Determination of Meropenem Stability Over 8 Hours in the Marketed Brands

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ABSTRACT

Meropenem is a Carbapenem antibiotic having a broad spectrum of activity against the majority of Gram negative, Gram positive, and anaerobic bacteria. Recently, carbapenemase-producing bacteria (Klebsiella pneumonia and Acinetobacter bomanii) have emerged showing resistance to all carbapenems including Meropenem. The treatment of critical infections caused by such microorganisms has become challenging to Infectious Diseases Specialists throughout the globe. The Meropenem continuous IV infusion protocol showed better pharmacodynamics profile which increases effectiveness of Meropenem for the treatment of such infections. In the present study, we have developed a UV-spectrophotometric protocol for the determination of Meropenem stability after reconstitution with Normal Saline at room temperature. We have also compared the stability of different Meropenem brands present in the Lebanese market as compared to the Originator product Meronem®(Astrazeneca™). During the 3 hours interval, only Meronem® & Aropem® have been stable, where as the rest showed more than 10% degradation. During the 8 hours interval, all Meropenem brands have showed a much greater than 10% degradation.

Introduction

Beta-lactam antibiotics are still the most common of antimicrobials used in the treatment of bacterial infections[1]. Meropenem is a Carbapenem antibiotic having a broad spectrum of activity against the majority of Gram negative, Gram positive, and anaerobic bacteria. It is Chemically named (4R,5S,6S)-3- [[(3S,5S)-5-dimethylcarbamoyl pyrrolidin-3-yl]- Thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylic acid[2]. Meropenem is more stable to human renal Dehydropeptidase-I (DHP-I) than Imipenem, thus it possesses a longer duration of action, and there is no need to associate a DHP-I Inhibitor (Cilastatin) to its formulation[3]. It has played a major role in the treatment of critical infections like intra-abdominal infections, bacterial meningitis, complicated skin & skin structure infections, lower respiratory tract infections, complicated urinary tract infections, gynecologic infections and septicemia. Recently, carbapenemase-producing bacteria *(Klebsiella pneumonia and Acinetobacter bomanii)* have emerged having resistance to all carbapenems including Meropenem. The treatment of critical infections caused by such microorganisms has become challenging to Infectious Diseases Specialists throughout the globe. After numerous researches to overcome this challenge, a new protocol was developed which consists of continuously infusing the Meropenem dose over 3-8 hours[4]. However, carbapenems are known to have low stability after dissolution, hence aroused the debate about the exact duration of infusion of this antibiotic to have maximal therapeutic outcome. Meropenem stability after reconstitution has been shown to be affected by the concentration of the resultant solution, the ambient temperature, and the time after reconstitution[5,6,7]. The European Pharmacopeia (EP), British Pharmacopeia (BP) and the United States Pharmacopeia (USP) recommend the UV absorbance assay for the identification of Meropenem[2,8,9]. In the present study, we have developed a UV-spectrophotometric protocol for the determination of Meropenem stability after reconstitution with Normal Saline at room temperature. We have also compared the stability of different Meropenem brands present in the Lebanese market together with the percentage of the Active Ingredient as compared to the Originator product Meronem® (Astrazeneca™).

Materials & Methods

Instrumentation

All experiments were conducted using Genesys 10S UV-Vis Spectrophotometer (Thermo Scientific™) and 1cm Quartz cuvettes.

Tested Samples

Our samples included Meropenem formulations from 5 different brands:

- Comparator formulation: Meronem® 1g vial (Astrazeneca™) – Lot nb. GY499.
- Meropenem® 1g vial (Hospira™) – Lot nb. 601C068B.
- Meropenem® Labatec 1g (Labatec Pharma™) – Lot nb. 0002D1.
- Ropenem® 1g vial (BPI™) – Lot nb. 7002.
- Aropem® 1g vial (Arwan™) – Lot nb. 010003.

Stability Testing

Meropenem 1g vials were reconstituted with 20ml of Normal Saline. 1ml was withdrawn and diluted with NS in a 100ml volumetric flask to get a concentration of 0.5mg/ml. Then, 1ml was withdrawn from the resultant solution and diluted with 100ml NS in a 100ml volumetric flask to get a testing concentration of 5 µg/ml. 50ml were transferred into a 50ml syringe pump connected to a 150cm extension tube and an IV catheter to exactly mimic the conditions in which Meropenem is used in the hospital. The rate of IV infusion was set at 6ml/hr. Samples were withdrawn from the IV catheter at the following time intervals: T0, T0.5, T1, T2, T3, T4, T5, T6, T7, & T8.

