Original Article

Compatibility of Cloxacillin Sodium with Selected Intravenous Drugs During Simulated Y-Site Administration

Thomas Sullivan, PharmD*; Jean-Marc Forest, MSc†; and Grégoire Leclair, PhD‡

Abstract

Background: Data regarding Y-site compatibility of intravenous (IV) cloxacillin sodium with other drugs are scarce and incomplete.

Objective: To establish the compatibility of IV cloxacillin with 89 injectable drugs during simulated Y-site administration.

Methods: Cloxacillin sodium (10 mL, 100 mg/mL) was combined with 89 undiluted IV drugs (10 mL, each). Tests were duplicated and performed at room temperature. Visual evaluation and a light obscuration particle count test were performed on 1 of the 2 solutions immediately after mixing. The second mixture underwent visual evaluation after 15 minutes, 1 hour, and 4 hours, followed by a particle count test at 4 hours. Drugs were considered incompatible if the mixture precipitated or became turbid within the 4-hour period or exceeded the particle count limit allowed by Test 1.B of USP <788> initially or at 4 hours.

Results: Of the 89 tested drugs, 64 were compatible for up to 4 hours. The remaining 25 drugs were incompatible. Of these incompatible drugs, 16 were identified visually, and 9 were identified by the light obscuration particle count test.

Conclusions: Sixty-four IV drugs were found to be compatible with cloxacillin via simulated Y-site, whereas 25 drugs were found to be incompatible with the antibiotic. The light obscuration particle count test should be used to complement visual evaluation when samples do not precipitate immediately.

Key Words—cloxacillin, compatibility, Y-site

Hosp Pharm—2015;50:214–220

Cloxacillin sodium is a penicillin derivative antibiotic indicated for staphylococcus and streptococcus infections. This antibiotic can be administered orally and intravenously.¹ In hospital settings, cloxacillin can be administered via Y-site injection with other intravenous (IV) drugs. Data regarding the Y-site compatibility of cloxacillin with other drugs are scarce and incomplete. Oxacillin sodium is the most chemically similar drug available in the United States, differing from cloxacillin only in the absence of a chlorine atom on the benzene ring.^{2,3} Despite the structural similarities, Y-site compatibility data for oxacillin cannot be extrapolated to

cloxacillin. There is therefore a need to evaluate the Y-site compatibility of cloxacillin with other IV drugs.

Chapter 788 of the United States Pharmacopeia (USP) recommends that injectable solutions be analyzed using a light obscuration particle count test.⁴ The USP criteria establish limits on the number of particles greater than 10 and 25 µm that are allowed in an injectable solution. USP has 2 sets of limits, depending on the volume of the solution to be administered; Test 1.A applies to volumes greater than 100 mL, and Test 1.B applies to volumes less than 100 mL. The USP particle limits are described in Table 1. For this study, the combined volumes of the

*Pharmacist, Jewish General Hospital, Montreal, Quebec, Canada; †Pharmacist, CHU Ste-Justine, Montreal, Quebec, Canada; ‡Assistant Professor, Université de Montréal, Montreal, Quebec, Canada. Corresponding author: Grégoire Leclair, PhD, Université de Montréal, C.P. 6128, succursale Centre-ville, Montréal, Quebec, H3C 3J7 Canada; phone: 514-343-6111; e-mail: gregoire.leclair@umontreal.ca

Table 1. USP particle limits for injectable solutions⁴

	No. of 10 µm particles	No. of 25 µm particles
USP Test 1.A (for volumes >100 mL)	<25 per mL	<3 per mL
USP Test 1.B (for volumes <100 mL)	<6,000 per container volume	<600 per container volume

solutions did not exceed 100 mL, therefore the Test 1.B limits were utilized.

The primary objective of this study was to determine the Y-site compatibility of cloxacillin with 89 IV drugs using visual evaluation and light obscuration particle counting.

METHODS

Test Materials

Cloxacillin sodium (Sterimax, lot 1CL1218CA) was supplied as a 2 g powder per vial and reconstituted with 18.8 mL of sterile water for injection, USP (Baxter, lot C880864) to yield a nominal concentration of 100 mg/mL. This reconstitution represents the practice at CHU Ste-Justine hospital center and does not match the recommendations of the manufacturer. The manufacturer suggests diluting with 6.8 mL to yield a nominal concentration of 250 mg/mL.⁵ CHU Ste-Justine hospital center has preferred to reconstitute to a 100 mg/mL concentration in order to simplify all dosing calculations.

