

jejunal ulcer cannot be stressed too emphatically, particularly because such complications as peritonitis, intestinal obstruction and small bowel obstruction can occur.

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SHORT COMMUNICATION

NOVOBIOCIN-TETRACYCLINE*
IN THE TREATMENT OF EAR, NOSE
AND THROAT INFECTIONS†

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SINCE ANTIBIOTICS play such an important role in the treatment of ear, nose and throat conditions, we must be alert to any means by which this therapy might be improved. The search for more effective antibacterial agents has led to the trial of various antibiotic combinations.

Admittedly, determination of bacterial sensitivity is the ideal way to select the proper antibiotic in each case, but it is hardly feasible in routine office

The combination of tetracycline and novobiocin has been shown to be effective in a variety of infections.⁴⁻¹⁰ The purpose of this study was to investigate the usefulness of such a combination in the treatment of otolaryngological infections. Furthermore, we wished to investigate the efficacy of a twice daily dosage schedule for the more commonly encountered ear, nose and throat infections.

Novobiocin, which was introduced in 1956, is active against Gram-positive organisms and certain Gram-negative organisms.¹¹ Of particular importance is its demonstrated efficiency in common infections including those caused by staphylococci and strains of *Proteus* which most often pose the problem of resistance to older antibiotics.¹²⁻¹⁴

TABLE I.—MINIMUM INHIBITORY CONCENTRATION OF NOVOBIOCIN AND TETRACYCLINE ALONE COMPARED WITH THE MINIMUM INHIBITORY CONCENTRATION WHEN THE TWO ARE COMBINED IN A RATIO OF 10 PARTS OF NOVOBIOCIN TO 1 OF TETRACYCLINE

Organism	Novobiocin	Tetracycline	Novobiocin-tetracycline combination
<i>M. aureus</i> , UC-391.....	0.09	100.0	0.04/0.004 µg./ml.
<i>M. aureus</i> , UC-76.....	0.09	0.4	0.04/0.004
<i>P. rettgeri</i> , UC-302.....	3.1	50.0	1.5/0.15
<i>S. fecalis</i> , UC-151.....	1.5	0.19	0.78/0.078

or home treatment. The most practical compromise appears to be the selection of medication which will be effective against the range of bacteria most often encountered in the type of infection to be treated. It should also effectively combat strains frequently resistant to other antibiotics, particularly staphylococci, which have been highlighted as a problem in today's antibacterial therapy.

Leading investigators^{1, 2} have taken fixed stands for and against some of the uses of antibiotic combinations. Clarification of these issues is desired by the confused and perplexed practitioner who wants to use those antibiotic preparations which will cure his patients most quickly and inexpensively. For these reasons the clinician looks with interest at some of the newer antibiotics, such as novobiocin,³ at the possible value of antibiotic combinations, and at the therapeutic value of preparations requiring less frequent administration.

The tetracyclines are active against a variety of Gram-positive and Gram-negative organisms. However, their potential and prime deficiency lies in the development of resistance by the staphylococcus. A report by Welch and associates¹⁵ on untoward reactions to antibiotics, as determined from a national survey, indicates that the most frequently encountered serious complication of tetracycline therapy is staphylococcus superinfection.

With the combination of novobiocin and tetracycline there is complementary antibacterial coverage. Each reinforces the other in their mutually shared range of activity. In addition, the combination should offer a wider range of activity than that afforded by either antibiotic alone.

Most important, however, novobiocin imparts to the combined therapy a high degree of effectiveness in staphylococcal infections which might be resistant to, or become resistant to, tetracycline alone.

Novobiocin and tetracycline are absorbed to different degrees in the gastrointestinal tract. The

*Supplied as Albamycin T by the Upjohn Company of Canada.
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TABLE II.—BACTERIA OBTAINED FROM SITES OF ENT INFECTION IN 80 PATIENTS. MORE THAN ONE ORGANISM WAS INVOLVED IN SIX OF THESE INFECTIONS

Organism cultured	Frequency of occurrence
<i>Streptococcus</i> (hemolyticus, non-hemolyticus, viridans).....	38
<i>Staphylococcus aureus albus</i>	23
<i>Proteus morganii mirabilis</i>	2
<i>Pseudomonas pyocyaneus aeruginosa</i>	12
<i>Paracolobactrum intermedium coliform</i>	2
<i>Klebsiella aerobacter</i>	1
<i>Escherichia intermedium</i>	1
Fusiform bacillus and spirochetes.....	2
No growth.....	5

blood concentrations attained are of the order of 10 parts of novobiocin to one of tetracycline.¹⁶ Thus, of all the laboratory data that have been amassed regarding combinations of the two antibiotics, those which hold the most significance are the data pertaining to inhibitory concentrations in a 10 to 1 ratio. Table I indicates how the minimum concentration of novobiocin alone and of tetracycline alone compare with the minimum 10 to 1 combination concentration that will inhibit the growth of several different organisms.¹⁷

In each instance the amount of novobiocin required in the novobiocin-tetracycline combination was about one-half that required with novobiocin alone. The tetracycline concentration in the combination was considerably less than half of that required with tetracycline by itself. This suggested

that a formulation containing 125 mg. of novobiocin with 125 mg. of tetracycline might possess the same therapeutic potential as that of 250 mg. of either antibiotic alone.

