Caroline Polo*, Elise D’Huart, Gwendoline Lesperlette, Jean Vigneron, Florence Meyer and Béatrice Demoré

Compatibility of injectable posaconazole with drugs commonly used in a hematology care unit

Abstract

Objectives: Concomitant administration of two incompatible drugs in the same infusion line can lead to a precipitation which could have clinical consequences for patients. The objective of this work was to study the physical compatibility of injectable posaconazole with other drugs commonly used in an adult hematology care unit.

Methods: The most widely used injectable drugs co-administered with posaconazole have been listed with a total of 19 drugs. For some drugs, different conditions have been tested. A total of 24 solutions were produced (not including the posaconazole). In the absence of compatibility data, the physical compatibility was tested for each pair including one of the 24 solutions and posaconazole. For each pair studied, three different ratios were prepared (9:1, 1:1, 1:9). Visual evaluations were performed after the mixture, after one and 4 h.

Results: Seventy two mixtures have been realised: 55.56% of pairs (n=40/72) resulted in a precipitation, against 44.44% (n=32/72) with no visual modification after a 4-h storage. On the 19 drugs tested, only filgrastim and tacrolimus showed no visual change with posaconazole during a 4-h storage.

Conclusions: In majority of cases, posaconazole was not compatible with drugs having alkaline pH, commonly used in a hematology unit.

Keywords: antifungal; anti-infectious; co-administration; physical compatibility.

Introduction

Posaconazole (Noxafil®) is a broad-spectrum triazole used to prevent and treat invasive mycoses due to Candida sp. or Aspergillus sp. This antifungal agent is widely used for patients with a high risk of developing invasive fungal infections as immune-compromised patients hospitalised in hematology departments with a prolonged neutropenia following chemotherapy. Posaconazole is available as different forms: gastro-resistant tablets, oral suspension, solution to be diluted for infusion. By intravenous (IV) infusion, posaconazole is administered through a central venous line over about 90 min. The posology used is a loading dose of 300 mg posaconazole twice a day on the first day, then 300 mg once a day thereafter [1]. There are several pharmaceutical forms:

Patients hospitalized in a hematology care unit can receive numerous injectable treatments. A majority of patients have a PICC-line (Peripherally Inserted Central Catheter) or an implantable port to administer these many injectable drugs. Concomitant administration of drugs in the same line is often mandatory [2]. Compatibility data are necessary to perform these co-administrations and to prevent undesirable effects: catheter obstruction, loss of efficiency, toxic derivatives formation, crystal deposition in the body or embolism risk, potentially deadly [3, 4]. Drugs must be physically compatible for Y-site administration [5].

In our hematology department, some cases of precipitation were notified. During an administration of posaconazole, a white precipitate in the infusion line was observed. Before the administration of the antifungal drug, the patient received an infusion of ganciclovir sodium. The hypothesis for an incompatibility with ganciclovir sodium was raised. Another case was reported after administration of piperacillin sodium/tazobactam sodium. In order to prevent other administration incidents, the objective of this study was to evaluate the physical compatibility of posaconazole with injectable drugs commonly administered in our hematology care unit.
Materials and methods

Observational analysis

An observational study was performed to establish a list of the drugs commonly used in a hematology care unit. First, using the prescribing software, the prescriptions of patients receiving injectable posaconazole and another intravenous drug were selected. A list of drugs administered by IV infusion concomitantly with posaconazole was realised. Then, in collaboration with several hematology nurses, a data collection was performed to understand care practices (concentrations, containers, solvent, time of infusion, co-administration in the same line).

Compatibility data available in the literature

Information on the physical compatibility of posaconazole with the injectable drugs of the established list was searched in posaconazole Summary of Product Characteristics (SmPC) and in two databases: the 19th edition of the Handbook on Injectable Drugs® and Stabilis® [1, 6–8].

The pH of each drug molecule was searched for in two databases: the 19th edition of the Handbook on Injectable Drugs® and Martindale – The Complete Drug Reference [9].

Laboratory tests

For Y-site mixtures with no compatibility information available in the literature, laboratory tests were performed. Drugs selected were evaluated in pairs, even if more than two drugs were administered simultaneously in the same IV line.

