concentration than in our study (5 mg/mL vs 2 mg/mL) and the formulation was not specified (Ambisome vs Fungizone).²

Some drugs found incompatible in our study were reported to be compatible in the literature. Dobutamine was reported compatible in an additive compatibility test but it was less concentrated in this study than in ours.² For Y-site compatibility test specifically, vancomycin was reported compatible in the literature, but was also tested at a lower concentration.²

The results of our study show that the particle count tests confirmed the results of the visual test and the validity of our results.

Conclusion

Of the 101 tested drugs, 83 were found to be compatible when mixed in a 1:1 ratio with meropenem, with both substances at their maximum, initial or original concentration (exceptions: Imipenem-cilastatin and cyclosporine). However, the test performed takes care of the physical criteria, which does not guarantee the clinical efficacy of compatible mixtures. It could also be interesting to perform the test at a lower concentration for mixtures demonstrated incompatible in this study.

Declaration of Conflicting Interests

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