An orchestra in need of a conductor

Doesburg, Frank

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CHAPTER 3B

A systematic procedure for Y-site compatibility analysis of intravenous drugs used in the intensive care unit

Frank Doesburg, Pieter A. Annema, Maurits H. Renes,
Maarten W. Nijsten, Wouter Bult, Daan J. Touw
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Supplementary material

Abstract

Background

Y-site compatibility testing of intravenous (IV) drug combinations is not standardized in the literature, and the compatibility of many common intensive care unit (ICU) drug combinations is still unknown. We combined and adapted existing Y-site compatibility testing procedures to better reflect ICU conditions.

Methods

Our testing procedure was defined based on previous Y-site compatibility studies. A total of 19 combinations of 13 IV drug solutions relevant to our ICU have an unknown or uncertain Y-site compatibility and were assessed according to this procedure. They were visually examined after 0, 30, 60, and 120 minutes, and quantitatively analyzed using HPLC-DAD analysis after a 2 h period at both 20˚C and 37˚C. Combinations were compatible when no visual changes occurred and quantitative analysis showed a recovery between 90% and 110%.

Results

Visual analysis indicated that 6 combinations were immediately incompatible. Quantitative analysis showed 4 combinations with at least one drug with a recovery <90%. The compatibility of 9 combinations could not be established using HPLC-DAD analysis.

Conclusions

According to our systematic procedure for the evaluation of simultaneous Y-site administration 6 combinations were incompatible and 4 combinations were compatible. A suitable analytical method must be developed for the remaining 9 combinations in order to determine their compatibilities.

Introduction

In the intensive care unit (ICU) patients commonly receive multiple intravenous (IV) drug solutions simultaneously.[1–3] When the number of drug solutions is larger than the number of available IV lumens, different intravenous drugs need to be administered concurrently through a single lumen and Y-site incompatibility is a major concern. The co-administration of incompatible drugs can lead to precipitation, inactivation, occlusion, catheter failure and embolism.[4] In order to avoid incompatibilities, additional IV catheters are often placed, increasing the likelihood of catheter-related complications such as catheter-related blood stream infection or (thrombo)phlebitis.[5] The ability to safely combine multiple drugs through a single lumen reduces the need for the placement of additional IV catheters. Therefore, knowledge of Y-site compatibility is essential for the prevention of IV therapy related complications.

ICUs frequently use a compatibility chart of common IV drug solutions to decide which drugs can be co-administered through the same lumen.[4,6,7]. Our university medical center maintains a parenteral drug guide (PDG) that contains instructions for the preparation and administration of over 585 different intravenous drugs, as well as known Y-site compatibilities. This PDG is the primary source for the compatibility chart used in our ICU (Figure 1) and is maintained by a team of pharmacy technicians and hospital pharmacists with Micromedex® as its primary source of information on drug compatibilities.[8] Unfortunately the chart we use is incomplete as many important combinations of drugs have not been studied or because contradictory results have been published.[9]

The Y-site compatibility analysis of IV drug pairs has not yet been standardized. According to a review of 93 compatibility studies, a wide variety of different procedures for assessing the Y-site compatibility of drug pairs is used.[10] There is neither consensus regarding which physicochemical parameters should be evaluated nor which acceptance criteria should be used to determine compatibility.[3] Hence, many compatibility studies present conflicting results or use drug concentrations and conditions that do not reflect ICU practice. We therefore developed a systematic procedure to establish the compatibility of pairs of intravenous drugs of which the Y-site compatibility is not known or uncertain according to the literature. We subsequently applied this procedure for some of the most commonly used drug pairs in our ICU.

