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Aureomycin in the treatment of brucellosis

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TABLE OF CONTENTS

Page

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General Considerations

Brucellosis is a not uncommon disease which tends to be chronic, recurring, and debilitating. Thus, since the advent of the "wonder drugs", many attempts have been made to find an agent therapeutically specific against the brucella organism. The sulfas, and the subsequent antibiotics have been tried singly and in combination, and all except chloromycetin leave something to be desired. Many cases become chronic and are apparently refractory to the sulfas; penicillin seems to have practically no antibrucella effect; and streptomycin, though sometimes effective, carries the threat of the well known toxic reactions, sometimes more severe than the disease itself. For these and other reasons the drugs mentioned have proven not to be completely satisfactory (3). Thus, a drug which could satisfy certain conditions was still being sought as late as 1948. Such a drug ideally would have the following properties:

1) It would be effective when given orally.

2) It would have no marked toxic side reactions.
3) It would be satisfactory given to ambulatory patients so that the expense of hospitalization may be avoided.
4) It would eradicate the brucella organism from the host tissues (2).

Such a drug may be aureomycin.

History of Development

Aureomycin is an antibiotic derived from cultures of Streptomyces aureofaciens. The discovery of this new agent was first described by Duggar in 1948. Though its antibacterial effects were noted by Duggar, the first thorough studies of its specific properties were conducted by Dr. Y. Subbarow at the Lederle Laboratory Division of the American Cyanamid Company. Under his direction, the development and experimental investigations were conducted. Important findings were that the drug was bacteriocidal against Brucella abortus and Brucella suis (6). Dr. J. Shaffer found, in addition, that aureomycin had a specific antibrucella effect against strains of Brucella abortus isolated from humans (2). Doctors Yow, Magoffin, and Braude, working at the University of Minnesota Hospital, further noted

that the drug was readily absorbed from the gastro-intestinal tract if given orally. Thus, a new antibiotic had been discovered, found to be satisfactorily absorbed if given orally, and found to have at least an antibrucella effect against cultures of the organism, including cultures isolated from patients with the disease. The efficiency of the drug in further experiments, its possible toxic effects, and, above all, its clinical potential were as yet unproven.

In Vivo Studies

After the above studies, other investigators began a more critical analysis of aureomycin. Doctors Yow and Magoffin, using chick embryos innoculated with various strains of Brucella organisms, found that weight for weight, streptomycin was considerably more effective against all three strains than was aureomycin (2). (Strangely, though, and for no known reason, this in vivo discovery was found to be reversed in clinical therapeutic trials using both agents.) Magoffin, Anderson, and Spink, again utilizing chick embryos, compared the in vivo efficiency of aureomycin, various sulfa preparations, and streptomycin. The agents were used separately and in all combinations upon chick embryos which had been

innoculated, and then incubated for twenty-four hours before drug administration. These workers concluded that:

1) Aureomycin prolonged the survival of the chick embryos, but didn't eradicate the organisms from the tissues.
2) Aureomycin combined with streptomycin or sulfadiazine was more effective than aureomycin alone (9).

Thus, in vivo studies, though they did show aureomycin to have a specific antibrucella effect, were misleading as to the true potency of the drug as later revealed by clinical results. First, laboratory studies indicated that streptomycin had a more pronounced effect against the Brucella organisms than did aureomycin. The contrary was found true in later therapeutic trials (5). Second, aureomycin failed to eradicate the organism from the tissues. To the contrary, exhaustive attempts by Bryer, Schoenbach, Wood, and Long failed to recover the organisms from a series of patients who had been treated with aureomycin (10). Third, chick embryo experiments indicated that aureomycin, though effective alone, was more effective when used in conjunction with streptomycin or sulfadiazine. Clinical findings from a

series of twenty-four patients later showed that those receiving aureomycin alone improved as rapidly as those receiving a combination with sulfadiazine (2). Though laboratory investigations were misleading, as later proven by clinical results, nevertheless, important facts were learned. An in vivo specificity of aureomycin against Brucella organisms was positively shown; however, the possibility of undesireable side reactions had yet to be investigated.

