Rational use of antibiotics

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CHAPTER 7

COLISTIN METHANESULFONATE INFUSION SOLUTIONS ARE STABLE OVER TIME AND SUITABLE FOR HOME ADMINISTRATION

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ABSTRACT

The stability of colistin methanesulfonate (CMS) was determined in quadruplicate in elastomeric home infusion pumps containing 1, 2 or 3 MU CMS and in infusion bags with 2 MU CMS all in 100 ml normal saline. Infusions were stored at room temperature (20°C–24°C) with or without exposure to natural light or refrigerated (4°C–8°C) and protected from light up to 2 weeks. In the initial solution of 2 MU CMS in 100 ml saline sampled immediately after reconstitution and dilution, 1.5% of CMS was hydrolysed to colistin. When stored at room temperature and exposed to natural light, colistin concentration in elastomeric infusion pumps increased to 2.6% in 8 days and to 2.1% when stored at 4°C. CMS stability increases at lower temperatures and higher concentrations. Based on the current data, chemical stability of CMS infusion solution is sufficient for a shelf life of 7 days refrigerated plus 1 day at room temperature.

INTRODUCTION

Colistin is an antibiotic used for the treatment of chronic infection with Gram-negative bacteria such as *Pseudomonas aeruginosa* which is the most common pathogen in cystic fibrosis (CF) lung disease. Colistin use by inhalation is widely practised for maintenance treatment. Due to increasing resistance of *P. aeruginosa* against other antibiotics, intravenous colistin can be incorporated in the treatment of exacerbations of CF lung disease.[1] Colistin is a multicomponent antibiotic, composed mainly of colistin A and colistin B.[2] For intravenous administration, colistin is marketed in the form of its inactive pro-drug colistin methanesulfonate (CMS), which hydrolyses *in vitro* and *in vivo* to active colistin.[3] Following intravenous administration of CMS, only a fraction is hydrolysed to colistin; preclinical and clinical studies have estimated that between 7% and 30% of CMS is converted to colistin.[4-6] The high variability regarding the extent of conversion might depend on differences in physiological processes and on factors related to storage conditions and administration of CMS infusions. In-depth knowledge of these factors is of importance as colistin has the potential to be used as prolonged maintenance (home) treatment, and colistin is known to be more toxic and causes more bronchial irritation compared with CMS.[3] A fatal complication with a CMS inhalation solution led to discussion about safety of in-advance prepared solutions of CMS.[7] Because of this, uncertainty has arisen about the stability and duration of storage of CMS solutions. Several studies have focused on the *in vitro* stability of colistin and CMS under different conditions, but these do not provide complete results.[8-11] Particularly, the stability of CMS in infusion bags was only studied for a period of 48 hours, which is a practical limitation for colistin if to be used in home treatment. In addition, CMS stability at room temperature and the influence of light have not been addressed. Therefore, extended *in vitro* stability testing of CMS is warranted. We tested stability during 14 days to cover a proposed shelf life of 8 days with a margin of more than 50%. A CMS concentration within the limits of 90%–110% at time of administration was used as the chemical stability specification. This paper reports stability data and the influence of temperature, concentration CMS and light on the *in vitro* stability of a standard CMS solution.

METHODS

In the current *in vitro* study, the stability of CMS was determined in infusion bags and elastomeric home infusion pumps at different concentrations and stored under different conditions, which were chosen to reflect clinically relevant conditions. Vials containing 1 MU CMS powder for infusion, corresponding to 80 mg CMS and 33.3 mg colistin, were used (Tadim, Profile Pharma, Chester, UK). These vials were reconstituted with 0.9% saline according to the summary of product characteristics. CMS was further diluted in 0.9% saline in infusion bags (100 ml, Baxter Viaflo) or elastomeric home infusion pumps (Intermate SV 200, Baxter) to achieve final concentrations of 800–2400 mg/l CMS. Infusions were stored at room temperature

