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Polymyxins for CNS infections: Pharmacology and neurotoxicity

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ABSTRACT

Central nervous system (CNS) infections caused by multi-drug resistant (MDR) Gram-negative bacteria present a major health and economic burden worldwide. Due to the nearly empty antibiotic discovery pipeline, polymyxins (i.e. polymyxin B and colistin) are used as the last-line therapy against Gram-negative 'superbugs' when all other treatment modalities have failed. The treatment of CNS infections due to multi-drug resistant Gram-negative bacteria is problematic and associated with high mortality rates. Colistin shows significant efficacy for the treatment of CNS infections caused by MDR Gram-negative bacteria that are resistant to all other antibiotics. In particular, MDR *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* which are resistant to expanded-spectrum and fourth-generation cephalosporins, carbapenems and aminoglycosides, represent a major therapeutic challenge, although they can be treated with colistin or polymyxin B. However, current dosing recommendations of intrathecal/intraventricular polymyxins are largely empirical, as we have little understanding of the pharmacokinetics/pharmacodynamics and, importantly, we are only starting to understand the mechanisms of potential neurotoxicity. This review covers the current knowledge-base on the mechanisms of disposition and potential neurotoxicity of polymyxins as well as the combined use of neuroprotective agents to alleviate polymyxins-related neurotoxicity. Progress in this field will provide the urgently needed pharmacological information for safer and more efficacious intrathecal/intraventricular polymyxin therapy against life-threatening CNS infections caused by Gram-negative 'superbugs'.

1. Introduction

1.1. Gram-negative 'superbugs': no magic bullets left?

The need for new antibiotics and the innovative use of current therapeutics to address antibiotic resistance was recently recognised as an urgent global health issue by the World Health Organisation (WHO), Infectious Diseases Society of America (IDSA), Centers for Disease Control and Prevention (CDC) and the Australian National Antimicrobial Resistance Strategy (Boucher, et al., 2013; Organization, 2017, Organization, 2016, 2013). As highlighted by the IDSA in the 'Bad Bugs, No Drugs' paper, "as antibiotic discovery stagnates, a public health crisis brews" (Boucher, et al., 2013). The situation is especially worrying with MDR *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*), against which no new antibiotics will be available for many years to come (Braine, 2011). WHO has placed these three problematic pathogens at the top of its '2017 Antibiotic-resistant Priority Pathogens List' (Organization, 2017). Clinicians worldwide are increasingly confronted with the reality of infections with Gram-negative pathogens that are resistant to all antibiotics, except polymyxins (Velkov, Roberts, Nation, Thompson, & Li, 2013).

Polymyxins (Fig. 1) were discovered in the 1950s, but were never subjected to contemporary drug development procedures. The clinical use of polymyxins waned in the 1970s, because the early experience in

Abbreviations: BBB, blood-brain barrier; CMS, colistin methanesulphonate; CNS, central nervous system; CSF, cerebrospinal fluid; ITH, intrathecal; IVT, intraventricular; MDR, multi-drug resistant

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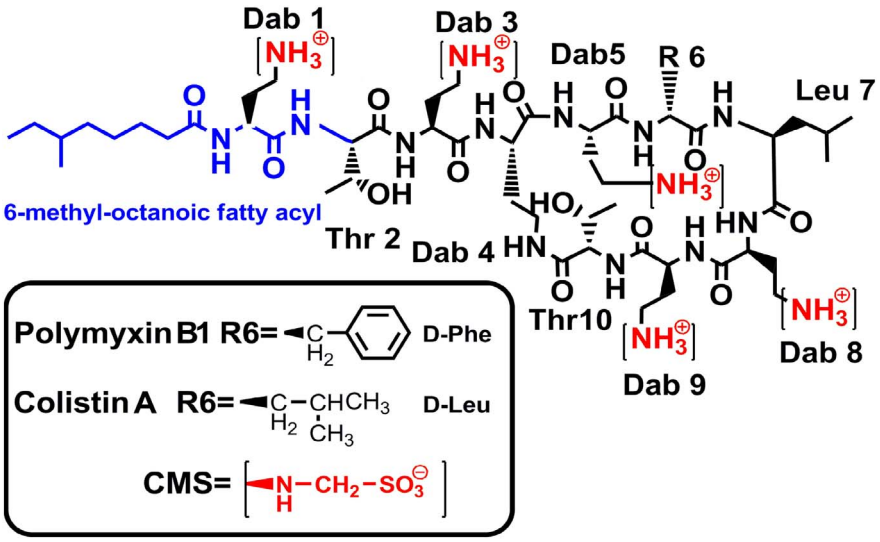

Fig. 1. Structures of polymyxin B, colistin and colistin methanesulphonate (CMS). Thr: threonine; Leu: leucine; Phe: phenylalanine; Dab:α,γ-diaminobutyric acid.

the 1960s with intravenous administration resulted in numerous cases of nephrotoxicity, which caused significant concern and thus newer antibiotics became first line treatment (Li et al., 2006). Recently, there has been a greatly renewed interest in the clinical use of polymyxins, because the three aforementioned very problematic Gram-negative pathogens are often resistant to all other antibiotics. Unlike polymyxin B which is available in the clinic as the sulphate salt, colistin is administered to patients as an inactive prodrug, colistin methanesulphonate (CMS) (Bergen, Li, Rayner, & Nation, 2006; Nation, Velkov, & Li, 2014; Nation et al., 2017). The current polymyxin resistance rate is low; however, resistance can emerge in patients because of suboptimal exposure with intravenous administration due to dose-limiting nephrotoxicity (Nation et al., 2014; Nation et al., 2017; Velkov et al., 2013).

