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Lincomycin: A New Antibiotic Active Against Staphylococci and Other Gram-Positive Cocci:

Clinical and Laboratory Studies

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ABSTRACT

Preliminary results suggest that the antibiotic lincomycin (a product of *Streptomyces lincolnensis* var. *lincolnensis*) possesses certain valuable properties which include good *in vitro* activity against many strains of hospital staphylococci resistant to many other antibiotics. During a study of this agent, a selected series of severe staphylococcal infections due to resistant organisms were treated with lincomycin, with encouraging responses. Favourable results were also noted in seven cases of osteomyelitis. Lincomycin may be administered by the oral or parenteral routes to adults and infants and satisfactory serum blood levels obtained. So far as the authors' limited experience enables them to conclude, and at the dose range tested, this antibiotic promises to be one of low toxicity.

SOMMAIRE

Il ressort des études préliminaires sur la lincomycine que cet antibiotique (produit par *Streptomyces lincolnensis var. lincolnensis*) possède certaines propriétés précieuses, parmi lesquelles une bonne activité *in vitro* contre de nombreuses souches de staphylococciques d'hôpitaux qui résistent à un grand nombre d'autres antibiotiques. Une série de cas d'infections staphylococciques graves, causées par des germes antibio-résistants ont été traités par la lincomycine et les résultats ont été encourageants. On a également noté des résultats favorables dans sept cas d'ostéomyélite. La lincomycine a été administrée par voies buccale et parentérale à des adultes et à des enfants. On a enregistré des concentrations sériques satisfaisantes. Pour autant que notre expérience actuelle, limitée du reste, nous permette de conclure, cet antibiotique promet d'être un agent thérapeutique de faible toxicité aux posologies appliquées.

THE search for new antibiotics continues with unabated vigour. Whereas certain organisms such as the streptococcus, the pneumonococcus and the meningococcus have received the *coup de grâce* from antibiotics in general, others defy attempts at eradication. In particular, two groups of bacteria, the staphylococci and the Gram-negative coliform bacilli, appear to have defied strenuous efforts to subdue them. Over the past two decades, several antibiotics have been developed for use against these bacteria, duly tested, found wanting, and a number unceremoniously discarded. Perhaps one should add that a few in the latter category have returned to favour at a later date. Of the antibiotics which have stood the test of time, the accumulated experience of prolonged usage has revealed that some possess toxic properties. These include undesirable side effects on the hemopoietic system, liver, kidneys, central nervous system, alimentary tract, skin and eighth cranial nerve. To this list must be added further unpleasant phenomena such as drug sensitivity and allergic reactions. Likewise during administration of an antibiotic, readjustment in the balance of the bacterial flora may encourage overgrowth of antibiotic-resistant bacteria and fungi, either commensals or those of obvious pathogenic potential.

Among the many desirable specifications for a successful antibiotic, it should yield good correlation between *in vitro* laboratory tests and *in vivo* clinical results. Unfortunately, such correlations are not always exact, and encouraging *in vitro* effects do not necessarily augur well for a satisfactory clinical response. Thus, despite the advent of new antibiotics, penicillin still remains for the clinician one of the safest and most effective antibiotics yet discovered.

A new antibiotic, lincomycin (Lincocin; Upjohn), was first made available to us for clinical testing in January 1963. This agent, a product of *Streptomyces lincolnensis* var. *lincolnensis*,[1, 2] is unique and is not related chemically to any other commercially available antibiotic. The single salt, lincomycin hydrochloride, can be administered orally, intramuscularly or intravenously. It may be termed a "narrow-spectrum" antibiotic according to the popular classification and, with certain exceptions, is effective only against Gram-positive bacteria. A

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detailed description of the chemical structure of lincomycin has been provided by Herr and Slomp.[3]

This present communication outlines our experience with lincomycin over the past 18 months in the Departments of Bacteriology, Medicine and Pediatrics at Dalhousie University in Halifax, Nova Scotia. We have concentrated on a study of the activity and safety of lincomycin as an antistaphylococcal agent.

