Stability and Compatibility of Combinations of Hydromorphone and a Second Drug

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ABSTRACT

The stability and compatibility of binary combinations of hydromorphone at three concentrations (2, 10 and 40 mg/mL) and seven other medications (ampicillin, cefazolin, ceftazidime, cloxacillin, diazepam, phenytoin and phenobarbital) were evaluated for 24 hours at room temperature. In addition to visual inspection and pH, the concentration of each component in the binary mixture was determined by a stability indicating liquid chromatographic method. Each test was completed at time zero, 4, 8 and 24 hours after mixing equal volumes of each medication.

Incompatibilities were observed when equal volumes of hydromorphone were mixed with either diazepam (5 mg/mL), phenobarbital (120 mg/mL) or phenytoin (50 mg/mL). Cefazolin was observed to be incompatible only when concentrations of cefazolin exceeded 200 mg/mL. Cloxacillin was observed to be incompatible with hydromorphone only when cloxacillin had been diluted with 5% dextrose in water (D5W) and the concentration exceeded 24 mg/mL. Cloxacillin is compatible with hydromorphone when an equal volume of a 250 mg/mL solution (reconstituted according to the manufacturer's directions) is mixed with hydromorphone. Ampicillin was observed to be compatible at concentrations of 20 mg/mL (diluted in D5W) and 250 mg/mL, but ampicillin retained more than 90% of the initial concentration for only four hours. Ceftazidime (40 mg/mL in D5W or 250 mg/mL) was physically compatible and chemical stable in the presence of hydromorphone. Hydromorphone was chemically stable in all solutions and never precipitated.

Key Words: *ampicillin, cefazolin, ceftazidime, cloxacillin, compatibility, diazepam, hydromorphone, phenobarbital, phenytoin, stability*

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RÉSUMÉ

Les stabilités et compatibilités d'associations binaires d'hydromorphone à trois concentrations (2, 10 et 40 mg/mL) et de sept autres médicaments (ampiciline, céfazoline, ceftazidime, cloxacillin, diazépam, phénytoïne et phénobarbital) furent évaluées pendant une période de 24 heures à la température de la pièce. En plus d'une inspection visuelle et au pH, la concentration de chaque élément du mélange binaire fut déterminée en utilisant la méthode d'un solvant chromatographique déterminant la stabilité. Chaque examen fut complété aux temps 0, 4, 8 et 24 heures après avoir mélangé en volumes égaux chaque médication.

Des incompatibilités furent observées lorsque des volumes égaux d'hydromorphone et de diazépam (5 mg/mL), de phénobarbital (120 mg/mL) ou de phénytoïne (50 mg/mL) furent mélangés. Il y eu incompatibilité seulement lorsque les concentrations de céfazoline dépassaient 200 mg/mL. La cloxacilline était incompatible avec l'hydromorphone, seulement quant elle était diluée dans l'eau avec 5 p.c. de dextrose (D5W) et que la concentration dépassait 24 mg/mL. Elle était compatible avec l'hydromorphone lorsque mélangée en volumes égaux d'une solution à 250 mg/mL (reconstituée selon les directives du fabricant). L'ampicilline était compatible (diluée dans le D5W) à des concentrations de 20 mg/mL et de 250 mg/mL, mais conservait retenu plus de 90 p.c. de la concentration initiale pendant quatre heures seulement. La ceftazidime était compatible physiquement (40 mg/mL dans D5W ou 250 mg/mL) et chimiquement stable en présence de l'hydromorphone. L'hydromorphone était stable chimiquement dans toutes solutions et ne précipitait jamais.