To simulate the administration, each drug tested was prepared separately before being mixed with posaconazole. For some drugs, different conditions have been tested (concentrations, containers, solvent).

As D’Huart E. et al. reports, this test consists in performing three mixtures with different ratios realised for each pair studied (drug X:posaconazole): (a) 9:1; (b) 1:1; (c) 1:9. These different ratios were performed to simulate different drug flows which can lead to lower or higher concentrations. Drugs were mixed and kept in glass tubes at room temperature (23 °C), not protected from light, to simulate the conditions of storage observed in a hematology unit [6]. Mixtures were manually stirred during 10 s by turning the tubes three times.

A pair of drugs with an absence of particulate formation, haze, colour change and gas evolution, was considered as physically compatible [5]. As recommended by the European Pharmacopeia, the samples were visually inspected against a white (colour shift) and black (precipitate) background [10]. And as D’Huart E. et al. reports, the observation was carried out with the unaided eye and a magnifying glass (×10) by two laboratory technicians after the mixture and after a 1-h and a 4-h storage [6]. Drugs were considered physically compatible if no visible change was detectable after 4 h.

pH was measured for solutions with no pH data in the literature and solutions with pH values not sufficiently precise in the literature. Measurements were carried out on with a Bioblock Scientific pH meter previously calibrated.

Results

Observational analysis

Table 1 lists injectable drugs and solvents commonly administered in the same IV line with posaconazole in our adult hematology unit. All powdered medicines have been reconstituted with the final solvent (0.9% sodium chloride or dextrose 5% in water).

Compatibility data available in the literature and laboratory tests

The SmPC of posaconazole indicates incompatibilities with Lactated Ringer’s solution, 5% dextrose with Lactated Ringer’s solution and 4.2% sodium bicarbonate without explanation on the type of incompatibility (chemical degradation, precipitation, change of colour). No incompatibility is noted with other drugs. It was also verified that posaconazole was compatible with a saline solution (0.9% sodium chloride) in the SmPC [1].

In the 19th edition of the Handbook on injectable drugs, only filgrastim (6 μg/mL tested in dextrose 5% in water or 0.9% in sodium chloride) and potassium chloride (0.04 mEq/mL tested in dextrose 5% in water or in 0.9% sodium chloride) have data of physical compatibility [7].

No data is available on the compatibility of posaconazole in the Stabilis database [8].

Table 2 gives pHs found in the Handbook of injectable drugs and the Martindale – the complete drugs reference [7, 9] and pH measurements carried out in our laboratory.

Table 3 regroups all products used during the compatibility study. This information makes it possible to detail the laboratory, the batch number and the expiry date of the products used.

In the laboratory, two drugs out of the 19 tested drugs showed no visual observation with posaconazole from the time of mixing to a 4-h storage: filgrastim and tacrolimus. Some drugs have been tested at different concentrations or in different containers. Therefore, 24 solutions have been performed and for each, three mixtures (9:1; 1:1; 1:9) have been prepared (total of 72 mixtures): 87.5% of solutions (n=21/24) presented a precipitation, against 12.5% (n=3/24) without visual modification. Out of 72 mixtures, 55.56% (n=40/72) resulted in a precipitation, against 44.44% (n=32/72) with no visual modification after 4-h storage.

All physical changes are presented in Table 4. Table 5 regroups ratio results without physical observation after a 4-h storage.
Table 1: List of preparations before mixture.