BACTERIOLOGY

Sensitivity tests.—The tests were performed using the disc-plate assay method employing three Lincocin paper discs of 2, 15 and 30 μg. strengths, respectively. Any strain which showed the slightest degree of resistance to the 2 μg. disc, but was sensitive to 15 μg. concentration, was designated as "moderately resistant" and classed as "resistant" for the purposes of this study.

TABLE I.—RESULTS OF COMPARATIVE *in vitro* DISC SENSITIVITY TESTS ON STAPHYLOCOCCI RECOVERED FROM PATIENTS AT THE VICTORIA GENERAL HOSPITAL, HALIFAX, NOVA SCOTIA, DURING 1963 AND 1964

Antibiotic	*Strains tested*	*Strains sensitive*	*Percentage sensitive*
Methicillin	1031	1031	100.0
Oxacillin	1031	1031	100.0
Lincomycin	1055	1005	95.2
Penicillin	1058	209	17.7
Streptomycin	1039	366	35.2
Erythromycin	1054	454	43.1
Chloramphenicol	1051	901	85.7
Tetracycline	1046	504	48.1
Novobiocin	1033	687	66.5

Note the high percentage of staphylococcal strains sensitive to methicillin, oxacillin and lincomycin, and the low percentage recorded for penicillin.

Tests on 1055 unselected cultures of coagulase-positive strains of *Staphylococcus pyogenes*, isolated from patients at the Victoria General Hospital, Halifax, and surrounding area, showed that 1005 were sensitive to lincomycin according to our standards, that is, 95.2% sensitive. Of the total of 1055, only three strains were resistant to the 30 μg. disc. Comparable susceptibility tests using other antibiotics against strains of *Staphylococcus pyogenes* recovered at the same institutions, at the same time and (wherever possible) from the same patients, revealed the sensitivity ratios summarized in Table I.

These results reflect the general rise in the resistance of staphylococci to penicillin as indicated by the figure of an 82.3% resistance rate to penicillin from *in vitro* tests in this area. Comparable values reported from England by Barber[4] revealed that in 1946 some 14% of staphylococci isolated at one London hospital proved resistant to penicillin. Subsequently, from the same hospital, Barber and Rozwadowska-Dowzenko[5] reported that the percentage of resistant strains rose to 38 and 59% during the years 1947 and 1948, respectively.

Preliminary results indicate that lincomycin is also active against most strains of *Streptococcus viridans* and *pyogenes* Groups A, C and G. Likewise, several strains of pneumococcus and also some strains of *Clostridium perfringens* appear to be inhibited. The antibiotic does not show *in vitro* activity against *N. meningitidis, H. influenzae,* the enterococcus or *E. coli.*

TABLE II.—LINCOMYCIN

Staphylococcus	*Lincomycin*	*Sensitivity pattern by disc method*					
Strain lab. No.	*M.I.C. (μg. ml.) by the dilution method*	*Penicillin*	*Tetracycline*	*Streptomycin*	*Erythromycin*	*Chloramphenicol*	*Novobiocin*
21880	1.25	R	R	R	R	S	MR
12676	0.62	R	R	R	R	S	S
21669	0.31	R	R	R	R	S	—
21677	0.62	R	R	R	R	S	MR
21651	0.15	R	R	R	R	S	MR
21853	0.15	R	R	R	R	S	—
21799	2.50	R	R	R	R	S	S
21626	0.31	R	R	R	R	S	MR
21842	0.62	R	R	R	R	R	MR

R—No zone of clearing.
S—Marked zone of clearing with high- and low-concentration discs.
MR—Moderate clearing with high-concentration disc and no clearing around low-concentration disc.
M.I.C.—Minimum inhibitory concentration, μg. per ml.

The minimum inhibitory concentration (M.I.C.) values ranging from 0.15 to 2.50 μg./ml. necessary for inhibition of staphylococcal growth *in vitro* lie well below the therapeutic serum blood levels attainable following administration of lincomycin.

