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ORIGINAL ARTICLE

Development of a Fourier transform infrared spectroscopy coupled to UV-Visible analysis technique for aminosides and glycopeptides quantitation in antibiotic locks

Développement d'une technique analytique par spectroscopie infrarouge à transformée de Fourier couplée à l'UV-Visible pour la quantification des aminosides et des glycopeptides dans les verrous antibiotiques

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Drug assay

Summary Antibiotic Lock technique maintains catheters' sterility in high-risk patients with long-term parenteral nutrition. In our institution, vancomycin, teicoplanin, amikacin and gentamicin locks are prepared in the pharmaceutical department. In order to insure patient safety and to comply to regulatory requirements, antibiotic locks are submitted to qualitative and quantitative assays prior to their release. The aim of this study was to develop an alternative quantitation technique for each of these 4 antibiotics, using a Fourier transform infrared (FTIR) coupled to UV-Visible spectroscopy and to compare results to HPLC or Immunochemistry assays. Prevalidation studies permitted to assess spectroscopic conditions used for antibiotic locks quantitation: FTIR/UV combinations were used for amikacin (1091—1115 cm^{-1} and 208—224 nm), vancomycin (1222—1240 cm^{-1} and 276—280 nm), and teicoplanin (1226—1230 cm^{-1} and 278—282 nm). Gentamicin was quantified with FTIR only

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(1045—1169 cm^{-1} and 2715—2850 cm^{-1}) due to interferences in UV domain of parabens, preservatives present in the commercial brand used to prepare locks. For all AL, the method was linear (R^2 = 0.996 to 0.999), accurate, repeatable (intraday RSD%: from 2.9 to 7.1% and interdays RSD%: 2.9 to 5.1%) and precise. Compared to the reference methods, the FTIR/UV method appeared tightly correlated (Pearson factor: 97.4 to 99.9%) and did not show significant difference in recovery determinations. We developed a new simple reliable analysis technique for antibiotics quantitation in locks using an original association of FTIR and UV analysis, allowing a short time analysis to identify and quantify the studied antibiotics.

MOTS CLÉS
Amikacine ;
Gentamicine ;
Vancomycine ;
Téicoplanine ;
Infrarouge à transformée de Fourier ;
IRTF ;
UV-Visible ;
Verrous antibiotiques

Résumé Les verrous antibiotiques de vancomycine, téicoplanine, amikacine ou de gentamicine sont des préparations hospitalières fabriquées en pharmacie à usage intérieur. Elles permettent de maintenir la stérilité des cathéters des patients sous nutrition parentérale à haut risque infectieux. Afin de garantir leur qualité et de se conformer aux exigences réglementaires, ces préparations sont soumises à des contrôles qualitatifs et quantitatifs avant leur libération. L'objectif de ce travail était de mettre au point une technique permettant de quantifier séparément chaque antibiotiques en utilisant la spectroscopie infrarouge à transformée de Fourier (IRTF) couplée à l'UV-Visible et de comparer les résultats à ceux obtenus par technique CLHP ou par immunochimie. Une première étude de pré-validation a permis de définir les conditions spectrales à utiliser dans l'analyse quantitative de chaque principe actif : couplage IRTF/UV pour l'amikacine (1091—1115 cm^{-1} et 208—224 nm), vancomycine (1222—1240 cm^{-1} et 276—280 nm) et téicoplanine (1226—1230 cm^{-1} et 278—282 nm), et l'IRTF seule (1045—1169 cm^{-1} et 2715—2850 cm^{-1}) pour la gentamicine, en raison de l'interférence dans le domaine de l'UV des parabens présents dans la spécialité de départ. L'étude de validation analytique a permis d'établir dans ces conditions pour les 4 molécules que la technique était linéaire (R^2 : 0,996—0,999), juste (CV% : 2,9—5,1 %), répétable (CV % : 2,9—7,1 %) et précise. Comparée à la CLHP ou l'immunochimie, la technique IRTF/UV montre des corrélations variant de 97,4 à 99,9 %. La nouvelle technique d'analyse ainsi développée est simple, fiable, rapide et associe une utilisation originale de l'IRTF couplée à l'UV-Visible permettant l'analyse qualitative et quantitative des 4 molécules étudiées.

Introduction

Central and peripheral venous catheters are essential for patients needing dialysis, cancer chemotherapy and parenteral nutrition [1—3]. It is estimated that more than 12,000 catheter-related blood stream infections are occurring annually in hospitalized-patients infections and mortality rate associated with the infections is 10—20% [4]. Their frequency and their management depend mainly on catheter's type, infecting organism and the patient's status. The main threat remains the systemic infection that can be limited by systemic antibiotic treatment, catheter's removal, or the Antibiotics Locks (AL) treatments [5,6]. AL treatments consists of filling the lumen of the catheter with antibiotics at concentrations 100- to 1000-fold higher than usual target systemic concentrations and allowing it to dwell for a period of time while the catheter is not in use in order to sterilize it, 24 h dwell time, or in parenteral nutrition 12 h every days during 14 days [1,7,8].

AL treatment technique is widely used in our institution, mainly with glycopeptides (vancomycin and teicoplanin) and aminosides (amikacin and gentamicin) locks. AL production is centralized in the hospital's pharmaceutical department. Locks consist in 2 mL prefilled sterile syringes with 2 to 8 mg/mL of glycopeptides or aminosides. Regarding regulatory and national Good Pharmacy Practices [9], AL batches are submitted prior to their use to quality controls, including AL concentration determination. Until recent date, assays were realized either with HPLC for vancomycin and gentamicin quantitation or immunochemical methods for teicoplanin and amikacin. These techniques are often time consuming and not cost-effective. Hence, we searched for a faster cost-effective method offering enough sensitivity and specificity to be applied easily in routine hospital pharmaceutical practice. Aminosides and glycopeptides have complex structures, consisting often in a blend of more than one component. While vancomycin [10,11], amikacin [12,13] and teicoplanin [14,15] are mainly constituted of one main component (Fig. 1A—C), gentamicin contains 4 major components (Fig. 1) [16,17]. Major and minor components are positional often isomers, have the same backbone and differ slightly in term of chemical structure and spectroscopic properties. This allows us to exploit the spectral proximity and attempt to set up an assay to quantify the components of one antibiotic without having to separate them.

To achieve this, we decided to combine two spectroscopic techniques, a tandem of Fourier Transform Infrared spectroscopy (FTIR) coupled to UV-Visible spectrophotometry, to improve the specificity and even sensitivity assays. [18]. The aim of this work was then to develop and validate an alternative quantitation method for these 4 antibiotics, using FTIR/UV-Visible multispectral analysis. The developed