| Drugs                                      | Concentration | Container   | Solvent        | Final volume |
|--------------------------------------------|---------------|-------------|----------------|--------------|
| Posaconazole                               | 1.2 mg/mL     | Infusion bag| 0.9% NaCl<sup>a</sup> | 250 mL       |
| Acyclovir sodium                           | 3.5 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |
| Alizapride hydrochloride                   | 3.0 mg/mL     | Syringe     | 0.9% NaCl      | 50 mL        |
| Cefepime hydrochloride                     | 40.0 mg/mL    | Syringe     | D5W<sup>a</sup> | 50 mL        |
| Filgrastim                                 | 0.3 MUI/mL    | Infusion bag| D5W            | 100 mL       |
| Furosemide                                 | 0.8 mg/mL     | Infusion bag| 0.9% NaCl      | 50 mL        |
| Ganciclovir sodium                         | 3.5 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |
| Insulin aspartate                          | 100.0 UI/mL   | Syringe     | 0.9% NaCl      | 50 mL        |
| Levetiracetam                              | 5.0 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |
| Methylprednisolone sodium succinate        | 20.0 mg/mL    | Syringe     | 0.9% NaCl D5W  | 12 mL        |
| Metoclopramide hydrochloride               | 0.4 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |
| Nefopam hydrochloride                      | 0.2 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |
| Ondansetron hydrochloride                  | 2.5 mg/mL     | Infusion bag| 0.9% NaCl      | 50 mL        |
| Pantoprazole sodium                        | 0.16 mg/mL    | Syringe     | 0.9% NaCl      | 50 mL        |
| Paracetamol                                | 0.08 mg/mL    | Infusion bag| 0.9% NaCl      | 100 mL       |
| Phloroglucinol dihydrate                   | 0.48 mg/mL    | Syringe     | 0.9% NaCl      | 50 mL        |
| Piperacillin sodium-Tazobactam sodium      | 0.4 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |
| Potassium chloride                         | 160.0 mg/mL   | Syringe     | 0.9% NaCl      | 50 mL        |
| Tacrolimus                                 | 100.0 mg/mL   | Syringe     | Without dilution| 40 mL        |
| Tramadol hydrochloride                     | 3.0 mg/mL     | Syringe     | D5W            | 50 mL        |
| Tramadol hydrochloride                     | 30.0 mg/mL    | Syringe     | D5W            | 50 mL        |
| Tramadol hydrochloride                     | 0.5 mg/mL     | Infusion bag| 0.9% NaCl      | 100 mL       |

<sup>a</sup>NaCl 0.9%: 0.9% sodium chloride. <sup>a</sup>D5W: dextrose 5% in water.

Table 2: pH values from the 19th edition of the Handbook on injectable drugs and Martindale – the complete drug reference and pH values measured in our laboratory.

| Drugs                                      | pH values in literature | pH values measured in our laboratory | Concentration | Solvent |
|--------------------------------------------|-------------------------|--------------------------------------|---------------|---------|
| Posaconazole                               | 2.6                     |                                      | 3.0 mg/mL     | 0.9% NaCl|
| Acyclovir sodium                           | 11.0                    |                                      |               |         |
| Alizapride hydrochloride                   | No data                 |                                      | 4.88          |         |
| Cefepime dihydrochloride                   | 4.0–6.0                 |                                      | 4.42          | D5W     |
| Filgrastim                                 | 3.8–4.2                 |                                      | 40.0 mg/mL    |         |
| Furosemide                                 | 8.0–9.3                 |                                      |               |         |
| Ganciclovir sodium                         | 11.0                    |                                      |               |         |
| Insulin aspartate                          | 7.0–7.8                 |                                      |               |         |
| Levetiracetam                              | 5.5                     |                                      |               |         |
| Methylprednisolone sodium succinate        | 7.0–8.0                 |                                      |               |         |
| Metoclopramide hydrochloride               | 4.5–6.5                 |                                      | 5.59          | 0.1 mg/mL|
| Ondansetron hydrochloride                  | 3.3–4.0                 |                                      | 5.34          | 0.2 mg/mL|
| Pantoprazole sodium                        | 9.0–11.5                |                                      | 4.15          | 0.16 mg/mL|
| Paracetamol                                | 5.5                     |                                      | 4.31          | 0.08 mg/mL|
| Phloroglucinol dihydrate                   | 4.0–6.0                 |                                      | 3.88          | 0.48 mg/mL|
| Piperacillin sodium-Tazobactam sodium      | 5.5–6.8                 |                                      |               |         |
| Potassium chloride                         | 4.0–8.0                 |                                      | 5.40          | 100.0 mg/mL|
| Tacrolimus                                 | 2.0–6.0                 |                                      | 4.26          | 3.0 µg/mL|
| Tramadol hydrochloride                     | No data                 |                                      | 4.24          | 30.0 µg/mL|

