

Physical Compatibility of Pantoprazole with Selected Medications during Simulated Y-Site Administration

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ABSTRACT

Rationale: Patients receiving IV pantoprazole often require concomitant IV drugs and solutions. A review of the product monograph, a search of the MEDLINE, International Pharmaceutical Abstracts, and EMBASE bibliographic databases, and communication with the manufacturer revealed no information about compatibility between pantoprazole and other medications during Y-site administration of drugs.

Objective: To complete a visual compatibility study of IV pantoprazole with 17 other IV medications, as well as with a mixture of 3.3% dextrose and 0.3% sodium chloride for injection, during simulated Y-site injection.

Methods: Seventeen drugs, each at 3 different concentrations (prepared in 5% dextrose in water [D5W] for injection), as well as a mixture of 3.3% dextrose and 0.3% sodium chloride for injection, were selected for physical compatibility testing with 3 concentrations (0.16 mg/mL, 0.40 mg/mL, and 0.80 mg/mL) of pantoprazole in 0.9% sodium chloride for injection (NS). The 17 drugs were ampicillin, cefazolin, ceftriaxone, dimenhydrinate, dobutamine, dopamine, epinephrine, esmolol, furosemide, insulin, midazolam, morphine, nitroglycerin, norepinephrine, octreotide, potassium chloride, and vasopressin. To simulate Y-site administration, equal volumes of pantoprazole (at each of the 3 concentrations) and each secondary drug (at each of the 3 concentrations) were mixed in a test tube. Solutions were inspected for colour change, clarity, visible precipitate, and evolution of gas immediately after mixing and at 15 min and 1, 4, and 12 h. The pH of each test drug was measured before it was mixed with pantoprazole. For combinations found to be physically incompatible, a range of concentrations was prepared to evaluate the extent of the incompatibility.

Results: Pantoprazole solutions were physically compatible with 12 of the 17 drugs tested and with the mixture of 3.3% dextrose and 0.3% sodium chloride for injection for up to 12 h at 23°C during simulated Y-site administration. Precipitation occurred with mixtures containing pantoprazole and dobutamine or norepinephrine. A colour change and a precipitate were observed when pantoprazole was mixed with esmolol, midazolam, or octreotide. In general, mixtures of pantoprazole with dobutamine,

RÉSUMÉ

Historique : Les patients qui reçoivent du pantoprazole par voie intraveineuse (IV) nécessitent également souvent l'administration concomitante d'autres médicaments et solutions par voie IV. L'étude de la monographie du pantoprazole, une recherche dans les bases de données bibliographiques MEDLINE, International Pharmaceutical Abstracts et EMBASE, et des échanges avec le fabricant n'ont permis d'obtenir aucune information sur la compatibilité entre le pantoprazole et d'autres médicaments pour une administration dans un raccord en Y.

Objectif : Mener une étude de compatibilité visuelle entre le pantoprazole IV et 17 autres médicaments IV, ainsi qu'avec une mixture de solutions injectables de dextrose à 3,3 % et de chlorure de sodium à 0,3 %, au cours d'une administration simulée dans un raccord en Y.

Méthodes : On a choisi 17 médicaments, chacun préparé selon trois concentrations dans une solution injectable de dextrose à 5 % dans l'eau (D5W), ainsi qu'une mixture de solutions injectables de dextrose à 3,3 % et de chlorure de sodium à 0,3%, à des fins de tests de compatibilité avec trois concentrations de pantoprazole préparées dans une solution injectable de chlorure de sodium à 0,9 % (NS) — 0,16 mg/mL, 0,4 mg/mL et 0,8 mg/mL. Les 17 médicaments étaient les suivants : ampicilline, céfazoline, ceftriaxone, dimenhydrinate, dobutamine, dopamine, épinéphrine, esmolol, furosémide, insuline, midazolam, morphine, nitroglycérine, norépinéphrine, octréotide, chlorure de potassium et vasopressine. Pour simuler l'administration dans un raccord en Y, on a mélangé en volumes égaux dans des éprouvettes le pantoprazole (à chacune des trois concentrations) et, de façon unitaire, chacun des autres médicaments (également à chacune des trois concentrations). Les solutions ont été inspectées pour un changement de couleur, la limpidité, la présence d'un précipité et l'émission de gaz immédiatement après leur préparation, puis après 15 min, 1, 4 et 12 heures. Le pH de chacune des solutions a été mesuré avant leur préparation. Pour les mélanges qui étaient physiquement incompatibles, on a préparé une série de concentrations afin d'en évaluer le degré d'incompatibilité.

