Original Article

Physical and Chemical Compatibility of Injectable Acetaminophen During Simulated Y-Site Administration

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Abstract

Purpose: The physical and chemical compatibility of intravenous acetaminophen with commonly administered injectable medications was evaluated.

Methods: Simulated Y-site evaluation was accomplished by mixing 2 mL of acetaminophen (10 mg/mL) with 2 mL of an alternative intravenous medication and subsequently storing the mixture in a polypropylene syringe for 4 hours. The aliquot solutions were visually inspected and evaluated for crystal content at 4 hours by infusing 4 mL of the medication mixture through a 0.45- μ m nitrocellulose filter disc. Medication mixtures that were selected for chemical stability testing were analyzed by high-performance liquid chromatography at 0, 1, and 4 hours using a Zorbax Eclipse Plus C18, 4.6 x 100 mm, 3.5- μ m column for separation of analytes with subsequent diode-array detection. Medications were considered chemically compatible if the concentrations of all components were >90% of the original concentrations during the 4 hour simulated Y-site compatibility test.

Results: U.S. Pharmacopeial Convention (USP) standards for physical particle counts were met for acetaminophen injection (10 mg/mL) when combined with cefoxitin, ceftriaxone, clindamycin, dexamethasone, diphenhydramine, dolasetron, fentanyl, granisetron, hydrocortisone, hydromorphone, ketorolac, meperidine, methylprednisolone, midazolam, morphine, nalbuphine, ondansetron, piperacillin/tazobactam, ranitidine, and vancomycin. Injectable acetaminophen is incompatible with acyclovir and diazepam and therefore should not be administered concomitantly with either of these products. Further testing confirmed the chemical compatibility of acetaminophen with ceftriaxone, diphenhydramine, granisetron, ketorolac, nalbuphine, ondansetron, piperacillin/tazobactam, and vancomycin.

Conclusion: All medications tested with acetaminophen were physically compatible except for acyclovir and diazepam. All 8 medications tested for chemical compatibility with acetaminophen were stable over the 4 hour simulated Y-site administration study.

Key Words—acetaminophen, compatibility, intravenous, Y-site

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In November 2010, intravenous acetaminophen was approved by the US Food and Drug Administration (FDA) for use in the management of pain and/or the reduction of fever.¹ Intravenous acetaminophen was initially approved for use in Europe in 2002, but the relatively recent US approval has prompted a resurgence of publications surrounding

the intravenous formulation. Scholarly articles have investigated its pharmacokinetics profile, safety, efficacy, role in the management of postoperative pain, and emergency room utility and have hypothesized concerning the economic advantages and disadvantages of using the intravenous formulation.^{2–6} A recent publication reports chemical and physical

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stability of acetaminophen (10 mg/mL) over 84 hours when stored in polypropylene syringes.⁷

To date, there is limited published information concerning the compatibility of intravenous acetaminophen with other parenteral drug products. Although Trissel's reports on the compatibility of acetaminophen with approximately 40 drugs and infusion solutions, the majority of the listings reference unpublished documents.⁸ Additionally, a document obtained by the pharmacy at Primary Children's Hospital (Salt Lake City, UT) from the manufacturer reports that the chemical compatibility for those compounds referenced in Trissel's was a one-way analysis that only assessed the chemical stability of acetaminophen, leaving the secondary component untested (Cadence Pharmaceuticals, personal communication, April 27, 2011). Patients who need multiple injectable medications and have limited intravenous access often require that these therapies be given through the same line. The purpose of this study was to determine and publish the physical compatibility of acetaminophen mixed with 22 separate injectable medications. Secondarily, 2-way chemical compatibility tests were performed on 8 of the drugs that were found to be physically compatible. Physical compatibility and chemical stability were performed using methods referenced in USP Chapters <788> and <797>.^{9,10}

