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Comparative Instabilities and Release of Colored Products from Original and Generics of Meropenem When Prepared in Concentrated Solutions for Prolonged Infusion to Patients

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Abstract (abridged)

Background and Aims
Economic pressures and legal requirements often force Hospital Pharmacies to purchase antibiotics based on minimal cost acquisition considerations (and to select generics) without real analytical capabilities for checking key quality properties of the chosen product(s). Meropenem is known for its limited stability in concentrated solutions [1], which may create uncertainties if using extended or continuous infusion [2] in environments with no efficient temperature control. Our aim was to compare the stability of meropenem commercialized in Europe by the original market authorization holder (OMAH) and generic producers.

Methods
Meropenem (powder for infusion) was purchased from the OMAH (AstraZeneca [AZ]) and from 4 generic producers active in Europe (Sandoz, Hospira, Fresenius Kabi, Aurovit). Solutions were prepared at 1g/48mL and 2g/48mL in 0.9% NaCl (pharmaceutical grade) and incubated at 25, 30, and 37°C for 0, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h. Meropenem was detected as molecular ion with mass/charge ratio of 384/141.32 by LC/MS-MS (with ^{2}H]-meropenem as internal standard), and rates of disappearance (with 95% confidence interval) calculated using linear regression of all experimental points with initial value set at 100%.

Results
Meropenem degradation proceeded on a time-, concentration- and temperature-dependent fashion, together with the appearance of a yellow color. The full results are presented in the poster but can be summarized as follows: Sandoz and Fresenius Kabi generics degraded more rapidly when tested at the lowest concentration, and Sandoz generic produced a more important release of yellow product(s).

Conclusions
Meropenem from different sources vary in stability when tested in concentrated solutions, and some may generate more colored degradation products(s). Detailed analytical studies are required for proper comparison and rational choice amongst the various sources of meropenem offered for clinical use especially if extended or continuous infusion is used.

References

[1] MERREM IV® Product information (10/06) - http://goo.gl/dLpMPX
[2] Roberts et al. J Antimicrob Chemother 2009;64:142-50 PMID 19398460.
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[4] Mattoes et al. Clin Ther 2004;26:1187-98 PMID 15476901
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[7] European Pharmacopoiea 9th edition (version 9.2) available on line at http://online6.edqm.eu/ep902/

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Background

Meropenem is a broad spectrum carbapenem with useful activity against a number of organisms resistant to other antibiotics. Like all β-lactams, the time during which its concentration remains above the MIC of the offending organism is the main driver for activity and needs to be optimized. In this context, administration of meropenem by prolonged or even continuous infusion has been advocated [1-3].

Meropenem, as MERONEM® (the original branded product) has limited stability (approx. 5-6h) when prepared in concentrated solutions such as those used in Intensive Care Units for prolonged (3h) or continuous infusion [5,6]. No detailed information, however, is publicly available for generics. Since Hospital Pharmacies are increasingly forced to purchase generics due to economic pressure, and within the context of a EU-sponsored programme aiming at monitoring β-lactams serum concentrations in patients with nosocomial pneumonia, we undertook to compare 4 generics of meropenem to the original branded product for stability and visible release of degradation products.

Methods

1. ***Origin of products:*** MERONEM® (original product) was from AstraZeneca Belgium; generics were from Sandoz and Hospira (Belgium), Fresenius-Kabi (Belgium and France, and Aurovit (Spain), all being approved and presented for intravenous administration.
2. ***Preparation of products:*** Solutions were prepared at 1 and 2g/48mL in 0.9% NaCl (pharmaceutical grade), mimicking the procedure used in Intensive Care Units when using meropenem by prolonged or continuous infusion.
3. ***Treatments:*** solutions were incubated at 25°C, 30°C, 37°C for up to 8h with samples taken at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h.
4. ***Stability assessment:*** Meropenem was detected as molecular ion with mass/charge ratio of 384/141.32 by LC/MS-MS (with ^{2}H]-meropenem as internal standard). Determination of rate of decay was determined by linear regression with initial point (0 h) set at 100% and calculation of the 95% confidence interval (Prism 7.02).
5. ***Liberation of visible degradation product(s):*** as all samples turned yellow (but to different extent) during incubation, optical density at 8h was measured at 405 nm (based on preliminary spectrum analysis to detect optimal absorption wavelength).

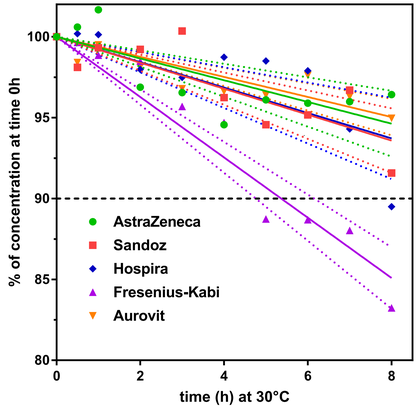
Main messages and Key Conclusion

- We confirm that meropenem is unstable in concentrated solutions, calling for caution when stored and/or used for infusion for more than 8h at temperature exceeding 25°C (see practical guide).
- Generics from Fresenius Kabi and Sandoz, are less stable than the original (MERONEM®) or the other generics tested. The Sandoz generic releases more colored product(s) than all other compound tested.

