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Stability of a highly concentrated solution of epirubicin for conventional transcatheter arterial chemoembolization

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ABSTRACT

Introduction: Epirubicin is widely used for conventional transcatheter arterial chemoembolization (cTACE) in patients with hepatocellular-carcinoma. However, there is no data about its stability in solution at concentration higher than 2 mg/L, yet needed when mixing it with a standard volume of Lipiodol® to produce an efficient water-in-oil emulsion. The aim of this study was therefore to evaluate the stability of a highly concentrated solution of epirubicin for cTACE and verify whether epirubicin solution could be prepared in advance.
Materials and methods: Fifty milligrams of epirubicin were dissolved in 6 mL of 0.9% sodium chloride and conditioned in brown polypropylene syringe. Physical and chemical stability assays including particles and HPLC-DAD analysis were performed in triplicate, using series of 5 syringes stored over 72 h at 4 ± 2 °C followed by 4 h at 22 ± 4 °C.
Results: Neither weight loss nor pH or spectrum change occurred. No haze or turbidity was observed and the number of subvisible particles was below the recommended limits. Epirubicin concentration remained above 95% of the initial value over the 72 h of storage at +4 °C followed by 4 h at 22 ±4 °C and no degradation was observed.
Conclusion: Epirubicin at 50 mg/6 mL in 0.9% NaCl conditioned in brown propylene syringe is stable for at least 72 h at 4 ±2 °C with additional 4 h at 22 ±4 °C allowing its preparation in advance for programmed cTACE and the standardization of its use in clinical practice.

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1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide (Murata et al., 2013). Since classical HCC (moderately-differentiated type) tumors receive nutritional blood flow mainly through the hepatic artery, trans-arterial chemoembolization (TACE) is proposed as nonsurgical palliative treatment for selectively deliver chemotherapy and embolic material to the tumor vascular bed, while sparing the surrounding hepatic parenchyma. Conventional TACE (cTACE) is performed in interventional radiology departments (IRD) and consists of the injection of a water-soluble anti-cancer drug along with Lipiodol® as water-in-oil type therapy that can be distributed according to the vascularity of the tumor, followed by the administration of an embolizing agent, such as gelatin sponge (Marelli et al., 2007). Despite the recent development of drug-eluting beads, which appeared to be better tolerated but more expensive and no more effective than cTACE, cTACE remains defined as the first-line therapy of unresectable HCC with an improved 2-year survival rate compared to best supportive care (Forner et al., 2014).

It is assumed that improved pharmacokinetic outcomes of cTACE are obtained by adjusting the mixing volume of Lipiodol® and highly concentrated anticancer drug solution to a 2–3:1 ratio (Lipiodol®/anticancer drug solution) (Shin, 2009). This requires dissolving a high dose of the drug in a small volume of aqueous solution (5–7.5 mL) before mixing it with a standard volume of

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Lipiodol® (10–15 mL) through the use of a pumping method to prepare an emulsion, which needs to be injected immediately (Idée and Guiu, 2013). Among anticancer drugs employed in cTACE, epirubicin (an epimer of doxorubicin), is commonly used at a median dose of 50 mg in treating advanced HCC worldwide (Marelli et al., 2007). But epirubicin is only commercialized as a 2 mg/mL solution or as a lyophilized formulation that have to be reconstituted with sodium chloride solution to achieve a similar final concentration. In fact, there is no data about its stability at higher concentration. Moreover, the reconstitution of lyophilized epirubicin implies being in adequacy with regulation requiring it to be performed in the hospital pharmacy according to the good practices of sterile reconstitution of the cytotoxic drugs. This constraint raises the dual problem of (i) the stability over time of the highly concentrated epirubicin solution from the end of preparation in the pharmacy to its used in the IRD and (ii) the delayed time of the cTACE procedure when the patient is admitted.

The aim of this study was therefore to evaluate the stability of a highly concentrated solution of epirubicin and verify whether the preparation can be performed in advance for a programmed cTACE.

