Physicochemical stability of voriconazole in elastomeric devices

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ABSTRACT

Objectives Voriconazole is the drug of choice for invasive aspergillosis (IA), a leading cause of mortality and morbidity in immunocompromised patients. Prolong intravenous administration of voriconazole is often needed in such patients due to high incidence of oral mucositis and unreliable bioavailability of oral dosage form. Administration of voriconazole through elastomeric pump may facilitate early hospital discharge of clinically stable immunocompromised patients needing prolonged intravenous treatment. Therefore, we investigated the physicochemical stability of voriconazole in one of the commonly used elastomeric pumps at three different temperatures for various time points.

Methods A total of 18 elastomeric pumps were prepared and 6 containing 2 mg/mL of voriconazole (3 in 0.9% sodium chloride and 3 in 5% glucose) were stored at either 4°C for 96 hours, 25°C for 4 hours or at 35°C for 4 hours. An aliquot withdrawn immediately before storage (time 0) and at various time points was analysed for chemical stability using high-performance liquid chromatography and for physical stability using visual, pH and microscopic analyses.

Results Voriconazole was stable for at least 96 hours, 4 hours and 4 hours at 4°C, 25°C and 35°C, respectively, when admixed with either 0.9% sodium chloride or 5% glucose. No evidence of particle formation, colour change or pH change was observed throughout the study period.

Conclusions These findings would allow early hospital discharge using elastomeric intravenous administration of voriconazole in patients in whom oral route of administration is not available.

INTRODUCTION

Invasive aspergillosis (IA) is responsible for significant mortality in immunocompromised patients. It is reported that approximately one in three patients die within 12 weeks of acquiring the infection.¹ Nearly half of the patients infected with IA do not respond to the antifungal treatment though newer antifungal agents have better treatment success. Voriconazole is a relatively newer triazole antifungal agent that has shown superior treatment response in IA when compared with amphotericin B.² Considering the high mortality associated with IA, most guidelines recommend intravenous administration of voriconazole for a prolonged period of time. Immunocompromised patients receiving chemotherapy and other immunosuppressant medications are at an increased risk of oral mucositis and often have erratic and unreliable absorption of nutrients and medications.^{3,4} Additionally, gastrointestinal side effects associated with oral voriconazole often

necessitate the need for its intravenous administration. Therefore, such patients require extended duration of hospitalisation or hospital outreach professionals need to visit the patient's home twice daily to complete their intravenous voriconazole treatment.^{5,6}

An elastomeric device is an easy and ready-to-use drug delivery system that can release intravenous medication at an accurate infusion rate and be managed by patients at their home. Empowering patients to manage their antimicrobial infusions at their homes will encourage their early mobility and better quality of life.⁷ Given the huge potential of these devices to offer seamless delivery of antibiotics, patients can be mobile and functional while receiving their treatment doses of an antimicrobial course.⁸ The use of these devices will also save nursing time and avoid delays in the timely administration of antibiotics allowing the allocation of valuable human resources to other competing priorities such as managing complex patients with acute health issues requiring close clinical follow-up by medical staff. Not to mention the cost savings from early discharge and reallocating stretched nursing staff will result in better utilisation of available healthcare resources.⁹ Also, an increased length of stay in the hospital is associated with a corresponding increased risk of hospital-acquired infections, with nearly 1 in 20 patients developing an infection during their hospital stay and this risk increases with every extra day spent in the hospital.¹⁰ Therefore, the use of elastomeric pumps will save costs depending on the local budget system. Given the lack of the stability data for voriconazole in elastomeric pumps, this approach cannot be used to administer prolonged courses of voriconazole. Therefore, the current study investigated the physicochemical stability of voriconazole in elastomeric pumps at three different temperatures for various time points.