A total of 89 secondary drugs, listed in **Table 2** and **Table 3**, were tested with cloxacillin. The secondary drugs requiring reconstitution were prepared using sterile water for injection unless otherwise indicated in the product's monograph. All liquid secondary drugs, with the exception of cyclosporine, were used without further dilution. Cyclosporine was diluted to a concentration of 5 mg/mL using sterile water for injection because the 50 mg/mL solution was too viscous for analysis. Drugs stored in breakable glass ampules were filtered using a 0.45 µm filter.

Test Solutions

All experiments were conducted in a laminar flow hood at room temperature under normal fluorescent light. Solutions were mixed in sterile 50 mL centrifuge tubes (Sarstedt, no. 62.547.004) until homogeneous. Upon mixing, each sample was immediately inspected visually, against both black and white backgrounds, with the unaided eye under normal fluorescent light for color changes, gas bubbles, haze, or precipitation.⁶ In the absence of precipitation, the sample was

immediately analyzed using the liquid particle counter and a second sample was similarly prepared. These second samples underwent further visual evaluation at 15 minutes, 1 hour, and 4 hours, followed by a final particle count test at 4 hours. Drugs that precipitated immediately were discarded without further evaluation.

Control Solutions

On each test day, 2 control solutions containing 10 mL of cloxacillin sodium and 10 mL of sterile water for injection, USP were prepared to ensure the quality of the cloxacillin solution. The first solution was immediately analyzed using the particle counter and the second solution was similarly analyzed after 4 hours.

Particle Count Test

Particle counts were determined using the LS-20 Liquid Particle Counter (Lighthouse Worldwide Solutions, Medford, OR). Chapter 788 of the USP recommends using a minimum volume of 20 mL and analyzing four 5 mL aliquots, discarding the results of the first aliquot.⁴ In this study, the first 4 mL were discarded and 3 analyses were performed using 5 mL; the last 1 mL was discarded. This minor modification was required to limit the aspiration of air bubbles at the end of each run, which are mistaken for particles by the apparatus.

The accuracy of the particle counter was verified once during the experiment using a control solution with a specific concentration of 15 µm particles (*Pharm-Trol* Particle Count Control solution, Thermo Scientific, lot 38713). The number of particles measured in the control solution was within the acceptable range, as described in the USP Reference Standard (USP Reference Standard: Particle Count - Suspension 25 mL, cat. no. 1500502, lot K0H089), therefore the particle counter was deemed accurate for the duration of the experiment.

Definition of Compatibility

Visual compatibility was defined as the absence of any particulate matter visible to the naked eye, substantial increase in turbidity or haze, or production of gas bubbles.⁷ Particulate matter compatibility

Table 2. Drugs compatible with cloxacillin sodium^a (100 mg/mL) in simulated Y-site administration (complied with USP specifications for particulate matter in injections)

	Drug name	Concentration (mg/mL)	Manufacturer	Lot
1	Acetylcysteine	200	AlvedaPharma	12025013
2	Acyclovir sodium	50	PPC	6002138
3	Adrenaline hydrochloride	1	Erfa	296823
4	Adrenaline	0.1	Hospira	06-433-DK
5	Albumin, human (Alburex-25)	250	Behring	4309900003
6	Amiodarone hydrochloride	50	Sandoz	CJ8512
7	Amphotericin B liposomal	4	Astellas	042227AA
8	Ampicillin sodium	250	Novopharm	CJ7690
9	Atropine sulfate	0.4	Sandoz	CF2473
10	Benztropine mesylate	1	Omega	1E656, 1B585
11	Calcium chloride	100	Hospira	96-345-DK, 96-208-DK
12	Calcium gluconate	100	PPC	6001828
13	Caspofungin acetate	5	Merck	2062040
14	Cefazolin sodium	10	Novopharm	360319
15	Cefotaxime sodium	95	Sanofi	121675
16	Cefoxitin sodium	100	Hospira	123B002
17	Ceftazidime	95	PPC	103820C
18	Ceftriaxone sodium	100	Sandoz	BR0011, BT8263
19	Cefuroxime sodium	90	PPC	8309
20	Clindamycin phosphate	150	Sandoz	CF4314
21	Cyclosporine	5	Novartis	S0065
22	Dexamethasone sodium phosphohate	4	Omega	2G034, 2G038
23	Dextrose 50 %	500	Hospira	15-439-OK
24	Digoxin	0.05	Sandoz	BK 4807
25	Dimenhydrinate	10	Sandoz	CL1904
26	Dopamine hydrochloride	3.2	Baxter	P290874
27	Esmolol hydrochloride	10	Baxter	071310Z
28	Fentanyl citrate	0.05	Sandoz	CJ3610
29	Fluconazole	2	Sandoz	CJ4307
30	Furosemide	10	Omega	2D951, 2F004
31	Heparin sodium	100 IU/mL	PPC	6003871
32	Hydrocortisone sodium succinate	125	Novopharm	821111
33	Hydromorphone hydrochloride	10	Sandoz	CJ7015
34	Insulin (Humulin R)	100 IU/mL	Lilly	A960330C
35	Isoproterenol hydrochloride	0.2	Sandoz	CM6492
36	Ketamine hydrochloride	50	Sandoz	CM9804
37	Levocarnitine	200	SigmaTau Pharm	91016
38	Levofloxacin	5	Hospira	11-165-JT