Résultats : Les solutions de pantoprazole étaient physiquement compatibles avec 12 des 17 médicaments testés et avec la mixture de solutions injectables de dextrose à 3,3 % et de chlorure de



esmolol, or midazolam were physically incompatible over clinically useful concentration ranges. Octreotide and pantoprazole were physically compatible when the octreotide concentration was less than 1.5 µg/mL. Norepinephrine was physically compatible with all pantoprazole concentrations when the norepinephrine concentration was less than 13 µg/mL.

Conclusions: Admixtures prepared in the clinical setting are subject to greater error than in the laboratory, and it is therefore recommended that practitioners avoid Y-site administration of pantoprazole with dobutamine, esmolol, midazolam, octreotide (at concentrations near or greater than 1.5 µg/mL), or norepinephrine (at concentrations near or greater than 13 µg/mL).

Key words: pantoprazole, Y-site, compatibility, dobutamine, esmolol, midazolam, octreotide, norepinephrine

sodium à 0,3 %, jusqu'à 12 heures à 23 °C au cours d'une administration simulée dans un raccord en Y. La formation d'un précipité est survenue avec les mélanges de pantoprazole et de norépinéphrine ou de dobutamine. On a observé un changement de couleur et la formation d'un précipité lorsque le pantoprazole était mélangé à l'esmolol, au midazolam ou à l'octréotide. Règle générale, les mélanges de pantoprazole et de dobutamine, d'esmolol ou de midazolam étaient physiquement incompatibles dans un éventail de concentrations cliniquement utiles. L'octréotide et le pantoprazole étaient physiquement compatibles lorsque la concentration d'octréotide était inférieure à 1,5 µg/mL. La norépinéphrine s'est révélée physiquement compatible avec toutes les concentrations de pantoprazole, lorsque ses propres concentrations étaient inférieures à 13 µg/mL.

Conclusions : Les mélanges préparés en milieu clinique sont sujets à une plus grande marge d'erreur que ceux préparés en laboratoire, et c'est pourquoi on recommande aux praticiens d'éviter l'administration de pantoprazole dans un raccord en Y avec la dobutamine, l'esmolol, le midazolam, l'octréotide (à des concentrations près de ou supérieures à 1,5 (g/mL), ou la norépinéphrine (à des concentrations près de ou supérieures à 13 µg/mL).

Mots clés : pantoprazole, raccord en Y, compatibilité, dobutamine, esmolol, midazolam, octréotide, norépinéphrine

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INTRODUCTION

Pantoprazole was the first proton-pump inhibitor for IV administration marketed in Canada. It is indicated when a rapid reduction in gastric acid secretion is required for patients who cannot tolerate oral medications; it has recently been approved for the treatment of Zollinger-Ellison syndrome.

It is also administered by continuous IV infusion for control of acute upper gastrointestinal bleeding,^{1,2} although it is not approved for this indication. Because patients receiving IV pantoprazole may be receiving other medications and solutions by the IV route, the potential exists for incompatibility when the pantoprazole is co-infused with other drugs via Y-site administration.

A review of the product monograph, a search of the MEDLINE, International Pharmaceutical Abstracts (IPA), and EMBASE bibliographic databases, and communication with the manufacturer's medical information department revealed no information about Y-site compatibility with other medications. Compatibility information is limited to that found in the product monograph, which indicates that pantoprazole may be reconstituted with 0.9% sodium chloride for injection (NS) and further diluted with either NS or dextrose 5% in water (D5W) for injection.^{3,4} The objective of this study was to determine, by visual observation during simulated Y-site administration, the physical compatibility of pantoprazole

with 17 medications that are commonly administered by the IV route and with a commonly prescribed IV solution (3.3% dextrose and 0.3% sodium chloride).