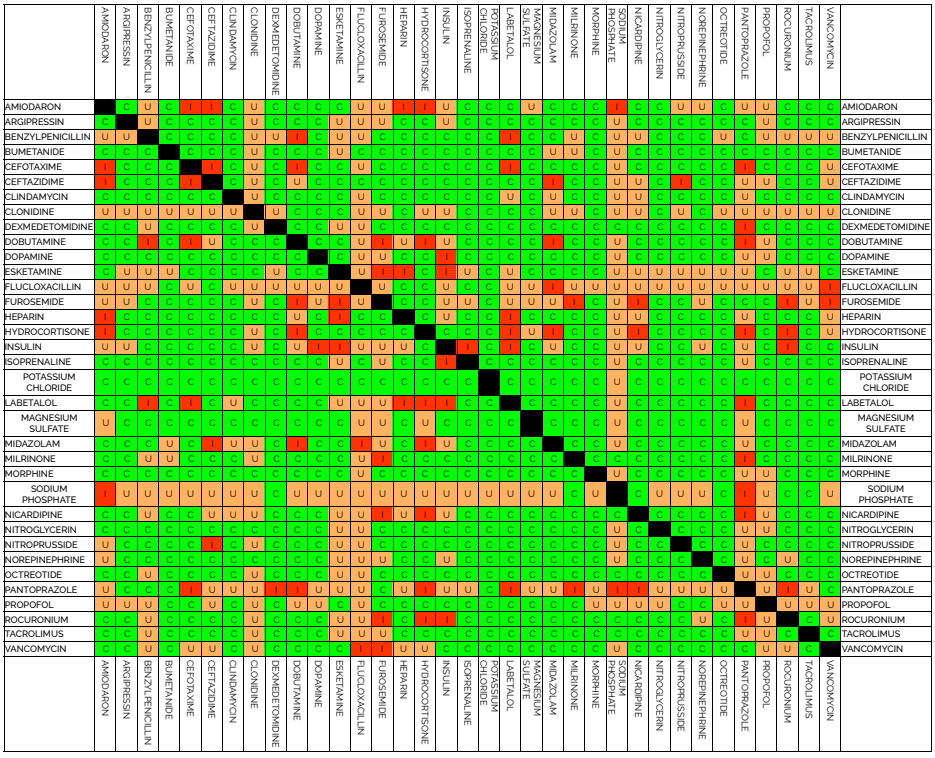


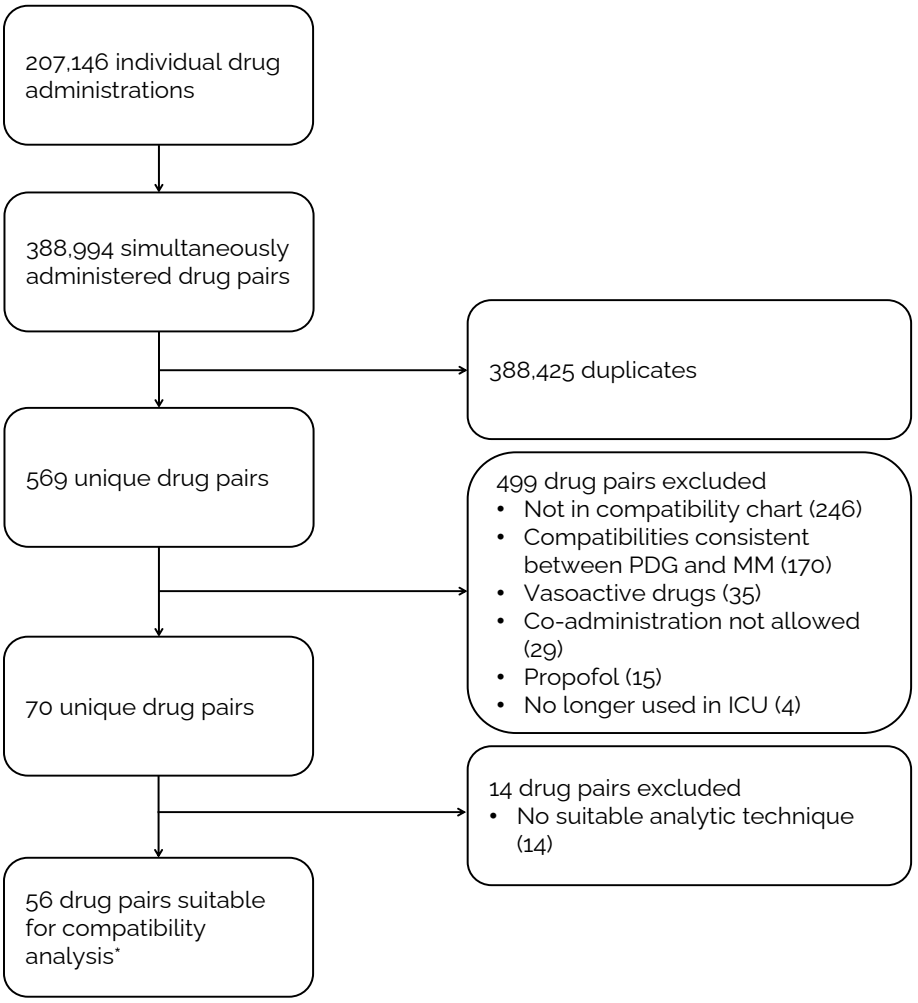
Figure 1. Compatibility chart. Green, red, and orange squares respectively indicate a combination of drugs that is compatible, incompatible or has an unknown compatibility.