METHODS

Materials

Acetaminophen,^a acyclovir,^b cefoxitin,^c ceftriaxone,^d clindamycin,^e dexamethasone,^f diazepam,^g diphenhydramine,^h dolasetron,ⁱ fentanyl,^j granisetron,^k hydrocortisone,^l hydromorphone,^m ketorolac,ⁿ meperidine,^o methylprednisolone,^p midazolam,^q morphine,^r nalbuphine,^s ondansetron,^t piperacillin/tazobactam,^u ranitidine,^v vancomycin,^w and syringes^x were obtained commercially. Acyclovir, clindamycin, and vancomycin were diluted with normal saline. Cefoxitin, ceftriaxone, and piperacillin/tazobactam were diluted with sterile water for injection. Ranitidine was diluted with 0.45% sodium chloride. All other injectable medications were utilized as obtained from the manufacturer. Nitrocellulose filter discs^y were used in particle count analysis. Acetonitrile,^z high-performance liquid chromatography (HPLC) grade water,^{aa} triethylamine,^{bb} and phosphoric acid^{cc} were used in preparation of the HPLC mobile phase. Forced degradation studies were performed with sodium hydroxide,^{dd} hydrochloric acid,^{ee} hydrogen peroxide,^{ff} and heat (60°C). Chromatographic analyses were conducted using an Agilent

1160 HPLC system with quaternary pump,^{gg} autosampler,^{hh} thermostatted column compartment,ⁱⁱ and diode-array detector^{jj} with ChemStation software^{kk} and Zorbax Eclipse Plus C18, 4.6 x 100 mm, 3.5- μ m column.^{ll}

Physical Compatibility

Simulated Y-site evaluation was accomplished by mixing 2 mL of acetaminophen (10 mg/mL) with 2 mL of an alternative intravenous medication and subsequently storing the mixture in a polypropylene syringe (Table 1). Compatibility was assessed as follows. Each aliquot mixture was tested in triplicate by visually inspecting each mixed solution at hours 0 and 4. Visual clarity was evaluated by comparing the solutions against a light and dark background. The aliquot solutions were evaluated for crystal content at 4 hours by infusing 4 mL of the medication mixture through a 0.45- μ m nitrocellulose filter disc. Each disc was analyzed quantitatively for crystal precipitates under 100x magnification and recorded. According to the USP standards, solutions are within particle count limits if an aliquot contains less than 12 particles/mL measuring ≥ 10 μ m and less than 2 particles/mL measuring ≥ 25 μ m in diameter.⁹ Therefore a 4 mL test solution should contain less than 48 particles ≥ 10 μ m and 8 particles ≥ 25 μ m in diameter to be considered physically compatible.

Chemical Compatibility

Of those drug entities exhibiting physical compatibility with acetaminophen, 8 drugs were additionally assessed to ensure chemical stability during simulated Y-site administration with acetaminophen. Duplicate samples of drug were prepared in polypropylene syringes as described previously. The concentrations of the analytes of interest were quantified using HPLC stability indicating assays. The mobile phase consisted of acetonitrile and aqueous 0.1% triethylamine adjusted to pH 3 with phosphoric acid. All analyses were performed on a Zorbax Eclipse Plus C18, 4.6 x 100 mm, 3.5- μ m column with 1 mL/min elution and diode-array detection. The column compartment was maintained at 25°C. Injection volumes, mobile phase ratios, and detection wavelengths for each analysis are listed in Table 2. Immediately prior to analysis, each sample was diluted 500-fold with sterile water. Each duplicate sample was analyzed in triplicate initially and at hours 1 and 4.