METHODS

Sample preparation

Voriconazole powder for injection (n=18, VFEND®BP) intravenous 200 mg, Pfizer Australia, New South Wales, Australia) was reconstituted with 19 mL of water for injection BP to obtain the stock solution of 10 mg/mL. The stock solution was then gently vortexed for 2 min to obtain the clear drug solution. The solution (20 mL) was then injected into a polyvinyl chloride bag (n=18) containing 80 mL of 0.9% sodium chloride (Baxter Healthcare Corporation, New South Wales, Australia) or 80 mL of 5% glucose (Baxter Healthcare Corporation,

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New South Wales, Australia). To ensure proper mixing, each bag containing 2 mg/mL of voriconazole was gently shaken for approximately 2 min. Voriconazole solution was then carefully withdrawn using a 50 mL plastic syringe from an infusion bag before injecting into an Intermate SV 50 mL/hour elastomeric infusion pump (Baxter Healthcare Corporation, New South Wales, Australia). Briefly, a pump was kept in a vertical position and the fill port cap was removed from the port present at the top of the elastomeric pump. The syringe containing drug solution was then connected to the port and the solution was injected into the pump by gently pushing the plunger of the syringe. A total of 18 pumps were prepared and 6 pumps containing 2 mg/mL of voriconazole (3 in 0.9% sodium chloride and 3 in 5% glucose) were stored (not protected from light) at either 4°C for 96 hours, 25°C for 4 hours or at 35°C for 4 hours. A control sample (n=3) was prepared the same way except that the voriconazole was omitted and stored as described above. An aliquot was withdrawn after 0 hour (baseline sample), 24 hours, 48 hours, 72 hours and 96 hours from the pumps stored at 4°C. Similarly, an aliquot was withdrawn after 0 hour, 1 hour, 2 hours, 3 hours and 4 hours from the pumps stored at 25°C and 35°C. The collected aliquot was then divided into four parts; one part was used to investigate the concentration of voriconazole using a stability indicating high-performance liquid chromatography (HPLC) method. The second and third parts were used to measure the change in pH (using a calibrated pH meter) and colour (visually against a black and white background) respectively. The fourth part was used to estimate the particle content.

HPLC assay

A newly developed stability indicating method was used on Dionex UltiMate 3000 HPLC system (Thermo Fisher Scientific, California, USA) to perform the chromatographic analysis. HPLC separation of voriconazole was carried out using an ACE® 3 µm C₁₈ (100 Å of pore size, 100×4.0 mm id) reversed-phase column (Advanced Chromatography Technologies, Aberdeen, Scotland). The temperature of the column compartment was set at 35°C. Two different types of mobile phases were used, mobile phase A was composed of Milli-Q water and 0.1% trifluoroacetic acid (Sigma-Aldrich, New South Wales, Australia) and mobile phase B was composed of acetonitrile (Sigma-Aldrich, New South Wales, Australia) and 0.1% trifluoroacetic acid. The gradient for mobile phase A was set as follows: 70% for the first 2 min, 45% for the next 3 min, 50% for another 2 min, followed by 70% for the last 3 min. The mobile phase flow rate was kept at 1.2 mL/min. The injection volume and the detector wavelength were set at 10 µL and 260 nm, respectively.

Validation of HPLC assay

The stability indicating nature of the method was determined by subjecting voriconazole (500 µL, 10 µg/mL) to acidic, basic and thermal stress conditions. Under acidic stress condition, an equal volume of voriconazole was mixed with 0.5 M hydrochloric acid before storing the sample at 40°C for 80 hours. Under basic stress conditions, voriconazole was mixed with 500 µL of 0.0125 M sodium hydroxide for 5 min. Under thermal stress conditions, voriconazole solution was kept at 65°C for 30 hours. Control samples were also prepared but voriconazole was omitted. Each sample was prepared in triplicate and analysed in triplicate.

Linearity of the method was investigated using 25 µg/mL, 12.5 µg/mL, 6.25 µg/mL, 3.125 µg/mL, 1.5625 µg/mL of voriconazole (using correlation coefficient r^2). Mean intraday precision and interday precision (over three consecutive days)

were calculated using peak areas with repeat analysis (n=6) of 6.25 µg/mL, 3.125 µg/mL, 1.5625 µg/mL of voriconazole. Mean intraday and interday (over three consecutive days) accuracy of voriconazole peak (25 µg/mL, 12.5 µg/mL, 6.25 µg/mL, n=6) were determined using the percentage recovery of voriconazole. Mean intraday reproducibility and interday reproducibility (over three consecutive days) were estimated based on retention time of voriconazole peak (25 µg/mL, 12.5 µg/mL, 6.25 µg/mL, 3.125 µg/mL, 1.5625 µg/mL, n=6). Each sample was analysed in triplicate.

