ELSEVIER

International Journal of Pharmaceutics 105 (1994) 83–87

international journal of pharmaceutics

Compatibility study of methotrexate with PVC bags after repackaging into two types of infusion admixtures

B. Benaji [a,*], T. Dine [a], F. Goudaliez [b], M. Luyckx [a], C. Brunet [a], M.L. Mallevais [b], B. Gressier [a], M. Cazin [a], J.C. Cazin [a]

[a] *Laboratoire de Pharmacologie, Pharmacocinétique et Pharmacie Clinique, Faculté des Sciences Pharmaceutiques et Biologiques, rue du Professeur Laguesse, B.P. 83, 59006 Lille Cedex, France,* [b] *Laboratoires Macopharma, rue du Pont-Rompu, B.P. 464, 59338 Tourcoing Cedex, France*

(Received 28 June 1993; Modified version received 29 September 1993; Accepted 8 October 1993)

Abstract

The stability and compatibility of methotrexate in admixtures for continuous intravenous infusion using PVC bags and administration set were studied. Methotrexate was reconstituted and diluted to 4.5 mg/ml for infusion in PVC containers, and to 0.225 and 24 mg/ml for storage in PVC bags containing 5% dextrose or 0.9% sodium chloride injections. Admixtures were stored at + 4°C and with protection from light for 30 days. Analyses were performed by HPLC. In every case, no significant drug loss was observed during storage or simulated infusions using PVC infusion bags and administration sets.

Key words: Compatibility; PVC infusion bag; Methotrexate; Storage

Methotrexate (MTX) belongs to the first class of compounds successfully used to produce remission of leukemia in man. Currently, high doses of MTX are used (Goldin, 1978) in the treatment of osteogenic sarcoma, acute lymphocytic leukaemia, cancer of the head and neck and other malignancies. Although the effectiveness of MTX appears to increase with higher-dosage regimens, the risk of haematologic and renal toxicity, often unpredictable and life-threatening, has also increased (Von Hoff et al., 1977). Since then it has been used in low doses in the management of psoriasis, cutaneous sarcoidosis, several rheumatic diseases and in the treatment of steroid-dependent asthma (Harrison et al., 1989; Tung and Maibach, 1990; Dyer et al., 1991; Kremer and Phelps, 1992; Webster et al., 1992).

There is evidence from recent studies that the therapeutic index of anti-cancer agents may be improved if traditional intravenous bolus injection schedules are replaced with continuous regimes (Lawrence et al., 1980; Adams et al., 1987). Other investigations indicate that drug concentration, duration of exposure and drug metabolism are major determinants of the effect of methotrexate (Pinedo and Chabner, 1977). Thus, MTX infusion must be carried out over a sufficiently long period (at least 18 h) in order to

* Corresponding author. Tel: 20.96.40.40 poste 4265; Fax: 20.96.97.52.

SSDI 0378-5173(93)E0310-M

attain a concentration of 10^{-6} mol/l which must be maintained for at least 6 h to be cytotoxic (Shapiro et al., 1975; Madelaine et al., 1991).

Continuous infusion therapy has been studied. Hence, the therapeutic advantages of continuous infusion vs intermittent small-volume infusion or intravenous (i.v.) push have been suggested (Carlson and Sikic, 1983). Now, for practical reasons, PVC containers are gradually replacing the conventionnal glass bottles used in continuous i.v. infusions. Therefore, with the increasing use of continuous i.v. infusion and intermittent small-volume i.v. infusion modes of administration, it is imperative that the stability and compatibility of antitumor agents in administration vehicles and PVC containers be investigated. Consequently, when drugs are administered by continuous i.v. infusion with PVC material, knowledge of the rate of drug delivery to the patient is essential (Moorhatch and Chiou, 1974; D'Arcy, 1983). Previous studies (Benvenuto et al., 1981; Illum and Bundgaard, 1982; Bosanquet, 1986) have reported the loss of certain drugs from aqueous solutions stored in PVC infusion bags for various periods of time. Generally, these losses have been attributed to interaction between the drug and the plastic infusion bag, and in some cases, may diminish the therapeutic response due to a reduced drug delivery to the patient.

We have used an HPLC analytical technique to investigate the compatibility of MTX with PVC containers and PVC infusion sets both during simulated infusions (1.5 g/m^2), and during storage (15 mg/m^2–8 g/m^2) at + 4°C in PVC bags used in a hospital pharmacy department where the reconstitution of cytostatics is centralized.

