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RESEARCH ARTICLE

STABILITY OF INTRAMUSCULAR INJECTION OF ERTAPENEM COMBINED WITH LIDOCAINE STORED IN POLYETHYLENE SYRINGES AT 4 ºC AND -20ºC

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ABSTRACT

Ertapenem is beta-lactam-type antibiotic with an exceptionally broad spectrum of activity, demonstrating broad-spectrum antimicrobial activity against many Gram-positive and -negative aerobes and anaerobes and is resistant to nearly all beta-lactamases. Ertapenem mixed with lidocaine can be administered intramuscularly, of great value as an outpatient antimicrobial therapy. However, the stability of this mixture has never been studied over time. The objective of this study was to evaluate the stability of 1g of ertapenem diluted in a 1% aqueous solution of lidocaine hydrochloride in a total volume of 3,2 mL stored in polyethylene syringes at 4ºC and -20ºC. Each preparation was analyzed using nuclear magnetic resonance method at the following time points: 0, 11 and 28 days. Dilutions were also observed for changes in appearance was tested at each time point. Syringes stored at -20ºC did not lead to any observable decomposition byproducts at least on day 11. Nevertheless, conservation at 4ºC for 11 days led to observed degradation byproducts in the solution.

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INTRODUCTION

Ertapenem is a group I carbapenem antibioticstructurally related to beta-lactam antibiotics. Its pharmacological properties allow an administration of one dose per day. It shares a common action mechanism with penicillins and cefalosporins as a bactericide blocking the bacterial cellular wall by means of blocking the penicillin binding proteins (PBPs). (Paterson *et al*., 2005; European Agency for the Evaluation of Medicinal Products, 2004) Ertapenem is secure and effective in adults with complicated intraabdominal infection (CII), acute pelvic infection (API), complicated urinary tract infection (cUTI) and skin and soft tissue infection (SSTI), including infections in diabetic foot, (Lipsky *et al*., 2005) and community acquired pneumonia (CAP). (Majumdar *et al*., 2002) It is also an effective antibiotic in profilaxys of surgesry associated infection after colorectal surgery. (Itani *et al*., 2006) The dose of ertapenem in adults and adolescents (13 to 17 years of age) is 1 gram (g) given once a day by the intravenous route. Infants and children (3 months to 12 years of age) the dose of ertapenem is 15 mg/kg given twice daily (not to exceed 1 g/day) by the intravenous route. Ertapenem is only commercially available in glass vials, each vial contains 1.0 g powder for concentrate for solution for infusion. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR) Another commercialized cabapenem have dosage regimen of every 8 hours or every 6 hours. Ertapenem is the only available for use carbapenem intramuscularly, representing a comfort for patients need home treatment. In clinical practice a great number of patients can continue ertapenem treatment at home with 1g or 500 miligrams (mg) every 24 hours given it is not necessary an intravenous administration. This is possible because ertapenem offers a simplified administration regime with intramuscular dosiffication available. There is only one recent clinical assay demonstrating ertapenem security and

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tolerability profiles with intramuscular (IM) administration of 1 g reconstituted in 1% lidocaine in a final volume of 3,2 mL. (Pedro Legua *et al*., 2002) Notwithstanding there are no available studies describing the physical-chemical stability of this mixture, l*et al*one it has been studied the physical-chemical stability during a prolonged conservation time. Our goal was to demonstrate the physical-chemical stability of this ertapenem and lidocaine combination over a long period (at least 28 days) to facilitate ambulatory use and decrease the time of hospital admission. To accomplish this we have analyzed an aqueous solution of lidocaine hydrochloride 1% mixed with ertapenem 1g, stored in polyethylene syringes at 4ºC and -20ºC during a period of 28 days. The selected analytical technique was Nuclear Magnetic Resonance (NMR). NMR is the gold standard for the structural analysis of organic compounds. This spectroscopical analytical tool is conventionally used in drug identification, but might as well be used in order to measure the extent of degradation of a given substance. This can be done by comparing the spectroscopical signal with that of an internal standard, as outlined in the International Conference on Harmonisation guidelines Q1A(R2) (www.fda.gov/downloads/regulatoryinformation/guidances/ucm128204.pdf) and Q3B (R2). (www.fda.gov/downloads/regulatoryinformation/guidances/ucm128204.pdf) Notwithstanding, the United States Pharmacopeia (USP) analytical methods are to be easily affordable, which is not the case of NMR, an expensive and high skilled tool. For this reason, NMR spectroscopy is commonly used only in case other easier and cheaper methods are not valid for a particular purpose. (Cardona *et al*., 2003) Studies demonstrate that NMR spectroscopy is an instrumental technique with analytical performance similar to reference methods like gas or liquid chromatography, and is recommended by the USP for drug stability studies. (Fernández-Ginés *et al*., 2016) Thus, the secondary aim of this work is to describe the possibilities of NMR in pharmaceutical analysis. (Iwona Wawer, 2008)