Mots clés: *ampicilline, céfazoline, ceftazidime, cloxacillin, compatibilité, diazépam, hydromorphone, phénytoïne, phénobarbital, stabilité*

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INTRODUCTION

In practice, pharmacists are often asked questions regarding the compatibility of medications. Our interest in compatibility of hydromorphone with other medications stems from recent advances in the management of chronic pain through the development of reliable portable infusion devices.[1] The use of these devices to deliver continuous intravenous or subcutaneous infusions of narcotics to control chronic pain in cancer patients has become an acceptable method of treatment.[2-6] In addition to improving the control of chronic pain, the use of portable infusion pumps allows patients to be managed at home with significant cost savings to the health care system.[7,8] Due to the problems associated with maintaining an intravenous site for long periods of time and the risks associated with long term intravenous therapy in this patient population, the subcutaneous route may be the preferred route. The ease of managing a subcutaneous site has promoted the use of this route for other drugs, including antibiotics, antineoplastics, antiemetics, and hormonal agents.[9] The success of the subcutaneous route with some of these agents has produced a desire for simultaneous administration of agents, and it is, therefore, not surprising that suggestions to simplify therapy include mixing medications in the same infusion container. Thus, questions concerning the compatibility between hydromorphone and other medications within an infusion container or at the site of injection arise. We have often discouraged the practice of mixing medications in the same infusion container for technical reasons (infusion solution formulation difficulties) or pharmacologic reasons (dose adjustment of one medication results in dosage changes for both medications or wastage of the remaining medication[10]) nevertheless, situations often arise when knowledge of medication compatibility is important.

The purpose of this investigation was to evaluate the compatibility and chemical stability over 24 hours of hydromorphone with seven other medications: ampicillin, cefazolin, ceftazidime, cloxacillin, diazepam, phenytoin, and phenobarbital. Compatibilities were evaluated visually as well as chemically, using liquid chromatographic equipment and keeping stability indicating assay methodology considerations[11-13] in mind during the development of a chromatographic separation.

METHOD

The intent of this study was to test the compatibility of the binary combinations of hydromorphone with seven other medications. In order to quantitate the concentrations of each compound accurately and specifically, liquid chromatographic separations were developed for each binary combination which allowed the separation of each parent compound from each other. The development of each method also considered the possibility of degradation productions and so was developed with stability-indicating assay methodologies in mind.[11-13]. Following the initial development of a chromatographic separation, the suitability of this system for use in a compatibility/stability study was tested by accelerating the degradation of each drug to be tested (ampicillin, cefazolin, ceftazidime, cloxacillin, diazepam, phenytoin phenobarbital and hydromorphone). Aqueous solutions of each product in the concentrations and pH's specified in Table I were prepared and placed in a 30 cc multidose vial with a rubber septum closure (Solopak Laboratories) and incubated in a water bath at 90°C. Samples were drawn just prior to incubation and at least eight other times over the study period. The study was stopped when degradation products could be detected. Chromatograms were inspected for the appearance of additional peaks and the peak of interest was compared between samples for changes in concentration, retention time and peak shape. No attempt was made to identify degradation products of any of the compounds. The final chromatographic conditions developed for each compatibility study is listed in Table I.

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves was tested. For each of the seven medications to be mixed with hydromorphone, six standards ranging in concentration from zero to the highest concentration to be encountered in the study (see Table II) were prepared and chromatographed in duplicate. Suitable accuracy and reproducibility was judged to have been attained when interpolation of two other samples of known concentration were within 3% of their known value and intra-day coefficient of variation for samples run at least twice, was less than 4%.

Stability/Compatibility Study

Each binary pair was evaluated separately and sequentially, such that the next compatibility/stability study was not initiated until the previous study was completed. For each initial study, 1 mL volumes of each available formulation of hydromorphone (2 mg/mL, 10 mg/mL and 40 mg/mL: Knoll Pharmaceuticals), were mixed with 1 mL of each of the following drugs; ampicillin, cefazolim, ceftazidime, cloxacillin, diazepam, phenytoin and phenobarbital (Manu-

