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Chloromycetin in typhoid and typhus

Robert Glen Murray
University of Nebraska Medical Center

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R. G. Murray

SOURCE

Chloromycetin, also known as Chloramphenicol, is an antibiotic drug which was isolated from a soil actinomycete by Burkholder (3) in 1947. The mold, discovered in Venezuela, was given the name Streptomyces venezuela and for a time was the main source of natural (fermented) Chloromycetin. It is not to be confused with Streptomyces lavendula, also a source of Chloromycetin but which has much less antibiotic activity. Ehrlich (4) presents an excellent article on the staining, morphology, technique of growing cultures, and differential features of these two species. The first cyrstalline Chloromycetin was filtered from submerged aereated culture by solvent extraction which yielded light yellow needles or plates. Later when the chemical structure was worked out it was found that here for the first time was a natural compound containing a nitrobenzene group, formerly thought to be harmful to animal life. Also found in the drug was a derivative of dichloacetic acid, another chemical unknown in natural products.

The structual formula was proven to be as follows:

Figure I

Chloromycetin [D-(-)- form]

The compound is unique in that it is neutral and contains both nitrogen and non-ionic chlorine. These four-isomers, the three not shown are esentially inactive in biological tests. Raistrick (10).

Synthesis was accomplished by H. M. Crooks, Jr. and his co-workers and a comparison of natural and synthetic Chloromycetin was made on chick embryos. Both were found to have the same effectiveness, low toxicity and clinical usefulness as shown by Smadel et al (13) on two cases of scrub typhus receiving the synthetic form over a sixteen hour period. One patient received two gm. initially, the other four gm. and both were then given 0.25 gm. every three hours for four doses.

PROPERTIES

Some of the properties of Chloromycetin are as follows. Solubability in water is low, about 2.5 mg. per ml. at 25°C. It is soluable in methanol, ethanol, butanol, propylene glycol and acetone. It is stable in aqueous solutions at room temperature over the pH range of two to nine for more than twenty-four hours and in distilled water is unaffected by boiling for five hours.

Biochemically it was found that the drug is rapidly absorbed from the intestinal tract and enters the blood stream unchanged as determined by blood tests on rats, dogs and later on man. Glazko-(6) in studies on dogs and rats, showed that the serum level rises rapidly following oral administration of the drug, and reaches a

peak in approximately two hours, and gradually falls over the next eighteen to twenty-four hours. Payne (8) represented this in a composite curve graf of blood concentrations determined on normal human volunteers.