Robustness of the method was investigated by injecting a calibration standard (6.25 µg/mL of voriconazole standard, n=6) and slightly changing the three chromatographic parameters; the temperature of the column was changed from 35°C to 30°C, the flow rate of the mobile phase was changed from 1.2 mL/min to 1.0 mL/min and the gradient for mobile phase A was changed to: 72% for the first 2 min, 42% for the next 3 min, 47% for another 2 min, followed by 72% for the last 3 min.

Sample preparation for HPLC analysis

A 1 mg/mL voriconazole stock solution was prepared by dissolving 170 mg of voriconazole powder in 10 mL of Milli-Q water. The stock solution was then used to prepare five standard solutions of voriconazole (25 µg/mL, 12.5 µg/mL, 6.25 µg/mL, 3.125 µg/mL and 1.5625 µg/mL). On each day of the analysis, a standard curve was generated by determining linear regression of the peak areas of voriconazole against its concentrations. An aliquot withdrawn from each elastomeric pump was diluted with Milli-Q water to a concentration of 5 µg/mL and subjected to HPLC analysis within 10 min of preparation. Each sample was analysed in triplicate. Voriconazole was considered to be chemically stable if it retained more than 90% of its initial concentration.

Microscopic analysis

An aliquot (50 µL) collected from each elastomeric pump was carefully placed on a Flex ICH microscopic slide (Dako, Agilent Technologies, New South Wales, Australia) and was covered with a cover slip. The samples were then analysed microscopically (Nikon Eclipse 50i, South Australia, Australia) using either 4×, 10× or 20× magnification objective. Particles were counted using Image J software (Wayne Rasband, NIH, Baltimore, USA). The positive control (n=3) was prepared by dissolving 10 mg of voriconazole powder in 400 µL of methanol. The mixture was then vortexed for approximately 2 min before microscopic analysis. Methanol without voriconazole powder was considered as a negative control. Each sample was analysed in triplicate.

Extraction of voriconazole

The solution remained in an elastomeric pump (n=2) after its storage at 35°C for 4 hours was carefully drained out. The reservoir of a pump containing rubber balloon and flow restrictor was taken out by removing the surrounding plastic housing. The balloon was then cut into small pieces using a surgical scalpel and kept in a sterile glass container along with the flow restrictor. The container was filled with 35 mL of methanol and then vortexed using a mixer (Lab-line Instruments, South Australia, Australia) for 840 min. An aliquot was withdrawn after 0 min, 60 min, 120 min, 240 min, 480 min and 840 min of vortexing. The withdrawn sample was subjected to HPLC analysis to determine the amount of extracted voriconazole.

Figure 1 Chromatographic profile of voriconazole before (A) and after subjecting it to acidic (B), thermal (C) and basic stress (D) conditions.

RESULTS

Validation of HPLC assay

Chromatograms of stressed and unstressed voriconazole are shown in [figure 1](#). Unstressed voriconazole was eluted at 4.5 min. Different types of chromatographic profiles were obtained before and after subjecting voriconazole to various stressed conditions. Storage of voriconazole at 65°C for 30 hours resulted in 14% loss of voriconazole. When stressed under acidic condition, the peak of a degraded product was eluted at 1.8 min. The area of this peak was increased by 3% after thermal degradation of voriconazole and was further increased by 18% when voriconazole was stressed under basic conditions. Importantly, degraded peaks did not elute with the voriconazole peak suggesting the newly developed method can be used for the chemical stability investigation of voriconazole.

The assay performance results are shown in [table 1](#). The linearity of the method estimated using correlation coefficient (r^2) was found to be greater than 0.999. The mean intraday accuracy and interday accuracy relative SD (RSD) at each concentration were found to be lower than 0.8% and 0.92%, respectively. The mean intraday and interday precision RSD at each concentration were estimated to be lower than 0.97% and 0.81%, respectively. The mean intraday and interday reproducibility RSD were found to be lower than 0.21% and 0.19%, respectively. No significant changes in the peak area and retention time of voriconazole peak were observed when three parameters (column temperature, mobile phase flow rate and composition of mobile phase A) were slightly changed.

