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COMPARATIVE STUDIES ON THE EFFECT OF ANTIBIOTICS AND GAMMA-GLOBULINS IN EXPERIMENTAL MELIOIDOSIS INFECTION.

by
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In recent years, in connection with the progress of the modern antibiotics and chemopreparations (drugs), the problem of melioidosis therapy became more perspective (prob ably meaning it has better perspectives or potentialities). However, it should be noted that positive comments on the effect of these substances belong essentially to the cases of treatment of subactue spe- aeptic forms (of the disease).

Among the various medicines, used in the treatment of melioidosis, the most promising proved to be, of the antibiotics, chloramphanol and pharmicetyn (spelling?), and of the sulfanilamide substances - sulfadiazine. spelling

According to Brygoo's data (1953), chloramphenicol, used in the twenty-four hour dose equal to 150 mg per 1 kg, inhibited the development of melioidosis infection in guinea pigs, whereas there was 100% fatal outcome in the control animals. At the same time, the author never observed any form of the causative agent

agent resisting therapy. Fournier and Chambon (1952) observed that one rarely succeeds in isolating strains from patients in the early stages of disease which would be resistant to chloramphenicol, and at the same time cases of the appearance of resistant forms of microbes are not uncommon in the process of their evolution. This resistance appears suddenly and most frequently in treatment with small doses of the substance. Similar findings were described by Nguyen-Hoai-Duc, Nguyen-Van-Ai and Nguyen-Ba--Khoi (1957).

Kobe (1952) and Durau (spelling?) (1952) reported on discovering some strains sensitive to aureomycin, but at the same time showing resistance to chloramphenicol. For the reason, these authors recommend combined use of chloramphenicol and aureomycin or terramycin (quoted in Fournier and Chambon).

Mirick's et al research studies (1946), and those of Harries et al, Miller et al (1948), Green and Mankikar (1949) and Fournier and Chambon (1958) established that penicillin, streptomycin, ielimyxin, bacitracin, magnamicyn and biomycin have a weak bacteriostatic effect on the melioidosis microbe. In this connection, these authors believe the use of the mentioned antibiotics is not expedient for the treatment of melioidosis.

Terramycin and aureomycin which have a bacteriostatic effect in vitro often are ineffective in vivo, as shown by Cruickshank, Chambon, Lajudie and Fournier (1954). Similar results were obtain ed by Brigoo who studied the antimicrobic

properties of neomycin.

From the standpoint of practical application, the new antibiotic pharamycetin (spelling?) present particular interest. From the data of Chambon (1956), the bactericetatic titer of this antibiotic is equal to 12.5 - 50 Mg per 1 ml of the medium. Based on this, Chambon believes it possible to use it in the treatment of chronic forms of melioidosis with the supporative process. This author also suggests that combined use of pharmycetin and penicillin, in the melioidosis therapy for disease caused by strains resistant to chloramphenicol. Such a combination may be permissible for with other antibiotics.

Of the sulfanylamide subetances, in their time, there have been tested sulfadiazine- sulfadiazine and sulfathiazole. According to Hirick's data and his collaborators (1946), sulfadiazine completely stops the growth of B. malleolyces pseudomallei in the concentration of 15 Mg per ml of medium. At the same time, Brigo and Henry (1953) deny any marked antimicrobic properties in this subetances.

Green and Sankikar (194) mention adequate effect of sulfadiazine in the treatment of melioidosis which is much superior to that of sulfathiazole.

Miller etal (1948) used sulfadiazine in the treatment of hamsters, experimentally infected with melioidosis. According to the data of these authors, sulfadiazine was responsible for about 50% survival of the animals, infected with virulent strains of melioidosis causative agent.

As regards the treatment of patients with melioidosis, we have at our disposal some data, indicating favorable outcome with the combined therapy with chloramphenicol and sulfadiazine (PARNAUD et al, 1958, Brygoo and Jaureguiberry 1952, Miller, Panell, Ingalls, 1948).

To sum up, experience with treatment of melioidosis patients and experimental research of the past few years permit us to include into the armory (storehouse) of therapeutic substances for melioidosis - chloramphenicol, phenycetin (spelling?) aureomycin and terramycin. Of the sulfanilamide substances, more or less hopeful results were obtained with sulfadiazine. ~~When~~ When treatment-resistant forms of disease appear, one should use combined treatment with several antibiotics (chloramphenicol, aureomycin, terramycin, etc.)