METHODS

Preparation of Test Mixtures of Drugs

Seventeen drugs (detailed in Table 1), each diluted in D5W at 3 different concentrations, were selected for visual compatibility testing with 3 concentrations of pantoprazole (0.16 mg/mL, 0.40 mg/mL, and 0.80 mg/mL) in NS. The 3 selected concentrations of each drug (noted in Table 1) represent the upper and lower limits of the range usually administered to adult patients and either a midpoint or the most commonly used concentration for adult clinical practice. The pantoprazole was prepared by first reconstituting a 40-mg vial of the drug (Pantoloc IV, lot 3011261; Altana Pharma Inc, Oakville, Ontario) with 10 mL of NS obtained from a 100-mL container of commercial NS (lot W2C06B3; Baxter Corporation, Toronto, Ontario). The reconstituted solution was further diluted with NS to prepare the 3 test solutions (0.16 mg/mL, 0.40 mg/mL, and 0.80 mg/mL). The 17 secondary drugs were initially prepared in accordance with the manufacturer's instructions and were further diluted in D5W to obtain the 3 test concentrations. To simulate the mixing of drugs during Y-site administration, a set volume (1 mL)



Table 1. Tested Concentrations and Initial pH of Medications before Mixing

Drug	Manufacturer	Lot No.	Lower Limit of Usual Range for Adult Use		Mid-Range		Upper Limit of Usual Range for Adult Use	
			Concentration Tested	pH	Concentration Tested	pH	Concentration Tested	pH
Pantoprazole	Altana Pharma Inc	3011261	0.16 mg/mL	8.02	0.40 mg/mL	8.06	0.80 mg/mL	8.25
2:1 NS-D5W mixture	Baxter Corporation	W2D30A1		4.60				
Ampicillin	Novopharm	112123	10 mg/mL	7.89	25 mg/mL	8.11	40 mg/mL	8.32
Cefazolin	Novopharm	3600400	20 mg/mL	4.52	30 mg/mL	4.73	40 mg/mL	4.81
Ceftriaxone	Hoffmann-La Roche Ltd	B24001	20 mg/mL	6.64	30 mg/mL	6.86	40 mg/mL	6.99
Dimenhydrinate	Astra Pharma Inc	E737	0.50 mg/mL	6.34	0.75 mg/mL	6.40	1.00 mg/mL	6.46
Dobutamine	Eli Lilly	5MG15M	1.0 mg/mL*	3.39	2.5 mg/mL*	2.93	4.0 mg/mL*	2.89
Dopamine	Dupont Pharma	1012-07	0.8 mg/mL	4.89	2.0 mg/mL	4.57	3.2 mg/mL	4.31
Epinephrine	Abbott Laboratories	70005NJ	16 µg/mL	5.94	24 µg/mL	5.74	32 µg/mL	5.52
Esmolol	Baxter Corporation	1041-59A	10 mg/mL*	4.21	15 mg/mL*	4.34	20 mg/mL*	4.46
Furosemide	Sabex Inc	112117	1.0 mg/mL	6.51	1.5 mg/mL	6.71	2.0 mg/mL	6.87
Insulin	Eli Lilly	5MR67P	5.0 unit/L	6.64	27.5 unit/L	7.04	50.0 unit/L	7.11
Midazolam	Sabex Inc	110414	1.0 mg/mL*†	3.74	1.5 mg/mL*	3.44	2.0 mg/mL*	3.45
Morphine	Abbott Laboratories	74029NJ	1 mg/mL	4.75	5 mg/mL	4.59	10 mg/mL	5.56
Nitroglycerin	Sabex Inc	109932	100 µg/mL	6.37	250 µg/mL	6.29	400 µg/mL	6.27
Norepinephrine	Sabex Inc	109551	6 µg/mL	6.02	8 µg/mL	5.89	64 µg/mL*	3.43
Octreotide	Novartis Pharma	C1F02611	5.0 µg/mL*	3.49	7.5 µg/mL*	3.51	10.0 µg/mL*	3.54
Potassium chloride	Astra Pharma Inc	E671	0.02 mEq/mL	6.70	0.21 mEq/mL	7.18	4.00 mEq/mL	7.14
Vasopressin	Ferring Inc	0M527	0.4 unit/mL	5.53	0.7 unit/mL	5.66	1.0 unit/mL	4.66

NS = normal saline (0.9% sodium chloride), D5W = 5% dextrose in water.

*This concentration was physically incompatible with at least 1 of the 3 tested concentrations of pantoprazole.

†The original concentration tested was the undiluted manufacturer's formulation

of each drug at each concentration, as listed in Table 1, was combined with an equal volume (1 mL) of each concentration of pantoprazole in a clean, dry glass test tube. Thus, a total of 9 concentration combinations were prepared for each secondary drug with pantoprazole. In addition, a mixture of 3.3% dextrose and 0.3% sodium chloride for injection was also tested with the 3 concentrations of pantoprazole. To ensure thorough mixing, all test samples were agitated manually after being combined.