Methods

Selection of drugs and concentrations for analysis.

A database of 207,146 intravenous drugs and fluids (administered between March of 2014 and February of 2016 on our adult ICU) was used to select 56 drug pairs suitable for analysis (see Figure 2).The original database contained fields for drug name, concentration, start time and date, end time and date, volume administered, and an anonymized patient identifier for each of the 3,361 patients. From these data, all simultaneously administered drugs could be retrieved on a patient level, from which the unique drug pairs were identified. Drug pairs that were not in our compatibility chart, or those that were consistently flagged as either compatible or incompatible in both our PDG and the Micromedex® database were excluded from further analysis. Vasoactive drugs (dobutamine, dopamine, isoproterenol, epinephrine and norepinephrine) and drugs that were not allowed as per summary of product characteristics to be co-administered with other drugs (e.g. insulin and nimodipine), were also excluded. Propofol was excluded as its opacity makes it unsuitable to perform a visual analysis. Drugs that were no longer in use in our ICU were also excluded from analysis. The above selection criteria led to 19 drug combinations that were tested in this study.

HPLC-DAD analysis was used for the quantitative compatibility assessment. In order for the analysis to be clinically relevant, concentrations of drugs administered in our ICU as described in our PDG were used in this study. Table 1 contains the concentration, type of solvent and the preparation method of each drug used in this study. Where possible, glucose 5% was preferred over NaCl 0.9% to comply with preferred practice in our ICU to minimize salt loading.



*19 of the 56 drug pairs were analyzed in this study.

Figure 2. Data flow for the selection of drug pairs suitable for compatibility analysis. PDG: parenteral drug guide, MM: Micromedex, ICU: Intensive care unit.

Table 1. Solvents, preparations and final concentrations of continuously administered ICU drugs

Drug	Preparation	Volume ml	Final concentration (mg/ml unless otherwise indicated)
clindamycin	12 ml (1,800 mg) + 36 ml glucose 5%	48	37.5
clonidine	4 ml (0.6 mg) + 46 ml NaCl 0.9%	50	0.012
dexmedetomidine	4 ml (0.4 mg) + 46 ml glucose 5%	50	0.008
esomeprazole	80 mg + 50 ml NaCl 0.9%	50	1.6
furosemide	25 ml (250 mg) + 25 ml NaCl 0.9%	50	5
heparin	4 ml (20,000 IU) + 46 ml glucose 5%	50	400 IU/ml
hydrocortisone	200 mg + 4 ml WFI + 46 ml glucose 5%	50	4
magnesium sulfate	50 ml (5,000 mg)	50	100
midazolam	50 ml (100 mg)	50	2
morphine	20 ml (200 mg) + 30 ml glucose 5%	50	4
nicardipine	-		1
potassium chloride	-		1 mmol/ml
sodium phosphate	10 ml (30 mmol) + 40 ml glucose 5%	50	0.6 mmol/ml