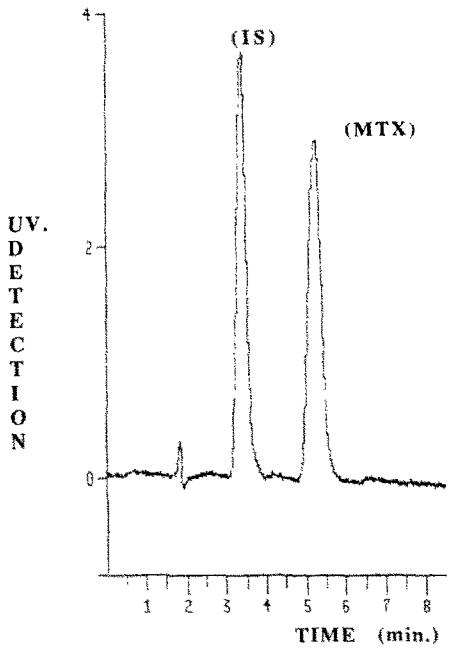

Fig. 1. HPLC analysis of MTX and aminopterin internal standard (IS). Operating conditions: C18 Ultremex ODS column (150×4.6 mm i.d). Mobile phase: (a) 96.5% 50 mM phosphate buffer (pH 4.85) and (b) 3.5% tetrahydrofuran. Flow rate, 1 ml/min; detection, at 365 nm; injected volume, 10 μl.

The method of HPLC separation is described in Fig. 1 and Table 1 summarizes the validation data of the assay procedure. The results demonstrate that this analytical method had acceptable accuracy and precision in every case.

Infusions of MTX were carried out under laboratory conditions simulating those routinely used in hospitals. For this purpose, we used a volumet-

Table 1
Validation data of HPLC assay procedure (n = 5)

Sample substance	Concentrations (μg/ml)	Average concentrations found ± SD (μg/ml)	CV interassay (%)	Accuracy (%)	Linear regression equation ($y = ax + b$)	Correlation coefficient (r)
MTX	10.00	9.99 ± 0.10	1.03	99.0		
	5.00	4.99 ± 0.04	1.64	99.8	$y = 0.213(x) + 0.042$	0.999
	2.50	2.59 ± 0.03	1.41	103.6		
	1.25	1.26 ± 0.08	1.72	100.8		

SD, standard deviation; CV, coefficient of variation.

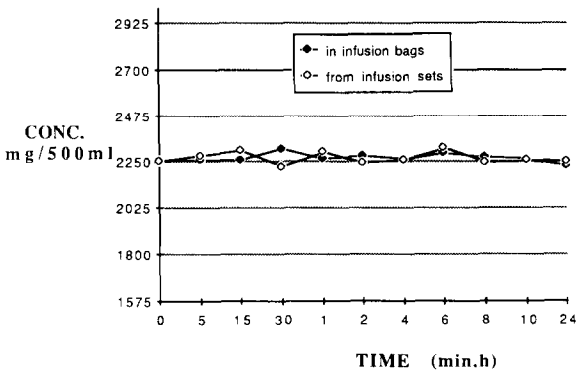

Fig. 2. Concentration kinetics of MTX during simulated infusions using: PVC infusion bags and sets ($n = 4$). Operating infusion conditions: infused dose, 2250 mg; infusion bag volume, 500 ml; infusion time, 24 h at room temperature and with protection from light.

ric infusion pump (ref. VIP II), opaque PVC infusion sets (ref. Perfecran 781547) for protection from light obtained from Fandre Laboratories (France) and Macoflex® infusion bags of PVC (100 and 500 ml) (Macopharma Laboratories, France). The bags were filled with 0.9% NaCl or 5% dextrose to study the possible influence of solvent on the interaction between drug and PVC.

The drug concentrations in solution and the conditions of simulated infusions are reported in Fig. 2. Infusion solutions of drug were prepared in PVC infusion bags containing 500 ml of 5% dextrose or 0.9% NaCl immediately before infusion. All admixtures were examined visually for clarity and colour, and tested for pH. The bag containing drug was then attached to an administration set connected to the infusion pump that allowed the solution to flow through at a constant rate. At specified times of infusion, samples (1 ml) were withdrawn at regular intervals from the PVC bags, and at the same time, an aliquot of effluent (1 ml) was collected from the administration set. Samples were kept frozen in polypropylene tubes at −20°C until analysis by HPLC. All simulated infusions were carried out at least in quadruplicate (two infusions in 0.9% NaCl and two infusions in 5% dextrose) at room temperature (20–24°C) with protection from light.

