

**Original Article**

## MAPPING OF INCOMPATIBILITY ASSAY: BRINGING METHOD TO PROBLEM IN CRITICAL CARE

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### ABSTRACT

**Objective:** This study aims to identify the methodology of incompatibility assay. This review is intended to inform further research into the management of these issues in a clinical setting in Indonesia.

**Methods:** A search was conducted of incompatibility studies through *International Pharmaceutical Abstract (IPA)* using the keywords 'compatibility' OR 'incompatibility' AND 'intravenous', "parenteral" OR "infusion".

**Results:** There are only two authors use in vivo setting and higher number of authors use in vitro setting. Among those who bring in vitro assays most of them use static approach between two drug combination.

**Conclusion:** A standardized procedure is meaningful for general judgement for incompatibility. However, particularly in critical care, setting up an evaluation procedure that mimics as closely as possible real practice within the clinical area should be undertaken to validate practice.

**Keywords:** Critical Care, Incompatibility Assay, Method, Database

### INTRODUCTION

Intravenous (IV) delivery is extensively used for many reasons; it has rapid onset, high bioavailability, rapid clearance once stopped, and therefore is suitable for dose titration and maintenance of effect. In particular, patients in intensive care, with multiple and complex conditions receive numerous intravenous medications. Frequently the number of IV medication is more than number of venous access lumens for these patients. Consequently, co- administration of more than one medication in the same container, or same line, is inevitable. Evidence shows adding of additional lumens increases opportunities for infection, and multi lumen CVC's increase the risk of catheter related blood stream infection [1]. A larger number of medications will increase the incompatibility risk geometrically [2]. However, this complex situation is poorly understood by health staff [3].

Previous studies found incompatibility problems in up to 18.6% of critical care patients and 18.7% of continuously infused medications [4]. This percentage differs from that found in general wards at only 3% [5]. The pivotal issue in compatibility problems is how to assess the evidence. This arises from up to 25% conflicting data in reference sources to determine compatible (C), incompatible (I), or compatible in the specific circumstances (C/I) [4].

Foinard also identified highly variable results in the frequency of incompatibility ranging from 0.2 to 25% of drug combinations used, resulting from differences of methodology of the compatibility studies [6]. This difference is induced by the variation in specific brand, concentration, flow rate, infusion device, and also circumstance [3]. Kanji also found a minimum of 10% difference with the practical setting in components assayed, conditions, and duration studied [4]. This creates difficulties for health professionals in making decisions related to incompatibility.

Incompatibility leads to technical and clinical complications such as occlusion, and reduced potency or even negation of the therapeutic effect of medications. It can also lead to local and systemic inflammatory reactions. The benefit of incompatibility studies therefore avoids these risks for the patient, and also possible lethal effects as in previous reports of the FDA and others [3, 4].

In analysing the problem, it was identified that incompatibility still happens as a result of conflicting incompatibility information. One of the causes of conflicting data relates to methodology. Underlying this problem is a question of how the examination of incompatibility was approached and how the method relates to practice in critical care. Studies on incompatibility began many years ago, but development of methods for the study of incompatibility has not progressed as quickly as medication discovery. This review aims to examine incompatibility assays and how they can be related to practical therapy.

### MATERIALS AND METHODS

A search was conducted of incompatibility studies through *International Pharmaceutical Abstract (IPA)*. From broad reports 406 publications were identified from 1970-2013 using the keywords 'compatibility' OR 'incompatibility' AND 'intravenous', "parenteral", OR "infusion". The studies were examined for methodology that they used.

### RESULTS

Incompatibility assays were identified using *in vitro* and *in vivo* methods. Most of the incompatibility assays identified used an *in vitro* approach.

#### *In Vivo* Approach

Only two studies were identified using this approach. Reyes and Jaimovich, both used porcine model [7,8]. Jaimovich measured compatibility in the mixture of diluted product, and also in the blood, from administration through a peripheral site using a double-lumen catheter [7, 8]. Meanwhile, Reyes used a triple lumen central venous catheter to understand the influence of infusion length toward the incompatibility. Ten domestic porcine weighing 10-20 kg were administered Total Parenteral Nutrition (TPN) through the distal port of the device and phenytoin as bolus or as an infusion. The experimental lumen was inserted into femoral vein. Samples were collected from other ports at 1, 5, 10, and 15 minutes. Particle was measured by phase-contrast light microscopy, and wright stain smears.