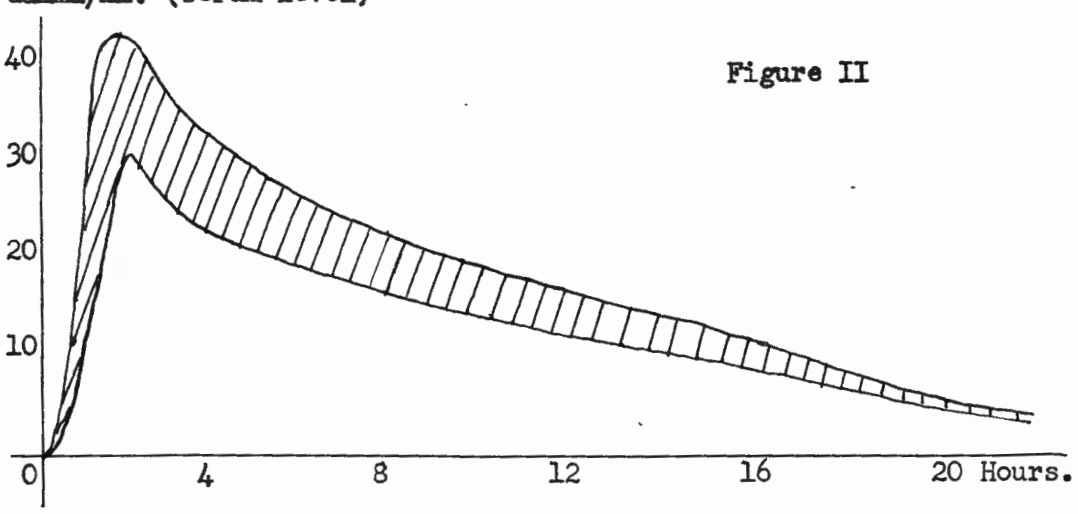


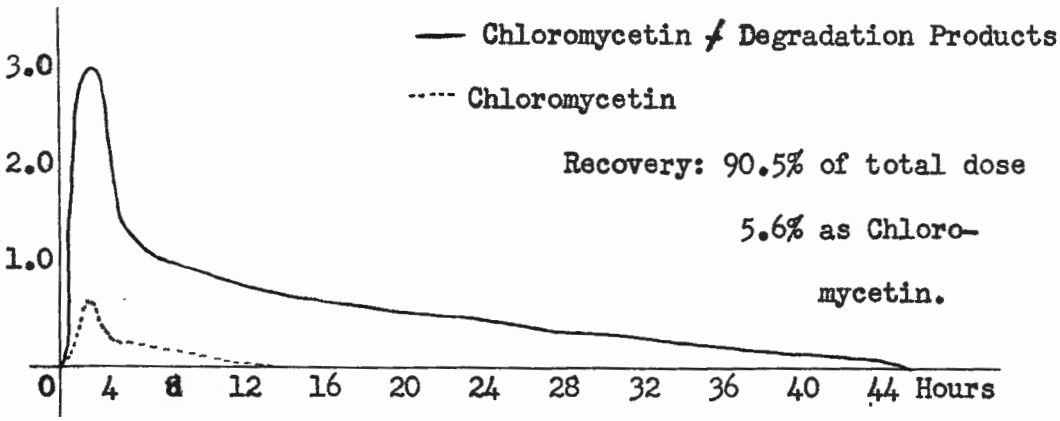
Figure II

Single Oral Dose of 2.5 Gm. of Chloromycetin

Long (7), in work on dogs, found that 4-5 Gm. given the first day would produce blood levels of forty to eighty micrograms per ml. in the first twenty-four hours, and that approximately 45% of the Chloromycetin binds to serum proteins. In man he found that the level of the drug in the cerebrospinal fluid was about 50% of that in the blood stream. As to tissue concentration of the drug Glazko (6) found them to be highest in the liver and kidneys and progressively less in lungs, spleen, heart, muscle, and brain.

Chloromycetin is excreted mainly in the urine as 80-92% of the administered dose can be accounted for in the urine over a twenty-four hour period. Ninety percent of it, thus excreted, is inactive

and represents degradation products with little or no bacteriostatic action. Renal clearance for active Chloromycetin (Uncorrected for protein binding) is about one-fourth the normal value for creatinine clearance while the degradation products are cleared at a much greater rate Glazko (6). Payne's work (8) on the rate of excretion seems to confirm this quite accurately (see fig. 3).



Normal Urinary Rate of Excretion of Chloromycetin

(Single Oral dose of 1.5 Gm.)

Figure III

Toxicity from Chloromycetin has not been observed in man either clinically or by laboratory examination. An occassional rare case of vomiting the initial dose has been reported but in no instance was it necessary to discontinue the drug Woodward-(17). The only toxicity noted in lab animals was in dogs (Long-7) receiving 72-80 mg. per Kg. per day intramuscularly for thirty-eight doses, five days a week. They were found to develop varying degrees of anemia, ranging from mild to moderately severe,

during the test period. There were no significant changes in the white blood count, blood sugar, or liver function tests in any of these animals. Woodward (18) reported that single doses up to 100 mg. per Kg. were well tolerated by dogs. It should be mentioned that some of the vomiting could possibly have been caused by the bitter taste of the drugs which has since been put up in gelatin capsules. Payne (8) wisely points out that side effects will probably be found after the drug comes into more extensive use.

ANTIBIOTIC ACTIVITY

When the original soil sample was discovered, agar streak cultures of this new mold were tested against various organisms and were found to inhibit adjacent inocula of Bacillus mycoides, Bacillus subtilis, Mycobacterium tuberculosis var hominis, (two strains tested against), Staphlococcus aureus, Staptococcus pyogenes, Brucella abortus, Escherichia coli, Klebsiella pneumoniae, Salmonella schottmuelleri and Shigella paradysenteriae (Sonne). This initial work was begun in the Park Davis Laboratories under Ehrlich and his associates (3). Smith and Joslyn (16) in testing two strains of B. subtilis found their relative sensitivity to Chloromycetin to be inversely proportionate to their sensitivity to Streptomycin. These men found that, in general, Chloromycetin is inactive against yeasts, filamentous fungi, and protozoa; moderately active against Gram positive bacteria and tuberculosis; and active against Gram negative Bacilli and Borrelia recurrentis. It gives moderate protection against Klebsiella and Shigella infections (in urine) and

remarkable protection against Rickettsia prowazeki (in chick embryos). It is also effective against certain strains of Proteus vulgaris (Long and Schoenback) (7).