Determination of pH

The pH of each drug at each concentration to be tested was measured to the nearest 0.001 pH unit before the drug was mixed with pantoprazole. The pH meter (Accumet 925, Fisher Scientific, Nepean, Ontario) was standardized on each day on which pH was to be measured with commercially available buffer solutions (Fisher Scientific, Nepean, Ontario). The pH is reported to 2 decimal places.

Visual Inspection of Physical Compatibility

Immediately after mixing of each pantoprazole-drug combination, the mixture was inspected visually

for particulate matter against a black and then a white background in diffuse fluorescent laboratory light. Each mixture was also inspected for changes in colour and clarity and for evolution of gas. These observations were repeated at 15 min and 1, 4, and 12 h after mixing. All mixtures were stored at room temperature (23°C) throughout the study.

For combinations that produced a change in colour or clarity and those in which a precipitate was observed, an expanded range of concentrations was prepared to evaluate the extent of the incompatibility. Physically compatible and incompatible combinations were plotted on a graph to determine the concentration of each drug at the interface between physical compatibility and incompatibility.

RESULTS

Initial Observations and pH

When the 17 secondary drugs, as well as the mixture of 3.3% dextrose and 0.3% sodium chloride for injection, were admixed with pantoprazole, the mixtures remained clear and colourless except in 5 cases. The exceptions, for which mixtures of the drug with pantoprazole developed a precipitate or a colour



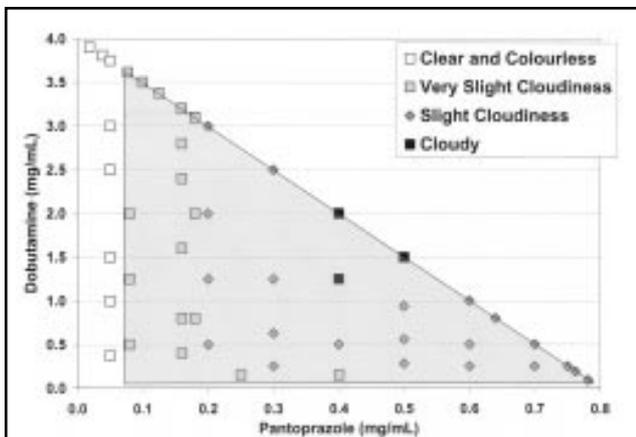


Figure 1. Observed compatibility of dobutamine with pantoprazole at 12 h after mixing. Because all of the initial 9 pantoprazole–dobutamine mixtures turned cloudy or slightly cloudy within 12 h of preparation (some within 15 min), a total of 50 mixtures of these 2 drugs were prepared to evaluate the range of incompatibility. Solutions of pantoprazole and dobutamine were physically incompatible over a wide concentration range. In general, the final pantoprazole concentration must be less than 0.05 mg/mL with any dobutamine concentration less than 4.0 mg/mL for the combination to be physically compatible.

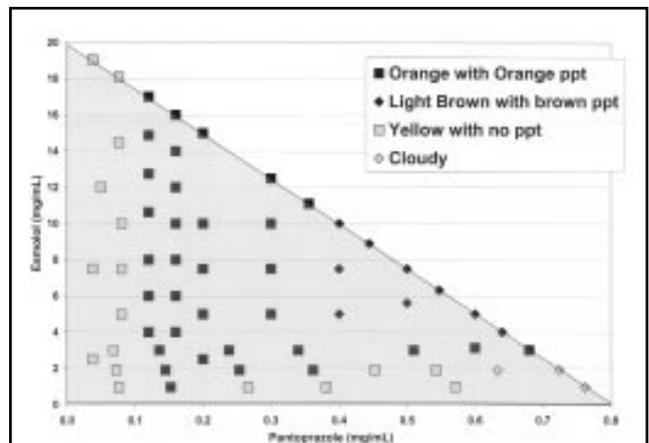


Figure 2. Observed compatibility of esmolol with pantoprazole at 12 h after mixing. Because all of the initial 9 pantoprazole–esmolol mixtures turned slightly yellow within 15 min of preparation, a total of 63 mixtures of these 2 drugs were prepared to evaluate the range of incompatibility. At room temperature, solutions of pantoprazole and esmolol produced a precipitate when the final concentration of pantoprazole exceeded 0.12 mg/mL and the final esmolol concentration exceeded 2 mg/mL. At lower concentrations of either medication, no precipitate was observed, but a colour change was observed within 12 h. ppt = precipitate.

change (or both) on mixing, were dobutamine, esmolol, midazolam, norepinephrine, and octreotide. In these combinations, the second drug was initially very acidic (2.89 to 4.46), whereas the initial pantoprazole solutions were slightly alkaline (greater than 8.00) (see Table 1). Therefore, pH may represent the underlying cause of the physical incompatibility.