Table I: Assay Validation Data

Parent Compound	Accelerated Degradation			Study Conditions*		Chromatographic Conditions		Intra-Day Reproducibility†	
(Manufacturer & Lot #)	Initial Conc.	Solvents‡	Initial pH	Study Duration (Minutes)	% Remaining	Initial %** Acetonitrile	Final % Acetonitrile	Hydromorphone	Secondary
Ampicillin (Penbritin-1000: Ayerst Laboratories; Lot #1SVW-FL)	5 mg/mL	W	7	195	32	17 (I-14)	17	0.82	0.40
Cefazolin (Ancef: Smith Kline and French Canada Ltd., Lot #05389)	10 mg/mL	W	7	210	29	15 (I-11)	15	1.23	2.27
Ceftazidime (Fortaz: Glaxo Canada Inc., Lot #83155)	10 mg/mL	W	7	128	27	17 (I-15)	17	1.48	0.84
Cloxacillin (Orbenin; Ayerst Laboratories Canada Inc., Lot #IZZA-HK)	100 mg/mL	W	7	170	47% at 45 min	35 (I-14)	35	3.12	0.34
Hydromorphone (Dilaudid; Knoll Pharmaceuticals, Lot #L50150269)	10 mg/mL	W	8.3	1632	70	13 (I-10)	13	0.69	0.56
Diazepam (Diazepam; Sabex International Ltd., Lot #249001)	1 mg/mL	W	1.8 3.5	1320 1320	15 100	14 (G-16)	39	1.14	0.99
Phenytoin (Aldrich Chemical Company Inc., Lot. #B030277) accelerated studies only; Phenytoin; (Abbott Laboratories, Lot #41-631-NJ)	5 mg/mL	M	2 6 11	120 120 120	100 100 100	20 (G-12)	50	0.59	1.63
Phenobarbital (BDH Fine Chemicals, Lot. #103537/20506) accelerated studies only; Phenobarbital; (Abbott Laboratories, Lot #41-631-NJ)	0.4 mg/mL	80% M 20% W	10	363	2% at 237 min	18 (G-16)	35	3.57	2.27

* All solutions were incubated at 90°C for the duration of the accelerated study.
† Reproducibility as estimated by coefficient of variation expressed as a percent.
‡ W indicates water, M indicates methanol.
** I indicates isocratic; G indicates that a gradient was used to elute compounds from the column, and following number indicates total chromatographic run time.

facturer, and lot # are listed in Table I, concentrations are indicated in Table II). Each mixture was vortexed to assure adequate mixing and then observed immediately for precipitate, colour change and evolution of gas. Upon observing a precipitate, varying proportions of each commercial formulation were mixed to evaluate the range of incompatible concentrations. The supernate of an aliquot of each solution which was observed to have a precipitation was chromatographed to determine the concentration of each component in solution and determine which component, if any, had precipitated. If no precipitate was visually apparent the solution was chromatographed and the pH determined. Physical inspection, pH and chromatographic analysis were repeated at 4, 8 and 24 hours.

Chromatographic Analysis

Six standards of hydromorphone and the second drug were prepared separately and chromatographed in duplicate. Volume injected depended on detector response for each drug in the binary combination and varied between 1 and 20 microlitres.

The chromatographic system consisted of a terniary gradient solvent delivery pump (Spectra Phys-

ics SP4200) which pumped a mixture of acetonitrile (Fisher: Cat. # A998), and 0.05 Molar phosphoric acid (pH 2.2) through a 25 cm x 4.2 mm reversed-phase C-18, 5 um column (Beckman Ultrasphere, ODS # 235329) at 2.0 mL/min. The ratio of acetonitrile to phosphate buffer for each chromatographic separation was different and is listed in Table I. All mobile phases contained 1 mg/mL heptane sulfonic acid as a counter ion. The column effluent was monitored with a variable wavelength ultraviolet detector (Schoeffel SF770) at 230 nm. The area of each peak produced by a standard of known concentration at 230 nm was reported and subjected to least squares regression. The actual concentration in solutions of unknown concentration, was interpolated from these curves and recorded. Concentrations were reported to the nearest 0.01 mg/mL.