WFI: water for injection

Materials

Table S1 (Supplementary material) lists all concentrations, volumes, manufacturers, batch numbers and expiration dates of drugs and solvents used in this study. All IV drugs were prepared in standard laboratory glassware. Polystyrene round bottom test tubes (16x95 mm) were used when measuring the pH and performing analyses. Another set of test tubes consisted of soda-lime glass flat bottom test tubes (Murray, S & Co Ltd, 75*16*0.85 mm; internal diameter 14.3 mm). A Memmert B30heating stove was used to heat the test tubes to 37 ±1˚C.

The pH was measured using a Metrohm 780 pH-meter coupled with a Metrohm 6.0238.000 glass electrode with an integrated Pt-1000 temperature sensor.

The HPLC-DAD setup comprised of a Hitachi (Hitachi Ltd., Tokyo, Japan) 5430 Diode Array Detector (DAD), a Hitachi 5310 column oven, a Hitachi 5210 autosampler and a Hitachi 5110 pump. The stationary phase was a Knauer LiChrospher 100-5 RP 18e (Knauer GmbH, Berlin, Germany) column, the eluent consisted of 470 ml acetonitrile, 150 µl triethylamine, 400 µl phosphoric acid (80%) and 530 ml ultrapure water. All used chemicals were HPLC grade.

Procedure

Temperature

The solubility and in particular the interaction of drugs may be influenced by changes in temperature. In case of IV lines being used in the ICU, the temperature may vary between room temperature and body temperature (approximately 20˚C and 37˚C, respectively). IV lines often partially run from the pump to the patient's bed and then under the bedsheets near or touching the patient's body. Consequently, each drug pair was kept for 2 h at 20˚C and at 37˚C respectively to reflect room temperature and the temperature under the patient's blanket, respectively. The test tubes were taken out for approximately 7 minutes for each measurement.

Visual analysis

Time was recorded from the moment of mixing the two drugs. At time points 0, 30, 60 and 120 minutes (T_0, T_{30}, T_{60}, and T_{120} respectively) a visual analysis was performed by checking for changes in clarity, degree of opalescence, coloration, number of particles and gas bubbles. All of the findings and results were immediately documented in a standard form (Supplementary material: File S1).

A total of three sets of three test tubes were used, where every set contained a tube with drug A, a tube with drug B and a 1:1 volume combination of drugs A and B. Visual analysis was performed in flat bottom soda glass test tubes and every tube was filled with 6.5 ml of solution.

All visual tests were performed with the unaided eye. In order to compare the clarity and degree of opalescence of the combination of drug A+B to that of drugs A and B separately, drug solutions were held against a black background in diffused daylight as described in monograph 2.2.1 'Clarity and degree of opalescence of liquids' of the European Pharmacopoeia 9.0.[11]

In order to determine a possible change in coloration the combination A+B was compared with the separate drugs A and B against a white background in diffused daylight as described in monograph 2.2.2 'Degree of coloration of liquids' from the European Pharmacopoeia 9.0.[12] Additionally, combination A+B was compared to the separate drugs A and B with regard to the presence of particles and gas bubbles.

A set of three round bottom polystyrene test tubes, each filled with 2 ml of solution, was vortexed prior to pH analysis. The pH of each solution was measured at 0, 30, 60 and 120 minutes. The pH measurements were only used to explain (in) compatibilities and were not used to determine whether two drugs were compatible.

Quantitative analysis
After passing the visual tests, drug combinations were subjected to HPLC-DAD analysis.

Another set of three round bottom polystyrene test tubes, each filled with 4 ml of solution, was used for quantitative analysis after the 2 h test period. This 2 h test period was considered to be sufficient to exceed the maximum time two drugs run simultaneously through an infusion line after being combined via Y-site in our ICU.