SCRUB TYPHUS

This infectious disease caused by Rickettsia tsutsugamushi (R. orientalis) and transmitted by mites is characterized by its sudden onset, fever of about two weeks duration, and a cutaneous rash which appears on about the fiftieth day. An eschar usually appears at the location of the insect bite and the patient usually develops agglutinins against proteus OX-K. Significance of the disease is realized in that there were approximately 6,685 cases observed among Army personnel during World War II with 284 deaths: this is contrasted with the sixty-four cases of epidemic typhus which occurred during the same period, with no deaths.

The first experimental use of Chloromycetin against scrub typhus was done by Smadel and Jackson (12) on mice which were infected by the intraperitoneal route. Chloromycetin was given either orally or intraperitonally and all mice were treated for two days after infection. Their results showed that 1.5 mg. intraperitonally or 3.0 mg. orally per day protected all the mice thus treated and that excellent results could be obtained even when treatment was delayed for ten days after infection. They used anywhere from 25 to 100 minimum lethal doses of R. orientalis.

In 1948 Smadel and Woodward (14) with a medical research team to study the clinical effects of Chloromycetin went to Kuala Lumpur,

Malaya where there was an epidemic of scrub typhus. They selcected twenty-four proven cases for treatment and twelve similiar cases for controls. Of the twenty-five cases accepted for treatment, twenty had rickettsemia and twenty-four had positive Weil-felix reactions to Proteus OX-K. Each patient received fifty mg. per Kilo. of body weight initially and then either 0.2 gms. or 0.3 gms. every two to four hours (orally). Total dosages ranged from 8.0 to 15.5 gms. The results are tabulated in the chart below.

		Treated	Untreated
No's of Patients	25	(18 males)	12 (all males)
Days after onset Rx begun	3-11	(ave. 6.2)	
Last febrile day of illness	4-12	(ave. 7.5)	13-29 (ave. 18.1)
Durative of fever (hrs.) after Rx begun	10-96	(ave. 31)	
Days after onset disch'd from hospital	9-28	(ave. 19.2)	17-53 (ave. 30.9)
Complications	0		1. Parotitis 1. Pneumonia
Deaths	0		1. (17th days)
Month of onset	March-April		February-March

Charts of typical cases showed marked drop in temperature to normal or subnormal levels the same day that therapy was begun. Pulse dropped more slowly to normal. Blood cultures became negative within the first twenty-four hours and the rash and eschar disappeared on the third day of treatment. Since this initial work on scrub typhus Smadel has collected sixty-nine cases treated with Chloromycetin and the results were being printed in November 1949.

EPIDEMIC TYPHUS

Epidemic typhus is caused by Rickettsia prowazeki and is transmitted from man to man by body and head louse. The disease is

characterized by sustained high fever, severe headache, generalized macular or maculopapular rash, and termination by rapid lysis in fourteen to eighteen days. Epidemic mortality rates are about twenty percent.

Late in 1947 Chloromycetin was given to twenty-two patients having typhus in a Bolivian epidemic, Raistrick (10). It was found that the patients usually entered convalescense within three days and all of them made rapid recovery. A control group of fifty cases in the same epidemic showed fourteen deaths from the disease. Payne and his associates (9) found that 10 mg. per Kg. of body weight per day given intravenously, or 15 mg. per Kg. of body weight per day given orally, for three days were effective in the treatment of this disease. Payne (8) states that in the treatment of scrub and epidemic typhus it appears that 5-6 gm. of Chloromycetin are necessary initially and that they should be given in the first twelve to eighteen hours. He also states the beneficial effects on the drug in treating epidemic typhus are so rapid that one suspects that Chloromycetin has an antitoxic activity in addition to a specific action against the organism.

MURINE TYPHUS

This relatively mild febrile disease, caused by Rickettsia mooseri, is transmitted from mice and rats to man by the rat flea and is characterized by fever, headache, and macular rash. The course of the untreated disease lasts from nine to fifteen days and the mortality rate is approximately two percent.