For storage studies, to infusion bags containing 100 and 500 ml of 0.9% NaCl or 5% dextrose solution, a known amount of drug was added to achieve the following two extreme concentrations which are most often used in hospitals: 22.5 mg/100 ml (0.225 mg/ml) and 12 g/500 ml (24 mg/ml) in the bags. After mixing the drug in the bag by rapid shaking, samples (1 ml) were withdrawn at regular intervals and stored in polypropylene tubes at −20°C until HPLC analysis. Infusion bags containing MTX were stored at + 4°C for a period of 30 days with protection from light. Drug storage in these bags was carried out in 0.9% NaCl ($n = 2$) and 5% dextrose ($n = 2$).

Fig. 2. depicts the concentration kinetics of MTX during simulated infusions using PVC infusion bags and sets ($n = 4$). When a solution of MTX was infused through PVC infusion sets from PVC infusion bags during the infusion pe-

Table 2
MTX concentrations present in solution after storage in plastic bags at 4°C in darkness

	Drug concentration			
	MTX (22.5 mg/100 ml)		MTX (12000 mg/500 ml)	
Infusion solution:	0.9% NaCl	5% Dextrose	0.9% NaCl	5% Dextrose
Initial	22.50	22.50	12000.00	12000.00
1 day	22.52 ± 0.07	21.98 ± 0.32	12457.20 ± 366.35	12437.69 ± 297.79
5 days	22.52 ± 0.94	22.76 ± 0.58	12607.20 ± 27.10	12556.40 ± 312.32
10 days	22.46 ± 0.38	23.00 ± 0.67	12567.18 ± 310.98	12084.94 ± 313.83
15 days	22.42 ± 0.53	23.15 ± 0.70	12252.37 ± 330.56	12350.99 ± 448.57
20 days	22.39 ± 0.93	22.58 ± 0.83	12196.73 ± 27.40	12060.29 ± 391.57
25 days	21.72 ± 0.57	22.25 ± 0.16	12106.54 ± 189.23	11887.39 ± 33.31
30 days	22.74 ± 0.46	22.43 ± 0.59	12550.98 ± 96.48	12447.66 ± 156.85

riod (24 h) used in chemotherapy, the variation in drug concentration in both the PVC bags and effluent in no case exceeded 10%. This demonstrates that MTX was not sorbed by the PVC infusion bags and sets during infusion at room temperature. No significant difference was observed with respect to drug stability during simulated infusions using 5% dextrose or 0.9% NaCl.

During storage at + 4°C with protection from light, the MTX admixtures have a yellow colour. The concentrations of MTX present in solution after various durations of storage in PVC infusion bags at +4°C with protection from light are listed in Table 2. Due to the large therapeutic range of MTX, two concentrations (15 mg/m^2 and 8 g/m^2) were studied. No substantial difference was observed between both concentrations. No significant disappearance of drug (exceeding 10%) was observed in PVC infusion bags, over a period of 30 days of storage, irrespective of the infusion solution (5% dextrose or 0.9% NaCl). No precipitation, change of colour or pH variation was observed during storage. On HPLC analysis, we observed neither loss nor degradation of the drug during storage in infusion bags over a period of 30 days. In the case of MTX, it is, however, necessary to use opaque PVC administration sets in order to avoid the degradation of the infusion solution.

In conclusion, the HPLC procedure described in this paper is both rapid and reproducible in the determination of MTX in parenteral solutions. With the increasing use of continuous i.v. infusion of cytostatic agents, the present study has examined the kinetics of MTX concentration during simulated infusion using PVC infusion bags and administration sets. The results demonstrate a satisfactory compatibility of this anticancer drug with PVC infusion material during an infusion period habitually used in hospital. After storage in PVC bags at + 4°C with protection from light, MTX at 0.225 and 24 mg/ml concentrations was shown to be stable for 30 days in 9% NaCl and in 5% dextrose. Consequently, MTX may be stored in PVC containers at concentrations ranging from 0.225 to 24 mg/ml without any interaction whatever the nature of the admixtures used. It is likely that other drugs interact with PVC infusion bags and administration sets, leading to a reduction in the clinical effectiveness of the drug (Kowaluk et al., 1981). This type of study is important concerning the packaging of pharmaceuticals in plastic containers in general (Magnam and Martin, 1988), and might be carried out for all drugs administered in PVC infusion bags.