For the 5 medications that were physically incompatible with pantoprazole, the range of physically incompatible concentrations was investigated further. The concentration range for physical incompatibility of pantoprazole with either midazolam or dobutamine spanned virtually all possible concentration combinations. For medications that were physically compatible with pantoprazole, no further investigations were conducted.

Pantoprazole and Dobutamine

Four of the dobutamine combinations (pantoprazole 0.16 mg/mL with dobutamine 1.0 mg/mL, 2.5 mg/mL, or 4.0 mg/mL, and pantoprazole 0.40 mg/mL with dobutamine 1.0 mg/mL) were initially clear and colourless and then showed slight cloudiness 12 h after mixing. The mixture of pantoprazole 0.80 mg/mL and dobutamine 1.0 mg/mL was also initially clear and colourless,

but it turned slightly cloudy 4 h after mixing. The other 4 mixtures tested (pantoprazole 0.40 mg/mL with dobutamine 2.5 mg/mL or 4.0 mg/mL, and pantoprazole 0.80 mg/mL with dobutamine 2.5 mg/mL and 4.0 mg/mL) turned cloudy within 15 min of preparation.

Because all of the initial 9 combinations turned slightly cloudy within 12 h of preparation, a total of 50 additional mixtures were prepared, with pantoprazole concentrations ranging from 0 to 0.80 mg/mL and dobutamine concentrations ranging from 0 to 4.0 mg/mL; the resulting compatibility profile is shown in Figure 1. Solutions of pantoprazole and dobutamine were physically incompatible over a wide concentration range. In general, the final concentration of pantoprazole must be less than 0.05 mg/mL with any final concentration of dobutamine less than 4.0 mg/mL for the combination to be physically compatible (see Figure 1).

Pantoprazole and Esmolol

All combinations of pantoprazole with esmolol were initially clear and colourless and turned slightly yellow within 15 min of preparation. Esmolol mixtures containing the lowest concentration of pantoprazole (0.16 mg/mL) turned yellow by 12 h after preparation. A reddish brown precipitate was observed after 12 h

in mixtures containing higher concentrations of pantoprazole (0.40 mg/mL and 0.80 mg/mL). Esmolol mixtures containing 0.40 mg/mL of pantoprazole turned orange, and those containing 0.80 mg/mL of pantoprazole turned light brown.

Because an incompatibility was observed between pantoprazole and esmolol, a total of 63 additional mixtures, with pantoprazole concentrations ranging from 0 to 0.80 mg/mL and esmolol concentrations ranging from 0 to 20 mg/mL, were prepared; the resulting compatibility profile is shown in Figure 2. At room temperature, solutions of pantoprazole and esmolol were physically incompatible over the entire concentration range tested (see Figure 2).

Pantoprazole and Midazolam

All mixtures of midazolam with pantoprazole 0.16 mg/mL and 0.40 mg/mL were initially clear and colourless but turned slightly yellow within 15 min of preparation. Mixtures of midazolam with pantoprazole 0.16 mg/mL turned a darker yellow and those with pantoprazole 0.40 mg/mL turned light brown by 12 h. A reddish brown precipitate was also observed in the mixtures containing pantoprazole 0.40 mg/mL. Mixtures of all 3 concentrations of midazolam (1.0 mg/mL, 1.5 mg/mL, and 2.0 mg/mL) with pantoprazole 0.80 mg/mL turned cloudy immediately upon mixing and gradually turned a light brown colour, eventually producing a reddish brown precipitate.

Because an incompatibility was observed between pantoprazole and midazolam, a total of 75 additional mixtures, with pantoprazole concentrations ranging from 0 to 0.80 mg/mL and midazolam concentrations ranging from 0 to 2.0 mg/mL, were prepared; the resulting compatibility profile is shown in Figure 3. Solutions of pantoprazole and midazolam were physically incompatible over a wide concentration range. In general, mixtures of midazolam and pantoprazole must contain a final concentration of less than 0.1 mg/mL midazolam and/or a final concentration of less than 0.01 mg/mL pantoprazole if they are to be physically compatible (see Figure 3). These concentrations are too dilute to be clinically useful for either drug.

