A REVIEW OF THE CLINICAL USES OF AUREOMYCIN

Lederle

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

Printed in U. S. A.

8265-150-AC-8/51

A review
of the clinical uses of

AUREOMYCIN

EDITION 1951

Lederle

A Review of the Clinical uses of

AUREOMYCIN

Table of Contents

	Page
Introduction	7
Pharmacology	11
CHAPTER I. Infections Seen Chiefly by Internists	15
CHAPTER II. Infections Usually Seen by Neurologists and Neurosurgeons	75
CHAPTER III. Infections Usually Seen by Pediatricians	86
CHAPTER IV. Infections Seen Chiefly by General Surgeons	106
CHAPTER V. Infections Usually Seen by Gynecologists and Obstetricians	139
CHAPTER VI. Infections Usually Seen by Orthopedic Surgeons	149
CHAPTER VII. Infections Seen Chiefly by Otolaryngologists	156
CHAPTER VIII. Infections Usually Seen by Urologists	164
CHAPTER IX. Infections Usually Seen by Dermatologists	176
CHAPTER X. Infections Usually Seen by Ophthalmologists	203
Bibliography	218
Index	242

A review of
the clinical uses of

AUREOMYCIN

Lederle

THE ADVANCES made by medical science, in the millennia that have elapsed since its first beginnings were recorded, have been overshadowed by the discoveries of the past hundred years. The elaboration of the theory of bacterial causation of disease, the recognition of antimicrobial substances and the establishment of the fundamentals of immunology, which were the contribution of the late nineteenth century, have led in the first half of the twentieth century to a degree of mastery of infectious disease which was unhoped for by our ancestors, although not undreamed of. In rapid suc-

cession have come the various sulfonamides and antibiotics, each one with something additional to offer, whether of higher potency, of wider versatility or of decreased toxicity. The advance has not reached its culmination and the achievements of the past entitle us to hope for even greater ones in the future.

In the fall of 1948, Dr. Benjamin M. Duggar of Lederle Laboratories Division, American Cyanamid Company, reported[202] to the New York Academy of Sciences the isolation of a new crystalline antibiotic from *Streptomyces aureofaciens*, a hitherto little-known soil organism. In a prolonged and tedious search by the Lederle research team, all known strains of this mold, most of which produce a yellow pigment, were tested, and extensive antibiotic studies were made *in vitro* against more than 50 species of microorganisms, including pathogenic and non-pathogenic bacteria, plant pathogens, fungi and yeasts. The *aureofaciens* isolates gave striking results with *Bacillus cereus*, *Bacillus subtilis*, *Micrococcus pyogenes var. aureus*, *Streptococcus pyogenes* and *Mycobacterium tuberculosis*, all of which are Gram-positive, and with the Gram-negative organisms, *Escherichia coli*, *Aerobacter aerogenes*, *Salmonella pullorum*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Neisseria catarrhalis*, and *Eberthella typhosa*. *Shigella gallinarum*, *Brucella abortus* and other species also showed fairly high sensitivity, while *Pseudomonas aeruginosa* and *Serratia marcescens* were somewhat resistant. In general, there was no effect on yeasts and fungi, except upon some of the *trichophyta*. Later work by Campbell, Saslaw and Strong[109] indicated that aureomycin also had a marked inhibitory effect on *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis*.

Although a comparative newcomer in the field of infectious disease, aureomycin has already given striking clinical indication of a scope and power beyond that indicated by this preliminary experimental work, often proving far more effective in actual human disease than would appear likely from *in vitro* tests on the pathogen concerned, although in some cases showing poorer

results, as in tuberculosis and typhoid. More important even than this, it has been found to be active against 2 hitherto resistant families of organisms, the rickettsiae and the large viruses of the psittacosis-lymphogranuloma group. Hobby, Lenert and Dougherty[338] have emphasized that the ideal antirickettsial and antiviral agents, when they are ultimately found, may be very different chemically from present antibacterial antibiotics.

