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Discussion

Multicomponent antibiotic substances produced by fermentation: Implications for regulatory authorities, critically ill patients and generics

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ABSTRACT

Teicoplanin and polymyxin E (colistin) are antibiotics consisting of multiple, closely related subcomponents, produced by fermentation. The principal components comprise a complex mixture of chemically related, active substances (teicoplanin $A_{2\text{-}1}$–$A_{2\text{-}5}$ and polymyxin $E_{1–2}$, respectively), which might be required to be present in specific ratios to ensure optimal antibacterial and clinical efficacy. These subcomponents differ in their fatty acid and amino acid composition and, as such, the lipophilic and protein binding characteristics differ between components. This has therapeutic implications for critically ill patients, as the volume of distribution of the teicoplanin A_2 and polymyxin E analogues at the onset of an intravenous infusion may impact on expected pharmacokinetics and influence outcome.

1. Introduction

Antibiotics are active substances that are classified on the basis of their chemical or biosynthetic origin into three main groups: first, those produced by fermentation; second, synthetic antibiotics produced by chemical synthesis (e.g. oxazolidinones and quinolones); and third, semisynthetic products (e.g. colistin methanesulfonate, tigecycline and cephalosporins) where the active ingredients obtained by fermentation are further modified by one or more chemical processes. Antibiotics produced by fermentation represent a very specific and highly differentiated group of antibiotics and include fusidic acid, colistin, daptomycin, fosfomycin, tobramycin, gentamicin, vancomycin and teicoplanin.

In comparison with synthetic processes, manufacture by fermentation is more difficult to control, thus it can lead to the formation of more variable antibiotic products with more complex and less predictable composition and impurity profiles [1–3]. This is due to the facts that:

- the purity of the active substances is dependent on the fungal or bacterial strains that produce the antibiotic;
- the conditions under which strains are processed may vary;
- the raw materials that are utilised, including the quality of water in which the strains grow, may also vary; and
- the extraction and purification processes may have limited selectivity.

Hence, the crude product obtained by fermentation might not be a single antibiotic substance or entity, but rather a complex mixture of analogues, as is the case with teicoplanin, colistin and gentamicin. It might therefore be difficult to compare apparently identical active ingredients unless they originate from the same manufacturer. Since there are more published data available for teicoplanin and colistin, this paper will focus on these two drugs with respect to the potential therapeutic implications for critically ill patients of the variations in chemical structure that exist between varying drug products.

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2. Teicoplanin

2.1. Composition of teicoplanin and disposition characteristics in patients

Teicoplanin is a glycopeptide antibiotic registered in many countries for the treatment of a variety of aerobic and anaerobic Gram-positive infections, including those caused by meticillin-resistant *Staphylococcus aureus* (MRSA). Although teicoplanin and vancomycin have a similar mode of action, their pharmacokinetics in patients are very different. With six ionisable groups, teicoplanin is predominantly hydrophilic but is still 50–100 times more lipophilic than vancomycin [4]. Therefore, cellular and tissue penetration are more favourable and the half-life ($t_{1/2}$) is prolonged to 168 h (versus 4–6 h for vancomycin). Although teicoplanin rapidly penetrates tissues, it is subsequently slowly released back into the serum.

Teicoplanin is produced by *Actinoplanes teichomyceticus* as an antibiotic complex and, as opposed to vancomycin that is a more 'homogeneous' fermentation product (i.e. a single moiety with a purity usually of >92%), the principal active component is teicoplanin A_2, which is comprised of a complex of A_2 group analogues ($A_{2\text{-}1}$, $A_{2\text{-}2}$, $A_{2\text{-}3}$, $A_{2\text{-}4}$ and $A_{2\text{-}5}$) accounting for 90–95% of total teicoplanin (Fig. 1) [3]. These analogue components are present in characteristic ratios (in conjunction with teicoplanin A_3) and collectively are responsible for the antibacterial activity and clinical efficacy of the antibiotic [3]. A high-performance liquid chromatography (HPLC) trace of the originator teicoplanin is depicted in Fig. 2 [3]. In a conventional reversed-phase HPLC system, less hydrophobic analogues would elute first. These subcomponents differ in length and branching of fatty acid moieties, both of which increase sequentially from $A_{2\text{-}1}$ to $A_{2\text{-}5}$. As a consequence, the lipophilicity and protein binding characteristics, and therefore the pharmacokinetic (PK) profile, of the teicoplanin components could be predicted to differ from product to product among various manufacturers.