<sup>a</sup>W: dextose, <sup>b</sup>% NaCl: 0.9% sodium chloride, <sup>c</sup>Wb: dextrose 5% in water.
Table 3: List of injectable drugs used for laboratory tests.

| Drugs                                           | Laboratory | Batch  | Expiry date |
|-------------------------------------------------|------------|--------|-------------|
| Posaconazole NOXAFIL® 300 mg/16.7 mL             | MSD        | S030468 | 10/21       |
| Acyclovir sodium 500 mg                          | Mylan      | B2139  | 04/22       |
| Alizapride hydrochloride PLITICAN® 50 mg/2 mL    | Sanofi     | H1503  | 06/22       |
| Cefepime dihydrochloride 2 g                     | Gerda      | P-09   | 04/22       |
| Filgrastim ZARZIO® 30 MUI/0.5 mL=300 µg/0.5 mL   | Sandoz     | KB9549 | 05/22       |
| Furosemide 20 mg/2 mL                            | Renaudin   | 206612 | 09/22       |
| Ganciclovir sodium CYMEVAN® 500 mg              | Cheplapharm| B8039B03 | 05/21     |
| Insulin aspartate NOVORAPID® 1,000 UI/10 mL     | Novo Nordisk| J5695Y8 | 11/21       |
| Levetiracetam 500 mg/5 mL                        | Mylan      | F2066  | 07/21       |
| Methyldapenosine sodium succinate 120 mg         | Mylan      | B3124  | 04/21       |
| Methyldapenosine sodium succinate 40 mg          | Mylan      | B2444  | 06/21       |
| Metoclopramide hydrochloride PRIMPERAN® 10 mg/2 mL| Sanofi    | HY022  | 06/22       |
| Nefopam hydrochloride 20 mg/2 mL                 | Mediso     | H1045  | 09/22       |
| Ondansetron hydrochloride 8 mg/4 mL              | Accord     | Y08562 | 04/22       |
| Pantoprazole sodium 40 mg                         | Arrow      | 891978 | 11/21       |
| Paracetamol 1,000 mg/100 mL                      | B Braun    | 1943451| 09/21       |
| Phloroglucinol dehydrate 40 mg/4 mL              | Arrow      | 206363 | 10/20       |
| Piperacillin sodium-Tazobactam sodium 4 g        | Pan Pharma | 305856 | 06/22       |
| Potassium chloride 2 g/20 mL                     | Lavoisier  | 8P371  | 06/21       |
| Tacrolimus PROGRAF® 5 mg/1 mL                   | Astellas   | 5A3419N| 01/21       |
| Tramadol hydrochloride TOPALGIC® 100 mg/2 mL    | Sanofi     | 1049   | 05/22       |

Solvants

| Dextrose 5% in water 100 mL Ecolifac®³          | Fresenius  | 15NLCS20 | 10/22       |
| Dextrose 5% in water 250 mL glass vial          | Lavoisier  | 9F561   | 02/22       |
| Sodium chloride 0.9% 100 mL EasyFlex®³          | MacoPharma | 19A09B  | 01/21       |
| Sodium chloride 0.9% 100 mL Ecolifac®           | Fresenius  | 15MNCS510 | 11/21     |
| Sodium chloride 0.9% 50 mL Ecolifac®            | Fresenius  | 15MD150 | 11/21       |
| Sodium chloride 0.9% 50 mL glass vial           | Lavoisier  | 9F561   | 09/22       |

³Ecolifac® is a low density polyethylene infusion bag. EasyFlex® is a polyolefin bag.

