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‘Old’ antibiotics for emerging multidrug-resistant bacteria

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Abstract

Purpose of review—Increased emergence of bacterial resistance and the decline in newly developed antibiotics have necessitated the reintroduction of previously abandoned antimicrobial agents active against multidrug-resistant bacteria. Having never been subjected to contemporary drug development procedures, these ‘old’ antibiotics require redevelopment in order to optimize therapy. This review focuses on colistin as an exemplar of a successful redevelopment process and briefly discusses two other old antibiotics, fusidic acid and fosfomycin.

Recent findings—Redevelopment of colistin led to an improved understanding of its chemistry, pharmacokinetics and pharmacodynamics, enabling important steps towards optimizing its clinical use in different patient populations. A scientifically based dosing algorithm was developed for critically ill patients, including those with renal impairment. As nephrotoxicity is a dose-limiting adverse event of colistin, rational combination therapy with other antibiotics needs to be investigated.

Summary—The example of colistin demonstrated that state-of-the-art analytical, microbiological and pharmacokinetic/pharmacodynamic methods can facilitate optimized use of ‘old’ antibiotics in the clinic. Similar methods are now being applied to fosfomycin and fusidic acid in order to optimize therapy. To improve and preserve the usefulness of these antibiotics rational approaches for redevelopment need to be followed.

Keywords

colistin; fosfomycin; fusidic acid; pharmacodynamics; pharmacokinetics

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Introduction

The worldwide problem of increasing antibiotic resistance is well documented [1–6]. At the same time, anti-infective development programmes are declining [3,7], forcing the reintroduction of previously abandoned ‘old’ antibiotics never subjected to the battery of contemporary drug development procedures now mandated by international drug regulatory authorities. This has resulted in a lack of important pharmacokinetic, pharmacodynamic and other scientific information with which to inform their rational use. To achieve optimal therapy, ‘older’ agents need to be subjected to scientific investigation akin to that required of their modern counterparts.

The most striking example of the reintroduction of previously abandoned antibiotics involves the polymyxins (colistin and polymyxin B). Having fallen out of favour in the 1970s due to reports of nephrotoxicity and neurotoxicity [8,9], a resurgence in their use began in the late 1980s when colistin (the most commonly used polymyxin) was reintroduced to manage infection or colonization by *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) [10]. More recently, as colistin (and polymyxin B) retains significant in-vitro activity against Gram-negative ‘superbugs’ [11], its use in critically ill patients as a last-line therapy has increased dramatically [10]. Over the past decade colistin in particular has been subjected to new investigations generating much information required to optimize clinical use. Other increasingly used ‘old’ antibiotics include fosfomycin, isepamicin, chloramphenicol, rifampicin and fusidic acid [12–14]. This review will focus primarily on colistin as the exemplar for the redevelopment process, highlighting experiences with this drug in order to provide insight that may assist in the redevelopment of other old agents. Fusidic acid and fosfomycin will be examined briefly.

The Redevelopment of Colistin

Colistin is a cationic antimicrobial peptide (Fig. 1a). Two different forms are commercially available: colistin sulphate (hereafter referred to as colistin) and sodium colistin methanesulphonate (CMS; Fig. 1b). CMS is ‘less toxic’ than colistin when administered parenterally [15] and hence it is CMS that is present in all parenteral (and most inhalational) formulations. In aqueous solutions CMS undergoes conversion *in vivo* [16–18] and *in vitro* [19] to form a complex mixture of partially sulphomethylated derivatives and colistin. Unfortunately, in Europe, product labels express the contents of CMS vials in international units (IU; there are ~12 500IU/mg of CMS [20]), whereas in North America, Australia, East Asia and some other regions vials are labelled with ‘colistin base activity’ (CBA); such confusing labelling significantly complicates the clinical use of CMS [21].

Colistin Pharmacokinetics and Pharmacodynamics

A striking example of the lack of information to guide rational dosing of CMS/colistin was the antibacterial activity assigned to each of CMS and colistin; the former was routinely reported as having reduced antibacterial activity compared with colistin [22–24]. It was only recently that CMS was revealed to be an inactive prodrug of colistin, showing separate determination of CMS and formed colistin concentrations are essential to fully understand the pharmacology of CMS/colistin [25]. However, pharmacokinetic studies conducted prior

to 2001 were undertaken using microbiological assay methods for the measurement of 'colistin' concentrations; such methods are neither able to separately quantify CMS and colistin nor differentiate between colistin present in a sample at collection from that formed by ongoing conversion from CMS during the incubation period [25]. Importantly, dosage regimens in manufacturers' package inserts even today were developed decades ago based upon pharmacokinetic and pharmacodynamic information derived using microbiological assays. The dearth of essential pharmacological information changed with the development of specific analytical methods capable of discriminating between CMS and colistin [26–32], the application of which over the past decade has greatly expanded our ability to define the pharmacokinetics, pharmacodynamics and integrated pharmacokinetics/pharmacodynamics of CMS/colistin.