Tube dilution minimum inhibitory concentration (M.I.C.) tests.—The results of these tests, summarized in Table II, show that a range of *S. pyogenes* resistant to many antibiotics show *in vitro* test-tube sensitivity to lincomycin in concentrations ranging from 0.15 to 2.50 μg./ml. Equivalent serum levels and still higher values were consistently recorded in the sera of seven patients whose serum levels were measured following oral doses of 1000 mg. every six hours (q.6h.); commonly obtained serum levels were 2.5 and 5 μg./ml., attained within six hours of the first dose. These figures are in substantial agreement with the data supplied by the manufacturer and show that blood levels of therapeutic value, adequate to deal with bacterial infections, may be attained following oral administration.

Clapper, Meade and Stewart[6] reported that serum levels from 0.67 to 3.9 μg./ml. were obtained in four hours following a single oral dose of 500 mg. administered to 10 subjects. Serum levels of 3.7 to 10 μg./ml. were achieved in half an hour and maintained at 2.8 μg./ml. or over for 12 hours in five subjects who received 600 ml. of lincomycin intramuscularly.

Cross-resistance with erythromycin.—Branch[7] of the D.V.A. Hospital, Lancaster, N.B., was unable to demonstrate spontaneous bacterial cross-resist-

ance* between staphylococci resistant to erythromycin and against lincomycin. We, too, have failed to show direct evidence of cross-resistance between these two antibiotics in strains of staphylococci recovered as primary isolates from hospital patients in Halifax. However, different results have been obtained by Barber and Waterworth[8] following the prolonged artificial growth of staphylococci in culture media containing lincomycin and erythromycin (these are referred to below).

The apparent lack of such cross-resistance is worthy of note since the chemical structure of lincomycin differs from that of erythromycin. Erythromycin is a member of the group of antibiotics which possess the macrolytic lactone ring type of chemical structure; oleandomycin and spiramycin are other members of this group. Moreover, it is pertinent to note that Mullins *et al.*[9] suggest that lincomycin is "antagonistic" to erythromycin and that the two should not be used in combination.

Barber and Garrod[10] and Lepper *et al.*[11] state that staphylococci develop resistance to erythromycin more rapidly than to any other antibiotic except streptomycin. Furthermore, Barber and Garrod[10] observed that there is considerable, but not complete, cross-resistance between erythromycin and other macrolide antibiotics. According to Lewis, Clapp and Grady,[2] the *in vitro* rate of development of resistance by staphylococci to lincomycin is comparable to that of erythromycin. Like erythromycin, lincomycin does not allow the "one-step" development of resistance. More recently, Barber and Waterworth[8] have reported development of *in vitro* cross-resistance between lincomycin and erythromycin, following cultivation of staphylococci in the presence of these antibiotics for 25 to 32 transfers. They concluded that, notwithstanding the dissimilarity in chemical structure between lincomycin and members of the macrolide group, there was similarity in antibacterial activity against staphylococci as well as evidence of cross-resistance between these two groups. It was also pointed out that cross-resistance among the macrolide antibiotics pursues a complex pattern which Garrod[12] contends may conform to either the double or dissociated variety of resistance. Further conclusions must wait until lincomycin has been subjected to extensive clinical usage.

A search for possible side effects.—Three patients complained of mild diarrhea early in the course of therapy, but this was not sufficient to interrupt their therapeutic regimen. Two others complained of vague generalized aches and pains which ceased at the end of the course of treatment. One patient complained of generalized itching of the skin which was directly related to the ingestion of the drug. In 10 patients complete examinations, serum blood urea nitrogen and serum glutamic oxalacetic transaminase tests were performed before and after lincomycin therapy. No significant changes were observed.

*Cross-resistance exists when an organism is resistant to one antibiotic and is also resistant to another antibiotic of the same chemical structure or to biologically related antibiotics.