Data Reduction and Statistical Analysis

All raw chromatographic data were archived on computer diskette. Means (± standard deviation) were calculated for all analyses. Reproducibility of methods was assessed by coefficient of variation (CV - standard deviation divided by the mean). Mean results from different study times of an identical test were compared statistically by least squares linear regression (or log-linear regression, if appropriate) to determine if an association existed between the observed result and time. Log-linear and linear-linear fits for the data from the accelerated degradation study (90°C) were compared for goodness of fit by the Maximum likelihood method of Box and Cox[14,15]. Analysis of variance and the least significant difference multiple range test was used to compare differences between times for similar analytical tests. The 5% percent level was used as the *a priori* cut-off for significance. Concentrations were considered "acceptable", or "within acceptable limits" if the concentration at any time of analysis was not less than 90% of the initial (time zero) concentration.

Table II: Compatibility Study Summary

Other Drug (mg/mL of original product)	Hydromorphone 2 (mg/mL original product)	10	40	Comments
Ampicillin				
20 mg/mL[1]	C*	C	C	Ampicillin is unstable both with and without the addition of hydromorphone. Compatible solutions retain 90% of the initial ampicillin concentration for less than five hours.
250 mg/mL[2]	C	C	C	
Cefazolin				
20 mg/mL[1]	C	C	C	Precipitation of cefazolin occurs when cefazolin is present in concentrations greater than 200 mg/mL.
300 mg/mL[2]	I**	I	I	
Ceftazidime				
40 mg/mL[1]	C	C	C	Ceftazidime and hydromorphone both retain more than 90% of their initial concentrations for 24 hours and no precipitation was observed.
180 mg/mL[2]	C	C	C	
Cloxacillin				
40 mg/mL[1]	I	I	I	Cloxaxillin and hydromorphone solutions are compatible, however, when cloxacillin is diluted in 5% dextrose in water, and then mixed with equal volumes of hydromorphone, cloxacillin will precipitate within 96 hours. Precipitation occurs immediately if the cloxacillin in D5W concentration exceeds 24 mg/mL.
250 mg/mL[2]	C	C	C	
Diazepam				
5 mg/mL[3]	I	I	I	Precipitation of diazepam occurs when water, in a volume exceeding 25% of the diazepam volume, is mixed with the diazepam formulation.
Phenobarbital				
120 mg/mL[3]	I	I	I	Precipitation of phenobarb occurs due to the presence of citric acid in the hydromorphone formulation.
Phenytoin				
50 mg/mL[3]	I	I	I	Precipitation of phenytoin occurs due to the presence of citric aid in the hydromorphone formulation.

* C = Compatible
** I = Incompatible
[1] Reconstituted solution diluted with 5% dextrose in water.
[2] Reconstituted according to manufacturers recommendations.
[3] Manufacturers commercially available solution.

RESULTS

Each parent compound could be degraded to produce degradation products which were observed in chromatograms. The percent remaining of each parent compound at the end of each accelerated study completed at 90°C is given in Table I. Reproducibilities, as estimated by coefficient of variation of duplicate analysis for each parent compound, was less than 4%. (Table I) As a result, each assay has the ability to detect changes

in concentration of less than 10% with duplicate analysis[16,17].

The compatibility studies are summarized in Table II. Only ceftazidime was observed to be compatible and stable at all concentrations evaluated.

Ampicillin

Ampicillin was reconstituted according to the manufacturers recommendations and then further diluted in 5% dextrose in water. All mixtures were initially clear and free of particulate matter and remained so for up to 72 hours. During the study period the pH was observed to drop by approximately 0.5 of a pH unit. No change was observed in the hydromorphone concentration, however, the ampicillin concentration was observed to decrease by more than 10% within 5 hours, regardless of the presence or absence of hydromorphone.

