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Spiramycin renaissance

E. Rubinstein* and N. Keller

Unit of Infectious Diseases, Chaim Sheba Medical Center, Tel Aviv University School of Medicine, Tel-Hashomer 52261, Israel

Recent years have witnessed an upsurge of interest from both clinicians and researchers in the use of macrolide antibiotics for the treatment of respiratory tract infections. This resurgence follows a period during which β-lactams were the predominant agents used to treat these common infections. The ability of macrolides to penetrate cells, which has been recognized partly as a result of increasing experience with 16-membered macrolides, has provoked considerable interest, particularly as potential agents for targeting the facultative/obligate intracellular pathogens that have emerged recently. The increasing incidence of resistance of certain pathogens, such as *Streptococcus pneumoniae*, to β-lactams, and the increasing number of immunosuppressed patients have also contributed to the revival.

Macrolides have been used extensively in the treatment of respiratory infections for a number of years, largely because of their efficacy in treating these infections and their lack of major side-effects.[1] Their activity against common respiratory pathogens, such as streptococci, pneumococci, *Legionella* spp., *Branhamella catarrhalis* and *Mycoplasma pneumoniae*, is well documented.[2] They are also well tolerated[3] and distributed throughout respiratory tract tissues.[4,5]

Macrolides such as azithromycin, dirithromycin, roxithromycin and clarithromycin have been developed recently. The main differences between these newer 14- or 15-membered-ring compounds and erythromycin result from their pharmacokinetic properties. The development of these new macrolides has renewed interest in the class as a whole and encouraged what could be described as a rediscovery of other macrolides, particularly the 16-membered macrolides, as exemplified by spiramycin.

Spiramycin has been available for some years. In countries where it has become established, it continues to enjoy a reputation for safety and efficacy.[6] This article examines the clinical evidence surrounding spiramycin, particularly with reference to respiratory tract infections.

The therapeutic activity of spiramycin is considerable, because (i) it is highly concentrated within body cells and is released very slowly from intracellular compartments; (ii) it exerts a probiotic effect by stimulating body defences against pathogens; and (iii) it has a substantial post-antibiotic effect.[7] Of particular significance is the fact that, along with other 16-membered-ring macrolides, spiramycin is active against many bacteria that have acquired resistance to erythromycin and other macrolides. This range of properties makes spiramycin especially suitable for the treatment of respiratory tract infections.

All macrolides have a similar mode of action: they inhibit protein synthesis by the large (50S) subunit of bacterial ribosomes by causing the growing polypeptide chain to dissociate from the ribosome.

The antibacterial spectrum of spiramycin is quite broad[8] and typical of the macrolides. It encompasses most of the pathogens involved in respiratory tract infections, including Gram-negative and Gram-positive cocci, Parvobacteriaceae, *Legionella* spp., *Chlamydia* spp., *Ureaplasma urealyticum*, *M. pneumoniae* and *Listeria monocytogenes*, but not Enterobacteriaceae. The activity of spiramycin against *S. pneumoniae* is similar to that of erythromycin and most other macrolides. Spiramycin is still active *in vitro* against strains with inducible resistance to erythromycin. While spiramycin exhibits borderline in-vitro activity against *Haemophilus influenzae* in conventional MIC tests, it is active against this organism *in vivo*.

The clinical management of respiratory tract infections with antimicrobial therapy should make use of appropriate drugs at timely intervals in the course of the illness. This is particularly relevant to non-hospitalized patients. Important considerations are the known activity against suspected pathogens, delivery route and the predicted frequency and severity of side-effects.

If the involvement of organisms such as *Mycoplasma*, *Legionella* or *Chlamydia* spp. is suspected, then macrolides should be used as first-line treatment. Spiramycin has significant activity against intracellular pathogens: infections where these organisms are involved which may be treated with spiramycin include legionnaires' disease; mycoplasma infections; toxoplasmosis; chlamydia infections and cryptosporidiosis.[9] It has been suggested that

*Tel: +972-3-5303500; Fax: +972-3-5347081.

intracellular pathogens may be responsible for nearly half of all cases of ambulatory community-acquired pneumonia.[10] Thus it is vital to ascertain the epidemiology of these intracellular pathogens in individual countries.

When considering the pharmacokinetic properties of an antibacterial agent, the concentration achieved at the site of infection (whether intracellular or extracellular) is very important. The ratios of serum and tissue concentrations are of particular interest; the data for spiramycin are shown in Table I. Other important pharmacokinetic parameters of spiramycin are shown in Table II. The absolute bioavailability of oral spiramycin is generally 30–40%. After an oral dose, serum levels were measured and C_{max} found to be between 0.4 mg/L and 1.4 mg/L.[11]

Intracellular penetration of spiramycin is also rapid and extensive, concentrations found in alveolar macrophages being 10–20 times greater than simultaneous serum concentrations. The post-antibiotic effect of spiramycin is quite marked, and is longer than that for erythromycin against *Staphylococcus aureus*. The inhibitory quotient (which takes into account the concentrations of antimicrobial agent in the tissues as well as the MICs for the pathogens) for spiramycin is always high, even for pathogens with high MICs of spiramycin.[4] Spiramycin also greatly reduces the capacity of strains of cocci to adhere to human buccal cells.[11] It is less metabolized than some other macrolides. The renal excretion of spiramycin is low, with 4–20% of a dose being excreted by this route.[12,13] High concentrations of spiramycin are achieved in bile, which is an important route of elimination.[14] The serum elimination half-life of spiramycin is between 6.2 and 7.7 h.