Toxic Manifestations

Bryer and his co-workers showed that aureomycin in therapeutic dosage caused no untoward effects in dogs. Massive doses did cause weight loss and anorexia, both of which were reversible when the drug was discontinued (1). Dr. Subbarow, giving as much as 1.5 grams of aureomycin per day to humans, found no severe toxic effects. His experiments included thorough renal, hepatic, and hematological tests (6). Bryer and co-workers also found renal, hepatic, and hematological tests not to be remarkable during the course of therapy of five patients. Furthermore, the only toxic reaction which was noted (nausea due to gastric irritation) was easily relieved by aluminum hydroxide (10). Spink, with similar dosages, noted

only mild nausea and vomiting and soft stools (4). Knight and co-workers did note a peculiar phenomenon in the treatment of a case of brucellosis. The patient, a twenty year old female, developed hyperpyrexia (40 degrees C.) accompanied by shaking chills thirty-six hours following the initiation of therapy (11). Spink and co-workers noted the same side effect in twelve of twenty-four patients receiving aureomycin therapy. Approximately twelve hours after the first dose, a temperature spike developed along with a fall in blood pressure and an increase in heart rate. This hyperpyrexia and general shock-like picture resolved itself with no consequences after a few hours. Spink noted that this effect didn't occur at all in patients receiving an initial dose of less than 0.5 grams. Further such reactions were avoided by smaller initial dosages (2). Laboratory and clinical tests thus reveal that the only toxic side effects of aureomycin therapy are mild and transient. The nausea is easily counteracted by aluminum hydroxide, the soft stools are of no consequence, and the hyperpyrexia accompanied with shock is avoided entirely by using initial dosages of less than 0.5 grams.

Thus far, clinical and laboratory evidence

revealed a new antibiotic with a specific anti-brucella effect, and one which carried little threat of serious side reactions. The clinical ability of the drug to improve or possibly cure the disease was still not known.

Clinical Efficacy

The following discussion of clinical usage of aureomycin in brucellosis will be, in part, made up of case histories for two reasons; first, the subject is so new that much of the literature consists of little but case reports, and second, the response to aureomycin was so utterly dramatic as to warrant the mention of case histories to emphasize the point.

1) Boyd and Prignano report the successful treatment of a nine year old girl who contracted the disease by drinking raw milk in Italy. Previous courses of streptomycin and of penicillin were ineffectual. A course of one 250 mg. capsule five times a day for eleven days was followed. Within four days the child was asymptomatic, and all traces of a previous hepatomegaly and splenomegaly had disappeared. They reported "prompt and permanent relief of a brucella

abortus case which was unaffected by penicillin or streptomycin" (1).

2) Bryers, Schoenbach, and co-workers reported equally gratifying results in a series of four patients with suis and one with abortus infestation. In all five patients, sulfadiazine, streptomycin, and polymixin had all been tried to no avail. Within twenty-four hours after the initiation of aureomycin therapy, blood cultures were negative, and after seventy-two hours all patients were afebrile and asymptomatic. All five patients had elevated sedimentation rates which decreased with therapy. Symptoms of headache, fatigue, myalgia, arthralgia, anorexia, and night sweats all regressed. Enlarged livers and spleens all decreased. Follow up studies one year later revealed all patients had gained weight and were working. There were no recurrences (10).

3) J. Galpine reports an equally remarkable case. A fifty-eight year old man was acutely ill with a positive diagnosis of brucellosis. His therapy was one 250 mg. capsule every twelve hours for two days, then two 250 mg.

capsule every six hours for seven days. He, too, had shown little response to other antibiotics, but was afebrile seventy-two hours after aureomycin initiation. There were no toxic reactions, and six months later the patient had had no recurrences (7).

4) H. Harris writes of very encouraging though not quite so dramatic results in a series of fifty-five patients. Forty-nine made a partial or complete recovery, and six showed no response. His conclusion was, "aureomycin favorably influences the course of brucellosis" (8).