Aureomycin is now recognized as the most versatile antibiotic yet discovered, with a wider range of activity than any other known remedy.[64,395] It is indicated for the treatment of acute amebiasis, bacterial infections associated with virus influenza, bacterial and virus-like infections of the eye, bacteroides septicemia, boutonneuse fever, brucellosis, chancroid, Friedländer infections (*Klebsiella pneumoniae*), gonorrhea, Gram-negative infections (including those caused by some of the coli-aerogenes group), Gram-positive infections (including those caused by streptococci, staphylococci, and pneumococci), granuloma inguinale, *H. influenzae* infections, lymphogranuloma venereum, peritonitis, pertussis infections (acute and subacute), primary atypical pneumonia, psittacosis (parrot fever), Q fever, rickettsialpox, Rocky Mountain spotted fever, sinusitis, subacute bacterial endocarditis resistant to penicillin, as an adjunct to adequate surgery in a wide variety of surgical infections, tick-bite fever (African), tularemia, typhus and the common infections of the uterus and adnexa.[101,113,307,317,436,463,756]

Cantor[110] remarks that aureomycin is likely to replace penicillin and the sulfonamides in the treatment of coccal infections and that, except for tuberculosis, it is perhaps superior to streptomycin in the control of bacillary infections.

Although aureomycin has been found relatively nontoxic and effective against a wide range of microorganisms, so that where accurate diagnostic facilities are not available, it is frequently given at the onset of an infection; nevertheless, it is very

important wherever possible to determine the causative organism and its sensitivity to the various chemotherapeutic agents. Even among organisms normally sensitive to a certain antibiotic, there may appear relatively or absolutely resistant strains, and if more than a single antibiotic is to be used, care must be taken to choose those which act additively. Spicer[675] has found that in a combination of a moderately effective antibiotic with one of high activity, the former either may have no effect or may impede the action of the latter. If an organism is resistant to one antibiotic, its growth may even be stimulated. Bacterial sensitivity tests are therefore of particular importance in combined therapy. Meleney[483] deplores the tendency towards the indiscriminate use of antibiotics. Much valuable time may be lost and irreparable damage done by this practice. He considers that no surgeon or physician should treat any infection with any antibiotic without the aid of a laboratory if there is one available, and that every patient has a right to this type of service.

Following the use of any antibiotic, a certain proportion of viable organisms remains. This accounts for many of the relapses observed when therapy is stopped too early, before the host's defense mechanism can subdue the invaders.

Pharmacology

Aureomycin is an amphoteric compound[338] that may be given by the oral or intravenous route. Hoffman, Wellman and Herrell[339] have observed little or no absorption into the blood stream when aureomycin is given as a retention enema. Oral administration is the preferred method. In urgent cases the intravenous administration is advisable, since maximum concentrations may thus be attained in 5 minutes.[437] The drug readily passes into the blood stream, whence it diffuses rapidly into all the tissues and fluids of the body, as well as into ascitic and pleural fluid,[194] and through the placenta into the fetal circulation.[288] Measurable serum levels are maintained for as long as 12 hours after oral administration, oral doses of 5 to 10 mg. per kilo at 6-hour intervals being adequate for this purpose. The drug appears rapidly and in high concentration in the urine, and can be detected for as long as 55 hours after a single oral dose of 0.5 or 0.7 Gm. Increasing the dose of aureomycin beyond 1.0 Gm. daily does not proportionally increase blood concentrations. Divided doses of 0.25 Gm. every 6 hours have given levels almost as satisfactory as those following doses of 0.5 Gm., 0.75 Gm. or 1.0 Gm. every 6 hours.[742] This may account for the fact that frequently good therapeutic results have been reported with small dosages.

