

Spectinomycin-Present, Future and Alternatives

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Received: March 21, 2015; Published: April 24, 2015

Abstract

Spectinomycin is an aminocyclitol antibiotic, closely related by chemical structure to the aminoglycosides. It has fewer side effects than aminoglycosides and has a comparatively broad antimicrobial spectrum of activity. Spectinomycin is used in human medicine for *Neisseria gonorrhoeae* treatment and in veterinary medicine for the treatment of infections caused by *Enterobacteriaceae* and *Mycoplasma* spp. However, its application in medicine is limited because of rapid development of *in vivo* and *in vitro* resistance. Therefore, the prolonged use of this antibiotic requires caution. An alternative for spectinomycin use could be trospectomycin - a new 6'-propyl spectinomycin analog. When compared with spectinomycin *in vitro*, trospectomycin has broader activity against aerobes and anaerobes such as *Staphylococcus* spp., *Streptococcus* spp., *Salmonella* spp., *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Chlamidia trachomatis*, *Ureaplasma* spp., *Mycoplasma* spp., *Bacteroides* spp., *Clostridium* spp., *Helicobacter pylori* and *Treponema pallidum*. However, the antibiotic is still not licensed for use in medicine, most likely due to the acquisition of resistance which is similar to that of spectinomycin. Because of this trospectomycin is possibly kept in reserve for future needs in medicine.

Keywords: Spectinomycin; Trospectomycin; Antimicrobial resistance; MIC; Antimicrobial activity

Abbreviations: MIC: Minimum Inhibitory Concentration; SPM: Spectinomycin; TRM: Trospectomycin

SPM is an aminocyclitol antibiotic, closely related in chemical structure to the aminoglycosides. It is produced by *Streptomyces spectabilis*. SPM has never exhibited the ototoxicity or nephrotoxicity associated with the aminoglycosides, but may sometimes cause neuromuscular blockade [1,2]. The drug is poorly absorbed from the normal gastrointestinal tract, but is well absorbed after intramuscular or subcutaneous injection. Following parenteral administration, effective concentrations are obtained in peri lymph, synovial, pleural, peritoneal, and pericardial fluid. It has usually bacteriostatic, comparatively broad spectrum activity that can become bactericidal at four times MIC concentrations [3].

In human medicine SPM is primarily used for treatment of urethritis caused by *Neisseria gonorrhoeae*. This is necessary because of the high rates of gonococcal resistance to penicillins, fluoroquinolones, oral cephalosporins and tetracyclines, which are mainly used for *Neisseria gonorrhoeae* treatment [4]. In some cases the susceptibility rate of *N. gonorrhoeae* against SPM was over 99% and in a three year study period only one spectinomycin-resistant strain was found [5]. In another study the clinical efficacy of spectinomycin was reported to be very high; the gonococcal eradication rate after a single-dose treatment of 2g SPM was 96.7%. Three of the isolated four strains from patients with treatment failure were susceptible to SPM and only one strain was highly resistant. Thus, the authors concluded that spectinomycin treatment failure in gonococcal urethritis is likely due not only to drug susceptibility, but also to other factors such as the pharmacokinetics and pharmacodynamics of SPM [6]. Other authors have also found that spectinomycin gonorrhoea treatment failure was not related to drug resistance [7,8].

Citation: Georgi Beev., et al. "Spectinomycin-Present, Future and Alternatives". *EC Microbiology* 1.2 (2015): 118-121.

In contrast, because of *Enterobacteriaceae* susceptibility, SPM is often used in veterinary medicine for the treatment of infections caused by *Escherichia* spp., *Salmonella* spp., and *Pasteurella* spp. (diarrhea, septicemia) [3]. In *in vitro* experiments the majority of strains of *Enterobacteriaceae* (with exception of *Serratiamarcescens* and *Proteus* spp.) were susceptible to SPM, whereas most staphylococci and group D streptococci were placed in an intermediate category. On the other hand only a few strains of *Pseudomonas aeruginosa* and *Herellea vaginicola* were in the intermediate category, most of them were highly resistant to SPM [9].

Other studies were performed regarding the *in vitro* activity of SPM against anaerobes. Phillips and Warren (1975) reported that all 38 strains of *Bacteroides fragilis* that they studied were susceptible to this antibiotic [10]. Other authors however found higher MICs of SPM for *B. fragilis* isolates. Because these values were close to peak levels of SPM after intramuscular injection of 2g of the drug they concluded that it is not likely that this drug would be effective in treatment of anaerobic infections. The controversy, therefore, could be settled with the performance of adequate *in vivo* studies [11,12]. Regarding other anaerobes, SPM exhibited higher *in vitro* activity against Gram-positive anaerobic cocci: *Bacteroides melaninogenicus*, *Fusobacterium*, *Clostridium ramosum* and lower activity against *Clostridium perfringens* [12]. To broaden the spectrum of activity against anaerobic as well as Gram-positive aerobic bacteria SPM is often combined with lincomycin in veterinary medicine [3].

SPM is an effective drug against respiratory tract infections caused by *Pasteurella multocida* and *Mannheimia haemolytica* [13]. It exhibits very high activity against *Mycoplasma* spp. *M. bovis*, *M. hyopneumoniae*, *M. hyorhinis*, *M. bovis genitalium*, *M. hyosynoviae* [3,14].

Regarding the antimicrobial activity, it could be said that SPM is a highly effective antibiotic against important pathogens in human and veterinary medicine, such as *Neisseria gonorrhoeae*, *Pasteurella multocida*, and *Mycoplasma* spp. Moreover, the drug has a unique property in some clinical cases SPM has a higher *in vivo* activity than *in vitro*, which has not been explained satisfactorily [15]. However, its long-term application in medicine is limited because of rapid development of *in vivo* and *in vitro* resistance in a manner similar to streptomycin [3].

Antimicrobial resistance is a major problem in veterinary and human medicine. Cosgrove (2006) found an association between the development of antimicrobial resistance and increased patient mortality, morbidity, length of hospitalization and cost of health care [16]. This necessitates the development of new forms of antibiotics, as well as, alternatives of the old antibiotics [17]. An alternative for SPM could be TRM-a new 6'-propyl spectinomycin analog under study. In human trials TRM showed high levels of tolerance and fewer adverse side effects than are generally seen with SPM [18]. When compared with SPM *in vitro* TRM has 2- to 50-fold higher activity against aerobes as well as anaerobes: *Staphylococcus* spp., *Streptococcus* spp., *Salmonella* spp., *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Chlamidia trachomatis*, *Ureaplasma* spp., *Mycoplasma* spp., *Bacteroides* spp., *Clostridium* spp. [19-21]. Moreover, this antibiotic is effective against important human pathogens such as *Helicobacter pylori* and *Treponema pallidum* [22,23]. Despite the broad spectrum activity, the drug is still not licensed for use in medicine. One reason is probably the acquisition of resistance similar to that of SPM. TRM also showed cross-resistance with SPM for spectinomycin-resistant *N. gonorrhoeae* [19]. Because of this TRM is possibly kept as a reserve for future needs in medicine.

Conclusion

Regardless of the comparatively broad spectrum of activity and lack of ototoxicity and nephrotoxicity, SPM should be used with caution in human and veterinary medicine because of the rapid development of resistance. A future alternative for SPM could be TRM; it has broader spectrum activity and fewer adverse side effects. However, because of rapid development of resistance TRM should also be used with caution in the future.

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Volume 1 Issue 2 April 2015

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