CLINICAL EVALUATION

The clinical trials herein reported are still in progress. Sixteen adult patients and 20 infants have been treated with lincomycin. These have been divided into four clinical groups.

Group I consisted of six patients suffering from severe staphylococcal infection, superimposed upon other critical illnesses. Of these, four had staphylococcal septicemia. After treatment with lincomycin, staphylococcal infection was eliminated in five of these cases. In the sixth case, overwhelming staphylococcal infection was found at postmortem examination after 11 days of combined lincomycin and oxacillin therapy. Previously, all cases in this group had received extensive treatment with other antibiotics. No other antibiotic was added at the time of exhibition of lincomycin, but in three of this group, penicillin therapy was continued concomitantly. Three of the patients in Group I died of the following causes: (1) postoperative cardiac arrest, (2) massive staphylococcal infection with metastasizing carcinoma of the bladder, and (3) massive gastrointestinal hemorrhage. The dosage used in the patients in Group I varied from 15.3 to 64 g. over periods of five to 15 days.

Group II consisted of seven patients with osteomyelitis. In all but one, surgical debridement was carried out before the initiation of lincomycin therapy. It is not possible to draw accurate conclusions under such circumstances. However, we were impressed by the overall response of the patients and by the effect on bacterial cultures. The duration of the osteomyelitis in these patients varied from three months to 60 years. From all cases coagulase-positive staphylococci were recovered. Four of these patients had no other antibiotic therapy whatsoever. The remaining three received the following: the first, 7.5 g. of chloramphenicol concomitantly; the second, local topical applications of neomycin and a wetting agent; the third, intravenous tetracycline for eight days—two months before lincomycin therapy. In three patients excellent clinical results were obtained. The fourth patient died following two episodes of pulmonary embolism. The lesions in the three remaining patients in Group II have not healed as of December 31, 1963, but the discharge from their sinuses remained free of all pathogenic staphylococci. Most patients in Group II were treated orally for three weeks with an average total dosage of 80 g.

The most gratifying results were obtained in the following cases:

CASE 1.—Mrs. L.T., a 20-year-old housewife, underwent a cholecystectomy in December 1962. The operation was followed by bacteremic shock and a prolonged

infectious illness characterized by thrombophlebitis, multiple abscesses and persisting staphylococcal septicemia. She was treated with many antibiotics, including methicillin, ristocetin and kanamycin, but without significant benefit. Ten weeks after surgery, she received a course of 15.5 g. of lincomycin orally over one week and made a complete recovery as evidenced by clinical and laboratory standards. She was re-evaluated at two- and four-month intervals following her hospital discharge and has continued in good health.

CASE 2.—F.N., a 70-year-old retired merchant, developed severe stabbing loin, groin and low-back pain in April 1963. Severe pulmonary emphysema and moderate prostatic hypertrophy were associated with these complaints. For three months, the correct diagnosis eluded his attendants despite many clinical consultations and laboratory procedures. An orthopedic consultant then suggested a review of radiographs of his lumbar spine and this revealed an area of slightly decreased opacity in vertebrae L1 and L2. Material obtained in needle aspiration of this area grew *Staphylococcus pyogenes*, and the patient was treated with lincomycin orally for 20 days. His symptoms disappeared 24 hours after exhibition of the drug, and he has remained clinically well ever since. Radiographs of his spine in November 1963 show fusion of the affected vertebrae. Encouraging results following treatment of patients with "closed" osteomyelitis have been reported by Geddes, Sleet and Murdoch.[13]

Group III was composed of three patients with respiratory infections, and one with a urinary tract infection. Brief case reports are presented below:

CASE 1.—Mrs. V.R., aged 69, was admitted to Victoria General Hospital on December 23, 1963, and discharged on January 28, 1964. Her complaints on admission were cough, pleuritic chest pain, chills and sweating. Dullness on percussion and limitation of expansion were noted in the right lower chest, accompanied by bronchial breathing and coarse rales. Diagnosis of pneumonia was made and her sputum repeatedly grew *Staph. pyogenes*. She was relatively afebrile throughout her hospital course and was treated with tetracycline, novobiocin and erythromycin, without response. She developed a severe dermatitis during the administration of these drugs, and this subsided when the drugs were withdrawn. On January 3, 1964, she was given lincomycin, 1000 mg. every six hours orally for five days, following which her clinical condition improved and bacteriological studies revealed eradication of staphylococci. Laboratory results obtained *before* lincomycin therapy were as follows: Hb. 12.1 g./100 ml., leukocyte count 11,225/c.mm. with 56% polymorphonuclear leukocytes, normal platelets, blood urea nitrogen (BUN) 9 mg./100 ml., and serum glutamic oxalacetic transaminase (SGOT) 88 units/ml. The following laboratory results were obtained *after* lincomycin therapy: Hb. 12.1 g./100 ml., leukocyte count 9025/c.mm. with 46% polymorphonuclear leukocytes, normal platelets, and a BUN of 17 mg./100 ml.

CASE 2.—Mrs. R.S., a 17-year-old married woman, was admitted to the Victoria General Hospital on December 9, 1963 and discharged on January 17, 1964. She was four months' pregnant and had been vomiting for three weeks. Physical examination revealed obesity, a uterus palpable 2 cm. above the umbilicus, and striae gravidarum. Urinalysis revealed a specific gravity of 1.025, hyaline casts, pus cells and red blood cells. On culture, the urine grew *A. aerogenes, E. coli* and *Staph. pyogenes*. She aborted on December 20, 1963, but continued to vomit. The urinary tract infection was treated with tetracycline and streptomycin, but this did not alter her clinical condition. On January 4, 1964, she was given lincomycin orally, 1000 mg. every six hours for 10 days. This eradicated the staphylococcus from her urine and she became clinically well. However, *E. coli* and enterococci persisted in her urine. It is to be noted that concomitantly with her antibiotic therapy she received intravenous fluids and electrolytes.

Before lincomycin therapy, the following laboratory data were obtained: Hb. 13.1 g./100 ml., leukocyte count 7900/c.mm. with 69% polymorphonuclear leukocytes, BUN 84 mg./100 ml., SGOT 84 units/ml. Following her drug therapy these values were: Hb. 11 g./100 ml., leukocyte count 11,500/c.mm. with 69% polymorphonuclear leukocytes, BUN 6 mg./100 ml. and SGOT 19 units/ml.

CASE 3.—L.K.S., aged 44, was admitted to the Victoria General Hospital for operative repair of a non-united fracture of the left leg. An operation was performed on May 16, 1964, and was immediately followed by fever, chills, sweats and left anterior chest pain, pleuritic in type. Daily fever elevations to 100° and 101° F. were noted. *Staph. pyogenes* and *A. aerogenes* were cultured from his sputum. His illness persisted in spite of penicillin and streptomycin therapy. He was given 1000 mg. of lincomycin every six hours for five days and became clinically well. The staphylococcus was eradicated from his sputum, but a light growth of coliform organisms remained. No toxic effects were observed. He was discharged on June 13, 1964.

Group IV consisted of 20 infants ranging in age from 4 to 22 months who had been given lincomycin intramuscularly. The dosage employed was 10 mg./lb. body weight, administered as a single injection every 24 hours. The duration of treatment varied from six to 10 days. These patients were selected from among those with respiratory illnesses who would otherwise have received penicillin therapy. The range of conditions treated included otitis media, upper respiratory infection and bronchopneumonia. All the infants showed a satisfactory response to treatment after two to three days. Bacteriological culture and sensitivity tests were conducted on the sputum of these infants before and after treatment.

Toxicity studies.—The following tests were performed before and after administration of lincomycin: hemoglobin; white cell counts, total and differential; assessment of platelets; serum glutamic oxalacetic and pyruvic transaminase (SGOT and SGPT); blood urea nitrogen and examination of centrifuged urine. The last included tests for protein, sugar, ketones, specific gravity and microscopic appearance of sediment. In three cases, a twofold increase in the SGOT level from a normal of 40 units/ml. to between 60 and 80 units/ml. was noted.