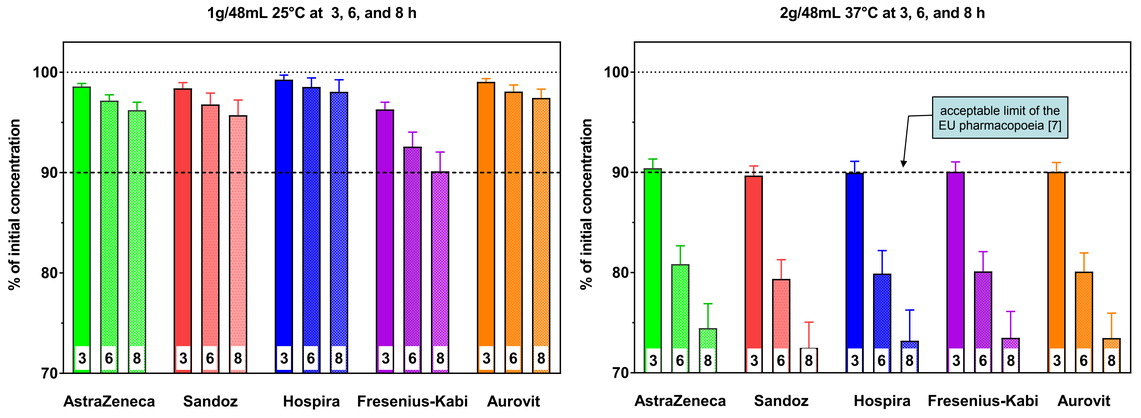
➢ **Detailed analytical studies beyond those giving legal rights of commercialization to generics of meropenem are needed to fully assess their quality when intended for use by prolonged or continuous infusion.**

Typical Results and Practical Guide

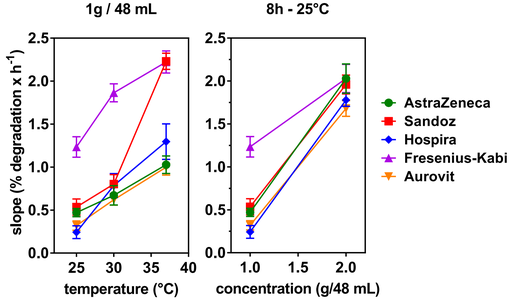
1. Typical degradation at 1g/48 mL and 30°C (95%CI)



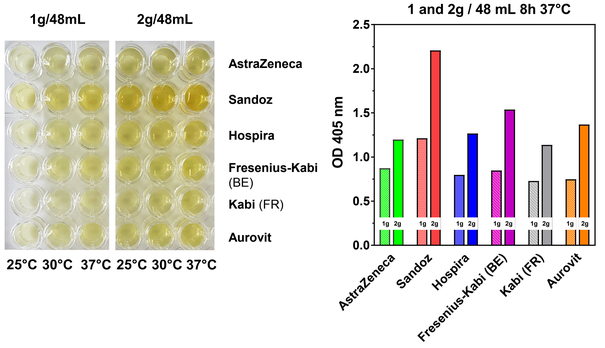
2. Stability at low and high concentrations and low and high temperatures



3. Influence of temperature and concentration



4. Release of colored degradation (?) products



5. A practical guide (ensuring > 90% stability)

1g /48 mL

Product	0.5-h inf.			3-h inf.			8-h inf.		
	25°C	30°C	37°C	25°C	30°C	37°C	25°C	30°C	37°C
AstraZeneca	✓	✓	✓	✓	✓	✓	✓	✓	✓
Aurovit	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hospira	✓	✓	✓	✓	✓	✓	✓	✓	xx
(Fresenius) Kabi	✓	✓	✓	✓	✓	✓	x	xx	xx
Sandoz	✓	✓	✓	✓	✓	✓	✓	✓	xx

2g /48 mL

Product	0.5-h inf.			3-h inf.			8-h inf.		
	25°C	30°C	37°C	25°C	30°C	37°C	25°C	30°C	37°C
AstraZeneca	✓	✓	✓	✓	✓	x	xx	xx	xx
Aurovit	✓	✓	✓	✓	✓	x	xx	xx	xx
Hospira	✓	✓	✓	✓	✓	x	xx	xx	xx
(Fresenius) Kabi	✓	✓	✓	✓	✓	x	xx	xx	xx
Sandoz	✓	✓	✓	✓	✓	x	xx	xx	xx

Key:	
OK	✓
Caution !	x
Don't do it !!	xx

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