Although there were early reports of gastrointestinal upsets, particularly in ambulant patients, during the first months of aureomycin therapy, it was rarely necessary to discontinue the drug. Side effects have been greatly diminished by increasing purification of the drug. Many physicians prefer to administer aureomycin at meal time, or with a glass of milk or buttermilk.[43,489,576,778] Rapid loss of activity in alkaline solution renders the combination of aureomycin with alkalies inadvisable, and the use of aluminum gels may decrease therapeutic activity

by interfering with aureomycin absorption,[189,277,648] although it tends to control gastrointestinal symptoms. Greenspan and coworkers[277] have found sodium carboxymethyl cellulose to be effective in controlling digestive disturbance, without interference with intestinal absorption or demonstrable effect upon serum aureomycin levels.

Hypersensitivity reactions to aureomycin have been reported, although they are relatively uncommon. Dermatitis, stomatitis and diarrhea have been reported. There will undoubtedly, however, be some persons who will develop more serious reactions. This is to be expected in allergic disorders and in those diseases which are characterized by a tendency towards Herxheimer reactions following any form of effective therapy. The frequency and seriousness of penicillin reactions appear to be increasing,[250] and aureomycin has been found useful in many cases showing sensitivity to this antibiotic.

When any orally administered antibacterial agent is given over extended periods, there is always the possibility of its interfering with bacterial intestinal synthesis of vitamins. It therefore seems advisable, when giving aureomycin or any similar remedy for long periods of time, to prescribe supplementary vitamins, especially those of the vitamin B complex.

There would appear to be little necessity to administer vitamins parenterally or intravenously to all patients receiving antibiotic therapy, unless without such therapy they would have required therapeutic vitamin supplementation. The consensus is that the ordinary daily requirement of vitamins, indicated as a supplement to those received in the diet, should be given to all patients who are receiving aureomycin daily for a period of 5 days or longer.[560]

Aureomycin is irritant to some tissues, but, in 0.5% solution as the borate, is without harmful effect on the sensitive conjunctival tissues, so that a solution of this strength is successfully used in the treatment of ophthalmic infection. Phlebitis,

which was noted as a result of intravenous administration, particularly into the veins of the lower extremities,[318] has been substantially decreased by the use of the present glycine diluent, although it is advisable to give the solution slowly.

In contrast to the observed tendency of other antibiotics to permit development of resistant strains of organisms, there is relatively little indication of such a trend with aureomycin. Increased drug resistance has been produced experimentally by serial culture, but this is of a low order and is not clinically important.[230] Fortunately, development of bacterial resistance to a single antibiotic does not necessarily involve simultaneous increase in resistance to others, so that many organisms which have developed marked resistance to penicillin or streptomycin can still be successfully attacked by aureomycin.[209]

Marked disparity has been observed between *in vitro* and clinical results with aureomycin, the result in all probability of its instability in the culture media employed. The observation of a relatively low effectiveness for aureomycin *in vitro* should not, therefore, deter the clinician from trying it where he feels that it may be useful.

A comprehensive review of the earlier literature on aureomycin from the standpoint of its history, its physical and chemical properties, its experimental activity, its pharmacology and its therapeutic applications, particularly in the treatment of brucellosis, forms the subject of a recent doctorate thesis, submitted to the Faculty of Medicine of Paris by Mouraret.[500]

AUREOMYCIN

Chapter One

Infections Seen Chiefly by Internists

Amebiasis

Aureomycin is an efficient amebicide, both experimentally[329] and clinically, comparing favorably with the standard remedies, without having their systemic toxicity.[290] Its immediate effect at least seems to be superior to that of other amebicides.[664] It destroys both the cysts and the trophozoite forms of *E. histolytica* and should therefore be an important aid in control of the carrier state.[726] The average therapeutic dosage appears to be 500 mg. every 6 hours, to a total of about 20 Gm. Negative stools have been obtained after as little as 6.75 Gm. Thus, aureomycin would appear to be the only amebicide which shows indications of activity against both forms of the parasite and most sites of invasion.

At present, its use as the sole remedy recommended for systemic amebiasis is still in the experimental stage. It seems to be of value in amebic hepatitis and is without serious toxic effects even in the presence of liver involvement,[290,387,494] but its present accepted usage is in intestinal amebiasis.

Thiodet and co-workers[708] found that in a case of suppura-