To understand the disposition of CMS and colistin, both clinical and preclinical investigations were required, the latter due to aspects of the overall pharmacokinetics of CMS and formed colistin that are only possible to be revealed by the separate administration of each; such studies are not easily performed in humans. Animal models revealed rapid conversion of administered CMS to colistin [the latter with an apparent elimination half-life ($t_{1/2}$) approximately twice that of the administered CMS] [17,33], extensive renal tubular reabsorption of colistin [32,34] and net tubular secretion of CMS [17]. Colistin showed potent, concentration-dependent bacterial killing which was subject to a substantial inoculum effect [23,35–39], the latter observation suggesting a potential need for higher colistin exposure or combination regimens to treat deep-seated infections with high inocula. Colistin heteroresistance, the situation in which colistin-resistant subpopulations are present within an isolate considered susceptible based upon minimum inhibitory concentrations (MICs), was also observed [35,38–41]. Regrowth with colistin concentrations well in excess of those safely achievable clinically was a consistent finding of in-vitro studies, with heteroresistance contributing to regrowth via amplification of colistin-resistant subpopulations [35,36,38,39,42,43]. Studies also revealed the area under the unbound concentration–time curve to MIC ratio ($fAUC/MIC$) was the pharmacokinetic/pharmacodynamic index most predictive of the antibacterial effect [43–45], indicating that time-averaged exposure to colistin is more important than the achievement of high peak concentrations from the administration of larger, less frequent doses.

Initial clinical investigations into the pharmacokinetics of CMS and formed colistin following intravenous administration of CMS were conducted in CF patients and, as with preclinical studies, revealed relatively rapid formation of colistin which, at steady state, had a $t_{1/2}$ approximately twice that of administered CMS (4.2 ± 1.3 versus 2.1 ± 0.87 h) [16,46]. Importantly, the steady-state plasma C_{max} values for colistin were low and, even without considering plasma protein binding, failed to reach the Clinical and Laboratory Standards Institute breakpoint of 2 mg/l for *P. aeruginosa* and *Acinetobacter baumannii* [47]. An early case report involving a critically ill adult patient requiring continuous venovenous haemodiafiltration (CVVHDF) highlighted the lack of pharmacokinetic information for CMS and formed colistin in critically ill patients [18]. With no guidance from the product information on whether CMS (or formed colistin) is cleared by dialysis [48–50], it was later shown in this patient that both CMS and colistin were cleared by CVVHDF and total plasma

concentrations of formed colistin were below the MIC for the infecting strain for the vast majority of the dosage interval; sadly the patient died. Subsequent studies have confirmed the efficient clearance of both CMS and colistin by intermittent haemodialysis and continuous renal replacement therapy (either CVVHDF or continuous veno-venous haemofiltration) [51■■■,52].

Over the past few years the gaps in our knowledge of CMS/colistin have begun to be filled. In critically ill patients formed colistin has a protracted $t_{1/2}$ (up to ~18 h) with little fluctuation in plasma colistin concentrations across a dosage interval (Fig. 2) [51■■■, 53,54,55■■■]; such a pharmacokinetic profile is substantially different to that observed in CF patients in whom the $t_{1/2}$ of formed colistin is substantially shorter [16,46], and emphasizes the need to understand the pharmacokinetics in each target group. Three of the studies in critically ill patients, which included between 10 and 18 patients, found renal function [as measured by creatinine clearance (CrCL)] was not a covariate for the clearance of formed colistin [53,54,55■■■] nor was CrCL a covariate for CMS clearance [55■■■]. In a much larger population pharmacokinetic study involving 105 patients with a wide range of renal function (including 16 patients receiving renal replacement therapy), Garonzik *et al.* [51■■■] showed an inverse relationship between the average plasma colistin concentration at steady state ($C_{SS,ave}$) achieved with a given daily dose of CMS and CrCL (Fig. 3). It is most likely that the small sample sizes and relatively narrow range of CrCL values ($>\sim 25$ ml/min) for the enrolled patients in the other studies [53,54,55■■■] resulted in an inability to detect a relationship between renal function and CMS/colistin clearances.