Cefazolin

Cefazolin reconstituted according to the manufacturers recommendations and then further diluted in 5% dextrose in water retained greater than 95% of the initial cefazolin concentration for 24 hours. When mixed with hydromorphone (2, 10 or 40 mg/mL) no precipitate was observed, and the concentration of both hydromorphone and cefazolin remained within 90% of the initial concentration. However, when an equal volume of hydromorphone and cefazolin in a concentration exceeding 200 mg/mL were mixed, cefazolin immediately precipitates. If the manufacturers vial is reconstituted to achieve a final concentration of 150 mg/mL, the mix is physically compatible and both hydromorphone and cefazolin retain greater than 90% of the initial concentration for the 24 hour study period. Degradation products observed during the accelerated study were not observed during the 24 hour study period.

Ceftazidine

Ceftazidine reconstituted according to the manufacturers recommendations to achieve a final concentration of 180 mg/mL is physically compatible and stable with hydromorphone solutions for a 24 hour period. If the ceftazidime solution (180 mg/mL) is further diluted in 5% dextrose and water to achieve a final concentration of 40 mg/mL and then mixed with an equal volume of a hydromorphone solution, the mixture is physically compatible and the concentration of both drugs remains within 90% of the initial concentration.

Cloxacillin

Cloxacillin reconstituted according to manufacturers recommendations as well as cloxacillin which is further diluted in 5% dextrose in water to achieve a final concentration 2000 mg/50 mL retains greater than 90% of the initial concentration for 24 hours. During this time, degradation products observed during the accelerated study were not observed. When cloxacillin (250 mg/mL) is mixed with an equal volume of a hydromorphone solution (2, 10 or 40 mg/mL), the mixture may turn milky white but vigorous agitation will prevent the formation of a precipitate. This solution will remain clear and colourless for up to 96 hours, and during this time neither cloxacillin nor hydromorphone will degrade. However, cloxacillin (2000 mg/50 mL 5% dextrose in water) when mixed with an equal volume of hydromorphone (2, 10 or 40 mg/mL) will turn milky white immediately and a water insoluble precipitate will form. This precipitate is readily soluble in methanol and can be shown to be cloxacillin, as the base. Cloxacillin solutions of lower concentrations (up to 24 mg/mL; 12 mg/mL after mixing with equal volumes of hydromorphone) remain clear and colourless for up to 24 hours. However, after 96 hours these solutions will also turn cloudy and a precipitate will be evident. Cloxacillin concentrations of 26 and 28 mg/mL in D5W will, when mixed with equal volumes of hydromorphone (2, 10 or 40 mg/mL), turn a hazy white. This precipitate can not be settled by centrifugation initially, but on standing a precipitate becomes apparent by 96 hours. The concentration dependent formation of cloxacillin base from a 5% dextrose in water solution can be shown to be due to the presence of citric acid in the hydromorphone formulation and does not occur when cloxacillin is mixed with a hydromorphone solution which does not contain citric acid, or when there is no dextrose (5% W/V) in the mixture.

Diazepam

Diazepam (5 mg/mL) was initially clear, and yellow in colour and remained so for up to 24 hours. However, upon dilution with an equal volume of hydromorphone (2 mg/mL, 10 mg/mL, or 40 mg/mL), samples became turbid immediately, and with mixing formed a milky, yellow, homogenous mixture. On standing (no centrifugation), a fine precipitate, which presented as a film adhering to the wall of the glass test tube was evident in all samples. The precipitate, which was identified as diazepam, was found in all samples containing hydromorphone, but could also be produced with the sodium citrate/citric acid buffer as well as water. In all samples, approximately 10% of the initial diazepam concentration was lost due

to precipitation. When mixed with water, no precipitate was formed in the mixtures in which less than 25% of the diazepam volume was added water. In samples in which precipitation did not occur (less than 25% of additional aqueous volume added) and in the supernate of samples in which a precipitate was formed, the concentration of hydromorphone and diazepam did not change over the subsequent 24 hour period, nor were degradation products that were observed in the accelerated study seen during this study period.

