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Stability and compatibility of 2.5 mg/ml methotrexate solution in plastic syringes over 7 days

A. Jacolot[a], Ph. Arnaud[a,*], D. Lecompte[c], S. Alamercery[d], E. Caroff[a], C. Naveau[b], Th. Guillot[c], M. Bousselet[c], F. Brion[a]

[a]*Hôpital R. Debré AP-HP, Service Pharmacie et Laboratoire de Toxico-pharmacologie, 48, boulevard Serurier, 75019 Paris France*
[b]*Hôpital du Mans, Service Pharmacie, 194, avenue Rubillard, 72000 Le Mans France*
[c]*Laboratoires Lederle, B.P. 58, 69922 Oullins cedex France*
[d]*C.N.R.S., Service Central d'Analyse, BP 22, 69390 Vernaison France*

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Abstract

The physico-chemical stability and the compatibility between a 2.5-mg/ml methotrexate solution and plastic syringes were studied over a 7 day period at +4 and 25°C. During this study, pH was determined and MTX degradation products were assayed by HPLC. The compatibility study consisted of the titration of reducing substances, TLC of extracted additives, assay of extracted ions by AAS, resistivity measurement, dynamometric test and UV, visible and IR absorption spectrophotometry. Stability and compatibility studies showed that 2.5 mg/ml methotrexate parenteral solution remained chemically stable in a plastic syringe over a period of 7 days under the tested conditions.

Keywords: Methotrexate; Stability; Plastic compatibility

1. Introduction

The necessity to provide reconstituted parenteral drugs early (for use during week-ends) requires rigorous stability and compatibility studies. Methotrexate, a folic acid antagonist widely used in cancer chemotherapy, is administered intrathecally for the treatment or/and prophylaxis of meningeal leukaemias. In vitro thermal and photolytic degradation kinetic studies of methotrexate parenteral solutions have been reported (Chatterji and Galleli, 1978; Hansen et al., 1983; Lorillon et al., 1992). A 1-mg/ml methotrexate parenteral solution mixed with cytarabine and hydrocortisone sodium succinate in several infusion fluids, kept in a disposable syringe at 20°C, was found stable over a period of 24 h (Cheung et al., 1984). At a concentration of 50 mg/ml, methotrexate parenteral solutions when stored in sealed plastic syringes protected from light at a temperature not exceeding 20°C were found stable for a period of up to 8 months (Wright and Newton, 1988). Infusion solutions of methotrexate can be prepared in PVC (Viaflex®

* Corresponding author.

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minibags), frozen immediately at −20°C, and stored for at least 3 months (Dyvik and Grislingaas, 1986). Methotrexate parenteral solutions, stored in glass and plastic containers, were found to be stable. Chen and Chiou, 1982 showed that the extent of adsorption was solvent- and concentration-dependent; the aqueous solution had no adsorption problem. Compatibility studies of methotrexate parenteral solutions in plastic syringes meet two obstacles: sorption of drug on the intravenous delivery systems (disposable plastic syringes); and leaching of plastic components or additives from the studied materials into the methotrexate parenteral solutions. The first point of interest is sorption of drugs on plastic materials (often plastic infusion containers) which has been observed for several drugs (Benvenuto et al., 1981). Until now, few reports have been published on drug sorption on plastic syringes. The second point of interest in compatibility/stability studies is the analysis of traces of plastic components or additives extracted by methotrexate parenteral solutions. In two commercially available disposable syringes, a contaminant (2-(2-hydroxyethylmercapto) benzothiazole) has already been found and identified in the extractive parenteral solutions (Petersen et al., 1981). Our procedure used several tests (Airaudo et al., 1987; Billon et al., 1990) to verify this ability to extract plastic components or additives. One commercially available parenteral dosage form of methotrexate is a 2.5 mg/ml parenteral solution (Ledertrexate, 5 mg/2 ml, injectable solution, Lederle Companies, France). Compatibility/stability of this parenteral solution was tested during our studies. Centralized preparation of these products in a hospital pharmacy avoids toxic effects for manipulators.

Data published do not fulfil our requirements. We have studied the stability of 2.5 mg/ml methotrexate parenteral solutions over a 7-day period (D0, D1, D2, D3, D4, D7) in 10-ml plastic syringes (Becton Dickinson, Grenoble, France) at 4 (two assays) and 25°C (one assay). Methotrexate and its degradation compounds were assayed on three syringes per day and with three different methotrexate dosages extracted per syringe. Syringes containing 2.5 mg/ml methotrexate parenteral solution were stored protected from light at two different temperature conditions (4 ± 2 and 25 ± 2°C). Compatibility studies were performed under different conditions after contact of plastic syringes with 2.5 mg/ml methotrexate parenteral solutions and compared to methotrexate placebo solutions.

