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Stability of Colistimethate Sodium in Aqueous Solution

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Colistimethate sodium, increasingly used to treat multidrug-resistant Gram-negative infections, spontaneously hydrolyzes to form colistin A (polymyxin E1) and B (polymyxin E2/B) when mixed with water. High levels of these active breakdown products at the time of administration have been associated with nephrotoxicity and even death. In this study, reconstituted colistimethate sodium was shown to be stable (<1.0% colistin A/B formation) for up to 24 h when stored at 21, 0, –20, and –70°C.

Colistimethate sodium (CMS) is a decades-old drug which has recently reemerged out of necessity to treat multidrug-resistant infections (6). Colistimethate sodium is FDA approved for injection in the United States, and is increasingly being administered adjunctively via a nebulizer to treat pulmonary infections (7). Intravenously administered CMS fell out of use in the years following its FDA approval due to its association with serious adverse events, particularly nephro- and neurotoxicities. However, these concerns are likely attributable to a lack of understanding of the drug's pharmacokinetics and pharmacodynamics and resultant inappropriately high dosing (9). The concerns regarding intravenous use of CMS have generally been mitigated by comprehensive safety and pharmacokinetic studies performed in recent years (6). On the contrary, there are few randomized-controlled trials regarding the appropriate use of nebulized CMS.

Regardless of the route, CMS must be reconstituted prior to administration. It is supplied by all major manufacturers as a lyophilized powder comprised of a complex mixture of methane sulfonated derivatives. When mixed with water, colistimethate sodium undergoes spontaneous hydrolysis to a heterogeneous mixture of partial sulfomethyl derivatives but primarily to the active compounds colistin A (polymyxin E1 or colistin “base”) and colistin B (polymyxin E2 or B) (4, 5). Thus, a solution prepared in advance may hydrolyze and result in administration of elevated levels of colistin A and B. This was the basis for a 2007 FDA Alert after a patient died following inhalation of a solution of CMS which was suspected to have hydrolyzed *in vitro* (2). It was not clear whether CMS was reconstituted in saline or water in this instance or how long the mixture sat prior to administration. Current recommendations state that colistimethate sodium should be reconstituted no more than 24 h prior to administration to avoid toxicity (3).

Methods, results, and discussion. In the present study, the stability of colistimethate in sterile water while stored under different temperatures was assessed. Colistins A and B were measured by liquid chromatography tandem mass spectrometry (modified from the method in reference 8). Colistin sulfate (USP catalogue number 1480C) and polymyxin B (USP catalog number 157007, 100 µg/ml) were used as colistin and internal standards, respectively. Colistin A has a quantitation range of 2.0 µg/ml to 40.0 µg/ml, and colistin B has a quantitation range of 0.5 µg/ml to 10.0 µg/ml. Colistimethate for injection (APP Pharmaceuticals, Schaumburg, IL) was reconstituted, according to package instructions, with 2 ml of sterile water to yield a 75-mg-CMS/ml solution. After a sample was taken for time zero analysis, the solution was

then divided and stored at four different temperatures: 21, 0, –20, and –70°C. The samples stored at –20°C and –70°C were divided into smaller aliquots to ensure only a single freeze-thaw cycle was performed. Samples were analyzed after 4, 8, and 24 h in quadruplicate, and the results were averaged. Stability was expressed as the percentage of CMS that hydrolyzed to liberate colistin A and colistin B during storage. Colistimethate was shown to be stable (<1.0% total colistin A and B formation) under all the tested conditions (Table 1).

The stability of colistimethate sodium in aqueous solution observed may provide some reassurance to health care providers. Many (especially smaller) hospitals and clinical trial units use outside pharmacies, and providing a premixed drug in frozen intravenous piggyback (IVPB) bags may have logistical advantages. Additional storage options may also serve as an advantage for patients self-administering nebulized CMS at home. The data suggest that CMS can be reconstituted in water and stored at 21, 0, –20, and –70°C for up to 24 h with minimal accumulation of colistins A and B. Additionally, freezing and thawing the solution a single time does not appear to significantly affect hydrolysis. This brief study supplements data which indicate <0.1% colistin A formation when CMS is reconstituted in water for up to 1 week when stored at 4°C or 25°C (11). This study quantifies the levels of the two major CMS breakdown products: colistins A and B. Given that CMS and its associated breakdown products have various antibacterial activities, an understanding of their stability in aqueous solution is of benefit for interpreting pharmacokinetic/pharmacodynamic studies (5).

It is important to note that sterile water is the immediate diluent recommended by the major manufacturers. Reconstituted CMS stored in saline is significantly less stable (11). Colistimethate sodium is also unstable in human plasma (5), particularly at elevated temperatures, which accelerate hydrolysis in all storage media tested. Colistin sulfate (a topical) also hydrolyzes to form colistin A. When stored at –80°C for 6 to 8 months in human plasma, colistin sulfate undergoes up to 7% colistin A formation (1).

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TABLE 1 Concentrations of colistin A and B formed over time under different storage conditions

Time (h)	Colistin concn at storage temp (°C) of ^a :											
	-70			-20			4			21 (room temp)		
	A	B	Total %	A	B	Total %	A	B	Total %	A	B	Total %
0	3.94 ± 0.37	0.73 ± 0.06	0.62%	3.94 ± 0.37	0.73 ± 0.06	0.62%	3.94 ± 0.37	0.73 ± 0.06	0.62%	3.94 ± 0.37	0.73 ± 0.06	0.62%
4	4.13 ± 0.13	0.77 ± 0.07	0.65%	4.20 ± 0.26	0.73 ± 0.03	0.66%	4.46 ± 0.09	0.79 ± 0.04	0.70%	4.55 ± 0.46	0.81 ± 0.06	0.72%
8	4.32 ± 0.49	0.72 ± 0.04	0.67%	3.91 ± 0.23	0.68 ± 0.07	0.61%	4.50 ± 0.23	0.80 ± 0.02	0.71%	4.21 ± 0.41	0.84 ± 0.12	0.67%
24	4.15 ± 0.15	0.78 ± 0.09	0.66%	4.23 ± 0.15	0.81 ± 0.11	0.67%	4.322 ± 0.29	0.83 ± 0.06	0.69%	4.832 ± 0.55	0.958 ± 0.11	0.77%

^a Levels of colistin A (A) and colistin B (B) are expressed in µg/ml ± SD. Total %, total proportion of colistin A and colistin B in sample.

Taken together, these data suggest that CMS may be reconstituted in water and stored at a variety of temperatures prior to administration. Colder temperatures are recommended to minimize spontaneous hydrolysis. Importantly, the levels of colistins A and B which would result in acute toxicity have not been thoroughly investigated. Regardless of the preparation and storage technique, colistimethate sodium should always be prescribed in terms of colistin base activity and ideal body weight to minimize the risk of overdosing (2, 10).

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