Pantoprazole and Norepinephrine

Two of the mixtures tested (pantoprazole 0.40 mg/mL and 0.80 mg/mL with norepinephrine 64 µg/mL) turned cloudy immediately upon mixing. All other combinations tested were clear and colourless throughout the 12-h study period.

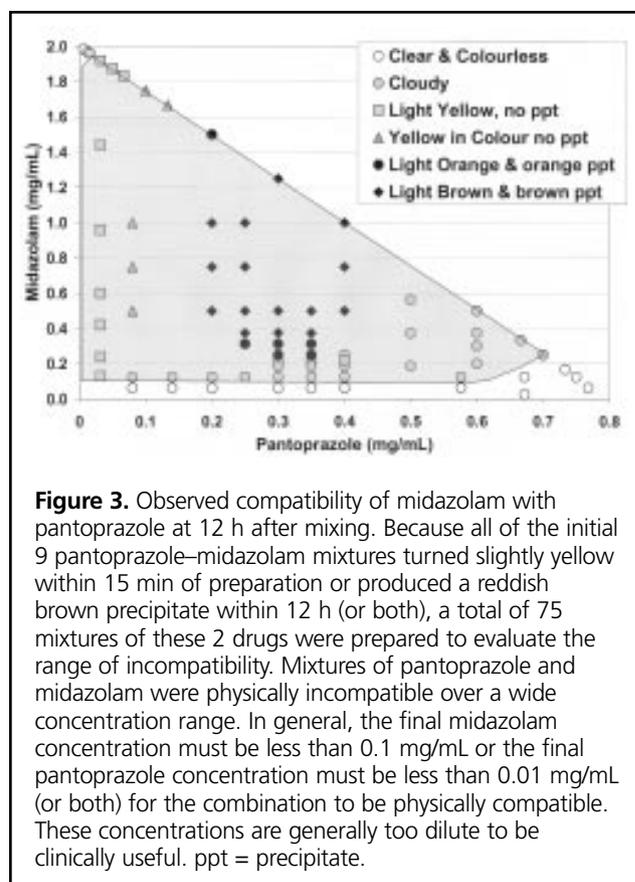


Figure 3. Observed compatibility of midazolam with pantoprazole at 12 h after mixing. Because all of the initial 9 pantoprazole–midazolam mixtures turned slightly yellow within 15 min of preparation or produced a reddish brown precipitate within 12 h (or both), a total of 75 mixtures of these 2 drugs were prepared to evaluate the range of incompatibility. Mixtures of pantoprazole and midazolam were physically incompatible over a wide concentration range. In general, the final midazolam concentration must be less than 0.1 mg/mL or the final pantoprazole concentration must be less than 0.01 mg/mL (or both) for the combination to be physically compatible. These concentrations are generally too dilute to be clinically useful. ppt = precipitate.

Because physical incompatibility was observed for some combinations, a total of 54 additional mixtures were prepared, with pantoprazole concentrations ranging from 0 to 0.80 mg/mL and norepinephrine concentrations ranging from 0 to 64 µg/mL; the resulting compatibility profile is shown in Figure 4. The final concentration of pantoprazole must be less than 0.10 mg/mL for this drug to be physically compatible with norepinephrine at final concentrations of 64 µg/mL or less; alternatively, the final concentration of norepinephrine must be less than 13 µg/mL for this drug to be physically compatible with pantoprazole at final concentrations of 0.80 mg/mL or less (see Figure 4).

Pantoprazole and Octreotide

All combinations of octreotide with pantoprazole 0.16 mg/mL were clear and colourless at time 0 and then turned slightly yellow within 15 min of preparation. Mixtures containing pantoprazole 0.40 mg/mL in combination with octreotide 5.0 µg/mL, 7.5 µg/mL, or 10.0 µg/mL turned slightly yellow at 12 h, 4 h, and 15 min after preparation, respectively. Pantoprazole 0.80 mg/mL combined with octreotide 7.5 µg/mL or