2. Materials and methods

Methotrexate parenteral solution (2.5 mg/ml): Ledertrexate, 5 mg/2 ml, injectable solution, Lederle Companies, Oullins, France. Methotrexate placebo solution: 8.6 g of sodium chloride in 1000 ml purified water adjusted to pH 8.3 ± 0.1 with 0.01 N NaOH solution. Methotrexate reference stock solution (0.25 mg/ml of known purity (92.27%) (Lederle Companies, Oullins, France)) was prepared in the mobile phase (phosphocitrate buffer (17.9 g sodium hydrogen phosphate anhydrous and 7.775 g citric acid monohydrate in 1 liter of purified water), pH 6.5/acetonitrile, 92:8 v/v). The HPLC analysis was performed on a Beckman Gold System apparatus (Beckman, Gagny, France) equipped with a piston pump (Beckman Module 126) delivering the mobile phase at a flow rate of 1.2 ml/min into a 250 × 4.6-mm Spherisorb® ODS-1 C_{18} column (Interchim, Paris, France). Prefilter (2 μm) (Beckman, Gagny, France) was replaced each week. An autosampler (Sedex 100, Sedere, Touzart et Matignon, Vitry/Seine, France) with a 20 μl loop was used. The column effluent was monitored at 302 nm by a UV spectrophotometric detector (module 166, Beckman, Gagny, France). The detector signal was computerized and integrated by the System Gold Program Beckman. Dynamometric tests allowed to evaluate possible modifications of sliding power after contact of the 2.5 mg/ml methotrexate parenteral solutions and methotrexate placebo solutions with plastic syringes. Sliding power is the ratio between work (W) and length of displacement (L). The Lhomargy apparatus (Lhomargy, DY20, Paris, France) is a 20 N captor and a syringe fixation system. The syringe plunger was pushed by the compression rod. The sliding force (F in Newton) was calculated by the ratio $F = W/L$. The work

Table 1
Ledertrexate (mg/ml) stored in syringe at +4°C (Assays 1 and 2) and at 25°C (Assay 3) during 7 days

		D0	D1	D2	D3	D4	D7
Assay 1	Mean	2.449	2.493	2.456	2.427	2.480	2.516
	CV (%)	0.79	0.62	1.85	1.59	5.46	3.19
Assay 2	Mean	2.453	2.497	2.537	2.525	2.490	2.584
	CV (%)	0.87	0.85	1.40	3.96	1.38	0.83
Assay 3	Mean	2.479	2.468	2.476	2.520	2.473	2.474
	CV (%)	1.69	1.25	1.53	1.13	1.33	0.68

was measured by the area under the curve (AUC) of the plotting. The length (L) of displacement was read on the 'X axis' of the plot.

3. Results and discussion

Methotrexate parenteral solution (2.5 mg/ml) is stable and compatible over 7 days when stored at 4 and 25°C in the tested plastic syringes (Table 1). No pH variation (8.1 $\pm$ 0.17) and no loss of organoleptic character modification were observed after 7 days storage. Determination of reducing substances and characterization of additives were compatible with the European Pharmacopoeia guidelines. Na^+, Ca^{2+} and Zn^{2+} ion concentrations were inferior to the detection limits of the atomic absorption spectrometric method (0.5 ppm around). If ionized compound extraction from the syringe into the content had occurred, values of resistivity would have decreased. The ionization degree of the methotrexate solution placebo was too high (low resistivity) for the sensitivity of the apparatus. Dynamometric tests allowed to characterize the type of force used to eject the solution with the plunger (Table 2). The results showed an initial resistance which appeared during the detachment of the plunger, and a regularity of forces during the ejection of the liquid. These reactions were not specific. No modification of the results was obtained for the different storage or accelerated stability conditions. The ultraviolet and visible absorption spectra showed the absence of extractable components from plastic syringes in methotrexate parenteral solutions. Infrared absorption spectra showed that polyethylene syringes are coated by a silicone oil layer without any significant absorption of methotrexate.

Table 2
Dynamometric test: methotrexate placebo solution after 1 h of contact with a 10-ml three-piece syringe at 25°C (D0T25), methotrexate placebo solution after 24 h of contact at 50°C with syringe (D1T50), methotrexate placebo solution after 7 days of contact with a 10-ml three-piece syringe at 25°C (D7T25)

	W (10^{-2} J)	l (10^{-2} m)	F (N)
DOT25			
Mean	13.4	5.3	2.5
CV (%)	9	2	11
D7T25			
Mean	11.3	5.4	2.0
CV (%)	13	4	13
D1T50			
Mean	10.7	5.4	2.0
CV (%)	17	4	18

4. Conclusion

According to our results, 2.5-mg/ml methotrexate parenteral solutions packed in plastic syringes and used for intrathecal injections remain chemically stable when stored for up to one week at room temperature.

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