Additional important findings have emerged from these recent pharmacokinetic studies in critically ill patients. The attainment of steady-state plasma colistin concentrations was shown to be a prolonged process (up to 3–4 days) [53], with total plasma colistin concentrations below the MIC breakpoint of 2 mg/l for the first few doses of the currently recommended dosing regimen, effectively delaying appropriate therapy. This highlights the importance of administering a loading dose of CMS in order to more rapidly achieve plasma colistin concentrations [51■■■,53,55■■■], and this is beginning to be used clinically [55■■■]. Garonzik *et al.* [51■■■] recently published the first scientifically based CMS dosing algorithms for patients with a large range of renal function (including patients on intermittent haemodialysis or continuous renal replacement therapy); the algorithms allowed calculation of the CMS loading and maintenance doses required to achieve a desired target plasma $C_{SS,ave}$ for colistin in critically ill patients. The recent population pharmacokinetic studies in critically ill patients [51■■■,53] demonstrated that in patients with moderate to good renal function it is not possible to achieve steady-state plasma colistin concentrations that are likely to be reliably efficacious with a daily dose of CMS at or close to the upper limit of the current product-recommended dose range (300 mg CBA per day) [48,50]; this is particularly the case for strains with MICs in the upper range of the susceptibility breakpoint for colistin (i.e. >1 mg/l) [51■■■]. As nephrotoxicity is a dose-limiting adverse effect of CMS in up to approximately 50% of patients [51■■■,56,57], increasing the daily dose may not be an acceptable option. Such a situation places patients at risk for clinical failure and the development of colistin resistance [36,38,39,42,43]. These factors suggest CMS/colistin

might best be used as part of a highly active combination and highlight the importance of investigating rational colistin combinations.

Where to with Colistin?

Although there is still much to learn about colistin a clearer picture on the appropriateness of currently administered CMS dosage regimens has slowly emerged. The development of a maintenance dosing algorithm for CMS incorporating renal function, translationally derived from murine pharmacokinetic/pharmacodynamic data, has provided clinicians for the first time with scientifically based guidelines to inform CMS administration. As clinical studies progress, the future incorporation of human pharmacokinetic/pharmacodynamic data into such algorithms, including information on colistin plasma protein binding, as well as studies examining colistin monotherapy versus combination therapy, will further optimize colistin therapy.

Fusidic Acid

Fusidic acid has been widely used for uncomplicated skin and skin-structure infections predominantly in Europe and Australia since the 1960s, with standard dosage regimens of 500 mg 12 or 8 hourly [58,59]. Owing to activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [60] it is currently undergoing redevelopment in the US [61]. As for colistin, there are major knowledge gaps relating to both its pharmacokinetics and pharmacodynamics. Fusidic acid has complex pharmacokinetics which includes a decrease in clearance with increasing dose and with multiple compared to single doses [59,62,63]. Administration with food decreases both the bioavailability (by ~18%) [63] and the rate of absorption [62]. It also has high between-patient variability in pharmacokinetics, is almost entirely nonrenally eliminated, is highly protein-bound (>97%) and appears unaffected by haemodialysis [59,64]. Population pharmacokinetic modelling of data from 75 healthy volunteers estimated a clearance of approximately 1.28 l/h and apparent $t_{1/2}$ of 14 h for single doses of up to 400 mg. However, with a substantial decrease in clearance to approximately 0.37 l/h at high concentrations due to auto-inhibition, the time required to reach steady state for a regimen of 500 mg 12 hourly was predicted to be approximately 3 weeks [63]. With such a slow attainment of steady state, efficacious concentrations may not be achieved during the first days of therapy which may lead to resistance. Therefore the use of front-loaded regimens was proposed. Simulations predicted loading doses of 1500 mg at 0 and 12 h followed by 600 mg every 12 h allow attainment of steady state within 24 h [63]. Based upon the population model, various human dosage regimens were simulated *in vitro* against a MRSA USA300 clinical isolate. The bacterial killing was well correlated with AUC/MIC, with a front-loaded regimen (1500 mg at 0 and 12 h followed by 600 mg 12 hourly) increasing killing and delaying the emergence of resistance (by up to 72 h compared to the 600 mg 12 hourly regimen) [61]. The prospectively identified front-loading regimen was subsequently tested in a phase 2 clinical study showing comparable efficacy to linezolid [61]. However, *S. aureus* develops resistance to fusidic acid when used as monotherapy primarily due to mutations in the *fusA* gene (which encodes elongation factor G, the site of action of fusidic acid) and plasmid-mediated resistance, and therefore, like colistin, may best be used in combination [65].

Rationally designed combination regimens (e.g. with rifampicin) will be critical to preserve the efficacy of fusidic acid into the future [58].