Long and his co-workers (17) have treated and reported three cases of murine typhus receiving Chloromycetin therapy. Diagnosis was confined by complement-fixation and rickettsial agglutinin tests. The main duration of illness before the patients were treated was 8.7 days and the persistence of fever, after therapy was begun, was fifty-three hours. Dosage and pattern of response coincided, in general, with cases of scrub typhus treated with Chloromycetin.

TYPHOID FEVER

This disease, caused by the bacteria, Eberthella typhosa, is the most common cause of enteric fever in the United States (Rene' Dubos) and carries with it a mortality rate of 15 to 20%, and it is against this organism that Chloromycetin has been found to be to highly effective.

While Smadel and Woodward were conducting their studies on scrub typhus in Malaya, Woodward accidently discovered that Chloromycetin was beneficial in the treatment of typhoid fever and presented his findings in a preliminary report (18). Ten cases were presented, all of which had positive blood cultures for E. typhosa. The initial dose of Chloromycetin was 50 mg. per Kg. of body weight, given orally which was followed by 0.25 gm. every two hours until the temperature became normal. After this occured 0.25 gm. were given every three or four hours for five days. The average total dose per patient was 19.1 gm. given over an average of 8.1 days. In all cases the drug was well tolerated and gave no evidence of clinical toxicity. Initial blood concentration levels were found

to be 40-80 gamma per cc. The mean duration of fever prior to treatment was 9.5 days. Improved general condition and lessened toxicity were usually apparent within twenty-four hours. Seven of the cases reached a permanent normal temperature level within three days and the mean duration of fever in all ten cases was 3.5 days. In eight of the ten cases blood cultures were taken for five days following the initial treatment. In two of those cases blood cultures were sterile in two, four and eight hours, following the initial dose. All eight cases maintained sterile blood cultures once they became negative. There were three instances of positive stool cultures after the fifth day of therapy but repeated tests thereafter were negative. Urine cultures in all of the cases remained sterile. Patients were not discharged until there were three consecutive negative stool cultures. There were two relapses, both causing bacteremia, on the tenth and sixteenth day respectively and both responded in two and three days respectively to a second course of Chloromycetin. It was noted from laboratory tests that there was no change in bacterial sensitivity to this second course of the drug, and that the clinical response was still as rapid as before. There were two serious complications is these patients. One developed all the clinical signs and symptoms of intestinal perforation with a spreading peritonitis on the second day of normal temperature. His therapy was supplimented with penicillin and streptomycin, no surgery was done. The otherpatient developed massive intestinal hemorrhage on the fourth day of normal temperature and was treated

with whole blood transfusions. Both cases recovered. A control group of eight cases had one death on the seventeenth day of the disease and the average total duration of fever in the remaining seven cases was thirty-five days.

Bradley (1) presented twenty-two cases of typhoid which broke out in a village in England. In all of the patients the diagnosis was confirmed. Enough Chloromycetin was available to treat ten of them. By the end of the third week of the epidemic he reported that two very elderly patients had died, one of them had been receiving Chloromycetin. Of the remaining nine cases treated, signs of resolution of the disease developed within forty-eight hours after 8 gms. of the drug had been administered. Seven of the patients became afebrile by the third day and the other two developed normal temperatures on the fourth day and the fifth day respectively. Resolution of the disease was complete in all nine cases. In his control group of twelve cases, four of them were mild illnesses, three had relapses, and in general the disease ran its usual course. Bradley remarked about the dramatic effects that Chloromycetin had on the typhoid headaches and other constitutional symptoms and the relatively lesser degree of effect on the temperature change. An unusual case of typhoid was reported by Foster and Condon (5) of a twenty year old, white, male, college student who accidently pipetted a typhoid culture into his mouth during a bacteriology laboratory. He went through the classical prodromal pattern undiagnosed, received three doses of penicillin