HPLC-DAD analysis was carried out according to the Systematic Toxicological Identification Procedure (STIP) setup which is the standard for toxicological screening in the Netherlands.[13] The STIP database contains retention times and UV-spectra for a standardized eluent and is used for the rapid detection of the 400 most common drugs and their metabolites used in the Netherlands.[14] In brief: a standardized C-18 column and a standardized mobile phase are used to separate compounds in a mixture. Retention times and UV-spectra of the separated peaks are compared to a library for positive identification.

A suitable dilution factor was determined for each drug to obtain an acceptable signal intensity with the HPLC-DAD analysis (Supplementary material: Table S2). A drug could be diluted with water for injection (WFI) and subsequently with mobile phase, or only with mobile phase if the dilution factor was low. However, esomeprazole was diluted with NaCl 0.9% to prevent degradation which would occur in mobile phase or in WFI. A calibration curve was made in triplicate for each individual drug and consisted of three points (75%, 100% and 125% of the theoretical concentration) after suitable dilution of the licensed product. Drug concentrations were calculated using integrated peak areas. Peak purity analysis was used to evaluate whether the API was separated from degradation or reaction products.

Two hours after drugs A+B were combined 2 samples of drug A, drug B and the combination of drug A+B were taken at 20˚C and 37˚C. The samples were subsequently analyzed with HPLC-DAD after dilution. The integrated HPLC-peaks were converted to concentrations with a 95% confidence interval (CI) using the above described calibration curve. A difference of <5% between results of the duplicate

samples of the same drug or combination taken at the same temperature was considered acceptable for HPLC-DAD analysis. The calculated recovery of drug A and B in a combination A+B was corrected for the (possible) decay of the separate drugs A and B after 2 h of analysis.

Final evaluation of compatibility results.
There were two criteria that had to be met in order for a drug pair to be qualified as compatible (Figure 3). First it was required to pass the visual analysis. This was achieved if the combination of drugs A and B did not have more particles or air bubbles, was not more opalescent, and was not more intense in color than drugs A and B separately.

Second, chemical compatibility was analyzed. If the amount of APIs of drugs A and B when combined remained between 90% and 110% after the 2 h at both 20 and 37°C the compounds were classified as compatible. This 10% deviation is in compliance with Dutch regulations.[15]

In cases where a drug A lacked a chromophore, API concentrations for drug A could not be measured and compatibility could not be concluded. Nevertheless, based on the chromatogram of drug B in the combination A+B *in*compatibility could still be concluded when in the chromatogram of B the API concentration was outside the 90-110% range.

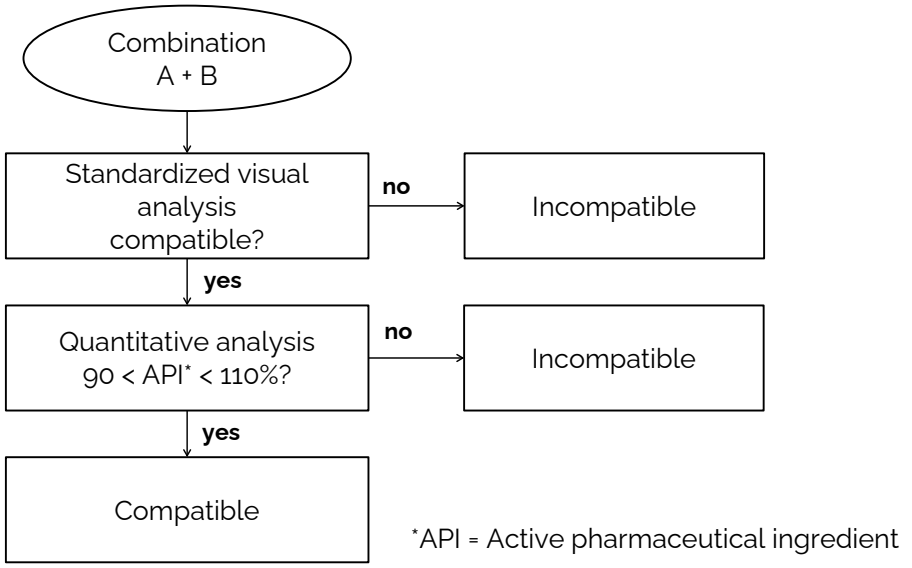


Figure 3. Flow chart representing the steps to determine the compatibility of a combination of drugs A and B.