Five-point linear standard curves were constructed with concentrations at 50%, 75%, 100%, 125%, and

Table 1. Physical compatibility for injectable antibiotics administered with acetaminophen 10 mg/mL

Antibiotic	Concentration	Visual check		Particle count	
		At hour 0	At hour 4	≥10 μm	≥25 μm
Acyclovir	5 mg/mL	C	C	> 40	8
Acyclovir	5 mg/mL	C	C	> 40	10
Acyclovir	5 mg/mL	C	C	> 40	11
Cefoxitin	100 mg/mL	C	C	7	3
Cefoxitin	100 mg/mL	C	C	5	0
Cefoxitin	100 mg/mL	C	C	10	6
Ceftriaxone	40 mg/mL	C	C	13	3
Ceftriaxone	40 mg/mL	C	C	12	3
Ceftriaxone	40 mg/mL	C	C	35	4
Clindamycin	10 mg/mL	C	C	22	3
Clindamycin	10 mg/mL	C	C	9	1
Clindamycin	10 mg/mL	C	C	7	0
Dexamethasone	4 mg/mL	C	C	3	2
Dexamethasone	4 mg/mL	C	C	2	0
Dexamethasone	4 mg/mL	C	C	4	2
Diazepam	5 mg/mL	I	I	>48	>22
Diazepam	5 mg/mL	I	I	>48	>22
Diazepam	5 mg/mL	I	I	>48	> 22
Diphenhydramine	50 mg/mL	C	C	20	0
Diphenhydramine	50 mg/mL	C	C	18	4
Diphenhydramine	50 mg/mL	C	C	6	2
Dolasetron	20 mg/mL	C	C	7	1
Dolasetron	20 mg/mL	C	C	6	3
Dolasetron	20 mg/mL	C	C	10	2
Fentanyl	50 mcg/mL	C	C	2	0
Fentanyl	50 mcg/mL	C	C	1	0
Fentanyl	50 mcg/mL	C	C	0	0
Granisetron	1 mg/mL	C	C	2	0
Granisetron	1 mg/mL	C	C	7	0
Granisetron	1 mg/mL	C	C	4	0
Hydrocortisone	125 mg/mL	C	C	16	2
Hydrocortisone	125 mg/mL	C	C	13	5
Hydrocortisone	125 mg/mL	C	C	20	4
Hydromorphone	2 mg/mL	C	C	2	0
Hydromorphone	2 mg/mL	C	C	7	0
Hydromorphone	2 mg/mL	C	C	8	1
Ketorolac	30 mg/mL	C	C	20	0
Ketorolac	30 mg/mL	C	C	18	0
Ketorolac	30 mg/mL	C	C	2	3
Meperidine	50 mg/mL	C	C	3	0
Meperidine	50 mg/mL	C	C	4	1

(continued)

Table 1. Physical compatibility for injectable antibiotics administered with acetaminophen 10 mg/mL (CONT.)

Antibiotic	Concentration	Visual check		Particle count	
		At hour 0	At hour 4	≥10 μm	≥25 μm
Meperidine	50 mg/mL	C	C	8	6
Methylprednisolone	62.5 mg/mL	C	C	6	1
Methylprednisolone	62.5 mg/mL	C	C	2	1
Methylprednisolone	62.5 mg/mL	C	C	8	2
Midazolam	5 mg/mL	C	C	2	0
Midazolam	5 mg/mL	C	C	5	0
Midazolam	5 mg/mL	C	C	2	0
Morphine	15 mg/mL	C	C	13	0
Morphine	15 mg/mL	C	C	7	0
Morphine	15 mg/mL	C	C	7	1
Nalbuphine	10 mg/mL	C	C	16	4
Nalbuphine	10 mg/mL	C	C	2	0
Nalbuphine	10 mg/mL	C	C	6	4
Ondansetron	2 mg/mL	C	C	2	0
Ondansetron	2 mg/mL	C	C	9	0
Ondansetron	2 mg/mL	C	C	12	0
Ranitidine	1 mg/mL	C	C	1	0
Ranitidine	1 mg/mL	C	C	0	0
Ranitidine	1 mg/mL	C	C	0	0
Piperacillin/tazobactam	100 mg/mL	C	C	6	1
Piperacillin/tazobactam	100 mg/mL	C	C	10	0
Piperacillin/tazobactam	100 mg/mL	C	C	12	0
Vancomycin	5 mg/mL	C	C	7	1
Vancomycin	5 mg/mL	C	C	14	1
Vancomycin	5 mg/mL	C	C	5	4

Note: C = clear and colorless; I = incompatible.