without effects, and finally with an accurate history of exposure and increasing signs and symptoms of the disease was admitted to the hospital. He developed the typical fever, bradycardia, dicrotic pulse, palpable spleen, and uncontrollable diarrhea. Laboratory cultures on urine and blood were negative on admission but blood cultures became positive two days later. Agglutination tests on the day of admission showed 1:80 for E. typosa, 1:20 for Paratyphoid A, and 1:10 for Paratyphoid B. Three days after admission the heart sound became blurred and the patient developed mild delerium and stupor. He was put on streptomycin therapy. Blood transfusions on the fourth day had no effects. On the sixth day the laboratory reported blood cultures to have E. typhosa, the streptomycin was stopped and Chloromycetin begun with an initial dose of 3.5 Gm. (50 mg/Kg.) which was followed by 0.25 Gm. every two hours. Twenty-four hours later he was completely conscious and oriented, and the temperature had dropped to 102°F. The diarrhea came under control shortly thereafter and by the third day of Chloromycetin therapy the temperature became normal and remained there. The same day he developed rales in the left chest and was given penicillin. Six days after the Chloromycetin was begun the rales and diarrhea had disappeared. The penicillin was stopped and the Chloromycetin was reduced to 0.25 Gm. every four hours. Three days later all therapy was stopped, stool and duodenal content cultures were negative. The patient was discharged the following day. A six month follow-up showed no remissions or complications. The results of this case

showed that penicillin and streptomycin were ineffective, but Chloromycetin caused a complete remission of the fever in ninety-six hours.

One case of chronic typhoid fever treated with Chloromycetin has been reported by Rumball and Moore (11). A nine year old white boy contracted typhoid in Egypt and made good clinical recovery, but was left a chronic fecal carrier of Salmonella typhi. Stool cultures were heavy with the organism but the urine was sterile. In vitro tests showed marked sensitivity of the bacteria to Chloromycetin. The child was given one half the adult dose initially which was followed by 0.25 Gm. every four hours day and night for seven days. The total dose was 10.5 Gm. The stool cultures, taken on alternate days, remained positive. Treatment was stopped and later begun at triple the original amount, giving a total dosage of 32.23 Gm. over a seven day period. Stools became negative almost immediately and remained so until two days after the Chloromycetin was stopped, after which he continued to excrete the organisms daily. While under treatment the blood serum inhibited growth of the organism (isolated) in dilutions rising from one in two the first day to one in thirty-two on the third day, but inhibition disappeared in sixteen hours after the last dose of the drug. The authors' comment on this case was that 30. mg. per Kg. for seven days failed to effect a cure, the dosage was three times the amount found necessary to cure acute cases of the disease, and the organism was sensitive to Chloromycetin. The question was brought up, would heavier doses over a longer period

of time produce a lasting cure? (No other literature on this subject was found at the time of this writing--R.G.M.).

It must be remembered that the remarkable response of acute typhoid fever to Chloromycetin does not eliminate the possibilities of complications such as intestinal perforation or hemorrhage, pneumonia, or as Woodward reported (17), a case which returned to the hospital ten days after discharge and died of a massive pulmonary embolus which was suspected to have originated from a late typhoid phlebitis.

PRESENT STATUS

Chloromycetin has been shown to give good results in the treatment of scrub typhus, both from a clinical and a laboratory standpoint and it markedly shortens the course of the disease. It produces rapid remission of signs and symptoms when used in the treatment of epidemic typhus. Early convalescence and recovery were noted in the patients who received this drug. Three cases of murine typhus produced beneficial results with Chloromycetin therapy.

Chloromycetin has produced excellent results in the treatment of acute typhoid fever and is unequivocally the drug of choice at this time as Aureomycin does not effectively alter the course of the disease (Woodward-17). Whether Chloromycetin will be effective in the treatment of chronic typhoid carriers remains to be seen.

Up to the present time no toxicity or intolerance to the drug has been observed in man either clinically or by laboratory tests. The optimum dosage at this time appears to be about 50. mg.per Kg.

of body weight as an initial dose and 0.2 to 0.3 Gm. given every two to three hours until the temperature becomes normal and then reducing the dose to every three to four hours. Recurrences of the disease, particularly typhoid fever, have been observed and are probably due to insufficient drug therapy. Payne (8) feels that the treatment of typhoid should be three to five days longer than is generally used with a total dosage of from 12 to 18 Gm., 5 or 6 Gm. of it being given initially. Appropriate laboratory tests have been the main criterion for cessation of the drug up to the present time. Chloromycetin does not preclude the possibility of complications from typhoid fever.

Evaluation of this new antibiotic must be reserved until larger series of cases are treated and reported on so that accurate conclusions may be reached. It also remains to be seen whether aureomycin will be competitive with or supplimentary to, Chloromycetin since these two antibiotics both contain chlorine and nitrogen and have somewhat similar biological properties.

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