Of the-rest- the published works in this country, we should mention research by Lutsenko (1930), compilation review by Chaliapov (1941), Poddubskii (1955), Popov (1957), Capochko, Carina, Lebedinskii (1957), Lebedinskii, Capochko, Gaisar-Garin (1957) and Levi (1960).

However, in spite of the attained success, the problem of therapy and special prophylaxis of melioidosis is far from solved. This is why in our work we set up the problem of comparative studies on the effect of various antibiotics of gamma-globuline for the purpose of selecting the most promising ones.

Experiments were carried out on 237 white mice, weighing

18 to 20 Gm. According to our own personal data and those from literature (Lajudie and Brygoo), the white mice are less sensitive to experimental infection than are guinea pigs and rabbits. Nevertheless, when using on these animals large doses of the virulent culture of B. malleolyces pseudomallei the corresponding disease developed with certain clinical manifestations (purulent conjunctivitis, suppuration of regional nodes, paralysis of the lower extremities, etc.). The animals dies, depending upon the amount of administered microbes and the method of infection in periods from one day (24 hours) to 2 weeks. On section, there were found some purulent necrotic foci and inflammatory nodules in the internal organs and lymph nodes, characteristic for the melioidosis infection. These data -adduce indicate the susceptibility of white mice to melioidosis and the possibility of using them, along with guinea pigs and rabbits, as experimental models.

For control the infection, we used the virulent strain of *B.* malleolyces pseudomallei with-141, brought from the South Vietnam. The animals were infected subcutaneously with 200mln microbes.

The experimental animals were kept for 18 days, after which those surviving were killed with chloroform, autopsied and examined bacteriologically.

As therapeutical agents were used in the experiments the following substances: tetracycline, levomycetine, biomycin, oxytetracycin, bacteriomycin and gamma-globulin, prepared from

the equine antimelioidosis serum by means of alcohol and weyer sedimentation of protein fractions on cold. The first (mentioned) three antibiotics were given per os, the remaining two antibiotics and gamma-globuline were administered subcutaneously.

Treatment was started after 16 hours from infection and continued during 12 dys; during the first 7 days, antibiotics were administered twice a day, and in the subsequent days, once; gamma-globulines were given only twice - after 16 and 48 hours since the moment of infection. The dailydose of tetracycline was 1 mg, that of levomycin 2 mg, biomycin 1 mg, colymycine 0.1 mg and bacteriomycine 0.1 mg, the single dose of gamma-globuline was 0.5 ml.

Therapeutic Activity of antibiotics and gamma-globulin in Experimental Melioidosis Infection

Substance	Number of animals in experiment	of these Dead	Survived	Survival of animals in %
Tetracycline ...	30	28	2	6/6
Levomycétine	30	11	19	63.3
Biomycin	30	10	20	66.6
Colymycin	28	25	3	10.7
Bacteriomycin	30	24	6	20
gamma-globulin	30	22	8	26.6
Control.....	30	26	4	13.3

As one can see from the data given in the Table, of the 6 substances used in treatments, the more or less effective ones proved to be levomycin and biomycin (63.3-66.6% of surviving animals). The remainder of the substances, including

gamma-globulin, proved to have little effect on experimental melioidosis.

In this manner, our data to a certain degree concur with those of Lajudie and Chambon, Erygoo, Kobe and Duro (Durau, Dureau, Dèrot? what have you - those crazy Russians give you phonetic spelling, the way they think it should be pronounced) and other research scientists, working on the susceptibility of certain melioidosis strains to chloramphenicol (or chloromycetin) and aureomycin.

Inasmuch as levomycetin, being a synthetic substance, is identical with the natural chloromycetin or chloramphenicol, and biomycin -- a natural antibiotic - in its structure and mechanis is identical with aureocycin, we could expect positive results from the use of ~~levomycin~~ as levomycetin and biomycin.

In conclusion, it should be noted that in bacteriological studies of the pathological material, the specific melioidosis causative agents were more or less regularly isolated from the site of administration, from the lymphnodes and internal organs and in this respect no ~~of~~ difference could be noted between the various groups of animals.

Conclusions

1. Of the 5 examined antibiotics, the most pronounced therapeutical properties were foun din levomycetin and biomycin which prevented death in 63.3 to 66.6% of animals, infected with 200 mln. of microbes of virulent culture melioidosis causative agent.

2. Treatment of experimental animals with gamma-globulin increased their survival twice as compared to the controls.

3. These experiments are preliminary, nevertheless, their results show the expediency in the use of domestic antibiotics (native to their country) in emergency cases - Mycin and levomycetin in combination with the gamma-globulin.

Literature is not transcribed

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For Dr. Joseph

Translated by Tatiana Boldyreff