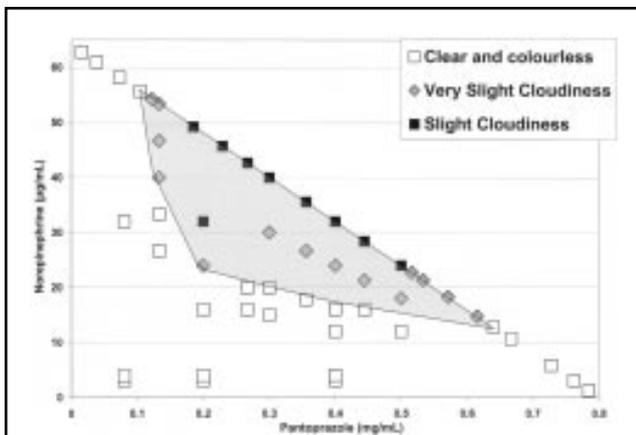


Figure 4. Observed compatibility of norepinephrine with pantoprazole at 12 h after mixing. Because combinations of equal parts of a solution containing 64 µg/mL of norepinephrine with either 0.40 mg/mL or 0.80 mg/mL of pantoprazole turned cloudy immediately upon mixing, a total of 54 mixtures of these 2 drugs were prepared to evaluate the range of physical incompatibility. In general, the final pantoprazole concentration must be less than 0.10 mg/mL to be physically compatible with any norepinephrine concentration of 64 µg/mL or less, or the final norepinephrine concentration must be less than 13 µg/mL to be physically compatible with any pantoprazole concentration of 0.80 mg/mL or less.

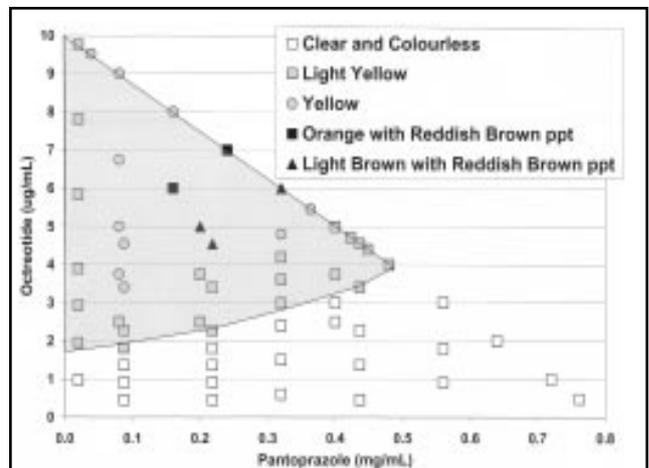


Figure 5. Observed compatibility of octreotide with pantoprazole at 12 h after mixing. Because a colour change was observed after mixing for 6 of the 9 pantoprazole–octreotide mixtures prepared initially, a total of 62 mixtures of these 2 drugs were prepared to evaluate the range of incompatibility. In general, the final octreotide concentration must be less than 1.5 µg/mL to be physically compatible with any final pantoprazole concentration under 0.80 mg/mL. Alternatively, the final pantoprazole concentration must be more than 0.50 mg/mL to be physically compatible with a final octreotide concentration of 4.0 µg/mL or less. ppt = precipitate.

10.0 µg/mL started to turn slightly yellow 4 h after mixing. However, the mixture of pantoprazole 0.80 mg/mL with octreotide 5 µg/mL remained clear and colourless throughout the entire 12-h study period. No precipitate was observed in any of the pantoprazole–octreotide mixtures. However, for all of the mixtures showing a colour change, the intensity of the yellow colour gradually intensified with time.

Because a colour change was observed with the pantoprazole–octreotide combinations, additional mixtures, with pantoprazole concentrations ranging from 0 to 0.80 mg/mL and octreotide concentrations ranging from 0 to 10.0 µg/mL, were prepared to more definitively determine the range of physical compatibility and incompatibility. A total of 62 mixtures were prepared to evaluate this relationship, and the resulting compatibility profile is shown in Figure 5. Solutions of pantoprazole and octreotide were physically incompatible over a wide concentration range. In general, the final concentration of octreotide must be less than 1.5 µg/mL for this drug to be physically compatible with pantoprazole at any final concentration less than 0.80 mg/mL; alternatively, the final concentration of pantoprazole must be more than 0.50 mg/mL for this drug to be physically compatible with octreotide at any final concentration of 4.0 µg/mL or less (see Figure 5).

