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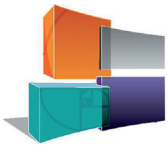

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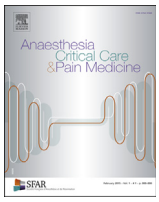

Original article

Compatibility of medications during multi-infusion therapy: A controlled in vitro study on a multilumen infusion device

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ABSTRACT

Objective: Drug incompatibilities can jeopardize the safety and effectiveness of intravenous drug therapies, especially in the field of anaesthesia and intensive care. Patients receive many drugs simultaneously through limited venous accesses. This study was designed to confirm the impact of a multilumen infusion device on the occurrence of known physical drug incompatibilities.
Study design: In vitro laboratory work.
Methods: Two infusion devices were studied: a standard single-lumen set and a multilumen infusion access device (Edelvaiss Multiline-8, Doran International). Up to six drugs were infused simultaneously: three acidic solutions of midazolam, amiodarone and dobutamine, and three alkaline solutions of furosemide, pantoprazole and amoxicillin/clavulanate. Saline, Ringer' solution and 5% dextrose were used as hydration vehicles with an infusion rate initially set at 100 mL/h and with stepwise decreases of 10 mL/h until precipitation. Two methods were used to highlight physical drug compatibility according to the European Pharmacopoeia: visual inspection of the extension set and an obscured-light sub-visible particle count test of infusions. The lowest infusion rate value for vehicle infusion to satisfy the two tests in all trials is reported for each infusion device.
Results: The standard set did not satisfy the test in 82% of the assessed drug combinations. The Edelvaiss Multiline-8 was able to prevent the occurrence of drug incompatibilities in 49% of the drug combinations tested. This device is therefore advantageous, especially when simultaneously infusing two or four incompatible drugs.
Conclusions: Infusion device characteristics have an impact on physical drug incompatibilities. Our results confirm that the Edelvaiss Multiline-8 device prevents physical drug incompatibilities under specified conditions.

1. Introduction

The safety and effectiveness of intravenous (IV) drug therapies can be hampered by various drug incompatibilities, especially in the field of anesthesia and intensive care. Patients in intensive care units (ICU) simultaneously receive many drugs through a limited number of venous accesses. Several IV therapies must be administered through the same central venous catheter (CVC), thus increasing the risk of physical incompatibilities [1]. Related knowledge among health workers is limited in this field and drug incompatibilities can have serious consequences for patients [2], especially in the case of particle infusion linked with precipitation: CVC obstruction, occurrence of potentially fatal embolism [3], crystals of calcium phosphate deposited in various organs during total parenteral nutrition [4]. Furthermore, particle contamination of infusion solutions can lead to a systemic inflammatory response syndrome (SIRS) [5–7]. In adult and pediatric ICUs, 18.6% and 3.4% of nursing errors are related to drug incompatibilities [8,9], respectively.

Preventing incompatibility is therefore important for the safe administration of injectable drugs. There are handbooks and

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databases on this subject, but usually for just two-drug mixtures at well-defined doses [10,11]. There are certain solutions that can help limit drug incompatibility. For example, the colour coding system for drug pH used in a Swiss hospital for five years made it possible to reduce the incompatible mixture risk from 15% to 2% with Y-site administration [12]. The use of an in-line filter prevents particle infusion when drug incompatibilities lead to a precipitate, particularly in neonatal ICUs [13–16]. The terminal filtration of solutes helps to prevent veinitis and phlebitis [17]. However, a data review of four randomized control trials recruiting a total of 704 neonates concludes that there is insufficient evidence to recommend the use of intravenous in-line filters to prevent morbidity and mortality in neonates [18]. On the other hand, a recent randomized control trial recruiting 807 subjects showed a decrease in overall complications and SIRS in pediatric ICUs thanks to filtration of intravenous fluids [7]. Furthermore, some studies show the advantage of using separate lumen catheters [19–21], but the number of catheter lumens is normally lower than the number of drugs infused. In a previous study, we showed that infusion device characteristics appear to have an impact on the physical compatibility of two drugs by investigating the impact of the Edelvaiss Multiline-8 on furosemide–midazolam incompatibility [22]. This nine separate lumen access infusion device allowed the simultaneously infusion of several drugs without contact mixing.

The aim of this study is to confirm the impact of the multilumen access infusion device used in our previous work, connected to a single-lumen CVC, on the occurrence of known drug incompatibilities through a controlled in vitro study, comparing a standard set with six-port-manifolds and a one-meter extension set.