Phenytoin

Phenytoin (50 mg/mL) was initially clear and colourless and remained so for up to 24 hours. However, upon addition of equal volumes of hydromorphone (2 mg/mL, 10 mg/mL and 40 mg/mL), samples turned milky immediately and a white precipitate formed. This precipitate was not soluble in water, but was readily soluble in methanol and was shown to be phenytoin, as the base. Precipitation of phenytoin was demonstrated to be due to the presence of citric acid in the hydromorphone formulation (precipitate was observed when the hydromorphone vehicle containing 2 mg/mL of sodium citrate and citric acid or 2 mg/mL of citric acid alone was mixed with phenytoin. No precipitate was observed when phenytoin was mixed with an equal volume of hydromorphone in a solution which contained neither sodium citrate or citric acid). During the 24 hours study period, the amount of white precipitate gradually increased. In all of these samples the concentration of phenytoin was less than theoretical. The hydromorphone concentration remained unchanged for the duration of the study.

Phenobarbital

Phenobarbital (120 mg/mL) was initially clear and colourless and remained so for up to 24 hours. However, upon addition of equal volumes of hydromorphone (2 mg/mL, 10 mg/mL, or 40 mg/mL), samples became turbid immediately, but mixed together to form a clear, homogeneous solution with no precipitate. However, after six hours all samples showed a white, crystalline, precipitate. Precipitation of phenobarbital was demonstrated to be due to the presence of citric acid and sodium citrate in the hydromorphone formulation. During the 24 hour study period, the amount of white precipitate gradually increased. The hydromorphone concentration remained unchanged for the duration of the 24 hour study period.

DISCUSSION

The syringe and IV injection site compatibility of binary combinations of hydromorphone with a second medication, as reported by various investigators[18-23] has been summarized by Trissel.[24] Most of these reports indicate that hydromorphone is compatible with these medications. However, in this study we observed cefazolin, cloxacillin, diazepam, phenobartital and phenytoin to be incompatible with hydromorphone. There are no previous reports concerning the compatibility of hydromorphone with these medications, except for cefazolin.[23] In that investigation Nieves-Cordero et al[23] reported that a 20 mg/mL solution of cefazolin in 5% dextrose in water was compatible with hydromorphone. In order to clarify this apparent discrepancy, we evaluated hydromorphone and cefazolin compatibility over a range of concentrations. Cefazolin was observed to precipitate from solution when the concentration of cefazolin exceeded 200 mg/mL. Concentration dependant compatibility was also observed with cloxacillin, and this incompatibility was also observed to be affected by other solutes in solution, namely dextrose and citric acid. Concentration dependant compatibility has also been recently reported for hydromorphone and dexamethasone[25], as well as dexamethasone and diphenhydramine.[25]

In this study we also observed an incompatibility between diazepam and hydromorphone. However, in this case the incompatibility was not due specifically to the hydromorphone, but rather to the amount of water added. Diazepam was observed to precipitate when the amount of water added exceeded 25% of the volume of the commercial diazepam product. This is similar to the incompatibility (insolubility) noted to occur when a commercially available intravenous pentobarbital solution (Nembutal; Abbott Laboratories) is mixed with either normal saline or 5% dextrose in water solutions.[26]

In this study we also observed a precipitate when hydromorphone was mixed with either cloxacillin, phenobarbital or phenytoin. When solutions containing 2 mg/mL of citric acid or 2 mg/mL of sodium citrate were mixed with each of these medications, each medication was also observed to precipitate in the presence of the citric acid. This incompatibility may not be due specifically to citric acid, but may likely be due to pH.

This and other studies[25,26] have demonstrated that compatibility of binary combinations of medications must be evaluated over a range of concentrations to completely evaluate the range of a mixtures' compatibility. Failure to evaluate a range of concentrations may result in an incompatibility being missed.