The clinical efficacy of spiramycin has been compared with that of amoxycillin in the treatment of acute community-acquired upper respiratory tract infections (C. Bunnag, personal communication). Adult patients with such infections were randomly assigned to receive either spiramycin 1 g (3 million IU) twice daily for 7 days or amoxycillin 500 mg three times daily for 7 days. A total of 93 patients were assessed: 45 patients received spiramycin and 48 amoxycillin. The investigators assessed both clinical and bacteriological responses at the end of drug therapy: 40 (89%) of the 45 cases treated with spiramycin, and 40 (83.3%) of the 48 treated with amoxycillin, were classified as successes. Adverse events were reported in two patients from the spiramycin group and one from the amoxycillin group. The investigators concluded that spiramycin and amoxycillin at the doses given were similarly effective with similar levels of tolerability.

In a randomized study of adult patients with acute sinusitis, the clinical and bacteriological efficacy and safety of spiramycin and doxycycline were compared.[15] Positive pretherapy cultures of samples taken by deep nasal aspiration along with radiological opacification of the nasal sinuses was taken as confirmation of the condition. Of the 33 patients enrolled, 15 were treated with spiramycin 1 g twice daily for 10 days and 18 were treated with doxycycline, administered as a single daily dose of 200 mg on day 1 followed by 100 mg/day for 9 days. At the end of the treatment period 27 patients were evaluable. Nine patients in each group were cured while three patients in the spiramycin group and five patients in the doxycycline group were clinical failures. As the numbers of patients were very small it is difficult to draw any firm conclusions from this study.

Table I. Spiramycin concentrations achieved in human tissues and fluids[4]

Tissue/fluid	Oral dosage (g/day × days)	Time since dose (h)	Tissue concentration (mg/kg)
Serum	3.75 (single dose)	12	1.5
Prostate	2 × 16	12	21
	3 × 10	240	1.7
Muscle	2 × 16	12	27
Bone	1	12	5.3
	3 × 10	240	1.7
Spleen	3 × 10	240	6.8
Liver	3 × 10	240	5.9
Kidney	3 × 10	240	6.1
Healthy lung	3 × 2	18	45 ± 18[a]
	3 × 2	18	30 ± 16.2[a]
Bronchial secretion	1 × 2	1	2
	1 × 2	6	6
Tonsil and adenoids	3 (single dose)		29.5
Tonsil	100 mg/kg (single dose)	36	45.3
	100 mg/kg (single dose)	84	2.5

[a]Standard error.

Table II. Pharmacokinetic parameters of spiramycin in healthy volunteers[4]

Parameter	Spiramycin dosage		
	1 g po	2 g po	0.5 g iv
C_{max} (mg/L)			
mean	0.96 (±0.32)	1.65 (±0.91)	2.28 (±0.38)
range	0.39–1.38	0.89–3.38	1.54–2.88
t_{max} (h)			
mean	3.0	4.0	ND
range	3–4	2–5	ND
$t_{1/2}$ (h)			
mean	5.37 (±1.33)	6.23 (±1.06)	5.54 (±0.61)
range	1.96–7.06	3.87–8.31	4.58–6.51
V_{ss} (L)			
mean	ND	ND	383 (±69.9)
range	ND	ND	268–516
Cl_r (mL/min)			
mean	ND	ND	144.2 (±47)
range	ND	ND	80–200
Cl_{nr} (mL/min)			
mean	ND	ND	887 (±96)
range	ND	ND	742–976
UE (% dose)			
mean	ND	ND	13.9 (±3.7)
range	ND	ND	7.6–20.0

Abbreviations: po, oral; iv, intravenous; $C_{max,}$ maximum plasma concentration; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state; Cl_r, renal clearance; Cl_{nr}, non-renal clearance; UE, urinary excretion; ND, not determined.