(continued)

Table 2. Drugs compatible with cloxacillin sodium^a (100 mg/mL) in simulated Y-site administration (complied with USP specifications for particulate matter in injections) (CONT.)

	Drug name	Concentration (mg/mL)	Manufacturer	Lot
39	Lidocaine hydrochloride 1%	1	AlvedaPharma	11401020
40	Magnesium sulfate	500	PPC	6003892
41	Mannitol	250	Hospira	15-140-DK
42	Meropenem trihydrate	50	Sandoz	0011D2
43	Methylprednisolone sodium succinate	62.5	Novopharm	G00030
44	Metoclopramide hydrochloride	5	Sandoz	CH6012
45	Metronidazole	5	Hospira	20-039-JT
46	Milrinone lactate	1	PPC	6003849
47	Multi-12 (multivitamin)		Sandoz	BT7797
48	Multi-12/K1 pediatric (multivitamin)		Sandoz	CJ7837
49	Naloxone hydrochloride	0.4	Sandoz	AY2119, CJ4230, AP8587
50	Sodium nitroprusside	25	Hospira	112463A
51	Norepinephrine bitartrate	1	Sandoz	CG8316, CK9591
52	Ondansetron hydrochloride dihydrate	2	Sandoz	CM7105
53	Oxytocin	10 IU/mL	PPC	6003582
54	Pantoprazole sodium	4	Sandoz	CL4631
55	Penicillin G sodium	500 000 IU/mL	PPC	105262
56	Piperacillin sodium/tazobactam	225	Sandoz	BW5242
57	Potassium chloride	2 mEq/mL	Hospira	07-019-DK
58	Propranolol hydrochloride	1	Sandoz	CM0580
59	Ranitidine hydrochloride	25	GlaxoSmithKline	C576195, C586632
60	Salbutamol sulfate (Albuterol)	1	GlaxoSmithKline	M462
61	Sodium bicarbonate	84	Hospira	19-193-EV
62	Sufentanil citrate	0,05	Sandoz	CN8916
63	Valproic acid	100	Abbott	10005DD
64	Voriconazole	10	Pfizer	Z040502

^aSterimax, lot 1CL1218CA.

was defined as an average number of particles no more than 300 per milliliter equal to or greater than 10 µm and no more than 30 per milliliter equal to or greater than 25 µm. These criteria are based on USP <788> Test 1.B specifications using a container volume of 20 mL: "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."^{4(p399)}

RESULTS

Control solutions made up of 10 mL of cloxacillin sodium 100 mg/mL and 10 mL of sterile water for injection, USP passed both the visual evaluation and the particle count test initially and after 4 hours during each day of testing. The average particle count of these control solutions immediately after mixing on all days was no more than 30 particles per milliliter equal to or greater than 10 µm and no more than 0.7 particles per milliliter equal to or greater

Table 3. Drugs incompatible with cloxacillin sodium^a (100 mg/mL) in simulated Y-site administration (did not comply with USP specifications for particulate matter in injections)