(20°C–24°C) and exposed to natural light and protected from light, or refrigerated (4°C–8°C) and protected from light up to 2 weeks. Aliquots of the solution were sampled into 2 ml polypropylene tubes to determine in quadruplicate in the pH and the concentration of formed colistin after 0, 3 and 6 hours and after 1, 3, 8 and 14 days. Samples were stored at –80°C until analysis. Quantification of colistin A and colistin B was performed with an LC-MS/MS assay using polymyxin B1 and polymyxin B2 as internal standards (IS). Quantification was carried out after diluting all samples to 16 mg/l of CMS with 10% trichloroacetic acid at 4°C. The compounds were separated on a Zorbax EclipsePlus-C18 (2.1×50 mm, 1.8 µm) column, using a linear gradient with a binary mobile phase of 0.1% formic acid in highly purified water (A) and 0.1% formic acid in acetonitrile (B). A triple quadrupole mass spectrometer (Agilent Technologies 6460) was operating in the ESI positive mode, and the double charged molecular ion was used as the precursor ion. The transition ions were m/z 585.4/101.1 for colistin A, m/z 578.4/101.1 for colistin B, m/z 602.4/101.1 for polymyxin B1 (IS for colistin A) and m/z 595.4/101.1 for polymyxin B2 (IS for colistin B). Good linearity was achieved ($r^2 \geq 0.99$) for colistin and intraday variation was 3.6%. Colistin A plus colistin B were expressed as colistin, and the amount hydrolysed was expressed as percentage of CMS. Conversion into molar units was done by intermediate calculations using 1749.82, 1735.79, 1169.46 and 1155.43g/mol as the molecular masses of CMS A, CMS B, colistin A and colistin B (free bases), respectively.[12]

RESULTS

In the initial solution of 2 MU CMS in 100 ml saline sampled immediately after reconstitution and dilution, 1.5% of CMS was hydrolysed to colistin. When stored at room temperature and exposed to natural light, colistin concentration in elastomeric infusion pumps increased to 2.6% in 8 days and to 2.1% when stored at 4°C as depicted in *figure 1*. In infusion bags (2 MU CMS in 100 ml saline) at day 8, 1.7% of colistin was formed when stored at 4°C and 2.1% when stored at room temperature and exposed to natural light, 3.7% of CMS was hydrolysed in 8 days in a 1 MU CMS in 100 ml solution, in a 2 MU in 100 ml solution this was 2.6% and in a 3 MU in 100 ml solution 2.3% of CMS was hydrolysed. The ratio of colistin A to colistin B was determined to be 3.7:1 and remained stable over time (*figure 2*). When stored at room temperature and exposed to natural light, the pH in elastomeric infusion pumps (2 MU in 100 ml) increased from 7.77 to 8.35 at day 1 and decreased to 7.87 at day 14.

DISCUSSION

This *in vitro* study showed that CMS was converted to 1.5% free colistin immediately after reconstitution and dilution. Eight days of storage in elastomeric infusion bags containing 2 MU CMS in 100 ml infusion solution (0.9% saline) at room temperature lead to 2.6% hydrolisation of CMS to colistin. Similar CMS stability was observed for CMS solutions kept in natural light and protected from light. CMS was more stable at lower temperatures and at higher concentrations.[13]

In addition, there was slightly more colistin formation in elastomeric infusion pumps than in infusion bags as shown in *figure 3*. Minor changes in pH were observed, with pH values ranging between 7.77 and 8.35. We cannot exclude some colistin formation during the analytical process, but this appears to be limited to a maximum conversion to colistin of 1.5%. Therefore, the current data are representative for the CMS solution administered in the clinical setting.[14]

Wallace *et al*[9] found <4% of colistin after 48 hours at 25°C and 0.3% at 4°C in a 4000 mg/l solution of CMS in glucose or normal saline. These results show a higher level of colistin formation at room temperature and a larger difference in colistin formation between room temperature and 4°C than our results. In comparison with our data, we must keep in mind the differences in concentration (800–2400 mg/l in our study) and in analytical technique. The HPLC assay applied by Wallace was able to distinguish colistin from (partially) sulfated colistin, but in-between formed derivates could not be excluded. Our LCMS assay only included colistin A and colistin B in unsulfonated form; other derivates were excluded due to separation on differences in molecular mass. Furthermore, the source of CMS differed (Coly-Mycin M vs Tadim).

Abdulla *et al*[13] found no CMS degradation (<0.5%) after 3 days at 4°C and <5% after 7 days and concluded a CMS solution of 800 mg/l can be stored up to 3 days at 4°C.

Our data and the data of Wallace and Abdulla cannot explain colistin formation as possible cause of the unfortunate death of a patient after CMS inhalation, which lead to an FDA warning and a restraint against in advance preparation of CMS solutions. In current practice, however, there is a need for safe, in-advance preparation of an intravenous medicine for home therapy, which can only be fulfilled when sufficient stability data are available.