Table 4: Final ratio results with physical modification after 4-h storage.

| Drug X/Posaconazole (1.20 mg/mL) | Concentration | Type of incompatibility | Ratio | Time       |
|----------------------------------|---------------|--------------------------|-------|------------|
| Acyclovir sodium                 | 3.5 mg/mL     | Precipitate              | 9:1   | After mixture |
| Alizapride hydrochloride         | 3.0 mg/mL     | Precipitate              | 9:1   | After 1 h    |
| Cefepime dihydrochloride         | 40.0 mg/mL    | Precipitate              | 9:1   | After mixture |
| Furosemide                       | 0.8 mg/mL     | Precipitate              | 9:1   | After mixture |
| Ganciclovir sodium               | 3.5 mg/mL     | Precipitate              | 9:1   | After mixture |
| Insulin aspartate                | 100.0 UI/mL   | Precipitate              | 9:1   | After mixture |
| Levetiracetam                    | 5.0 mg/mL     | Precipitate              | 9:1   | After mixture |
| Methyldapenosine sodium succinate| 20.0 mg/mL    | Precipitate              | 9:1   | After mixture |
| Metoclopramide hydrochloride     | 0.1 mg/mL     | Precipitate              | 9:1   | After 4 h    |
| Nefopam hydrochloride            | 0.2 mg/mL     | Precipitate              | 9:1   | After mixture |
| Ondansetron hydrochloride        | 0.16 mg/mL    | Precipitate              | 9:1   | After 1 h    |
| Paracetamol                      | 10.0 mg/mL    | Precipitate              | 9:1   | After mixture |
| Phloroglucinol dehydrate         | 0.8 mg/mL     | Precipitate              | 9:1   | After mixture |
| Piperacillin sodium–Tazobactam sodium | 160.0 mg/mL | Precipitate              | 9:1   | After mixture |
| Potassium chloride               | 100.0 mg/mL   | Precipitate              | 9:1   | After mixture |
| Tramadol hydrochloride           | 0.5 mg/mL     | Precipitate              | 9:1   | After mixture |
In the majority of cases, a white precipitate after mixture appeared. Figure 1 shows a white precipitate which occurred instantly after mixing posaconazole and ganciclovir. After mixing posaconazole with pantoprazole, a precipitate was observed for the 9:1 ratio, a precipitate and a yellow colouring for 1:1 ratio are visual and for the 1:9 ratio, only a yellow colouring can be observed (Figure 2).

**Discussion**

In the 19th edition of the Handbook on injectable drugs, only filgrastim (6 μg/mL in 0.9% sodium chloride and dextrose 5% in water) and potassium chloride (0.04 mEq/mL=2.98 mg/mL, in 0.9% sodium chloride and D5W) were physically compatible with posaconazole [7]. During the observational study in hematology care unit, higher concentrations of potassium chloride have been observed and used for the compatibility tests in this study. These drugs were tested with different concentrations in our laboratory: filgrastim 3 μg/mL and potassium chloride 100.0 mg/mL. This current study highlighted an incompatibility with potassium chloride 100.0 mg/mL.

In the majority of cases, this study demonstrated that posaconazole is responsible for many incompatibilities not previously published. Critical molecules with high precipitation potential were identified in the drug list established in the first step of this study. Out of 19 drugs, 17 were identified as physically incompatible with posaconazole.

For the drugs tested, posaconazole was compatible only with filgrastim and tacrolimus for any dilution studied (9:1, 1:1 and 1:9). These different ratios were performed

| Drug X/Posaconazole (1.20 mg/mL) | Concentration | Ratio   |
|---------------------------------|--------------|--------|
| Alizapride hydrochloride        | 3.0 mg/mL    | 1:1, 1:9 |
| Filgrastim                      | 0.3 μM/mL    | 9:1, 1:1, 1:9 |
| Furosemide                     | 0.8 mg/mL    | 1:9 |
| Insulin aspartate               | 100.0 UI/mL  | 1:9 |
| Levetiracetam                   | 5.0 mg/mL    | 1:9 |
| Methylprednisolone sodium succinate | 20.0 mg/mL | 9:1 |
| Metoclopramide hydrochloride    | 0.1 mg/mL    | 1:1, 1:9 |
| Nefopam hydrochloride           | 0.2 mg/mL    | 1:1, 1:9 |
| Ondansetron hydrochloride       | 0.16 mg/mL   | 1:1, 1:9 |
|                                 | 0.08 mg/mL   | 1:1, 1:9 |
|                                 | 0.48 mg/mL   | 1:9 |
| Paracetamol                     | 10.0 mg/mL   | 1:9 |
| Phloroglucinol dihydrate        | 0.8 mg/mL    | 1:1, 1:9 |
| Piperacillin sodium – Tazobactam sodium | 160.0 mg/mL | 9:1 |
| Potassium chloride              | 100.0 mg/mL  | 1:1, 1:9 |
| Tacrolimus                      | 3.0 μg/mL    | 9:1, 1:1, 1:9 |
|                                 | 30.0 μg/mL   | 9:1, 1:1, 1:9 |
| Tramadol hydrochloride           | 0.5 mg/mL    | 1:1, 1:9 |