Fosfomycin

Fosfomycin is a broad-spectrum bactericidal antibiotic known for more than 40 years but abandoned in several parts of the world. It displays a unique mechanism of action by inhibiting an early step in bacterial cell wall synthesis [66], making cross-resistance unlikely and allowing fosfomycin to retain significant in-vitro activity against many Gram-positive and Gram-negative pathogens, including multidrug resistant (MDR) strains [67,68]. Fosfomycin is primarily administered orally for treatment of uncomplicated urinary tract infections. Fosfomycin tromethamine, the oral formulation, is rapidly absorbed achieving serum concentrations of approximately 22–32 mg/l following the standard single 3 g oral dose, with very high concentrations (range 1053–4415 mg/l [69]) achieved in urine after 3 h [70]; urinary concentrations remain high for several days. Elimination is almost entirely via glomerular filtration (serum $t_{1/2}$ 2.4–7.3 h) [69]. In some countries fosfomycin disodium is used intra-venously for systemic infections [71]. A $C_{\max}$ of approximately 250 mg/l is achieved following intra-venous administration of a 4 g dose [72,73]. Given the susceptibility breakpoints for fosfomycin, when specified, range from 32 to 64 mg/l [47,74], oral therapy for systemic infections should be avoided until more information is forthcoming. Fosfomycin is almost entirely unbound in serum [75] with its low molecular weight facilitating good distribution into many tissues (e.g. muscle, lung and bone) [76–78]. Although fosfomycin crosses the blood–brain barrier [79], activity against Gram-negative bacteria is significantly reduced in human cerebrospinal fluid [80].

Concerns over the potential for rapid resistance development with fosfomycin have resulted in it primarily being used in combination for treatment of systemic infections [81], with in-vitro combination studies displaying excellent activity against both Gram-negative and Gram-positive pathogens [82]; clinical studies demonstrating the effectiveness of combination therapy, however, are lacking. Fosfomycin exhibits in-vitro synergy with carbapenems as well as with aminoglycosides, colistin and tigecycline against serine carbapenemase-producing and extended spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae* [83]. Combinations of fosfomycin with aminoglycosides, colistin or tigecycline were effective against ESBL-producing *Escherichia coli* and a considerable subset of MDR *P. aeruginosa* [83]. Against *P. aeruginosa* biofilms, fosfomycin has shown good in-vitro activity in combination with fluoroquinolones or aminoglycosides, making it a potential option to treat CF patients [84–88]. Activity against biofilms may be due to the ability of fosfomycin to penetrate deeply into the biofilm, along with enhanced activity under anaerobic conditions [87,88]. Given the limited available evidence from clinical and other studies, this old antibiotic may be a viable alternative for treatment of infections due to both Gram-positive and Gram-negative pathogens, especially MDR pathogens. However, as fosfomycin has not been used widely there is a shortage of clinical efficacy and safety data and further research is warranted.

Conclusion

So what lessons can be learned from the colistin experience? The first is that pharmaceutical companies are generally disinterested in funding research for off-patent anti-infectives. Consequently, the redevelopment task will fall to publicly funded granting bodies such as the US National Institutes of Health (NIH). Additionally, the redevelopment process takes time – perhaps a decade or more – so the redevelopment process needs to start early. Fosfomycin and fusidic acid are two promising ‘old’ antibiotics. The example of colistin has shown that much is to be gained from the redevelopment of ‘old’ antibiotics by employing contemporary analytical and pharmacokinetic/pharmacodynamic methods to maximize bacterial killing and minimize the occurrence of adverse events as well as the emergence of resistance.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 720).

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Key Points

- Due to increased emergence of bacterial resistance and declining development of new antibiotics, previously abandoned 'old' compounds active against multidrug-resistant bacteria are being reintroduced into the clinic.
- As these 'old' antibiotics have never been subjected to the contemporary drug development process, their redevelopment using contemporary analytical and pharmacokinetic/pharmacodynamic methods is critical in order to optimize therapy.
- Colistin is an example of successful redevelopment in which the use of new state-of-the-art bioanalytical, microbiological and pharmacokinetic/pharmacodynamic approaches has generated an improved understanding of its clinical pharmacology, and has enabled rational optimization of patient therapy.
- Other old antibiotics such as fosfomycin and fusidic acid will benefit from redevelopment based on the lessons learnt with colistin.

Figure 1.

(a) Structures of colistin A and B; (b) structures of colistin A and B methanesulphonate (CMS). Fatty acyl: 6-methyloctanyl for colistin A and 6-methylheptanyl for colistin B; Thr, threonine; Leu, leucine; Dab, α,γ-diaminobutyric acid. α and γ indicate the respective -NH₂ involved in the peptide linkage.

Figure 2.

Steady-state plasma concentration–time profiles of (a) CMS or (b) formed colistin in 105 critically ill patients (89 not on renal replacement, 12 on intermittent haemodialysis and 4 on continuous renal replacement therapy) [51■■■]. The physician-selected daily dose ranged from 75 to 410 mg colistin base activity; the dosage intervals ranged from 8 to 24 h and hence the inter-dosing blood sampling interval spanned the same range. CMS, colistin methanesulphonate. Reproduced with permission from [51■■■].

Figure 3. Relationship of (a) physician-selected daily dose of colistin base activity (CBA) and (b) the resultant average steady-state plasma colistin concentration with creatinine clearance in 105 critically ill patients [51■■■]. Reproduced with permission from [51■■■].