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Review

Colistin loading dose: evaluation of the published pharmacokinetic and clinical data

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ABSTRACT

Colistin (polymyxin E) has been widely used since the beginning of the century as a last-option antibiotic for the treatment of patients with multidrug-resistant and extensively-drug resistant bacterial infections. However, colistin dosing is troublesome because each batch of the drug contains a mixture of components and because it is administered as the inactive pro-drug colistimethate sodium (CMS), which has different pharmacokinetic (PK) properties from the active drug. Significant inter-individual and intra-individual variability in colistin plasma concentrations have been observed in all available studies. Low plasma concentrations of the drug during the first hours from initiation of administration suggested that a loading dose would be appropriate. However, other PK studies challenge this approach. Clinical data from randomised controlled trials are not available, whilst data from observational studies do not support higher effectiveness of a loading dose. In this review, we summarise the available data regarding the administration of a loading dose and discuss the issues surrounding the potential advantages and disadvantages as well as the context within which such an approach could be beneficial to patients.

1. Introduction

Colistin (polymyxin E) has been widely used as a last-option antibiotic for patients with multidrug-resistant (MDR) and extensively-drug resistant (XDR) bacterial infections [1]. However, its effectiveness has been questioned, its safety was challenged, its pharmacokinetic (PK) parameters have been debated, and its dosing scheme is not standardised [doses between 3 million international units (MIU) to 12 MIU per day have been recommended] [2].

Colistin dosing is troublesome. First, being a fermentation product of *Bacillus polymyxa*, each dose contains a mixture of ca. 30 components, with colistin A and B accounting for up to 100% of the dose [3–5]. Most of the PK parameters of colistin A and B are similar (body clearance, volume of distribution, elimination half-life), but protein binding in rats was higher for colistin A than colistin B (65% vs. 48%), presumably due to its longer fatty acid chain [6]. Furthermore, in intensive care unit (ICU) patients, the fraction of colistin A bound to proteins was inversely associated with the colistin plasma concentration, whilst that of colistin B was constant (ca. 43%) [7]. These differences in lipophilicity of the subcomponents might affect the PK parameters of colistin brands/batches and ultimately the attainment of plasma levels. Whether these differences might also impact the antibacterial activity or the synergistic effects of the subcomponents is not known [3]. However, this may be true, as the activity and synergy of the polymyxin B components against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were different [8].

Second, owing to its toxicity (irritation and pain when administered intramuscularly and subcutaneously owing to the five free amine groups), colistin is administered as the inactive pro-drug colistimethate sodium (CMS). A different amount of amines becomes methylated in every molecule during CMS production, on which the rate of CMS hydrolysis depends, leading to disparities in the time to achieving therapeutic plasma concentrations when different amine groups are methylated [9]. Third, CMS and colistin have different PK properties. CMS is mainly excreted by the kidneys, whereas colistin is removed mainly by non-renal routes. Thus, in patients with high creatinine clearance (CL_{Cr}), CMS removal may be too fast to allow for adequate colistin plasma concentration to be achieved, and vice versa [10]. Finally, inter-individual and intra-individual variability in colistin plasma concentrations have been observed in all studies, suggesting that therapeutic drug monitoring may be required [10].

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On the other hand, colistin demonstrated rapid, concentration-dependent killing against *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* [11]. The PK parameter that best describes its activity is the time-averaged, free drug exposure [area under the free drug concentration–time curve (*f*AUC)] over the minimum inhibitory concentration (MIC) ratio (*f*AUC/MIC). *f*AUC/MIC values of 50–65 mg·h/mL have been associated with bactericidal activity against *P. aeruginosa*, which correlate on average with colistin plasma concentrations two-fold higher than the pathogen's MIC [12,13]. Newer data suggest that depending on the site of the infection and the offending pathogen, the *f*AUC/MIC could be as low as 12 mg·h/mL in the thigh and as high as 48 mg·h/mL in the lungs, corresponding to steady-state plasma concentrations of 1 μg/dL and 4 μg/dL, respectively [14].

Using liquid chromatography–tandem mass spectrometry (LC–MS/MS) [15,16], several studies showed that colistin either did not achieve adequate (i.e. above the bacterial MIC) concentrations in plasma or tissues [17,18] or in order to do so required up to 48 h [19,20]. However, any delay in time to antibiotic administration has been associated with increased mortality [21]. Thus, following the publication of studies depicting an improvement in colistin initial plasma concentration with higher initial doses, experts concluded that there is good evidence for initiating colistin therapy with a loading dose [10]. The European Medicines Agency (EMA) endorsed recommendations for a 9 MIU loading dose in critically ill patients only, but the US Food and Drug Administration (FDA) has not made any changes to its recommendations [22,23]. Administration of a loading dose has become common practice in several countries, including the USA [24].

A loading dose appears a reasonable option for all the good reasons and, at least theoretically, a higher initial dose would assist in eradicating bacteria in a more timely manner and prevent the development of resistance. Here we will review the evidence regarding a colistin loading dose. Unless otherwise stated, the colistin concentration refers to plasma values [24].