150% of the 500-fold dilution for each intravenous product analyzed. Precision of each analytical method was evaluated for every compound by assaying 10 replicate injections and reporting the resultant coefficient of variation. Each drug entity was subjected to forced degradation with 1N hydrochloric acid, 1N sodium hydroxide, 3% hydrogen peroxide, and heat. Degradation peaks did not interfere with the corresponding analytes of interest for any of the drug compounds. A drug entity was considered chemically compatible if its concentration was >90% of the original concentration during the 4 hour simulated Y-site compatibility test.

RESULTS AND DISCUSSION

The use of injectable acetaminophen has increased within our institution since its US market debut. The

intravenous formulation provides an alternative route of administration for individuals who require pharmacotherapy for pain and/or fever but cannot take enteral or rectal acetaminophen. Patients often require the administration of multiple intravenous products with limited intravenous access. Therefore, pharmacists and nurses regularly consult tertiary literature sources to assess the compatibility of intravenous products to ensure that safe and optimal therapy is provided to the patient. We chose to study the physical compatibility of acetaminophen with 22 compounds within 3 broad categories: 6 antibiotic/antiviral, 8 pain/sedation, and 8 additional medications commonly used in a postoperative patient care setting. Visual clarity was maintained in all aliquots at 0 and 4 hours, except for diazepam. Physical compatibility for microscopic disc measurements at hour 4 indicated

Table 2. Chemical compatibility of acetaminophen 10 mg/mL with selected injectable medications

	Ceftriaxone	Diphenhydr- amine	Granisetron	Ketorolac	Nalbuphine	Ondansetron	Piperacillin	Tazobactam	Vancomycin
Concentration, mg/mL	40	50	1	30	10	2	89	11	5
Mobile phase, buffer:ACN	87.5:12.5	60:40	75:25	50:50	87.5:12.5	70:30	gradient ^a	gradient ^a	87.5:12.5
Wavelength, nm	254	210	210	210	210	254	230	230	210
Injection volume, μ L	5	5	20	5	5	5	5	5	5
Retention time, min	3.67	1.45	1.88	2.03	4.38	1.54	9.75	1.86	1.27
Degradants, min	1.12, 1.27, 1.52, 1.78, 1.96, 2.30	ppt with base	0.90, 2.85	ppt with acid	1.02	not detected	0.99, 3.99, 5.9-7.9, 8.67, 9.07 ppt with acid		0.88, 1.46
Initial concentration, mg/mL	38.99 $\pm$ 0.13	50.05 $\pm$ 0.26	0.97 $\pm$ 0.01	29.62 $\pm$ 0.49	9.86 $\pm$ 0.05	2.17 $\pm$ 0.02	91.07 $\pm$ 1.12	10.87 $\pm$ 0.05	4.88 $\pm$ 0.11
Hour 1, % remaining	100.58 $\pm$ 0.32	99.67 $\pm$ 0.49	102.00 $\pm$ 1.71	100.48 $\pm$ 0.53	99.03 $\pm$ 0.68	99.96 $\pm$ 1.65	99.52 $\pm$ 1.23	99.11 $\pm$ 0.87	99.81 $\pm$ 0.61
Hour 4, % remaining	100.23 $\pm$ 0.99	100.14 $\pm$ 0.41	98.50 $\pm$ 4.79	100.05 $\pm$ 1.24	99.36 $\pm$ 0.23	98.66 $\pm$ 0.85	98.36 $\pm$ 1.91	98.71 $\pm$ 0.57	99.19 $\pm$ 0.65
Linearity, r^2	>0.9999	0.9986	>0.9999	0.9998	0.9999	0.9985	>0.9999	0.9982	0.9997
Precision, %RSD	0.301	0.270	1.122	0.245	0.354	0.978	0.352	0.909	0.536
Acetaminophen 10 mg/mL analyzed at 254 nm									
Retention time, min	2.13	1.07	1.31	1.00	2.14	1.19	2.09	2.09	2.16
Degradants, min	0.96, 3.32	0.84, 1.65	0.88, 2.17	0.82, 1.42	0.96, 3.32	0.86, 1.94	0.96, 3.22	0.96, 3.22	0.96, 3.32
Injection volume, μ L	5	5	5	5	5	5	5	5	5
Initial concentration, mg/mL	9.88 $\pm$ 0.01	9.89 $\pm$ 0.09	10.00 $\pm$ 0.01	9.82 $\pm$ 0.11	9.84 $\pm$ 0.02	9.78 $\pm$ 0.03	10.00 $\pm$ 0.02	10.00 $\pm$ 0.02	9.83 $\pm$ 0.03
Hour 1, % remaining	100.43 $\pm$ 0.22	99.94 $\pm$ 0.52	99.61 $\pm$ 0.49	101.23 $\pm$ 0.43	99.03 $\pm$ 0.57	101.28 $\pm$ 0.31	99.46 $\pm$ 1.03	99.46 $\pm$ 1.03	100.06 $\pm$ 0.70
Hour 4, % remaining	100.86 $\pm$ 0.65	100.34 $\pm$ 0.62	99.15 $\pm$ 0.61	101.02 $\pm$ 1.27	99.67 $\pm$ 0.31	101.28 $\pm$ 0.47	99.83 $\pm$ 0.39	99.83 $\pm$ 0.39	100.39 $\pm$ 0.17
Linearity, r^2	>0.9999	0.9997	0.9997	0.9997	>0.9999	>0.9999	0.9999	0.9999	0.9999
Precision, %RSD	0.234	0.381	0.167	0.693	0.145	0.161	0.105	0.105	0.101