2. Materials and methods

2.1. Drugs

Epirubicin hydrochloride (Farmorubicine®), supplied by Pfizer (New York, NY, United States), the only pharmaceutical product of epirubicin available in powder form, was employed as vial containing 50 mg of epirubicin mixed with 10 mg of methyl parahydroxybenzoate (methylparaben) and 250 mg of lactose, to prepare High Performance Liquid Chromatography (HPLC) quality controls (Batch 8Y6026-B) and samples required for the stability study (Batch 8Y60191). Epirubicin hydrochloride that does not contain methyl parahydroxybenzoate and lactose (Epirubicin Ebewe®, Batch 12551304) was supplied by Sandoz (Holzkirchen, Germany) as a solution of 100 mg of epirubicin hydrochloride in 50 mL sodium chloride 0.9% and was used for HPLC calibration.

2.2. Preparation of epirubicin solution

Syringe containing highly concentrated epirubicin solution for cTACE was prepared in a pharmaceutical isolator (Ref. N1000 4SSB, JCE Biotechnologies, Hauterive, France), in a controlled atmosphere area, according to the French Good Practices for Preparation of Medicinal Products in Pharmacies (Guideline of the French National Agency for Medicines and Health Products Safety, July 2007). Fifty milligrams of epirubicin hydrochloride lyophilized powder were reconstituted in 6 mL of 0.9% sodium chloride achieving a final concentration of 8.33 mg/mL. Epirubicin solution was then conditioned in a brown 50 mL polypropylene syringe (Ref. 300869, BD Medical, Le Pont-de-Claix, France). Immediately after filling, each syringe was closed with a female luer lock polypropylene cap (Ref. OBTFB, Didactic, Etainhus, France) and put in a sterile bag that stops UV radiations (Ref. SRUV2000, JCE Biotechnology, Hauterive, France).

2.3. Design of the stability study

A series of 5 syringes was prepared. A first syringe was analysed immediately after preparation (see below). Three other syringes were stored undisturbed at 4 ± 2 °C for 24, 48 or 72 h before analysis. Temperature conditions of storage were monitored and recorded using a temperature measuring probe (Thermo-client Ref. V3.2.2.4, Oceasoft, Montpellier, France). In addition, a fifth syringe was stored at 4 ± 2 °C for 72 h and then maintained at room temperature 22 ± 4 °C for 4 h before analysis. These conditions were intended to simulate those found in pharmaceutical and clinical practice, prior to administration to patient. Series of five syringes was prepared in triplicate and all syringes were analyzed.

Table 1
Physical stability assays.

Time (h)	Clarity	Degree of opalescence	Particulate contamination	Turbidity (absorbencies) Mean [CI 95%]		Weight of filled syringes (g) Mean [CI 95%]	% of initial weight
0		No more pronounced than reference suspension I	No visible mobile undissolved particles	350 nm	0.030 [0.029;0.031]	51.65 [50.36;52.94]	100.0
	No haze			410 nm	0.054 [0.051;0.057]		
	No precipitate			530 nm	0.099 [0.093;0.105]		
24	No change in appearance	No more pronounced than reference suspension I	No visible mobile undissolved particles	350 nm	0.031 [0.030;0.032]	51.92 [50.68;53.16]	100.5
	No haze			410 nm	0.055 [0.055;0.055]		
	No precipitate			530 nm	0.103 [0.101;0.105]		
48	No change in appearance	No more pronounced than reference suspension I	No visible mobile undissolved particles	350 nm	0.031 [0.030;0.032]	51.72 [50.38;53.06]	100.1
	No haze			410 nm	0.054 [0.052;0.056]		
	No precipitate			530 nm	0.101 [0.095;0.107]		
72	No change in appearance	No more pronounced than reference suspension I	No visible mobile undissolved particles	350 nm	0.031 [0.030;0.032]	52.02 [49.99;52.05]	100.7
	No haze			410 nm	0.055 [0.053;0.057]		
	No precipitate			530 nm	0.101 [0.098;0.104]		
72 + 4	No change in appearance	No more pronounced than reference suspension I	No visible mobile undissolved particles	350 nm	0.030 [0.029;0.031]	52.02 [49.99;52.05]	100.7
	No haze			410 nm	0.054 [0.051;0.057]		
	No precipitate			530 nm	0.100 [0.094;0.106]		

Fifty milligrams of epirubicin were reconstituted in 6 mL of NaCl 0.9% and stored in brown polypropylene syringe for 24, 48, 72 h at 4 ± 2 °C or 72 + 4, *i.e.* 72 h at 4 ± 2 °C and additional 4 h at 22 ± 4 °C before assays (see Section 2). CI: confidence interval.

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