2. Pharmacokinetic data (Table 1)

A loading dose was originally considered for drugs with a long half-life that require more treatment days to achieve steady-state. However, since delayed administration of antibiotics and fluctuating or suboptimal antibiotic concentrations during the first treatment days have been associated with worse clinical outcomes and development of resistance (high bacterial inocula, higher probability for resistant subpopulations at the beginning of the infection), attention was given to the administration of loading doses even for antibiotics with shorter half-lives [13,25–27].

In general, the magnitude of the loading dose is proportional to the volume of distribution (V_d) and the desired antibiotic concentration; it is not influenced by renal function. For a hydrophilic agent such as colistin, the predicted V_d during sepsis is usually large (increase in extracellular volume due to fluid administration and increased permeability of the endothelium). The desired concentration depends on the MIC of the causative microbe [27]. Therefore, with increasing V_d and MIC, the required loading dose would be higher.

Plachouras et al showed that following administration of 3 MIU of CMS, almost none of the ICU patients achieved a colistin concentration >1 mg/L within the first 8 h [20]. Modelling these observations, the authors predicted that a CMS loading dose of 9–12 MIU would significantly improve initial colistin concentrations [20]. Based on these findings and using Monte Carlo simulations, Garonzik et al (measurements of colistin concentrations were not performed after the initiation of colistin administration but only at steady-state) concluded that the loading dose required to rapidly achieve the desired colistin concentration was a function of the patient's weight (the lower of ideal or actual) [dose of colistin base activity (CBA) (mg) = colistin average steady-state plasma concentration ($C_{ss,avg}$) target × 2.0 × body weight (kg)] and that maintenance dosing should be initiated 24 h after the loading dose owing to concerns for nephrotoxicity [19].

These suggestions were studied in two subsequent studies in Greek patients. A CMS loading dose of 6 MIU improved colistin concentrations at 8 h (mean 1.34 mg/L, range 0.37–2.59 mg/L), but still only 3 of 10 recruited patients achieved a concentration >2 mg/L at 8 h and 5 patients achieved a concentration >1 mg/L [7]. Additional modelling showed that the higher the loading dose, the faster the bacterial killing for a wild-type *P. aeruginosa* strain with a MIC of 1 mg/L. However, due to the inter-individual variability observed in colistin disposition, it was predicted that only a 12 MIU loading dose would allow for adequate colistin concentrations for an individual achieving a low colistin concentration. The authors recommended 'a loading dose of 6 to 9 MIU in critically ill patients' [7].

In another study, a 9 MIU CMS loading dose was administered in 19 ICU patients. The maximum colistin concentration after the loading dose (mean 2.65 mg/L, range 0.95–5.1 mg/L) was achieved 8 h later, but concentrations of 1 mg/L and 2 mg/L were predicted after 1.6 h and 4 h, respectively. Specific data on the number of patients achieving the goal of plasma concentration >1 mg/L or >2 mg/L were not provided. For the first time, colistin concentrations were above the breakpoints (i.e. 2 mg/L) after the first dose [5]. Inter-individual and intra-individual variability continued to be present, albeit lower than in previous studies, but still some patients did not reach the desired level of 1 mg/L. The most concerning finding of these two studies was that the loading dose achieved one of the desired goals, i.e. higher concentrations, but at least 4 h after infusion initiation [5,7].

In contrast to the aforementioned studies, in a French study of 73 ICU patients the rationale for a loading dose was challenged [28]. Following a CMS dose of 2 MIU, predicted colistin concentrations reached 3 mg/L within 3 h from initiation of the infusion, 5 times higher and 16 times faster than observed in the study by Plachouras et al [20]. The inter-individual variation in colistin concentration remained. A study performed in India reported higher colistin concentrations (median 4.6 mg/L, range 2.5–23.2 mg/L) following a 2 MIU first dose and the levels were achieved near the end of the infusion. Fifteen young, low-weight ICU patients with intact renal function were included. Differences in the methodology were observed compared with other studies [29]. Data from patients with cystic fibrosis as well as healthy, young, non-obese male volunteers also support that maximum colistin concentrations can be achieved at 2–5 h following the first dose, but the reported maximum concentrations varied [30–32].

Several differences between the French and Greek studies are worth mentioning. The common features in the studies including Greek patients were median/mean body weight of ca. 80 kg, inclusion of patients with mainly preserved renal function and use of the same colistin brand. On the other hand, the non-Greek studies enrolled patients with variable body weight and renal function and they used different colistin brands. For example, a different CMS brand was used in the Greek studies (Colistin; Norma) and the French study (Colimycine; Sanofi-Aventis). The use of different brands may have contributed to the interstudy discrepancies. In support of this view, a study in rats reported that different brands may result in different colistin exposure [9]; however, none of the Norma or Sanofi-Aventis brands was evaluated in this study. Invoking unpublished data, Karaiskos et al commented that 'in a comparison of CMS from six different providers in plasma in vitro, we have, however, observed that colistin formation was slow for all six brands, including the brand used by Grégoire et al, with similar rates and extents of colistin formation' [5].