Indeed, several studies that have investigated the impact of the originator teicoplanin A_2 analogue distribution in healthy volunteers and patients have concluded that there was a highly significant correlation between lipophilicity and PK parameters

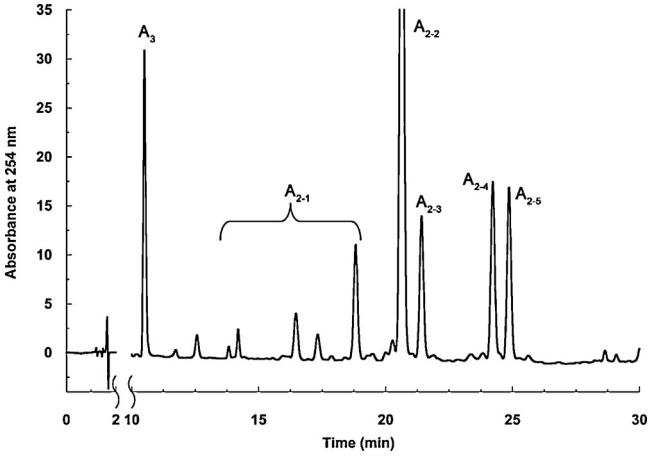

Fig. 2. High-performance liquid chromatogram obtained from analysis of teicoplanin standard solution. The figure has been adapted with permission from Rossi et al. [3].

[2,3,5–7]. The various teicoplanin subcomponents have different protein binding properties and as such have high interpatient variability with regard to total and unbound plasma concentrations [5]. Lipophilicity affects the protein binding and volume of distribution (V_d). As the lipophilicity of the teicoplanin components increases, the initial unbound plasma fraction, the initial V_d, the total clearance (CL) and renal clearance, and the fraction of the administered dose excreted in urine all decrease. In contrast, the unbound steady-state V_d and unbound non-renal clearance increase [3,6,8]. Accumulation of teicoplanin components occurs in plasma following repeated intravenous (i.v.) administration and this varies from one analogue to the other during treatment, with the more lipophilic components ($A_{2\text{-}4}$ and $A_{2\text{-}5}$) showing slightly higher accumulation [6]. Recently, a study utilising two teicoplanin dosage regimens (three loading doses of 6 mg/kg i.v. every 12 h followed by 6 mg/kg/day versus three loading doses of 12 mg/kg i.v. every 12 h followed by 15 mg/kg every other day) confirmed the abovementioned changes in A_2 analogue composition in serum

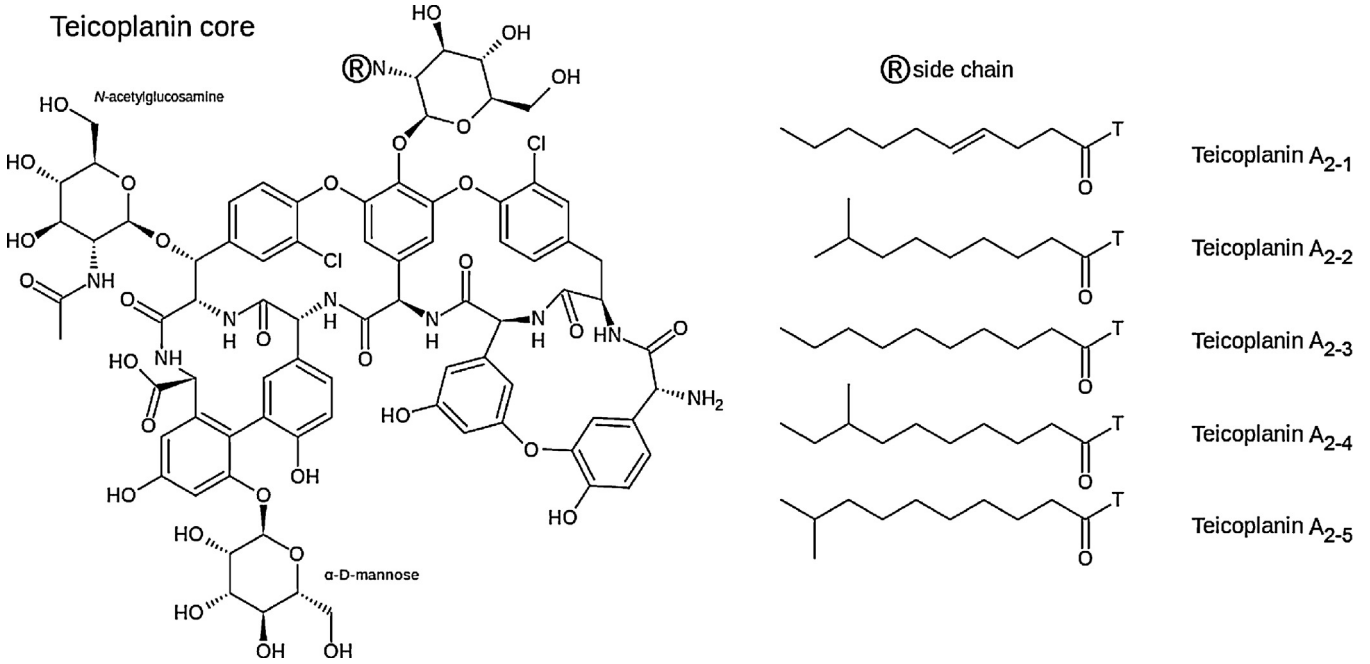

Fig. 1. Chemical composition of the teicoplanin core and A_2 subcomponents. The figure is original and reproduced with permission from Rossi et al. [3].