While the SPC of Tadim states a shelf life of 24 hours after reconstitution and dilution, and several dosing guidelines also indicate that CMS infusion solutions should be used within 24 hours, based on the current data, chemical stability of CMS infusion solution was sufficient for a shelf life of 7 days refrigerated plus 1 day at room temperature.[4-6,15]

These data support the administration of colistin using elastomeric home infusion pumps. The difference in colistin concentration immediately after preparation (1.5%) and after 8 days storage at room temperature (2.6%) was small, and the remaining CMS concentration was well within the specification of 90%–110%.[16] The formation of colistin was limited when compared with the reported *in vivo* conversion of 30%. Potential tolerability issues cannot be entirely excluded based on this *in vitro* study and should be monitored by pharmacovigilance in clinical practice.[6]

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FIGURE 1 Time course of colistin formation in elastomeric infusion pumps containing 2 MU colistin methanesulfonate in 100 ml 0.9% saline when stored under different conditions.

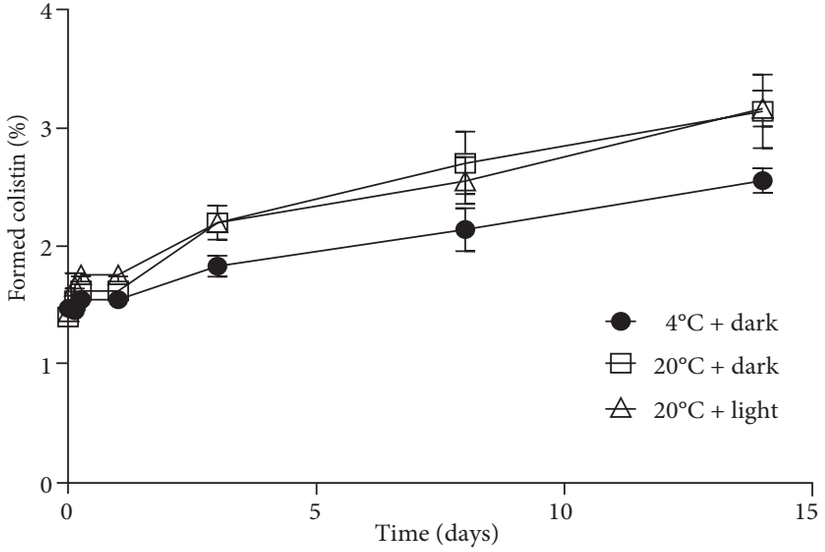

FIGURE 2 Time course of ratio colistin A to colistin B in elastomeric infusion pumps containing colistin methanesulfonate in 100 ml 0.9% saline when stored under different conditions.

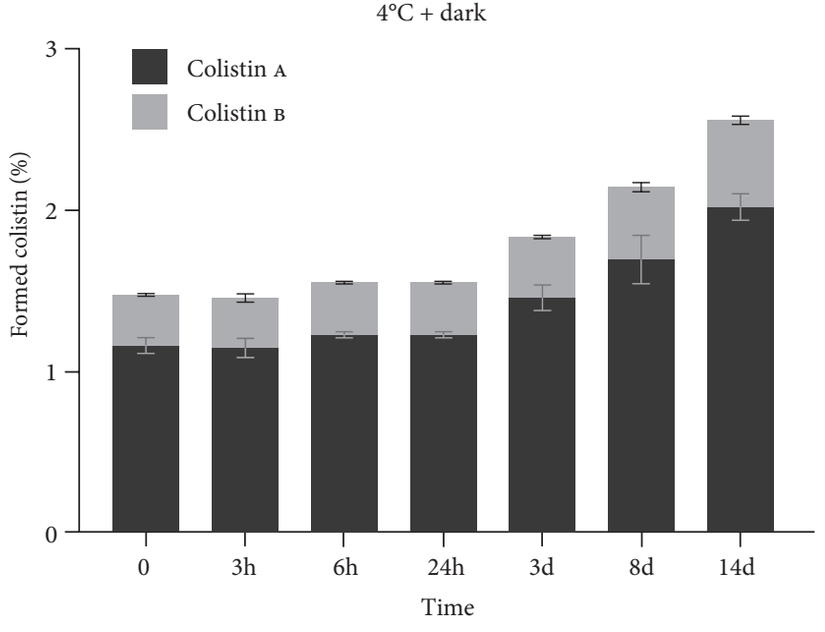

FIGURE 3 Colistin concentration 8 days after preparation (baseline delta) in elastomeric infusion pumps containing 1, 2 and 3 MU CMS in 100 ml 0.9% saline and in infusion bags containing 2 MU CMS in 100 ml 0.9% when stored under different conditions. CMS, colistin methanesulfonate.