Results

Visual compatibility

The visual compatibility results are summarized in Table 2. Full visual compatibility test results for all time points T_0, T_{30}, T_{60}, and T_{120} are available in the supplementary material (Supplementary material: Table S3). Most of the analyzed drug pairs appeared to be compatible for at least 2 h at both 20˚C and 37˚C. Combinations 8 and 9 showed a slight discoloration into pale yellow after 2 h of testing at both 20˚C and 37˚C. Combinations 1, 10, 13, 15, 17, and 19 directly turned opalescent, and therefore were considered incompatible at T_0.

Quantitative analytical compatibility

The quantitative analytical compatibility results are summarized in Table 2, and a more detailed overview is available in the supplementary material (Supplementary material: Table S4).

For most drugs it was possible to identify the active pharmaceutical ingredient (API) peak by comparing retention times from the STIP library to the measured retention times (clindamycin, clonidine, furosemide, heparin, labetalol, midazolam, morphine and nicardipine). The API peaks of hydrocortisone and nitroglycerin could be confirmed by consulting Clarke's Analysis of Drugs and Poisons Fourth Edition.[16] The API peaks of dexmedetomidine and esomeprazole could not be retrieved from the STIP database or from other databases, therefore they were determined based on their respective chromatograms after injection of a reference sample.

Magnesium sulfate, potassium chloride and sodium phosphate lack a chromophore, and could not be analyzed with HPLC-DAD. The concentration of midazolam in combination 1 was less than 90% after 2 h at both 20˚C and 37˚C. In combination 3 the peak of furosemide overlapped with the peak of clonidine. In combination 5 the peak of clonidine partially overlapped with the peak of hydrocortisone. In combination 6 the peak of midazolam overlapped with the peak of clonidine. In combination 8 the peak of hydrocortisone overlapped with the peak of esomeprazole. The API peak of nicardipine could not be detected using HPLC-DAD in combination 10 but other peaks were visible instead. In combination 13 both furosemide and midazolam reached concentrations below 90%. The difference between duplicate measurements for midazolam at 37˚C was 8.4%. The spectrum of hydrocortisone in combination 18 when combined with sodium phosphate contained API peaks which were significantly lower and wider compared to the peaks in the spectrum of hydrocortisone. However, as the area under the curve (AUC) indicated concentrations between 90-110% and the API concentration of magnesium sulfate could not be determined, the compatibility was considered to be unknown. Combination 19 showed a concentration of midazolam <90% at both 20˚C and 37˚C. All of the other combinations contained API concentrations between 90% and 110 % and all differences between duplicate measurements were <5%.

Table 2. Overall results of physicochemical analysis on combinations of drugs in ICU concentrations

ID	Drug	Visual	Quantitative	Total	Conclusion
1	clindamycin + midazolam	I	I	I	Incompatible[a]
2	clonidine + dexmedetomidine	C	C	C	Compatible[a,b]
3	clonidine + furosemide	C	U	U	Unknown
4	clonidine + heparin	C	C	C	Compatible[a,b]
5	clonidine + hydrocortisone	C	U	U	Unknown
6	clonidine + midazolam	C	U	U	Unknown
7	clonidine + nicardipine	C	C	C	Compatible[a,b]
8	esomeprazole + hydrocortisone	P	U	U	Unknown
9	esomeprazole + magnesium sulfate	P	U	U	Unknown
10	esomeprazole + nicardipine	I	I	I	Incompatible[a]
11	esomeprazole + potassium chloride	C	U	U	Unknown
12	furosemide + magnesium sulfate	C	U	U	Unknown
13	furosemide + midazolam	I	I	I	Incompatible[a]
14	furosemide + morphine	C	C	C	Compatible[a,b]
15	heparin + nicardipine	I	C	I	Incompatible[a]
16	hydrocortisone + magnesium sulfate	C	U	U	Unknown
17	hydrocortisone + nicardipine	I	C	I	Incompatible[a]
18	hydrocortisone + sodium phosphate	C	U	U	Unknown
19	midazolam + sodium phosphate	I	I	I	Incompatible[a]