### **In Vitro Approach**

There are many studies in drug compatibility using *in vitro* methods. There are two major sub-sets for this approach; static and dynamic methods;

#### **a. Static method.**

Many investigators have used this approach to measure incompatibility in IV admixtures. Some of medications are mixed in the same container or syringes before administration into an infusion set. This method is commonly used for parenteral nutrition, and also for antibiotics with diluents [9]. In a practical setting, such mixtures are mostly prepared by pharmacists and delivered by a nurse at the bedside, so they require validated storage time before administration. During storage, an incompatibility reaction may occur amongst the components of the mixture. Prior admixing was associated with a higher risk of incompatibility compared to 'y-site' administration, where medications are added into separate tubes which come together at a common 'y' connection close to the patient. It is often believed by many health professionals that this method avoids physical and chemical incompatibility issues.

In detailed methods, the *in vitro* approach uses a glass container or syringe to blend all of the components. A filter is commonly used for reducing particulate matter before mixing as this may 'scratch a precipitate' that otherwise might not occur. To ensure homogeneity, the mixture also is getting vortexes. All procedures were undertaken at room temperature and sterile conditions in a biological safety cabinet with range of 18-24° Celsius. Most observations were undertaken at time 0 and 24 hours. This is intended to reflect the probable maximum time of storage of this mixture before delivery to patients.

#### **b. Dynamic method**

The dynamic method is mostly used to describe the incremental step method. For incompatibility studies, this term is frequently related to assay methods for incompatibility at 'y-site' connections or in tubing where the components of IV medications may possibly come into contact with one another. This method was initiated by Allen in his 1977 study [3]. The study was designed to more closely simulate the actual conditions in hospital. It uses an infusion set that is filled with a large volume IV solution, to which is added primary additives (such as vitamin B, Potassium Chloride, or heparin) into the carrier solution and also secondary additives (medications) from syringes through syringe-ports. Contact between the medications was predicted in y-site injections. Incompatibility was assessed from a sample from the needle tip in 0 and 4 hours.

Allen reported that incompatibility will be expected at the y-site when the resultant mixture is in a 1:1 ratio. This finding becomes important for incompatibility assay. Most study that followed Allen's procedure used the same ratio of 1:1 and an observation window of 4 hours. This was also reinforced by Trissel and Martinez as the basis for a fixed method for incompatibility testing [11]. Trissel is a major author in this subject area. His paper is widely cited to identify y-site incompatibility using methodology described as 'simulated y-site'. Trissel used the term 'simulated y-site' to classify the incompatibility test for medication that is mixed in the same tubing or line. The difference of procedure compared to Allen is Trissel's method does not use an infusion set. This method is therefore closer to the static method. Using same assumption as Allen, it utilises a vial or glass flask for mixing medications in a ratio 1:1. To minimize risk, drug concentration is maintained below the maximum concentration that can be used in the clinical situation [12]. In this method, medications are mixed in a clear glass tube and measured in 0 minutes, 30 minutes, 60 minutes, and 4 hours. All manipulation takes place in a class 100 biological safety cabinet at room temperature in duplicate. Here it is important to note that many critical care areas will typically be warmer than normal room temperature (25°C). A modified method was conducted by Husson, et al. that used a continuous infusion via an infusion line and extracted samples at the end of tube for assessing incompatibility [13]. This approach takes place in a dynamic way. Husson assembled an infusion line as in practical setting. The evaluation was observed along the line and in

the collection bag at the distal end of the line at 0, 30, 60, and 75 minutes. This approach is more accurately termed dynamic rather than Trissel's approach. It used an infusion line flowing at a specific rate.

Servais and Tulkens also developed a similar method to Husson by mimicking as closely as possible the projected routine used in a Belgian hospital [14]. They used an infusion line to measure incompatibility between ceftazidime and other drugs that were commonly delivered in the same line. This study is closer to modelling the true clinical situation. Not only modelling the clinical area set-up with a running infusion line, but also for the brand name of drugs, diluents, concentration, flow rate, and circumstances following the routine procedure in their hospital.

Collins and Lutz developed a method of incompatibility study utilizing not only in a single lumen but also in multi-lumen catheter [15]. Previously, there has been a presumption that when another medication is co-administered separated in a different lumen of a multi-lumen device, it will not be in contact with any other medication and incompatibility will be avoided. However, this study concluded that adjacent lumens particularly in a double lumen device, gives a possibility for rapid incompatibility reactions for example between phenytoin and parenteral nutrition. Precipitation was identified in the double lumen system, but it did not appear in the triple lumen system.