Table 2 The percentage of voriconazole remaining in elastomeric pumps stored at various temperatures and time intervals. Each sample was prepared in triplicate and analysed in triplicate. Results are presented as mean $\pm$ SD

Time (hours)	% initial concentration remaining					
	4°C		25°C		35°C	
	0.9% sodium chloride	5% Glucose	0.9% sodium chloride	5% Glucose	0.9% sodium chloride	5% Glucose
1	-	-	98.7 $\pm$ 0.4	99.6 $\pm$ 0.3	98.6 $\pm$ 0.1	99.1 $\pm$ 0.8
2	-	-	98.2 $\pm$ 0.4	99.3 $\pm$ 0.9	98.7 $\pm$ 0.5	98.6 $\pm$ 0.4
3	-	-	98.3 $\pm$ 0.0	98.8 $\pm$ 0.5	98.2 $\pm$ 0.5	97.6 $\pm$ 0.2
4	-	-	98.1 $\pm$ 0.1	98.9 $\pm$ 0.3	97.9 $\pm$ 0.5	98.5 $\pm$ 0.7
24	99.5 $\pm$ 0.3	99.6 $\pm$ 0.3	-	-	-	-
48	98.9 $\pm$ 1.0	99.4 $\pm$ 0.2	-	-	-	-
72	99.5 $\pm$ 0.5	97.9 $\pm$ 0.3	-	-	-	-
96	98.1 $\pm$ 0.2	97.2 $\pm$ 0.1	-	-	-	-

Chemical stability of voriconazole

The mean concentration of voriconazole at time zero when admixed with 0.9% sodium chloride or 5% glucose was found to be 2.01 mg/mL or 1.99 mg/mL and was considered as 100%. The percentage of voriconazole remaining at different temperatures for various time points is shown in [table 2](#). At 4°C, voriconazole diluted with either 0.9% sodium chloride or 5% glucose solution retained more than 97% of its initial concentration after 96 hours of storage. After 4 hours of storage at 25°C, voriconazole lost less than 2% of its initial concentration when admixed with either type of diluent. Voriconazole-0.9% sodium chloride or 5% glucose admixture retained more than 97% of its initial concentration after 4 hours of storage at 35°C.

Physical stability of voriconazole

The baseline pH of a sample admixed with 0.9% sodium chloride or 5% glucose was found to be 6.14 $\pm$ 0.021 (mean $\pm$ SD) or 5.56 $\pm$ 0.028, respectively. No major change in pH was observed when the samples were kept at different temperatures for various time points. The maximum change in pH was found to be 0.20 and 0.15 when voriconazole was admixed with 0.9% sodium chloride and 5% glucose, respectively. No change in colour was observed in any of the samples when inspected visually against the white and black backgrounds under bright light. Microscopic images of the control samples are shown in [figure 2](#). The number of particles estimated to be present in a positive control was found to be 1800 particles/mL of sample. The microscopic analysis did not show the presence of particles in any of the samples.

Table 1 HPLC assay performance determined by analysis of voriconazole peak

Concentration of voriconazole (μ g/mL)	Precision (%RSD)		Accuracy (%RSD)		Reproducibility (%RSD)	
	Intraday*	Interday* [†]	Intraday*	Interday* [†]	Intraday*	Interday* [†]
25	-	-	0.45	0.52	0.09	0.1
12.5	-	-	0.79	0.66	0.18	0.08
6.25	0.78	0.66	0.83	0.91	0.08	0.15
3.125	0.51	0.47	-	-	0.17	0.17
1.5625	0.96	0.80	-	-	0.20	0.18

*=for all intraday and interday, n=6

[†]=for all interday, 3 consecutive days

Figure 2 Microscopic images of positive control (A) and negative control (B) samples.

Extraction of voriconazole

The amount of voriconazole extracted after 60 min, 120 min, 240 min, 480 min and 840 min of vortexing was found to be 1.16 mg, 3.31 mg, 4.04 mg, 4.83 mg and 5.1 mg, respectively.