2. Methods

A well-documented incompatible combination of drugs was used to perform the study [1,23–26]. In our case, incompatibilities result from acid–base reactions. Mixing an alkaline solution with an acidic solution alters the pH of the final mixture to the point of immediate precipitation with the formation of a visible precipitate. Six commonly used drugs in the ICU were selected:

- three alkaline drug solutions: furosemide (10 mg/mL, lot number 122134; Renaudin, France), pantoprazole (40 mg, lot number 180795; Nycomed, Paris, France) and amoxicillin/clavulanate (1 g/200 mg, lot number BW4397; Mylan, Saint-Priest, France);
- three acidic drug solutions: midazolam (5 mg/mL, lot number F3039; Mylan, Saint-Priest, France), amiodarone (50 mg/mL, lot number 1A101; Sanofi-Aventis, Paris, France) and dobutamine (12.5 mg/mL, lot number 10520; Panpharma, Fougères, France).

Each drug was reconstituted with the solvent according to the manufacturers' recommendations and was infused at a fixed concentration and infusion flow rate, according to clinical practices (Table 1). Drugs were simultaneously infused with:

- saline solution (Viaflo 1 L, Baxter, Maurepas, France, lot number 12C05T2F);
- Ringer's solution (Macoflex 500 mL, Baxter, Maurepas, France, lot number 12A13E);
- 5% dextrose (Viaflo 1 L, Baxter, Maurepas, France, lot number 12E18T2B).

The pH of initial drug solutions, infusion vehicles and the mixed solution at the outlet of the infusion device were measured, using a pH meter (SB70P Symphony, VWR International, Singapore). Two, four, and then six drugs associated with saline were infused simultaneously, using an Orchestra infusion station (Fresenius Vial, Brezins, France) consisting of a base unit (Base Intensive), syringe pumps (DPS modules) and a volumetric pump for the infusion vehicle (MVP module), through two infusion devices, which differ in conception and dead space volume (V) (Fig. 1):

- a standard single-lumen set with a six-port manifold and a 150 cm extension set, volume (V) = 8.55 mL (ref. RPB6315, Cair LGL, Civrieux d'Azergues, France), which is commonly used in the ICU;
- a new multilumen access infusion device (Edelvaiss Multiline-8, Doran International, Toussieu-Lyon, France) with eight accesses connected to nine separate lumens in a single tube (outside diameter = 4 mm, length = 150 cm). Seven accesses are reserved for drug infusions and each is connected to a peripheral lumen (V = 0.9 mL). The eighth access with high flow (HF) rate capacity is intended for the infusion vehicle. It is connected to two lumens (one peripheral and one central) for a total dead space volume of 2.9 mL. The fluids administered through the eight ports mix at the extension set outlet.

Fifty-millimeters syringes filled with the drugs were prepared before each test and connected to a specified access on each infusion device. For the standard device, all alkaline drug solutions were placed in proximal positions (accesses 1 to 3) and acidic drug solutions in distal positions (accesses 4 to 6), whereas all acidic and alkaline drug solutions were placed on either side of the HF access for the Edelvaiss Multiline-8 (Table 2). Access 4 was not used (Fig. 1). Simultaneous infusions were performed using previously purged syringe pumps and extension lines to connect the syringes to the infusion device. A transparent extension line (length = 25 cm, V = 0.50 mL) simulating a single-lumen CVC was added at the distal end of the infusion device. All tests were made at room temperature between 18 and 22 °C.

For each infusion condition, the hydration vehicle rate was initially set at 100 mL/h, corresponding to the maximum daily

Table 1
List of drugs selected for the study with the characteristics of the drug solutions used.

Drug	Lot number (manufacturer)	Concentration (mg/mL)	Infusion flow rate (mL/h)	Visual aspect	pH (median [min–max]) of the drug solution
Furosemide	122134 (Renaudin, France)	10.0	2	Clear	9.05 [8.96–9.30]
Pantoprazole	177626 (Nycomed, France)	0.8	10	Clear	9.30 [8.91–9.32]
Amoxicillin/clavulanate	BW4397 (Mylan, France)	20.0	6	Pale yellow	8.82 [8.77–8.89]
Midazolam	F3039 (Mylan, France)	1.0	2	Clear	3.61 [3.59–3.64]
Amiodarone	1A101 (Sanofi-Aventis, France)	6.0	10	Clear	4.18 [4.16–4.40]
Dobutamine	10520 (Panpharma, France)	5.0	12	Clear	3.66 [3.64–4.40]