REFERENCES

1. Coons CE, Sone M. Portable narcotic infusion devices in Canada. *Can J Hosp Pharm* 1989. 42: 235-8.

2. Citron ML, Johnson-Early A, Fossieck BE et al. Safety and efficacy of continuous intravenous morphine for severe cancer pain. *Am J Med* 1984; 77: 199-204.
3. Portenoy RK, Moulin DE, Roger A, et al. IV infusion of opiods for cancer pain: clinical review and guidelines for use. *Cancer Treatment Reports* 1986; 70: 575-81.
4. Kerr IF, Sone M, DeAngelis C, et al. Continuous narcotic infusion with patient controlled analgesia for chronic cancer pain in outpatients. *Ann Intern Med* 1988; 108: 554-7.
5. Bruera E, Brenneis C, MacDonald RN. Continuous SC infusion of narcotics for the treatment of cancer pain: an update. *Cancer Treatment Reports* 1987; 71: 958-73.
6. Swanson G, Smith J, Bulich R, New P, Shiffman R. Patient-controlled analgesia for chronic cancer pain in the ambulatory setting: A report of 117 patients. *J. Clin Oncol* 1989; 7: 1903-8.
7. Wodinsky HB, Sone M, and Kerr IG. Outpatient palliative pain control. *Dimensions in Health Services* 1988; 65: 10-17.
8. Wodinsky HB. Outpatient vs inpatient palliative pain control. Proceedings of Cancer Pain 88. May 31, 1988.
9. Hillman RS. The subcutaneous space. A route for continuous administration of drugs? *Trends in Pharmacological Sciences* June 1983. 245-7.
10. Walker SE, Coons CE, DeAngelis C, Iazzetta J, Matte D, Schueller T, Kolos C. Continuous subcutaneous infusion (CSCI) of narcotics for the treatment of cancer pain: A guide for pharmacists. Pamphlet distributed by Knoll Pharmaceuticals Canada. 1988.
11. Trissel LA. Avoiding common flaws in stability and compatibility studies of injectable drugs. *Am J. Hosp Pharm* 1983; 40: 1159-60.
12. Trissel LA and Flora KP. Stability studies: five years later. *Am J Hosp Pharm* 1988; 45: 1569-71.
13. Anon. (Eds. Tremblay SJ, Walker SE, O'Brodovich M, Murdock L). Policy for publication of chemical stability study manuscripts. *Can J Hosp Pharm* 1990; 43: 3-4.
14. Box GEP, Cox DR. An analysis of transformations. *Jr. Statist Soc Series B* 1964; 26: 211-43.
15. Sclove SL. (Y vs X) or (Log Y vs X)? *Technometrics* 1972; 14: 391-403.
16. Frieman JA, Chalmers TC, Smith H, et al. The importance of beta, Type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978; 299: 690-4.
17. Stolley PD and Strom BL. Sample size calculations for clinical pharmacology studies. *Clin Pharmacol Therap* 1986; 39: 489-90.
18. Ingallinera T, Kapadia AJ, Hagman D et al. Compatibility of glycopyrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; 36: 508-10.
19. Anon. Vistril IM, table of physical compatibilities. Pfizer Laboratories. New York, New York. July 1979.
20. Cutie MR. Letters. *Hosp Formul* 1980; 15: 502-3.
21. Souney PF, Solomon MA, Stancher D. Visual compatibility of cimetidine hydrochloride with common preoperative injectable medications. *Am J Hosp Pharm* 1984; 41: 1840-1.
22. Parker WA. Physical compatibility of ranitidine HC1 with preoperative injectable medications. *Can J Hosp Pharm* 1985; 38: 160-1.
23. Nieves-Cordero AL, Luciw HM, and Souney PF. Compatibility of narcotic analgesic solutions with various antibiotics during stimulated Y-site injection. *Am J Hosp Pharm* 1985; 42: 1108-9.
24. Trissel LA, Handbook on Injectable Drugs. 5th ed. American Society of Hospital Pharmacists. 1988; 224-7.
25. Walker SE, DeAngelis C, Iazzetta J, Eppel JG. Dexamethasone compatibility with hydromorphone or diphenhydramine. *Am J Hosp Pharm* 1991; 48: 2161-6.
26. Walker SE, Iazzetta J. Compatibility and Stability of Pentobarbital Infusions. *Anesthiol* 1981; 55: 487-9.