C: compatible, I: incompatible, U: unknown, P: partly.
[a]at 20°C and 37°C
[b]for at least 2 hours

Discussion

From existing Y-site compatibility studies we propose a systematic procedure for the investigation of Y-site compatibilities for drug combinations used in the ICU. Using this procedure, a visual analysis is performed over a period of 2 h at both 20˚C and 37˚C. Subsequently, a quantitative analysis using HPLC-DAD was performed. Using this stepwise procedure 19 drug-drug combinations with unknown or unclear compatibility were analyzed. Four drug combinations were determined to be compatible and six combinations were considered incompatible. For the remaining nine combinations compatibility could not be assessed.

The application of a standardized methodology for compatibility assessment was pioneered by Lawrence Trissel, who studied Y-site compatibilities of hundreds of drug combinations using both visual and quantitative analysis.[17] Despite these efforts a major problem in the body of research on Y-site compatibility is the inconsistency in the methodology that is applied.[3,10] A systematic review of 93 compatibility studies revealed that of 820 possible combinations of 41 commonly used drugs, quantitative analysis was only performed in 75 (9%) cases.[10] Quantitative methods, in addition to visual analysis, may yield opposite results as incompatibilities are not always visible. Only a few studies combine visual and quantitative methods, however they have employed widely varying concentrations.[2,10,17–20] In addition, durations of compatibility studies range from 2 to 24 h and do not always reflect clinical practice.[2,17,19,21–28]

Our local ICU protocols advise a minimum combined infusion rate of 3 ml/h. The volume of our standard IV tubing is 2 ml, corresponding to a maximum contact time of 40 minutes. Kanji et al. mention the practice of piggybacking a secondary fluid at 10 ml/h to preserve catheter patency when the primary infusion is set at a low rate.[10] This practice results in contact times less than 15 minutes at much lower drug concentrations. Even at low infusion rates and considering intermittent pausing of infusions, the contact time will not exceed 1 hour, hence a testing period >2 h is considered not clinically relevant.[10] Many studies are only performed at room temperature, which is not representative for clinical practice as IV lines often run under blankets where the temperatures may vary from 20˚ to 37˚C. We therefore propose a streamlined and reproducible procedure for the assessment of Y-site compatibility using both visual and quantitative analysis at 20˚C and 37˚C, and a maximal contact time of 2 h. To our knowledge, the current study is the first to propose such a systematic procedure for the assessment of Y-site compatibility specifically aimed drug combinations used in the ICU.

Compared to other departments, ICU patients typically receive more intravenous drugs simultaneously, hence our focus on frequent ICU drug combinations.[29] A common approach to compatibility testing is to simply analyze frequently used drugs without regard to the frequency of their combined use. Many combinations of frequently used drugs are rarely administered simultaneously in clinical practice. In this study, we therefore targeted the most frequent combinations of drugs that were actually administered simultaneously in practice using a large dataset of drug administrations. We believe that this approach results in a selection of drug combinations that is more clinically relevant.

Concentrations and methodology for the combinations examined in the current study vary greatly in literature. For example, in four studies examining the combination of furosemide and morphine, four different concentrations were used, and temperatures ranged from 23˚C to 27˚C, rendering conflicting compatibilities.[17,26,27,30] Remarkably, none of these studies used quantitative analytical methods. Of the 19 combinations analyzed in this study, (conflicting) compatibilities of 6 (32%) combinations are reported in literature, and with the exception of 2 (10%) combinations, only visual analysis was used.[2,17,19–27,30,31]