DISCUSSION

This study has demonstrated that pantoprazole diluted in NS is physically compatible for up to 12 h at 23°C with 3.3% dextrose and 0.3% sodium chloride for injection and with 12 of 17 drugs diluted in D5W during simulated Y-site administration. Precipitation occurred with mixtures containing pantoprazole and dobutamine or norepinephrine. A colour change and a coloured precipitate were observed when pantoprazole was combined with esmolol, midazolam, or octreotide. The cause of the incompatibility between pantoprazole and these 5 drugs (esmolol, dobutamine, midazolam, norepinephrine, octreotide) may be due to the difference in pH between pantoprazole (pH greater than 8.0) and the other medications (pH less than 4.5).

The protocol used here for investigating potential concentration-dependent physical incompatibility involved an initial test of 9 concentration combinations of pantoprazole with a second drug. If the common method of mixing equal volumes of a more limited number of concentrations of each drug had been used in this study, pantoprazole might have been judged physically compatible with dobutamine, midazolam, octreotide, and norepinephrine. Protocols using limited concentration combinations fail to account for the

possibility of a concentration-dependent incompatibility, as was observed in this study (Figures 1 to 5). These figures are similar to those developed by Henry and others⁵ for calcium salts in the presence of phosphate in total parenteral nutrition solutions; similar compatibility profiles have now been reported for numerous drug combinations.⁶⁻¹⁰

These results are limited by a lack of chemical stability data. A physically compatible combination may be chemically incompatible, even in the absence of a colour change or the appearance of a precipitate. With 3 of the drugs tested in combination with pantoprazole (esmolol, midazolam, and octreotide) a change in colour was observed during the 12-h period after mixing, a likely indicator of a chemical change. In fact, in mixtures involving all 3 of these drugs a slight change in colour was observed within 15 min. Nonetheless, a clinically relevant degree of decomposition is unlikely to occur during the period of contact after mixing of 2 medications at a Y-site, since contact time in the shared tubing beyond the Y-site is generally extremely short.

Most Y-sites have less than 15 cm of tubing beyond the point of mixing, but even a relatively long IV tubing set (32 in. or 70 cm in length) of normal diameter will contain less than 2 mL of solution. Therefore, at usual flow rates for the adult clinical setting, the period of contact will be less than 2 or 3 min in most cases, even if the tubing is very long. Under these circumstances clinically important degradation is unlikely to occur. However, in some clinical situations, including pediatric practice or patients with extreme fluid restriction, lower flow rates could result in greater contact time. In situations where prolonged contact (more than 15 min) occurs between the point of first mixing and entry into the body, all drug combinations for which physical compatibility has been confirmed should ideally undergo chemical analysis with a stability-indicating method to confirm the stability of the combination.

In the studies reported here, the solutions were not protected from light at any time. The solutions were prepared and mixed in clear glass test tubes and were continuously exposed to fluorescent light of normal intensity, conditions that closely simulate those in most patient care areas. However, visual inspection, such as that used for samples in this study, can detect only large, visible particles. Although each combination was placed in a clear glass test tube to avoid misinterpretations, the possibility exists that an incompatibility expressed as a microprecipitate was not detected because of small particle size.

The results of this study are limited to the drug products used and the conditions under which the study was conducted. Furthermore, although the range of physically compatible concentrations was carefully delineated, admixtures prepared in the clinical setting may be subject to some concentration errors, unlike solutions prepared in the controlled laboratory setting. Therefore, concentrations that approach or are close to the identified physically incompatible concentrations should be avoided.

In conclusion, pantoprazole for IV administration was physically compatible with 3.3% dextrose and 0.3% sodium chloride for injection and with 12 of 17 drugs diluted in D5W and tested for up to 12 h at 23°C during simulated Y-site administration. Precipitation occurred with mixtures containing pantoprazole and dobutamine or norepinephrine. A colour change and a coloured precipitate were observed when pantoprazole was combined with esmolol, midazolam, or octreotide. In general, mixtures of pantoprazole with esmolol, dobutamine, or midazolam were physically incompatible over concentration ranges used in the clinical setting. Octreotide and pantoprazole were physically compatible when the octreotide concentration was less than 1.5 µg/mL. Norepinephrine was physically compatible with pantoprazole when the norepinephrine concentration was less than 13 µg/mL.

Routine Y-site administration of pantoprazole with esmolol, dobutamine, midazolam, norepinephrine, or octreotide is not recommended; however, for 4 of these drugs (dobutamine, midazolam, norepinephrine, and octreotide) co-infusion may be considered if appropriate concentrations are selected.

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