5) Knight and co-workers add more evidence as to aureomycin's specific, immediate antibrucella effect with an additional series of five patients. At the start of treatment, four were febrile with an acute brucellosis infection, and one was afebrile with a chronic form of the disease. The presence of the disease in all five was verified by tests for bacteremia and antibody titres. The course of therapy was six grams of drug in divided doses the first day, and four grams thereafter for each of the succeeding five days.

Within four days, all four acutely febrile patients had normal temperatures and had lost all symptoms of joint pains, malaise, and anorexia. Of interest is the fact that the fifth patient who was suffering with chronic brucellosis showed absolutely no clinical response to therapy. His arthralgia and anorexia persisted in spite of treatment (11).

6) Spink and co-workers have submitted probably the most thorough studies of the subject. His series consisted of twenty-four patients infested with B. melitensis. The patients ranged in age from four to fifty-four years. The duration of their respective illnesses ranged from a few days to one year. Dosages for the twenty-four patients varied from 1-2 grams/day, and course of therapy from 9-15 days. Spink treated half of these patients on an ambulatory basis and the other half was hospitalized. To his gratification, the half treated as out patients showed just as satisfactory a clinical response as those that were hospitalized. One half of the patients was given aureomycin

in conjunction with streptomycin, the other half aureomycin alone, since, as previously discussed, in vivo studies had misleadingly indicated streptomycin to be much more effective against brucellosis than aureomycin. Again, Spink was pleased to note that those who combined therapy exhibited a response in no way superior to the response of those treated with aureomycin alone. Results exceeded all hopes in that all twenty-four patients were totally asymptomatic and afebrile within two or three days.

One patient with severe chronic brucellosis of one year's duration showed total recovery in one week.

Another patient, a riding instructor who had been incapacitated, was back at work in one week.

A pregnant woman with a melitensis bacteremia (which usually leads to abortion) was asymptomatic within five days, and carried her pregnancy to term and a normal delivery.

Possibly the most dramatic response was that of a severely ill older woman. She had temperature spikes as high as 105 degrees,

purpura hemorrhagica, splenomegaly, and anemia. Five days later, her temperature was normal, her purpura receeding, her spleen no longer palpable, and her blood cultures sterile.

All patients in the series became afebrile, gained weight, and maintained sterile blood cultures. Symptomatic relief was uniformly prompt. Toxic effect were minimal. Of no consequence were the mild, transitory nausea, vomiting, and soft stools. Of a more serious nature was the hyperpyrexia and shocklike picture observed in twelve patients as described earlier. Spink noted that this reaction was peculiar to patients receiving initial doses in excess of 0.5 grams every six hours. He was successful in avoiding this untoward effect by smaller initial dosage (0.1 gram the first day) gradually increased to two grams per day by the fourth day.

Spink summarized his findings by stating that toxic reactions were mild and controllable, and therapeutic results

excellent in treatment of brucellosis due to melitensis. Aureomycin was "far better than any other specific drug" (2).

Summary

Carefully conducted clinical trial by many investigators indicates aureomycin to be an exceedingly effective antibrucella agent. Cases reported included three due to abortus, four to suis, twenty-four due to melitensis, and sixty due to unspecified brucella organisms. Of these ninty-one patients, all but seven showed a prompt, complete, and probably permanent eradication of the disease. The drug is apparently equally effective against all the species of the brucella organism, though melitensis was the causative agent in the majority of cases.

Furthermore, aureomycin seems to meet all the requirements of the ideal hypothetical antibrucella agent;

1) It may be satisfactorily given orally.
2) It has few severe toxic side reactions, and none that aren't easily obviated.
3) It eliminates the expense and inconvenience of hospitalization since it is equally effective when given to ambulatory patients.

4) It promptly eliminates the brucella organism from the tissues.

Optimum dosages are approximately 0.1 gram the first day, 0.5 grams the second, one gram the third, and two grams on each of the successive six to fourteen days. This dosage course, though not standardized, avoids all toxic reactions without sacrificing any therapeutic benefits.

In contrast to the discouraging results achieved with vaccines, sulfas, penicillin and streptomycin alone and in combination, aureomycin yields a consistent and abrupt change in the course of the disease.

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