In the visual analysis nicardipine and esomeprazole (combination 10) were incompatible. The pH values of nicardipine and esomeprazole before mixing were roughly 3.5, and 10, respectively. When combined the pH was 8.9, which may have affected the stability of nicardipine, which precipitates at a pH >6.0.[32]

Most of the overlap between peaks in the chromatogram could be explained by concentration differences. A large difference in concentration could cause one peak to (partially) overlap with another peak, this phenomenon is difficult to predict and turned out to be present in combinations 3, 5 and 6. In combination 3 (clonidine and furosemide), peaks partially overlapped causing the inability to integrate the peaks properly. In combination 6 there retention times for the peak of clonidine and one of the peaks of midazolam were identical. A suitable alternative analytical method should be found to determine the compatibility when such an issue occurs.

For some combinations peak overlap was caused by the formation of degradation products. Esomeprazole for instance was unstable in the mobile phase used for HPLC-DAD analysis and degraded quickly. In combination 8 a degradation peak overlapped with the hydrocortisone peak causing the inability to integrate the hydrocortisone peak.

A limitation to this study and many other studies is that there is little knowledge on the activity of the API's after combining drugs.[2,18–20] We assumed that when our method revealed that there was no visible incompatibility and the concentration of API was within the 10% analytical margin, the activity of the drugs remained the same. The use of visual analysis is limited as the human eye cannot be calibrated, hence visual analysis is generally only helpful in cases where incompatibility is obvious because precipitation or color change occurred. Nevertheless, the reliability of the visual testing procedure can be improved by using a standardized procedure. Therefore, in this study visual inspection was performed following the guidelines described in the European Pharmacopoeia 9.0, which is currently considered to be the state of the art.[11,12] Visual testing was only used to conclude that a combination is incompatible. Passing visual testing should always be confirmed by an quantitative test before compatibility may be concluded. In the quantitative analysis acetonitrile was used as eluent instead of solvents commonly used in the ICU. When for example NaCl 0.9% or glucose 5% is used as eluent, the reversed phase analysis will result in very long retention times. Fortunately, most drugs are not affected by acetonitrile and in the case of esomeprazole it was known beforehand that degradation would take place, hence in this case acetonitrile was not used.

In this study we determined incompatibility based on precipitation, color change, and changes in peak areas relative to a calibration line using visual analysis and HPLC-DAD. Knowing not only that a change occurred, but also knowing what caused the change could help predict (in)compatibilities of similar drug solutions. Further analysis using LC-MS/MS could also help explain the findings in this study. A limitation of our study is that drug solutions were not filtered and sub-visible particles may have been present in the drug combinations. A test for sub-visible particles could be added, but most hospitals lack the equipment to perform this test. A solution could be filtering the solution using 0.2 micrometer membrane filters. Comparing filtered and unfiltered drug combinations could demonstrate the impact of sub-visible particles on the quantitative analysis of a drug. Drug solutions were tested in a 1:1 ratio. In addition, also ratios such as 1:10 and 10:1 might be tested to further substantiate compatibility, since one drug solution may be delivered at a much higher infusion rate than the other in clinical practice. This may for example result in more extreme pH values when drugs with a large pH difference are combined. To our knowledge this approach has not been described in literature before. Likewise, for practical reasons, we did not evaluate combinations of three or more drugs. However in daily ICU practice Y-site combinations of three or even more drugs are employed, where the pairwise combinations (AB, AC and CB) are all compatible. Pairwise compatibility is, however, no guarantee for compatibility of all drugs combined.

Conclusion

An improved and systematic procedure for Y-site compatibility analysis of ICU drugs was developed by combining previous Y-site compatibility studies. Using this procedure 19 drug-drug combinations with yet unknown or uncertain compatibilities were analyzed. Four combinations were found to be compatible and 6 combinations were found to be incompatible for Y-site co-administration. We were unable to conclude on 9 combinations of drugs. A suitable analytical method must be developed for these combinations in order to determine their compatibilities.

Supplementary material

Supplementary material can be downloaded from https://ivcompatibility.org/thesis/supplements.html.

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