UV Spectroscopy

Withdrawn samples were scanned for absorbances at wavelengths ranging from 190 to 400nm at a reading interval of 1nm with special focus at the 200nm wavelength for stability testing because the latter wavelength is considered as a reference for stability/purity testing of the Active Meropenem quantity before degradation[10].

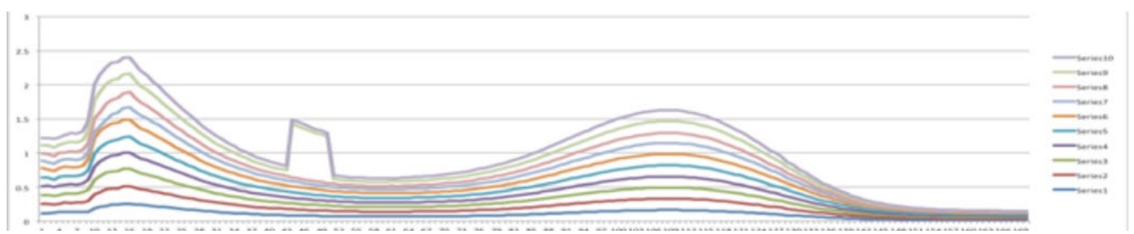
Results

The scanning absorbances of the five different Meropenem brands are shown in Figure 1.

At the wavelength of 200nm, degradation was calculated from the corresponding absorbance values from T0 to T8 for each brand of the Meropenem formulation. The percentage of Meropenem degradation over 3 and 8 hours in each product was calculated. Please refer to the following Table 1.

Product	% Deg. 3hrs	% Deg. 8 hrs
Meronem®	6.25	19.14
Aropem®	8.04	22.19
M.Hospira®	12.76	21.27
M.Labatec®	22.99	42.59
Ropenem®	19.13	26.51

Table 1. *Percentages of degradation of Meropenem over 3 hours and 8 hours in each of the five different brands.*