Note: ACN = acetonitrile; ppt = precipitate; %RSD = percent relative standard deviation.

^aGradient: time 0 min, 87.5/12.5 (buffer/ACN); 4 min, 87.5/12.5; 6 min, 70/30; 12 min 70/30; 13 min, 87.5/12.5; 20 min, 87.5/12.5.

that the crystalline particulate count exceeded the USP recommendations for acyclovir and diazepam (Table 1). Eight of the medications were further tested to assess chemical compatibility. Acetaminophen retained greater than 99% of its original concentration throughout all testing. The secondary compounds evaluated during the simulated Y-site administration analysis were also found to be stable, retaining greater than 95% of their original concentrations over the 4-hour study duration (Table 2).

CONCLUSION

Commercially available acetaminophen injection (10 mg/mL) is physically compatible with cefoxitin, ceftriaxone, clindamycin, dexamethasone, diphenhydramine, dolasetron, fentanyl, granisetron, hydrocortisone, hydromorphone, ketorolac, meperidine, methylprednisolone, midazolam, morphine, nalbuphine, ondansetron, piperacillin/tazobactam, ranitidine, and vancomycin. Injectable acetaminophen is incompatible with acyclovir and diazepam and therefore should not

be administered concomitantly with either of these 2 products. Further testing confirmed the chemical compatibility of acetaminophen with ceftriaxone, diphenhydramine, granisetron, ketorolac, nalbuphine, ondansetron, piperacillin/tazobactam, and vancomycin.

ACKNOWLEDGMENTS

The authors have no conflicts of interest to disclose.

^aAcetaminophen injection 10 mg/mL, 100 mL, Cadence Pharmaceuticals, San Diego, CA, lot V006510.

^bAcyclovir 50 mg/mL, 10 mL, APP Pharmaceuticals, Schaumburg, IL.

^cCefoxitin for injection, USP 10 g, Apotex, Weston, FL, lot 112B001.

^dCeftriaxone for injection, 10 g, Hospira, Lake Forest, IL, lot 100098M.