MATERIALS AND METHODS

Sample preparation

Commertial Ertapenem glass vials (Invanz® 1 g, Laboratoire Merck Sharp & Dohme – Chibret (Mirabel), France.) were reconstituted with a solution prepared with 3,2 mL of 1% lidocaine prepared from 40 mg of lidocaine hydrochloride (Acofarma, Barcelona, Spain.) in 4 mL of deuterated water. The solution was passed through a 0,22-µm microfilter (Millipore, Madrid.). This mixture was portioned in 0,5 mL aliquots and put into 6 polyethylene syringes with a sterile closing cap (Fresenius Kabi AG, Germany). The syringes were randomly divided in two groups of 3 syringes refrigerated at 4ºC and at -20ºC. All the samples were prepared under sterile conditions in a horizontal laminar airflow cabinet (Telstar BH10, Terrasa, Spain).

Physical assessment

Samples were visually inspected for particulate matter, clarity, and color changes. This inspection was conducted against a light background and without instruments or magnification.

NMR analysis

Proton nuclear magnetic resonance (^{1}H-NMR) spectra of the samples were acquired on a Bruker AVANCE III HD 600MHz® spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany). A capillary filled with hexadeuterated DMSO (DMSO-d6) was inserted into each NMR tube to obtain a lock signal. All NMR experiments were performed at room temperature. The first measurement was recorded immediately after mixing and then on day 11 and 28 of storage at both temperatures (4ºC and -20ºC). Characteristic ^{1}H signals were

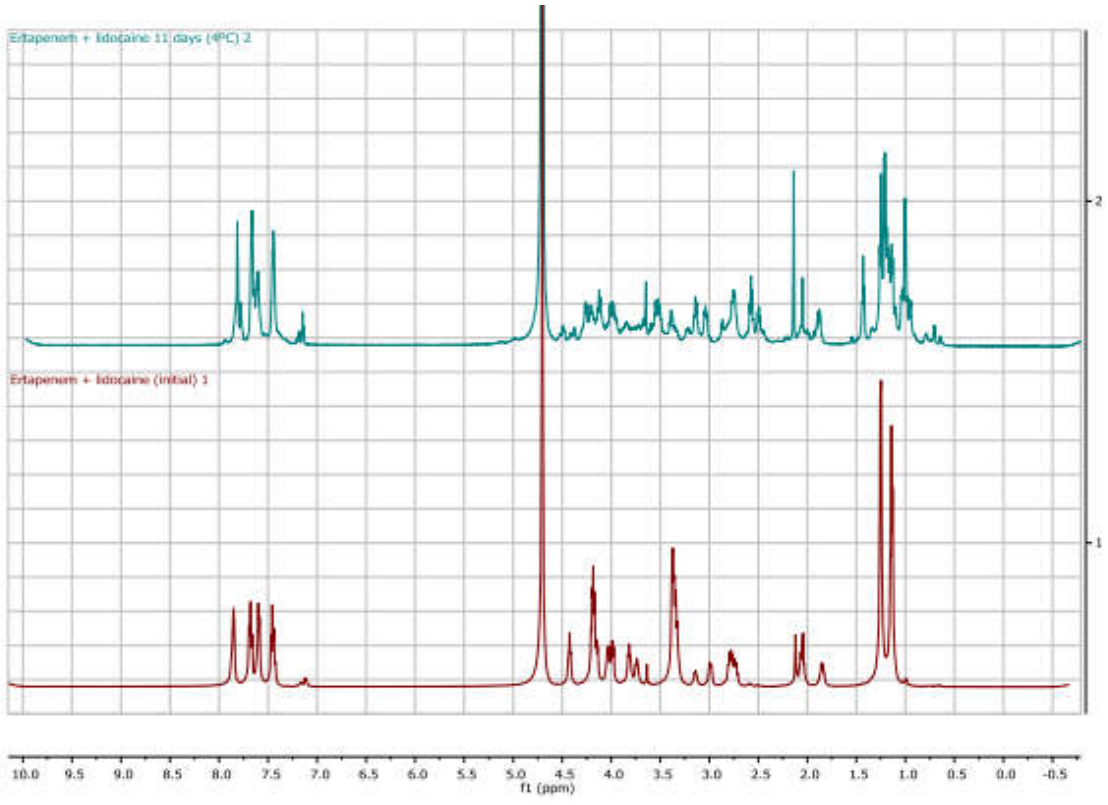

Figure 1. Bottom spectrum shows the mixture at initial time. Top spectrum shows the same after 11 days at 4ºC with visible byproduct formation