DISCUSSION

IA is considered as one of the most difficult to treat invasive fungal infections and requires prolonged treatment with appropriate antifungal agents. Most guidelines recommend a duration of at least 6 weeks to 12 weeks with a suitable antifungal agent.¹¹ Voriconazole has become the antifungal of choice because of its superior efficacy and safety when compared with the other antifungal agents.¹² Additionally, the availability of its oral dosage form allows the continuation of the treatment beyond the initial intravenous treatment.¹³ However, most immunocompromised patients suffering from IA often have concomitant oral and/or intestinal mucositis, and suffer from poor and erratic oral bioavailability due to extensive use of chemotherapy and other immunosuppressant drugs.^{14–15} As such, the use of intravenous voriconazole for extended periods of time in immunocompromised patients with IA is not an uncommon occurrence in clinical practice. The need for prolonged intravenous administration of voriconazole often results in extended hospital stay. This would increase financial burden to the healthcare system and the risk of nosocomial infections.^{16–18} Therefore, elastomeric infusion of voriconazole in such patients can provide a much needed alternative.

The current study investigated the stability of voriconazole in two of the most commonly used diluents used in clinical practice to ensure the generalisability of the results to everyday practice. The majority of available HPLC methods are indicated for the determination of voriconazole in different types of commercially available formulations rather than 0.9% sodium chloride or 5% glucose solution. Therefore, a new stability indicating method was developed and validated for the stability determination of voriconazole when admixed with either 0.9% sodium chloride or 5% glucose solution. We found that voriconazole is physically and chemically stable for at least 96 hours at 4°C. Therefore, the pumps can be prepared in advance by healthcare professionals and stored at an appropriate temperature avoiding the necessity for frequent preparation. This approach could reduce the possibility of errors and the cost associated with preparation process.¹⁹ The drug-loaded pumps can be supplied in bulk to the patients avoiding the need to travel to the hospitals every day to get the daily dose of voriconazole. A study conducted by Vallière *et al* suggested that the temperature of the elastomeric device often exceeds 25°C and can go as high as 35°C.²⁰ Therefore, we investigated the stability of voriconazole at 25°C and 35°C and found that voriconazole is stable for at least 4 hours

allowing home-based elastomeric administration of voriconazole in patients who are optimised on voriconazole predischARGE and in whom the oral route of administration is not available.

This is the first study that investigated particle content in an elastomeric solution stored at various temperatures. Previously reported studies have used visual examination for such an assessment.^{21–22} Microscopic analysis enabled us to view small sized particles that may otherwise be invisible through unaided vision. If undetected then the infusion small particles can contribute to harm. For example, it has been reported that particles smaller than 2.5 µm can cause cardiac damage including promotion of atherosclerotic lesions.²³ A recent study used an instrument method to determine the number of particles in an elastomeric device containing an antibiotic solution. The instrument method required considerable dilution of the sample which may allow the possible dissolution of some particles that may be present. On the other hand, microscopic analysis allowed direct examination of the particles without their possible dissolution.

Chromatographic analysis showed that approximately 3% (6 mg) of voriconazole was lost when a pump containing voriconazole-0.9% sodium chloride admixture was stored at 35°C for 4 hours. However, HPLC chromatograms did not show any degradation peaks indicating potential adsorption of voriconazole on the surface of elastomeric balloon and/or flow restrictor. The adsorption was confirmed by extracting more than 85% of adsorbed voriconazole. Given the low minimum inhibitory concentration of voriconazole for the susceptible fungi,²⁴ it is unlikely that the clinical effectiveness of voriconazole will be compromised due to such a small decrease in the administered dose. Nevertheless, such an assumption needs to be tested in a follow-up clinical study.

The current study did not investigate the stability of voriconazole when exposed to direct sunlight or kept beyond 35°C. Therefore, patients are recommended to avoid sun exposure and, to keep the pump inside a thermal control container where temperature is expected to exceed 35°C.

In conclusion, this study provides crucial information to healthcare professionals on the stability of voriconazole in one of the commonly used elastomeric devices.

What this paper adds

- Long-term intravenous infusion of voriconazole is often required in patients with cancer who are infected with invasive aspergillosis (IA) and in whom oral route is not available.
- Extended intravenous courses of voriconazole require prolonged hospitalisation leading to increased healthcare cost and the risk of nosocomial infections.
- Stability of voriconazole in elastomeric devices is currently unknown and therefore such devices cannot be used as an alternative to the hospital-based administration of intravenous voriconazole.

What this study adds?

- Voriconazole admixed with either 0.9% sodium chloride or 5% glucose is physically and chemically stable in one of the commonly used elastomeric devices.
- Daily administration of voriconazole through the elastomeric device can provide an economical and safe alternative to the hospital-based administration of this antifungal agent.

Competing interests None declared.

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