### **DISCUSSION**

Each of the identified approaches to the identification of incompatibility has limitations in terms of answering problems in a clinical setting. *In vivo* studies are superior in terms of the complex considerations including physiological considerations. It tries to consider intravascular pressure, respiratory cycles, neurovascular, and also thermoregulatory factors that may influence vascular size and flow. Vasculature and blood flow may affect the infusion stream, although to what extent requires further investigation. These changes can influence particle formation through flow turbulence. The major limitation is that it is expensive, requires an animal or human subject and the associated ethical issues. Consequently the majority of incompatibility assays are conducted in the *in vitro* setting. This is reflected in the incompatibility definition. The US National Coordinating Committee on Large Volume Parenteral (NCC-LVP) defines incompatibility as a phenomenon which occurs when one drug is mixed with others to produce, by physicochemical means, a product unsuitable for administration to the patient [2]. Bergman also stated that is only *in vitro* incompatibilities pertaining to LVP systems that are considered, while potential *in vivo* effects are termed by drug-drug interactions.

An *in vitro* study is simpler and less expensive. The main reason to use this approach is that many incompatibility reactions happen in an *in vitro* setting. The medications in the mixture react in the container or in the line before entering to human body. It assumes that there is no correlation between physiological change and *in vitro* reaction outside the body. However, Jaimovich demonstrated that direct clinical applicability is limited for *in vitro* testing. It doesn't reflect the changes in the body that may affect vessels and flow in the vessel [8]. He also found that precipitation is influenced by turbulence in blood flow with changing vascular structure. Unfortunately this assumption has not yet been confirmed with other studies. *In vitro* modelling is therefore limited but the risk of incompatibility can be assessed in an advanced methodology bringing some modelling of the *in vivo* situation. Currently, the commonly referenced studies for incompatibility use an *in vitro* approach with simulated 'y-site' as described by Trissel. This type of study is useful for the judgement of incompatibility within a fixed procedure. Practitioners can interpret the data more readily, but applicability is limited to the conditions prevailing within those studies. This approach tends to use a static rather than a dynamic model that is not illustrating the real conditions. Currently, most of databases used to inform critical care use different study conditions to the projected routine use in critical care. In addition, the European Pharmacopoeia recommends assaying incompatibility in triplicate rather than the duplicate as used by Trissel [12,17].

Critical care patients are especially vulnerable to incompatibility issues due to the number of medications, the use of multi-lumen devices, changing flow rate of infusion including changeover of medication, interruption and resumption of drug flow, and also the specific circumstances of temperature or humidity and light. At present, critical care patients require multi-lumen catheters for their multiple medications. They typically receive around 10 different medications. Currently, there is assumption that multi-lumen divided medications can avoid incompatibility. However, incompatibility studies using multi-lumen devices are underreported [15].

Typically more than 60% of medication for critical care patients is continuous or intermittent intravenous [16]. However this is a dynamic situation with specific rate for each individual, not a static standardised approach. Few of the studies identified that flow rate impacts on incompatibility. Yet a simple physicochemical theory shows that flow rate impacts upon the number and quantity of medications that may come into contact within the infusion system. For a medication that has an incompatibility reaction which is dose-dependent, flow rate may influence the reaction. The study from Foinard acknowledged that physical incompatibility is influenced by drug concentration, flow rate, and infusion device [6]. Foinard confirmed that flow rate influenced incompatibility, and that dynamic models that also consider flow-rate have been underutilised to date. It appears clear that there is a need for more controlled *in vitro* studies mimicking common situations in clinical practice in order to address directly this issue in hospital practice.

Regarding the use of published information, practitioners need to be aware of study methodology issues. It must also be recognised in this age of proliferation of generic products that existing studies relate to a specific brand name, concentration, duration, and also temperature. Trissel highlighted the need to interpret carefully before applying the data in his data base [16]. For example, incompatibility that occurred in 4 hours cannot be concluded that the drug is safe before 4 hours. The observation may be not done before 4 hours. More than 60% of studies observed the incompatibility during up to 4 hours. In the most of study, the incompatibility was measured previously at 1 hour then at 4 hours. The reaction may have happened in the interval. Increasing temperature also raises the reaction rate. Many reports only performed a partial evaluation; physical or chemical incompatibility. They did not investigate incompatibility comprehensively. There remains a need for more studies, modelling closely the actual conditions of use. These need to be stated in the publications along with all the equipment used within the model infusion system. This can be collated into a central resource. Practitioners also need to understand that there should be no substitution or extrapolation of these studies without validation.