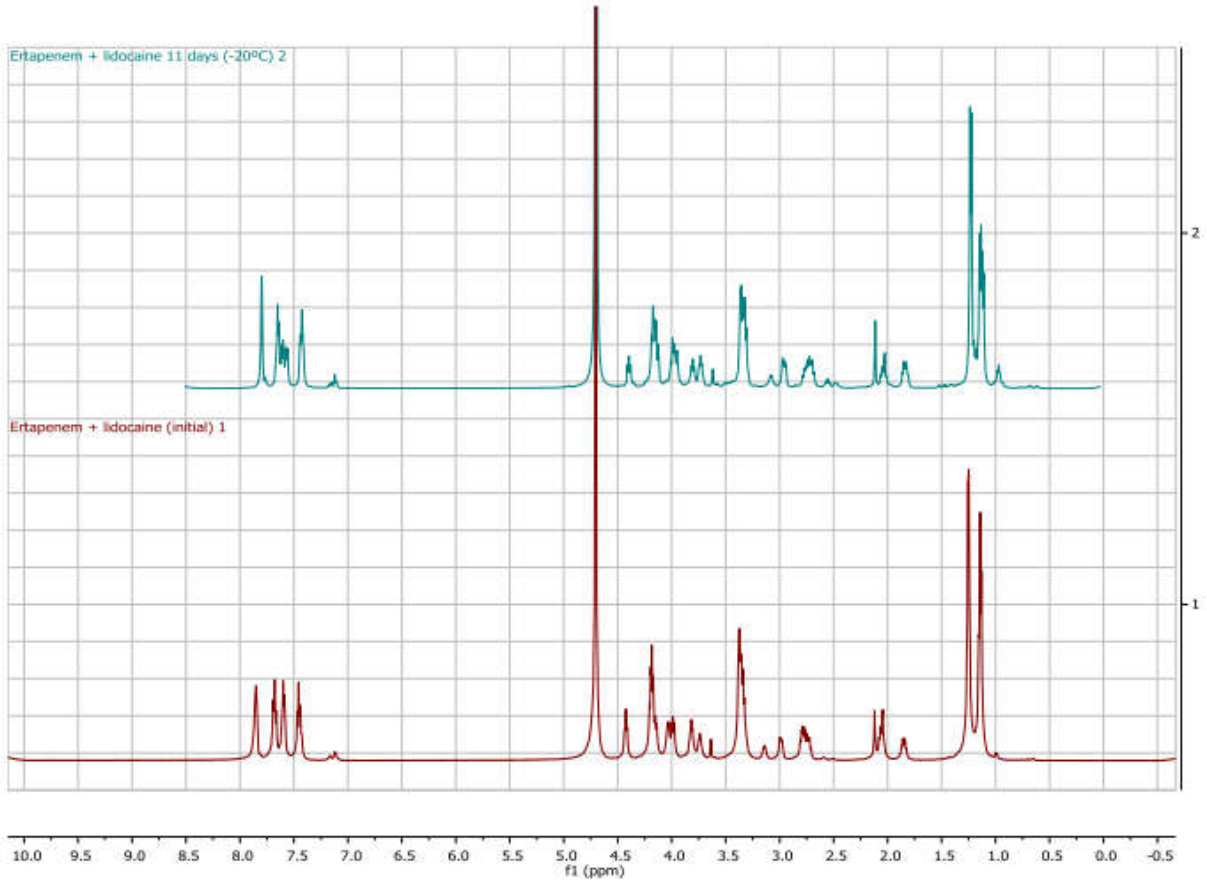

Figure 2. Bottom spectrum shows the mixture at initial time. Top spectrum shows the same after 11 days at -20ºC. All signals are compatible with the chemical structures of both compounds and remain unchanged

obtained for both compounds, with signals of lidocaine being 3% of those of ertapenem.

RESULTS AND DISCUSSION

The physical inspection of the samples revealed a darkening of color in those days maintained at 4ºC. Only the samples kept at -20ºC were colorless along the storage. The NMR analysis demonstrated that several byproducts appeared in the sample stored at 4ºC on day 11 (Figure 1) and at -20ºC on day 28, while that stored at -20ºC remained unchanged until day 11 (Figure 2). The findings of this study can be very useful for home patients that have to prepare a customized dose of ertapenem. This fractionation can be made in pharmacy services for hospitals, assuming a patient greater safety. In addition, it could represents a savings for the national health system. Our results demonstrate that a mixture of 1g of ertapenem diluted in a 1% aqueous solution of lidocaine hydrochloride in a total volume of 3,2 mL and stored in polyethylene syringes at -20ºC did not lead to any observable decomposition byproducts at least on day 11. The integrity of both molecules is maintained unchanged from both the physical and chemical points of view until day 28. Nevertheless, conservation at 4ºC for 11 days led to observed degradation byproducts in the solution.

Conclusion

The mixture of 1 g of ertapenem solution with 1% lidocaine hydrochloride in a total volume of 3,2 mL was stable when stored in polyethylene syringes for up to 11 days at -20 °C.

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