	Drug	Concentration (mg/mL)	Manufacturer	Lot	Incompatibility
1	Amikacin sulfate	250	Sandoz	CB8036	>30 x 25 µm particles/mL at T=0
2	Azithromycin monohydrate	100	Sterimax	7005545	Precipitation at T=0
3	Chlorpromazine hydrochloride	25	Sandoz	AY5529	Precipitation at T=0
4	Ciprofloxacin lactate	2	Omega	A020282	>30 x 25 µm particles/mL at T=0
5	Diazepam	5	Sandoz	BB9997, 159114, CA4470	>30 x 25 µm particles/mL at T=0
6	Diphenhydramine hydrochloride	50	PPC	6004001, 6003080	Precipitation at T=0
7	Dobutamine hydrochloride	12.5	Hospira	12-088-DK	Precipitation at T=0
8	Droperidol	2.5	Sandoz	BT 9146	Precipitation at T=0
9	Erythromycin lactobionate	50	Amdipharm	88-409-TB-23	Precipitation at T=0
10	Gentamicin sulfate	40	Sandoz	CG2537	Precipitation at T=0
11	Hydralazine hydrochloride	20	Sterimax	00501B10	Yellow opaque at T=4h
12	Labetalol hydrochloride	5	Sandoz	CN4355	Precipitation at T=0
13	Lorazepam	4	Sandoz	CA7061	>30 x 25 µm particles/mL at T=4h
14	Midazolam	5	PPC	6003319, 6003849	Precipitation at T=0
15	Morphine sulfate	50	Sandoz	BX6159	Precipitation at T=0
16	Nitroglycerin	5	Omega	1F690	>30 x 25 µm particles/mL at T=4h
17	Phenytoin sodium	50	Sandoz	CH9389, BK8196, CG2519, BT9159	Precipitation at T=1h
18	Piperacillin sodium	300	Hospira	1P301MC1	>30 x 25 µm particles/mL at T=0
19	Potassium phosphate	3mmol/mL	PPC	6103592	>30 x 25 µm particles/mL at T=4h
20	Promethazine hydrochloride	25	Sandoz	BP2439	Precipitation at T=0
21	Rocuronium bromide	10	Merck	179835	Precipitation at T=0
22	Ticarcillin/clavulanic acid	200/6.7	GSK	553181	>30 x 25 µm particles/mL at T=0
23	Tobramycin sulfate	40	Sandoz	CB9754	Precipitation at T=0
24	Trimethoprim/Sulfamethoxazole	16/80	Aspen Triton	1L255	>30 x 25 µm particles/mL at T=0 & 4h
25	Vancomycin hydrochloride	50	PPC	6103664	Precipitation at T=0

Note: T=0 = initial time; T=1h = time at 1 hour; T=4h = time at 4 hours.

^aSterimax, lot 1CL1218CA.

than 25 µm. After 4 hours, the average particle count of control solutions on all days was no more than 15 particles per milliliter equal to or greater than 10 µm and no more than 1.1 particles per milliliter equal to or greater than 25 µm.

Of the 89 tested drugs, 64 were compatible (Table 2). These drugs were visibly compatible throughout the 4-hour period and complied with the particle count criteria immediately after mixing and also after 4 hours. The number of particles per mil-

liliter equal to or greater than 10 μm of these 64 compatible drugs ranged from 0.9 to 72.1 at the time of mixing and from 0.9 to 191.7 after 4 hours. The number of particles per milliliter equal to or greater than 25 μm of these same drugs ranged from 0.0 to 28.5 at the time of mixing and from 0.0 to 21.4 after 4 hours.

A total of 25 drugs were incompatible (Table 3). Visual incompatibility was observed for 16 of these drugs (14 precipitated immediately, phenytoin sodium precipitated after 1 hour, and hydralazine hydrochloride became turbid after 4 hours). A total of 6 drugs passed the visual evaluation throughout the 4-hour period, but failed the particle count test either initially or at 4 hours. These drugs included amikacin sulfate, diazepam, lorazepam, nitroglycerin, piperacillin sodium, and potassium phosphate. The 3 remaining incompatible drugs (ciprofloxacin lactate, ticarcillin/clavulanic acid, and trimethoprim/sulfamethoxazole) were suspected incompatible when examined visually and were confirmed to be incompatible using the particle count test. Of the incompatible drugs that underwent the particle count test, the number of particles per milliliter equal to or greater than 10 μm ranged from 31.3 to 247.5 at the time of mixing and from 55.7 to 20756 after 4 hours. For these same solutions, the number of particles per milliliter equal to or greater than 25 μm ranged from 11.1 to 243.1 at the time of mixing and from 25.9 to 7003 after 4 hours.