1. Acknowledgement

The authors wish to thank Macopharma, Roger Bellon Laboratories for cooperation in this study.

2. References

Adams, P.S., Haines-Nutt, R.F., Bradford, E., Palmer, A. and Rowland, C.G., Pharmaceutical aspects of home infusion therapy for cancer patients. *Pharm. J.*, 4 (1987) 476–478.

Benvenuto, J.A., Anderson, R.W., Kerkof, K., Smith, R.G. and Loo, T.L., Stability and compatibility of antitumor agents in glass and plastic containers. *Am. J. Hosp. Pharm.*, 38 (1981) 1914–1918.

Bosanquet, A.G., Stability of solutions of antineoplastic agents during preparation and storage for in vitro assays: II. Assay methods, adriamycin and the other antitumour antibiotics. *Cancer Chemother. Pharmacol.*, 17 (1986) 1–10.

Carlson, R.W. and Sikic, B.I., Continuous infusion or bolus injection in cancer chemotherapy. *Ann. Int. Med.*, 99 (1983) 823–833.

D'Arcy, P.F., Drug interactions and reactions update. *Drug Intell. Clin. Pharm.*, 17 (1983) 726–731.

Dyer, D., Vaughan, R. and Weber, R.D., Methotrexate in the treatment of steroid-dependant asthma. *J. Allergy Clin. Immunol.*, 88 (1991) 208–212.

Goldin A., Studies with high-dose methotrexate – historical background. *Cancer Treat. Rep.*, 62 (1978) 307–312.

Harrison, P.V., Orrell, D.H., James, R., Peat, M. and Stones, R.N., Short-term methotrexate administration by low-dose infusion-does it influence clearance of psoriasis? *Clin. Exp. Dermatol.*, 14 (1989) 291–294.

Illum, L. and Bundgaard, H., Sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 10 (1982) 339–351.

Kowaluk, E.A., Roberts, M.S., Blackburn, H.P. and Polack, A.E., Interactions between drugs and polyvinyl chloride infusion bags. *Am. J. Hosp. Pharm.*, 38 (1981) 1308–1314.

Kremer, J.M. and Phelps, C.T., Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. *Arthritis Rheum.*, 35 (1992) 138–145.

Lawrence, J.R., Steele, W.H., Stuart, J.F.B., McNeill, C.A., McVie, J.G. and Whiting, B., Dose dependent methotrexate elimination following bolus intravenous injection. *Eur. J. Clin. Pharmacol.*, 17 (1980) 371–374.

Madelaine, I., Baruchel, A., Faure, P., Bellenger, P. and Schaison, G., Hight dose methotrexate concentration in plasma and cerebrospinal fluid after 24 h infusion (3 g/m^2 versus 8 g/m^2). *J. Pharm. Clin.,* 10 (1991) 153–158.

Magnam, J. and Martin, J.P., Les anticancéreux sont-ils compatibles avec les matières plastiques? *Lett. QS Cancérol.,* 72 (1988) 1–6.

Moorhatch, P. and Chiou, W.L., Interactions between drugs and plastic intravenous fluid bags: I. Sorption studies on 17 drugs. *Am. J. Hosp. Pharm.,* 31 (1974) 72–78.

Pinedo, H.M. and Chabner, B.A., Role of drug concentration, duration of exposure, and endogenous metabolites in determining methotrexate cytotoxicity. *Cancer Treat Rep.,* 61 (1977) 709–714.

Shapiro, W.R., Young, D.F. and Mehta, B.M., Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lombar injections. *N. Engl. J. Med.,* 293 (1975) 161–166.

Sullivan, M.P., Moon, T.E. and Trueworthy, R., Combination intrathecal therapy for meningeal leukemia: two versus three drugs. *Blood,* 50 (1977) 471–479.

Tung, J.P. and Maibach, H.I., The pratical use of methotrexate in psoriasis. *Drugs,* 40 (1990) 697–712.

Von Hoff, D.D., Penta, J.S., Helman, L.J. and Slavik, M., Incidence of drug-related deaths secondary to high-dose methotrexate and citrovorum factor administration. *Cancer Treat Rep.,* 61 (1977) 745–748.

Webster, G.F., Razsi, K., Sanchez, M. and Shupack, J.L., Weekly low-dose methotrexate therapy for cutanuous sarcoidosis. *J. Am. Acad. Dermatol.,* 24 (1992) 451–454.