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Review

Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health

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ABSTRACT

Since its introduction in the 1950s, colistin has been used mainly as a topical treatment in human medicine owing to its toxicity when given systemically. Sixty years later, colistin is being used as a last-resort drug to treat infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella pneumoniae*), for which mortality can be high. In veterinary medicine, colistin has been used for decades for the treatment and prevention of infectious diseases. Colistin has been administered frequently as a group treatment for animal gastrointestinal infections caused by Gram-negative bacteria within intensive husbandry systems. Given the ever-growing need to retain the efficacy of antimicrobials used to treat MDR infections in humans, the use of colistin in veterinary medicine is being re-evaluated. Despite extensive use in veterinary medicine, there is limited evidence for the development of resistance to colistin and no evidence has been found for the transmission of resistance in bacteria that have been spread from animals to humans. Since surveillance for colistin resistance in animals is limited and the potential for such transmission exists, there is a clear

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need to reinforce systematic monitoring of bacteria from food-producing animals for resistance to colistin (polymyxins). Furthermore, colistin should only be used for treatment of clinically affected animals and no longer for prophylaxis of diseases, in line with current principles of responsible use of antibiotics.

1. Introduction

Colistin (polymyxin E) is a cationic, multicomponent, lipopeptide antibacterial agent discovered soon after the end of the Second World War (1949). An antibiotic originally named 'colimycin' was first isolated from the broth of *Paenibacillus (Bacillus) polymyxa* var. *colistinus* in 1950 [1]. Colistin has been used for decades in veterinary medicine, mainly to treat Gram-negative infections of the intestinal tract. For the treatment of human infections, colistin was restricted initially to ophthalmic and topical use [2,3] owing to its systemic toxicity [2,4,5]. A recent global increase in Gram-negative bacteria that are multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) [6] has forced clinicians to re-introduce systemic colistin treatment in the form of its inactive prodrug, colistin methanesulfonate (CMS), as a last-resort drug for infections with such bacteria, which are frequently the cause of healthcare-associated infections [7]. Human infections with such highly resistant bacteria are associated with higher patient morbidity and mortality, higher costs and longer length of hospital stay [8,9].

Due to its importance in human medicine, the public health impact of current or future use of colistin products in animals needs to be re-assessed at this time. The use of colistin in human and veterinary medicine is reviewed here, including a description of its toxicity profile, antibacterial spectrum, resistance mechanisms that render bacteria non-susceptible to polymyxin products, issues related to susceptibility testing, as well as the relationship between its use and antimicrobial resistance.

2. Use in human and veterinary medicine

2.1. Human medicine

Colistin belongs to the antimicrobial class of polymyxins. In human medicine, colistin-containing products are commercially available in two forms, colistin sulphate and the prodrug CMS (syn. colistin methanesulphate, colistin sulphonyl methate, pentasodium colistimethanesulphate). CMS is microbiologically inactive [10] and is less toxic than colistin sulphate [11]. It is administered predominantly as parenteral formulations and via nebulisation [3]. Following administration, CMS is hydrolysed to colistin, which is the base component responsible for its antibacterial activity [12]. Besides colistin, polymyxin B is also used widely in human medicine but only for topical use in the European Union and European Economic Area (EU/EEA). Colistin differs from polymyxin B by only one amino acid in position 6 (D-leucine in colistin, phenylalanine in polymyxin B). Polymyxin B has similar toxicity when administered systemically [4,13].

Colistin sulphate is available in tablets and syrup for selective digestive tract decontamination (SDD) and as topical preparations for skin infections. CMS is available for administration intravenously, intramuscularly as well as topically via aerosol (nebulisation) and by intraventricular administration. Polymyxin B is available in parenteral formulations and can be administered intravenously, intramuscularly or intrathecally.

Major adverse effects that may arise from the parenteral use of colistin are nephrotoxicity (acute tubular necrosis) and neurotoxicity such as paraesthesia, dizziness/vertigo, weakness, visual disturbances, confusion, ataxia and neuromuscular blockade, which can lead to respiratory failure or apnoea [3]. Compared with more recent studies, older studies have shown a much higher frequency of neurotoxicity and nephrotoxicity (ca. 7%), the latter being occasionally irreversible [14]. In up to 29% of cystic fibrosis patients, adverse (neurological) effects have been found [15,16].

Despite the toxicity issues, patients with cystic fibrosis and other pulmonary diseases, e.g., chronic obstructive pulmonary disease (COPD), can be treated with parenteral or nebulised colistin to control lower airway bacterial infections and related complications [17,18].

Recent studies [19–21] support the administration of a loading dose and higher doses of CMS than suggested previously in order to achieve adequate colistin concentrations for a therapeutic effect. This raises the concern of a higher risk of nephrotoxicity [14]. Parenteral use of colistin to treat serious human infections is complicated by different ways of describing and expressing the dose [in grams of colistin base activity or as International Units (IU)]. To limit toxic side effects following parenteral use, close monitoring of renal function and avoidance of co-administration with other nephrotoxic agents (e.g., aminoglycosides) is recommended [3]. A recent study with four different brands of CMS [22] showed differences in the pharmacokinetics in rats in the amount of colistin formed from the various products. This is worrisome considering the narrow therapeutic index of colistin and the risk of therapeutic failure due to the emergence of resistance associated with exposure to low concentrations. The European Pharmacopoeia monograph for CMS is not detailed and specifications are quite broad [23]. Another concern is that the minimum titre for CMS is specified in IU (potency test is based on turbidimetric and/or agar diffusion techniques), which requires an update or re-evaluation considering that CMS itself is found to be an inactive prodrug [10]. New derivatives of polymyxins with a more favourable toxicity profile are under evaluation [24].

Infections caused by MDR, XDR and PDR Gram-negative bacteria are reported increasingly, especially in vulnerable patient populations, e.g., those in intensive care units (ICUs) and haematology/oncology wards [25]. Thus, colistin has re-emerged as a last-resort therapeutic option to treat infections due to MDR, XDR and PDR, lactose-fermenting and non-fermenting Gram-negative bacilli, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Colistin has been used for the treatment of infections at different body sites, e.g., bacteraemia and ventilator-associated pneumonia due to carbapenemase-producing bacteria [26,27]. In most cases, such carbapenem-resistant organisms produce a serine-based carbapenemase (e.g., the KPC or OXA enzymes) [28] or a metalloenzyme [e.g., the New Delhi metallo-β-lactamase 1 (NDM-1)] [29–31]. These bacterial strains appear to be spreading within the EU and have become a major problem in some health centres and countries [32,33]. In addition to increased use in adult populations, paediatric use of colistin has also been reported for the treatment of MDR Gram-negative infections in children and was shown to be safe and effective, provided renal function is monitored closely [18].

Colistin in combination with other antibiotics such as tigecycline or carbapenems is used as preferred treatment particularly for carbapenemase-producing Enterobacteriaceae and other carbapenem-resistant Gram-negative bacteria [26,34,35]. A recent randomised trial failed to demonstrate a clinical benefit for the