^eClindamycin injection, USP, 150 mg/mL, 6 mL, APP Pharmaceuticals, Schaumburg, IL.

^fDexamethasone sodium phosphate injection, USP, 4 mg/mL, 1 mL, APP Pharmaceuticals, Schaumburg, IL.

^gDiazepam 5 mg/mL, 2 mL, Hospira, Lake Forest, IL, lot 02-553-EV.

^hDiphenhydramine hydrochloride 50 mg/mL, 1 mL, West-Ward, Eatontown, NJ, lot 091323.

ⁱDolasetron mesylate injection, 20 mg/mL, 5 mL, Sanofi-aventis, Bridgewater, NJ.

^jFentanyl citrate injection, USP, 50 mcg/mL, 2 mL, Hospira, Lake Forest, IL.

^kGranisetron hydrochloride injection, USP 1 mg/mL, 1 mL, Wockhardt, Parsippany, NJ, lot DL12716.

^lHydrocortisone sodium succinate for injection, USP, 125 mg/mL, 2 mL, Pfizer, New York, NY.

^mHydromorphone hydrochloride injection, USP 2 mg/mL, 1 mL, West-Ward, Eatontown, NJ.

ⁿKetorolac tromethamine 30 mg/mL, 1 mL, Hospira, Lake Forest, IL, lot 09-026-DK.

^oMeperidine hydrochloride injection, USP, 50 mg/mL, 1 mL, Hospira, Lake Forest, IL.

^pMethylprednisolone sodium succinate for injection, USP, 62.5 mg/mL, 2 mL, Pfizer, New York, NY.

^qMidazolam injection, USP, 5 mg/mL, 1 mL, Hospira, Lake Forest, IL.

^rMorphine sulfate injection, USP, 15 mg/mL, 1 mL, West-Ward, Eatontown, NJ.

^sNalbuphine hydrochloride injection 10 mg/mL, 10 mL, Hospira, Lake Forest, IL, lot 03-413-DK.

^tOndansetron 2 mg/mL, 2 mL, Wockhardt, Parsippany, NJ, lot DL12598.

^uPiperacillin and tazobactam, 4.5 g, Wyeth, Philadelphia, PA, lot F72631.

^vRanitidine injection 25 mg/mL, 40 mL, Bedford Labs, Bedford, OH.

^wVancomycin hydrochloride injection, 500 mg, Hospira, Lake Forest, IL, lot 068218E02.

^xBecton-Dickinson (BD) Luer-Lok Syringe, 10 mL, Franklin Lakes, NJ, Ref. No. 309605.

^yMillipore nitrocellulose membrane black gridded, 0.45 μ m, lot R0SA24676.

^zAcetonitrile, for HPLC, Acros, NJ, lot B00L1555.

^{aa}Water, HPLC grade, Fischer Scientific, Fair Lawn, NJ, lot 114379.

^{bb}Triethylamine 99% pure, Acros, NJ, lot A0295058.

^{cc}Phosphoric acid, for analysis 85 wt% solution in water, Acros, NJ, lot A0295482.

^{dd}Sodium hydroxide, 1N, Acros, NJ, lot B00L6551.

^{ee}Hydrochloric acid, 1N, Acros, NJ, lot B00L1741.

^{ff}Hydrogen peroxide, 3%, JT Baker, Phillipsburg, NJ, lot E21H29.

^{gg}1260 Infinity quaternary pump, Agilent Technologies, Santa Clara, CA, model G1311B.

^{hh}1260 Infinity standard autosampler, Agilent, model G1329B.

ⁱⁱ1260 Infinity thermostatted Column Compartment, Agilent, model G1316A.

^{jj}1260 Infinity diode-array detector, Agilent, model G4212B.

^{kk}HPLC ChemStation, version B.04.03, Agilent.

^{ll}Zorbax Eclipse Plus C18, 4.6 x 100mm, 3.5- μ m column, Agilent.

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