No associated changes were observed in the patient's condition, and the SGOT levels were interpreted as falling within the normal range of fluctuation.

Discussion

Some nine years ago, lincomycin was discovered during the course of a routine soil screening program. This suggests that man has not yet exhausted nature's store of naturally occurring antibiotics which can be derived from soil. Thus contrary opinions, which favour a search for new antibiotics through modification of the chemical structure of existing and older antibiotics would seem to be premature. When new antibiotics are introduced to the medical profession and public, a variety of predictable and unpredictable, long- and short-term factors must be considered. With the passage of time and progressive increase in use of penicillin, the number of allergic reactions to this agent and its derivatives among the exposed population is more likely to increase than to diminish.

From the immediate and practical point of view, lincomycin offers an alternative antibiotic for use against those organisms which are either sensitive or resistant to erythromycin. Likewise, lincomycin may offer a substitute for penicillin, in subjects sensitive to the latter. By virtue of its apparent low toxicity, even in high dosage (where such is necessary), lincomycin possesses some advantages over other antibiotics for the treatment of severe staphylococcal infections complicated by renal, hemopoietic or ear damage, and where vancomycin, ristocetin, chloramphenicol or kanamycin may be contraindicated.

Summary

Preliminary results suggest that lincomycin possesses certain valuable properties; these include good *in vitro* activity against many strains of hospital staphylococci resistant to many other antibiotics. A selected series of severe staphylococcal infections due to resistant organisms have been treated with encouraging results. Lincomycin may be administered by the oral or parenteral route to adults and infants. Satisfactory serum blood levels have been obtained. As far as our limited experience enables us to conclude, this antibiotic promises to be one of low toxicity at the dose range tested.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE WAR AND THE WOUNDED

The first contingent of the Canadian Expeditionary Force has arrived safely in England and is undergoing a further period of training preparatory to leaving for the front. Another contingent of 10,000 men will follow, and the recruiting is proceeding rapidly; in fact applications are coming in so quickly that it is doubtful whether all those who now volunteer will be able to go with the next contingent. Arrangements are being made, however, to continue the training of troops after the embarkation of the next contingent and until the cessation of hostile activities. It is understood that 10,000 men will leave about the end of December. But it is not sufficient to send the men; provision must be made for the care of those who are wounded or fall ill from exposure and hardship. With exclusion of the Russian and Austrian armies, there are more than two millions now fighting in Europe. The loss of life and the number of wounded must be enormous, greater than in any previous war, not only because of the numbers participating but because of the deadly perfection of the modern invention; and from experience in former battles it is to be expected that the sick and wounded will number at least 20 per cent of the armies engaged in conflict, probably more. In the South African war, the British invalided 73,977 men out of an army of 325,000, which means that in the next few months there will be 400,000 sick and wounded soldiers in the armies taking part in the European war. This percentage among the British troops may be decreased somewhat by the general inoculation against typhoid fever, but whether the same precaution has been taken in the other armies is uncertain, and as every wounded man becomes a subject for medical attention no matter what his nationality, the treatment may have less effect upon the numbers requiring medical care than might have been expected.

The Canadian government has provided that 2090 beds shall accompany the first two contingents; about half of these have been sent with the troops now in England. That is, provision has already been made for two general hospitals each with 520 beds, two stationary hospitals each with 200 beds, one clearing hospital with 200 beds, and three field ambulances each with 150 beds. The personnel of medical officers, nurses, orderlies, drivers, and cooks will number about 1100.

The work of the Army Medical Corps is largely supplemented by the Red Cross. Five hospitals have been organized in Paris, and the wounded are brought to them from the field hospitals. The Canadian Red Cross Society has already transmitted $50,000 to the Central British Committee at London and lesser sums have been sent by local branches in the Dominion.—Editorial, *Canad. Med. Ass. J.*, 4: 994, 1914.