LETTER

Pemetrexed stability: additional information about microparticles

INTRODUCTION

The chemical stability of pemetrexed solutions diluted in 0.9% sodium chloride (0.9% NaCl) and 5% dextrose (D5%) in PVC infusion bags at 2–8°C was determined by High Performance Liquid Chromatography (HPLC) for 1 month by Zhang and Trissel¹ and Rondelot *et al.*² However, subvisual examination shows an increase in turbidimetry and in the number of microparticulates after storage at 2–8°C. The hypothesis of an interaction with PVC was advanced and the use of an inline filter was advised.¹ The discrepancy between the nephelometric evaluation and HPLC analysis could be due to the requirement to dilute the samples with the HPLC method. Dilution before analysis increases the solubility, a microprecipitate can be dissolved, and the results give a concentration near 100% of the initial concentration. This was well demonstrated in a recent article on the stability of co-trimoxazole.³

The objective of the present work was to investigate the hypothesis of the presence of a microprecipitate and to validate the feasibility of using an administration line with a 0.2 µm microfilter on pemetrexed infusions.

MATERIALS AND METHODS

As chemical stability has been previously demonstrated, we used a more rapid analytical method based on ultraviolet detection. The technique selected was flow injection analysis (FIA), which uses an HPLC apparatus without a separating column. The column is replaced by tubing and the sample is pushed by ultra-pure water towards a diode array detector.

Pemetrexed 500 mg vials were reconstituted with 20 mL 0.9% NaCl to obtain a concentration of 25 mg/mL. The solution was injected in 0.9% NaCl and D5% polyolefin bags to obtain a final concentration of 5 mg/mL in 25 mL. Five infusions were prepared for each solvent.

Table 1 Concentrations of pemetrexed 5 mg/mL after storage at 2–8°C and filtration of the solution via a 0.22 µm inline microfilter

	Mean concentration (mg/mL)	Mean±SD % of initial concentration*			
0.9% NaCl	Day 0	Day 7	Day 14	Day 21	Day 28
Bag 1	4.884	99.1±0.10%	99.6±0.02%	97.6±3.32%	99.7±0.02%
Bag 2	4.708	100.9±0.48%	100.3±0.01%	100.1±0.02%	99.9±0.04%
Bag 3	4.574	†	99.6±0.08%	100.4±0.12%	100.4±0.05%
Bag 4	5.111	89.4±0.08%	98.3±0.03%	99.5±0.06%	99.6±0.01%
Bag 5	4.961	100.3±0.01%	100.3±0.01%	100.3±0.01%	100.3±0.01%
5% Dextrose	Day 0	Day 7	Day 14	Day 21	Day 28
Bag 1	5.088	98.9±0.06%	99.6±0.01%	99.4±0.13%	99.2±0.10%
Bag 2	5.047	100.0±0.13%	100.4±0.01%	100.1±0.21%	100.1±0.09%
Bag 3	4.839	104.7±2.94%	99.9±0.14%	100.7±0.14%	101.1±0.12%
Bag 4	4.915	98.5±0.01%	99.3±0.09%	100.0±0.03%	100.0±0.13%
Bag 5	5.050	100.2±0.17%	100.3±0.28%	99.5±0.10%	100.4±0.12%

*The results are expressed as the mean of three injections.

†Error on sample preparation.

After preparation, 1 mL was removed and analysed by FIA without dilution. The bags were stored at 2–8°C. On day 8, an infusion line with a 0.2 µm microfilter was applied to the bags; 1 mL was taken and analysed by FIA to evaluate the concentration. At days 14, 21 and 28, 1 mL was taken after the purge of the line and analysed.

RESULTS

The results of sample analysis by FIA are presented in table 1.

DISCUSSION

As the chemical stability of pemetrexed has already been demonstrated,^{1,2} we focused our study on the formation of microparticles at 2–8°C. The objective was to investigate the hypothesis of the formation of a microprecipitate. The concentrated solution filtered at different time points during 28 days did not show any decrease in concentration, which does not support the presence of a microprecipitate. The use of the inline filter did not result in adsorption of the drug on the filter material. In view of the results, the administration of pemetrexed solutions at 5 mg/mL in non-PVC 0.9% NaCl or D5% bags, stored for 28 days at 2–8°C, using an administration set with an inline microfilter was perfectly feasible. Potential microparticles have no importance in daily practice and have no negative impact for the patient if the solution is filtered. These data allow advance preparation and minimise drug wastage.

Elise D'Huart, Jean Vigneron, Sophie Morice, Pauline Lider, Béatrice Demoré

Department of Pharmacy, Centre Hospitalier Universitaire de Nancy, Vandœuvre-lès-Nancy, France

Correspondence to Elise D'Huart, Department of Pharmacy, Centre Hospitalier Universitaire de Nancy, Vandœuvre-lès-Nancy, 545411, France; dhuartelise@gmail.com

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