**Figure 1:** Mixture of ganciclovir sodium (G) 3.5 mg/mL diluted in 0.9% sodium chloride with posaconazole (P) 1.2 mg/mL diluted in 0.9% sodium chloride after the mixture (G:P (v:v)): glass tube left to right, n°1: 9:1, n°2: 1:1, n°3: 1:9.

**Figure 2:** Mixture of pantoprazole sodium (PS) 0.4 mg/mL diluted in 0.9% sodium chloride with posaconazole (P) 1.2 mg/mL diluted in 0.9% sodium chloride after a 4-h storage (PS:P (v:v)): glass tube left to right, n°1: 9:1, n°2: 1:1, n°3: 1:9.
because the drugs flows can be modified leading to higher or lower concentrations. If the three ratios are compatibles, it is possible to extrapolate over all the concentration ranges. As notified in the Handbook [7] or in Martindale [9], these two drugs have an acidic pH like posaconazole. As described by Vu N. et al., knowledge of pH is really useful in stabilization of preparations. The pH affects the solubility of a basic or an acid drug. An optimal pH range is necessary for solubilizing drugs [11]. The pH could be a precipitation factor, since two opposite pHs are more likely to form a precipitate as illustrated by Perez M et al. during their experiment [12]. This present study shows that posaconazole does not present a precipitate directly after mixing with an acidic drug (the pH of posaconazole ± 2 pH units), cefepime being an exception. In our laboratory, pH posaconazole was measured at 4.42 pH units. Another parameter may come into play concerning the stability between posaconazole and cefepime. All drugs that precipitate instantly after mixing with posaconazole, have a basic pH (above 9.0, except for cefepime dihydrochloride): acyclovir sodium: 11.0 pH units, ganciclovir sodium: 11.0 pH units, pantoprazole sodium: 9.0–11.5 pH units. The hypothesis to explain the formation of a precipitate for these molecules after mixing with posaconazole is a pH too far from the pH of posaconazole.

Posaconazole is a weak base which cause a low aqueous solubility. To increase the solubility by ionization a cyclodextrin used as complexing agent: sulfobutylether-β-cyclodextrin (SBECD) is added to the formulation [1]. As described in the literature by Dhruve P. et al., this complexing agent improved the solubility of the drug [13]. The balance between the complexed molecule and the complexing agent could be very weak and therefore lead to precipitation when a chemically active element is added.

The compatibility between posaconazole and cefepime could be due to the presence of excipients (sodium edentate, L-arginine). However, we did not find any information to confirm this hypothesis. This hypothesis needs further investigations.

Posaconazole should not be administered simultaneously with these commonly intravenous drugs. In addition, as explained by Perez M et al., the use of a new multilumen access device could prevent physical incompatibility between several drugs with different pH levels (acid and basic), for example the Edelvaiss Multiline-8®, which confirms that the infusion set has an impact on the physical compatibilities drugs [12]. A grouping of drugs of similar pH may also be considered, or a delay in the administration of the least essential injectable drugs [14]. In case of available specialties and for a patient able to swallow, it is possible to change the route of administration [15].

Conclusion

This study provides new data on the physical compatibility of posaconazole with drugs commonly used via Y-site infusion in a hematoloy care unit. Among the 19 drugs tested, only filgrastim and tacrolimus were physically compatible with posaconazole. In majority of cases, posaconazole was not compatible with drugs having alkaline pH, commonly used in our hematology unit.

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