DISCUSSION

The simulated Y-injection site model used in this study is based on those used in previous compatibility studies.^{6,7} The models from these previous studies stem from the findings of Allen et al. They suggested that when 2 solutions are simultaneously administered via Y-injection, those solutions will mix in a 1:1 ratio.⁸ The solutions were tested at high concentrations following the principle that, in general, 2 drugs that do not precipitate at high concentration are unlikely to precipitate at lower concentrations. It is understood that this methodology may not accurately reflect the conditions in Y-site administration and may be interpreted by some to reflect the conditions of 2 drugs mixed in a syringe.⁹ Samples were analyzed for up to 4 hours as is typical in Y-site compatibility experiments.^{6,7,10}

The results from this study concerning amikacin sulfate and pantoprazole sodium are not consistent with published data on these 2 molecules.^{11,12} Amikacin was previously listed as compatible with cloxacillin,¹¹ but it failed the particle count test in

this study. Pantoprazole has been previously listed as incompatible, but it passed both the visual examination and the particle count test in this study.¹² Consultation with one of the authors (J.M. Forest, oral communication, August 2013) responsible for the previous pantoprazole data confirms that a different formulation of pantoprazole was used in their study. These findings reinforce the disparity in compatibility of different formulations of the same drug and the importance of retesting new formulations for compatibility.

The results of this study demonstrate the value of the light obscuration particle test in evaluating the compatibility of 2 drugs. Nine of the 89 drug mixtures tested would have been considered compatible if evaluated by visual observation alone. The light obscuration particle test should be considered for those drugs that do not precipitate immediately upon mixing.

CONCLUSION

Sixty-four IV drugs were found to be compatible with cloxacillin via simulated Y-site, whereas 25 drugs were found to be incompatible with the antibiotic. The light obscuration particle count test should be used to complement visual evaluation when samples do not precipitate immediately.

ACKNOWLEDGMENTS

This study was jointly funded by CHU Ste-Justine and Université de Montréal.

The authors declare no conflicts of interest.

REFERENCES

1. Katzung BG, Masters SB, Trevor AJ. *Basic and Clinical Pharmacology*. 11th ed. New York: McGraw-Hill; 2010:779.
2. National Center for Biotechnology Information (US). PubChem Compound Database; CID=6098 (cloxacillin). Bethesda, MD: National Center for Biotechnology Information (US). 2005. <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6098>. Accessed February 22, 2013.
3. National Center for Biotechnology Information (US). PubChem Compound Database; CID=6196 (oxacillin). Bethesda, MD: National Center for Biotechnology Information (US). 2005. <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6196>. Accessed February 22, 2013.
4. <788> Particulate matter in injections. In: *United States Pharmacopeia. USP 36*. Rockville, MD: United States Pharmacopeia; 2012:350-353.
5. SteriMax Inc. Cloxacillin for injection [prescribing information]. Mississauga, ON: Author; 2012.

6. Kumar A, Mann HJ. Visual compatibility of oritavancin diphosphate with selected coadministered drugs during simulated Y-site administration. *Am J Health Syst Pharm.* 2010;67:1640-1644.
7. Bramm MK, Chan P, Heatherly K, et al. Compatibility of doripenem with other drugs during simulated Y-site administration. *Am J Health Syst Pharm.* 2008;65:1261-1265.
8. Allen LV, Levinson RS, Phisutsinhrop D. Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets. *Am J Hosp Pharm.* 1977;34:939-943.
9. Truven Health Analytics: Trissel's 2 clinical pharmaceuticals database (parenteral compatibility): Cloxacillin - pantoprazole compatibility detail. www.micromedexsolutions.com/micromedex2. Accessed February 24, 2013.
10. Trissel LA, Leissing NC. *Trissel's Tables of Physical Compatibility*. Lake Forest, IL: MultiMatrix, Inc.; 1996.
11. Nunning BC, Granatek AP, Ricci RA. Physical compatibility and chemical stability of amikacin sulfate in combination with antibiotics in large-volume parenteral solutions – part III. *Curr Ther Res Clin Exp.* 1976;20:369-416.
12. Péré H, Chassé V, Forest JM, Hildgen P. Compatibilité du pantoprazole injectable lors d'administration en Y. *Pharmactuel.* 2004;37:193-196. ■