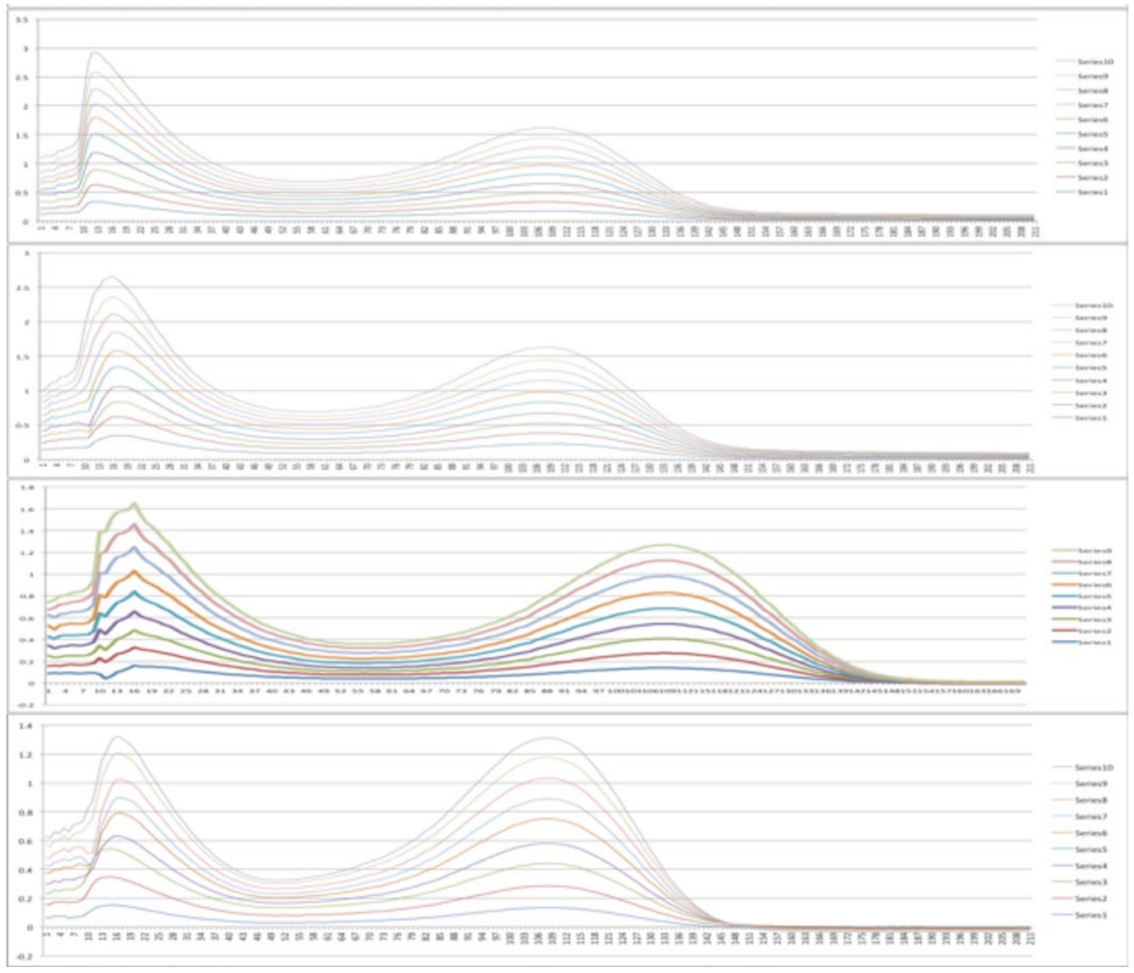


Figure 1. *Scanning curves of Meronem® (First), Aropem® (Second), Meropenem Labatec® (Third), Meropenem Hospira® (Fourth), & Ropenem® (Fifth). These curves show the pattern of Meropenem degradation with time. The highest curve corresponds to T0 (Series 10), while the lowest curve corresponds to T8 (series 1).*

Discussion

We have used a stability working concentration of 5 µg/ml which is a very low concentration compared to the concentrations used clinically (20mg/ml). So, we should expect a lower stability profile of Meropenem in clinical practice. Meropenem is considered to be stable if there is degradation of no more than 10% of the original amount. During the 3 hours interval, only Meronem® & Aropem® have been stable, where as the rest showed more than 10% degradation. At the 8 hours interval, all Meropenem brands showed a much greater than 10% degradation, thus it is considered unstable over 8 hours at room temperature. Meropenem degradation increases with time, temperature, and concentration. After thorough analysis of our results during the 8 hours interval, we can conclude that Meropenem is stable for a maximum of 4 hours after reconstitution and dilution with Normal Saline. After examining the graphs in Figure 1, we can conclude that only Ropenem® has a different pattern of absorbance values even at T0, that may be due to a difference in the raw material processing. All others four brands show an almost similar graph, however, absorbance values throughout the tested time tend to be higher with Meronem®, Aropem®, & Meropenem Labatec®.

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Infos

Obésité: Un Anticorps Trouble la Régulation de l'Appétit

De nombreuses formes d'obésité sont liées à une prise alimentaire trop importante appelée hyperphagie. Que ce dérèglement soit d'origine psychologique, génétique ou environnementale, les mécanismes physiologiques à l'œuvre restent mal connus. Des chercheurs de l'unité INSERM «Nutrition, inflammation et dysfonction de l'axe intestin-cerveau» de l'Université de Rouen pensent qu'un anticorps présent dans le sang joue un rôle clé. Avec des collègues japonais de l'université de Kagoshima, ils présentent leur théorie, étayée par des expériences menées sur des souris, dans un article publié vendredi dans la revue "Nature Communications".

En théorie, après une période de surabondance alimentaire, un système complexe de régulation de l'appétit doit conduire une personne «normale» à manger moins. Chez beaucoup de personnes obèses, ce mécanisme semble défectueux: alors que le rapport entre réserves et besoins est déjà très déséquilibré, ils continuent à ressentir une grande sensation de faim. Pourtant on ne retrouve pas dans leur sang, comme on aurait pu s'y attendre, de taux plus important de ghréline, l'hormone de la faim qui agit sur l'hypothalamus pour stimuler l'appétit. Ce taux est même parfois légèrement plus bas que la normale. Une situation tout à fait paradoxale.

Un type d'anticorps présent dans le sang, les immunoglobulines, permettraient d'apporter une réponse élégante à cette apparente énigme. Ces molécules ont en effet «des propriétés différentes chez les patients obèses», explique Sergueï Fetissov, principal auteur de l'étude. «Elles ont une «attirance» plus forte pour la ghréline que celles observées chez des sujets de poids normal ou chez des patients anorexiques. Cette différence d'«affinité» conduirait à transporter un plus.