MATERIALS AND METHODS

Two preparations of the antibiotic combination (Albamycin T) were supplied to us—tablets and flavoured granules for suspension. Each tablet contained novobiocin 125 mg. and tetracycline 125 mg. The granules were prepared for administration by adding 50 c.c. of tap water to the bottle in which they were contained. Each 5 c.c. teaspoonful of the suspension provided novobiocin 62.5 mg. and tetracycline 62.5 mg.

A total of 80 office and hospital patients with ear, nose and throat infections were treated by these preparations. Since Pinto⁹ and Birkett¹⁰ reported good results in a number of clinical infections after twice daily doses of novobiocin-tetracycline, we felt that this dosage schedule could be applied in the treatment of otolaryngological infections. Accordingly, 68 patients received two tablets twice daily for a total of 1 g. of the combined antibiotics per day. Twelve children, ranging in age from nine weeks to 10 years, were treated by the suspension. Dosage of this preparation was calculated to provide at least 15 mg. of the combined antibiotics per kg. body weight per day. Ten children were on a twice-daily dosage schedule and two received the drug every six hours.

Bacteriological studies were made in all patients. Material for culture was obtained by swabs from the pharynx and, in the cases of otitis media, from the exudate of the middle ear made available by

TABLE III.—DIAGNOSES AND ORGANISMS ENCOUNTERED IN 80 PATIENTS TREATED WITH NOVOBIOCIN-TETRACYCLINE COMBINATION. MORE THAN ONE DIAGNOSIS WAS MADE IN A NUMBER OF PATIENTS

Number of cases	Diagnosis	Organisms cultured	Frequency of organisms
60	Acute purulent or catarrhal otitis media.....	<i>Staphylococci</i>	22
		<i>Streptococci</i>	18
		<i>Pseudomonas</i>	12
		<i>Proteus morganii</i>	1
		<i>Proteus mirabilis</i>	1
		<i>Paracolobactrum intermedium</i>	1
		<i>Paracolobactrum coliforme</i>	1
		<i>Escherichia intermedium</i>	1
		<i>Klebsiella aerobacter</i>	1
		No growth of organisms	4
			Total 62
18	Acute tonsillitis.....	<i>Streptococci</i>	19
4	Acute (maxillary or pan-) sinusitis.....	<i>Streptococci</i>	4
20	Acute pharyngitis.....	<i>Paracolobactrum coliforme</i>	1
		<i>Streptococcus</i>	20
		<i>Staphylococci</i>	1
			Total 22
2	Laryngitis.....	<i>Streptococci</i>	2
2	Acute tracheitis.....	<i>Streptococci</i>	2
2	Cellulitis (auricle and nose).....	<i>Streptococci</i>	1
		No growth	1
1	Vestibulitis.....	No growth	1
2	Vincent's angina.....	Fusiform bacillus	2

spontaneous rupture or surgical drainage of the drum.

RESULTS

Seventy-four of the 80 patients responded satisfactorily to treatment by novobiocin-tetracycline. The other six patients, four of them children, had been treated elsewhere by all types of antibiotics. Albamycin T therapy was immediately begun and when x-ray results revealed definite necrosis of the mastoid cells, simple mastoidectomy was performed. Postoperative courses were uneventful.

In seven patients with acute purulent otitis media in which myringotomy was indicated, the antibiotic combination was also administered, and in all patients recovery was complete.

There were no gastrointestinal disturbances, but in two patients an annoying pruritic, maculopapular rash appeared. This disappeared upon withdrawal of the drug and after treatment with antihistamines as well as corticosteroids.

The frequency of occurrence of various organisms encountered in this series of patients is presented in Table II. It is noteworthy that staphylococci were cultured from sites of infection in more than one-fourth (28.5%) of the 80 patients.

SUMMARY

The effectiveness of a novobiocin-tetracycline combination for the treatment of a variety of ear, nose and throat infections was demonstrated in this series of 80 patients. The antibacterial spectrum of this combination encompasses the organisms commonly encountered, including staphylococci often resistant to other antibiotics. Novobiocin plus tetracycline is effective in a combined dosage equal to the usual dose of either component employed singly. It permits the physician to employ a convenient twice daily dosage schedule in most cases.

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