From our recently completed multi-centre multi-national study on the pharmacokinetics/pharmacodynamics/toxicodynamics (PK/PD/TD) of colistin in critically-ill patients, it is evident that the currently recommended intravenous dosage regimens are suboptimal (Nation et al., 2017). In the majority of patients, it was not possible to achieve a colistin plasma concentration of 2.5 mg/L, which is required for effective bacterial killing based on our PK/PD data (Cheah et al., 2015; Nation et al., 2017; Sandri et al., 2013). Notably, a very large proportion of patients experienced nephrotoxicity, regardless of whether colistin concentrations were above or below 2.5 mg/L. We have observed a similar inability to achieve adequate concentrations of polymyxin B in critically-ill patients (Sandri et al., 2013). It is now evident that nephrotoxicity is the major dose-limiting factor impacting the effective clinical use of polymyxins. The consequences caused by suboptimal intravenous polymyxins are even more significant in the treatment of CNS infections, since very low brain penetration represents an additional limiting factor when polymyxins are administered parenterally.

2. Intrathecal and intraventricular polymyxins for CNS infections

CNS infections caused by MDR *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* are particularly difficult to treat, since as discussed above, only a small proportion of the intravenous polymyxin dose can reach the infection site (Antachopoulos et al., 2010; Jimenez-Mejias et al., 2002; Markantonis et al., 2009; Ziaka et al., 2013). Consequently, high intravenous doses are required to achieve bacterial killing. However, due to extensive renal tubular reabsorption, severe nephrotoxicity has been frequently reported in up to 60% of treated patients, even with the current intravenous dosage regimens (Nation et al., 2014, 2017; Sandri et al., 2013). Thus, peripheral administration in case of CNS infection is neither effective nor safe. The intrathecal (ITH, via the lumbar cistern of the spinal canal) or intraventricular (IVT, via insertion of a catheter into the lateral ventricle of the brain) delivery of antibiotics bypasses the blood-brain barrier (BBB); and are commonly used clinical procedures (Remeš, Tomáš, Jindrák, Vaniš, & Šetlík, 2013; Shofty et al., 2016). Clinical experience has shown that ITH/IVT colistin methanesulphonate (CMS) and polymyxin B are the only therapeutic option for the treatment of MDR Gram-negative CNS infections that are resistant to all other antibiotics (Bargiacchi & De Rosa, 2016; Bargiacchi et al., 2014; Khawcharoenporn, Apisarnthanarak, & Mundy, 2010; Ng, Gosbell, Kelly, Boyle, & Ferguson, 2006). Summary tables detailing the diagnosis, treatment and outcome of patients who received ITH/IVT therapy have been published (Bargiacchi & De Rosa, 2016; Khawcharoenporn et al., 2010). ITH/IVT administration of polymyxins produces cerebrospinal fluid (CSF) exposure that cannot be achieved with intravenous delivery which would in any case lead to unacceptable nephrotoxicity. However, current ITH/IVT polymyxin therapy has never been optimised with respect to PK/PD. In some instances, excessively high-doses of ITH/IVT CMS have been used for CNS infections which may result in side-effects (Bargiacchi & De Rosa, 2016; Imberti et al., 2012; Khawcharoenporn et al., 2010; Ng et al., 2006). Neurotoxicity (e.g. seizures, aseptic meningitis, hypotonia, diaphragmatic paralysis, and cauda equine syndrome) has been reported in patients that received the currently recommended dosage regimens of ITH/IVT CMS (Koch-Weser J Fau - Sidel et al., 1970; Ng et al., 2006). Adverse effects following ITH/IVT high-dose antibiotics can lead to poor therapeutic outcomes due to complications in critically ill patients (Grill & Maganti, 2011). The current IDSA guidelines for ITH/IVT CMS suggest a dose of 10 mg CMS once daily for at least 14 days. Notwithstanding, in clinical practice both dose and duration are often empirically chosen and range widely between 1.6 and 40 mg, either as a single dose or in divided doses (Ng et al., 2006). The duration of therapy reported is also variable and can span from 1 to 4 weeks, although treatment duration of < 1 week correlates with higher mortality rates (Ng et al., 2006). It is very important to note that these guidelines are empirical and not based on clinically investigated dosage recommendations. A major difficulty relates to the lack of established PK/PD readouts for ITH/IVT polymyxins treatment. Therefore, identifying a practical PD readout for optimising dosage regimens for ITH/IVT polymyxins is urgently required and was recently identified as a research priority in antimicrobial chemotherapy (Nation et al., 2015).

3. Pharmacokinetics of intrathecal and intraventricular polymyxins

We have shown that the ratio of the area under the unbound