The clinical and bacteriological efficacy of spiramycin and penicillin V have been compared in the treatment of streptococcal tonsillitis in children.[16] A group of 299 children suffering from acute tonsillitis and with a positive rapid antigen test for Group A β-haemolytic streptococci (GABHS) were randomized to receive either a 5 day course of spiramycin 100,000 IU/kg twice daily or a 7 day course of penicillin V 25,000 IU/kg three times daily. Clinical and bacteriological assessments were performed at inclusion (day 1), at the end of treatment (days 8–10) and at the follow-up visit (days 25–35). Of the 237 children with positive GABHS culture on day 1, 210 were available for clinical and bacteriological evaluation at the end of treatment. In the spiramycin group, treatment was judged to be 96.1% effective while in the penicillin group the treatment was assessed to be 98.1% effective (not significantly different). Bacteriological eradication was achieved in 79.4% of cases treated with spiramycin and 89.8% of cases treated with penicillin V (not significantly different). At follow-up, 182 children were available for evaluation and clinical cure was observed in 97.7% of the group treated with spiramycin and in 89.4% of the group treated with penicillin V (not significantly different). Three relapses and one reinfection occurred in the penicillin V group. Adverse events, mainly intestinal, occurred in 10.7% of the group treated with spiramycin and in 12.8% of the group treated with penicillin V. The authors concluded that a 5 day treatment with spiramycin is effective and safe for GABHS tonsillitis and is an alternative to penicillin V in children.

The efficacy and safety of spiramycin have also been compared with those of penicillin V in the treatment of 55 patients with acute bacterial tonsillitis.[17] Patients older than 12 years, presenting with acute tonsillitis, were randomly assigned to receive either spiramycin (1 g twice daily) or penicillin V (600 mg three times daily) for a minimum of 4 days and a total treatment duration of 8 days. The most frequently isolated pathogens were streptococci; about one-third were GABHS. There were no clinical failures in the patients treated with spiramycin and only one in the patients treated with penicillin. No side-effects were reported in either of the treatment groups. The authors concluded that spiramycin exhibited efficacy equivalent to that of penicillin V in the clinical cure of bacterial tonsillitis in adults.

In a double-blind, randomized, multicentre trial in general practice, the relative efficacy of spiramycin and doxycycline were compared in 221 adult patients (mean

age 49 years) suffering from pneumonia or acute exacerbations of chronic bronchitis.[18] The spiramycin regimen was 1 g three times daily on day 1 followed by 1 g twice daily for 4.5 days. The doxycycline regimen involved a single dose of 200 mg on day 1 followed by 100 mg/day for 8 days. The investigators were able to evaluate 91 patients treated with spiramycin and 100 treated with doxycycline. There were no significant differences between the cure rates or incidence of adverse events in the two treatment groups. The adverse events in each group were mainly related to the gastrointestinal tract.

In another trial, the efficacy of spiramycin in treating community-acquired pneumonia was investigated[19] in an open study of 188 patients, including 39 who had not responded to other antibiotic therapies. They were treated with spiramycin at the recommended dose of 1 g twice daily for 10 days in general practice. The mean age of the patients was 44.7 years. Clinical and radiological cure was evident in 83% of the patients following the spiramycin treatment and a further 14% of the patients showed clinical and radiological improvement which did not require a change in the treatment regimen. The regimen was modified for five patients (3%) because of treatment failure.

The efficacy and safety of oral spiramycin, 2 g daily, were compared with those of oral erythromycin, 2 g daily, in the treatment of lower respiratory tract infection.[20] The trial was an open, randomized, prospective, multicentre investigation involving 198 outpatients and institutionalized elderly patients with a mean age of 61.7 years. Bronchitis was diagnosed in 155 patients, 96 of whom had acute exacerbations of chronic bronchitis. Bronchopneumonia was diagnosed in 26 patients and pneumonia in 17. The patients were assessed before therapy, and after 3 and 10 days of treatment. In the spiramycin group 76.3% of the patients were considered cured and 6.2% failed therapy. In the erythromycin group 63.4% were cured and 17.8% failed therapy. The differences between groups were significant ($P < 0.05$). Treatment was prematurely withdrawn in four patients treated with spiramycin (all due to lack of efficacy) and in 13 patients in the erythromycin group, due to of lack of efficacy (two cases), adverse events (nine) or both (two). Adverse events were mostly of a gastrointestinal nature. In the spiramycin group 11.8% of patients complained of side-effects whereas in the erythromycin group 41.4% of patients reported these effects ($P < 0.001$).

Since the introduction of spiramycin there have been very few reports of severe adverse reactions. Any gastrointestinal disorders reported have been usually mild and transient,[20] and allergic reactions quite uncommon. Liver injury has been described only once.[21] In contrast to many macrolide derivatives, particularly erythromycin, spiramycin does not bind to cytochrome P450 and does not interact with theophylline or cyclosporin in pharmacokinetic studies.[22] It has not been reported to interact with any other drug. The number of atoms in the ring may affect the safety profile: 14-membered-ring macrolides, such as erythromycin, induce more frequent and severe adverse reactions (particularly gastrointestinal disorders[3] and hepatitis[24]) and drug interactions than spiramycin, which has a 16-membered ring.

The clinical evidence thus demonstrates that, in those countries where it is available, spiramycin is worthy of consideration in the treatment of both upper and lower respiratory tract infections.

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