## CONCLUSION

*In vitro* assay is recommended for incompatibility study. A standardized procedure following the methods of Allen and Trissel are meaningful for general judgement for incompatibility. However, particularly in critical care, setting up an evaluation procedure that mimics as closely as possible real practice within the clinical area should be undertaken to validate practice.

## Authors' Contributions

The literature review was prepared by SH and edited and commented upon by RAK, PAB and KL.

## Peer Review

Not commissioned; externally peer reviewed.

## CONFLICTS OF INTEREST

The authors SH, RAK and KL declare that they have no known competing interests. Patrick Ball has presented internationally on

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## REFERENCES

1. Templeton A, Schlegel M, Fleisch F, Rottenmund G, Schobi B, Hens S, Eich G, Multilumen Central Venous Catheters Increase Risk for Catheter-Related Bloodstream Infection: Prospective Surveillance Study. *Infection* 2008;36(4):322-27
2. Bergman H. Incompatibilities in Large Volume Parenterals. *The Ann of Pharmacother* 1977;11(6):345-60
3. Bertsche T, Mayer Y, Stahl R, Hoppe-Tichy T, Encke J, Haefeli WE, Prevention of Intravenous Drug Incompatibilities in an Intensive Care Unit. *AJHP* 2008;65(19):1834-40
4. Kanji S, Lam J, Goddard RD, Singh A, Goddard R, Fairbairn J, Lloyd T, Monsour D, Kakal J, Inappropriate Medication Administration Practices in Canadian Adult ICUs: A Multicenter, Cross-Sectional Observational Study. *The Ann of pharmacother* 2013;47(5):637-43
5. Westbrook JL, Rob MI, Woods A, Parry D. Errors in the Administration of Intravenous Medications in Hospital and the Role of Correct Procedures and Nurse Experience. *BMJ quality & safety* 2011;20(12):1027-34
6. Foinard A, Decaudin B, Barthelemy C, Debaene B, and Odou P, The Impact of Multilumen Infusion Devices on the Occurrence of Known Physical Drug Incompatibility: A Controlled In Vitro Study. *Anesth & Analges* 2013;116(1):101-06
7. Reyes G, Mander GS, Husayni TS, Sulayman RF and Jaimovich DG, In-vivo Evaluation of Simultaneous Administration of Incompatible Drugs in a Central Venous Catheter with a Decreased Port to Port Distance. *Critical Care* 1999;3(1):51
8. Jaimovich D, G, Rose W, W. In Vivo Evaluation of Simultaneous Administration of Incompatible Drugs via a Double-Lumen Peripheral Catheter. *Critical Care Medicine* 1990;18(10):1164-66
9. Trissel LA, Gilbert DL, Martinez JF, Baker MB, Walter WV, Mirtallo JM, Compatibility of Medications with 3-in-1 Parenteral Nutrition Admixtures. *Journal of Parenteral and Enteral Nutrition* 1999;23(2):67-74
10. Allen L, Levinson R, Phisutsinphop D. Compatibility of Various Admixtures with Secondary Additives at Y-injection Sites of Intravenous Administration Sets. *AJHP* 1977;34(9):939-43
11. Trissel L, Martinez J. Physical Compatibility of Melphalan with Selected Drugs during Simulated Y-Site Administration. *AJHP* 1993;50(11):2359-63
12. Trissel L, Bready B. Turbidimetric Assessment of the Compatibility of Taxol with Selected other Drugs during Simulated Y-site Injection. *AJHP* 1992;49(7):1716-19
13. Husson E, Crauste-Manciet S, Hadj-Salah E, Jean-Christophe S, Brossard D, Compatibility of Parenteral Drugs with Commercialized Total Parenteral Admixtures during Simulated Y-site Infusion. *Nutrit Clin et Metabol* 2003;17(2):72-79
14. Servais H, Tulkens PM. Stability and Compatibility of Ceftazidime Administered by Continuous Infusion to Intensive Care Patients. *Antimicrob Agents and Chemother* 2001;45(9):2643-47
15. Collins J, Lutz R. In vitro Study of Simultaneous Infusion of Incompatible Drugs in Multilumen Catheters. *Heart & Lung: the J of Crit Care* 1991;20(3):271
16. Ministry of Health and Long-Term Care, Intravenous Monitoring Program. Provider Guide. Emergency Health Services Branch. 1993.
17. Trissel LA. Handbook on Injectable Drugs. 15<sup>th</sup> edition, Bethesda, MD: American Society of Health-System Pharmacists, 2009, p.xiii-iv.