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L.E. Khundanov, E.I.Kuptsevich, E.K.Demidova, L.A.Smirnova, & E.D.Shkurko: O kombinirovannoi terapii eksperimental'nogo melioidoza antibiotikami i sul'fodimezinom. Antitiotiki, Vol. VI@1013-16, 1961.

Translated from Russian:

COMBINED TREATMENT OF EXPERIMENTAL MELIOIDOSIS WITH ANTIBIPTICS AND SULFADIMESIN

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Combined administration of antibiotics with other drugs was completely justified in many diseases. In particular, in case of anthrax, tuberculosis, mixed infections and infections, caused by drug-resistant microbes.

The advantages of the combined therapy consist of the synergism, lowered toxicity, prevention of the appearance of drug-resistant forms of microorganisms and, finally, of possible successful treatment of gavely ill patients without preliminary bacteriological diagnosis.

The purpose of the present work was the study of possible use of antibiotics in comination with sulfodimezine (spelling?) in/ the treatment of experimental melioidosis infection.

As therapeutical agents we used in the experiments the following antibiotics: monomycin (footnote: monomycin is a new domestic antibiotic, obtained at the laboratory of Prof. G.F. Gause at the Institute for the Study of New Antibiotics, Academy of Medical Sciences, USSR).

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tetracyclin (footnore: in this experiment we used series of tetracyclin, especially prepared for intramuscular injections); oxytetracyclin, chlortetracyclin, bicyllin, streptomycin, mycerin (spelling?) and llevomycetin (spelling?). Of the sulfamide substances, sulfodimezin was tested.

Experiments were carried out on white mice weighint 18-20 Gm. The animals were infected by means of subcutaneous injection of 0.5 ml suspension of one-day agar culture of the B. strain of <u>malcomyces pseudomallei</u> (4). The infecting dose was 5 mln. of microbe cells (1 Dol).

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Therapy was started after 14-15 hours since infection, i.e. during the stage (phase) of generalization of the infection. The substances being tested were dissolved in the physiological solution and administered twice a day (?blur) in the amount of 0.2 ml. Insoluble substances (chlortetracyclin, levomycetin and sulfodimezin) were given to the animals per os. The course of treatment lasted 10 days. Observations of the animals were continued for 3 weeks.

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The criterion of effectivity of the therapy was: survival of the animals, average longevity of those who died (of the dead animals), as well as the data of bacteriological examinations.

Preliminarily, toxicity of all drugs was checked upon and on the same animals tolerated dose of each substance was established. As a result of this check-up it was found that the tolerated daily dose for monomycin was 2.5 mg., and for

tetracyclin, oxytetracyclin, chlortetracyclin, streptomycin, mycerin, bicyllin - 2 mg (burred text, looks like 2), for levomycetin, 4 mg. and for sulfodimezin, 6 mg.

Results of experiments are represented in Table 1.

As one can see from the Table 1, in spite of somewhat milder conditions of experiment, monomycin, streptomycin, mycerin and bicyllin proved to be poorly effective in the treatment of melioidosis. In the groups of mice which received the mentioned antibiotics, there was observed death of animals in 70% to 90% of cases. At the same time, longevity of the treated dead mice was somewhat greater, than that of the controls which did not receive treatment.

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In the groups of mice of this experiment, the therapy of which was carried out with chlortetracyclin, levomycetin, sulfodimezin, there was observed survival of 75% to 90% animals with average longevity of the dead animals from 13.4 - to 16 days, whereas the control mice lived on the average 8 days.

Table 1

Therapeutical Effect of Antibiotics & Sulfodimezin in Experimental Melioidosis

Drug	Method of administration	Single dose in mg.	Number of mice in exper.	Dead	Survived	Average longevity of dead mice in days
Monomycin	Intramuscular					
Tetracyclin	"					
Oxytetracyclin						
Bicyllin						
Streptomycin						
Mycerin						
Chlortetracyclin	peroral		figures not retyped, see. p. 1014			
Levomycetin						
Sulfodimezin						
Control						

Among the animals treated with tetracyclin and oxytetracyclin, survival was from

cyclin, survival was from 45 to 55%, with average longevity of the dead animals being from 11.7 to 15.7 days.

In this manner, of the 9 tested substances, the most effective drugs in melioidosis were levomycetin, sulfodimezin and chlortetracyclin. The therapeutical effect of these substances was reflected not alone in the high percentage of survival of the animals, but in considerable postponement of the time of death of the treated mice.

Tetracyclin and oxytetracylin, had therapeutic effect but it was much weaker than that of lecomycetin, sulfodimezin and chlortetracyclin. Nevertheless, these antibiotics may be recommended, especially in such cases, when we are dealing with antibiotic-resistant forms of pathogenic agent, requiring combined effect of several antibiotics. As for other antibiotics (monomycin, bicyllin, streptomycin, mycerin), these, in contrast to other drugs, possessed equally low therapeutical effect, although among the animals treated there was observed prolonged survival as compared to the controls.

Bacteriological examination of material from animals, dead during the course of treament, showed melioidose microbes more or less regularly eliminated from the site of infection, lymph nodes and internal organs; in this respect, no difference was noted in separate groups of animals, receiving one or other drug.

The second part of our research studies was dedicated to investigating the possibility of using antibiotics in

combintaion with sulfodimezin in the treatment of experimental melioidosis infection.

These experiments were done on white mice infected with the same dose as used in the first series of experiments /1/ (5 mln. of microbe cells).

Considering the fact that chemotherapy of melioidosis produces sufficiently marked effect only under conditions of treatment with large doses, which maintain sufficiently high level of concentration of the drug in the organs and the blood, we were forced to confine to the same doses which were used in testing each substance separately.

Of the substances tested, sulfodimezin, chlortetracyclin and levomycetin were used perorally; monomycin, tratacyclin oxytwtracyclin, bicyllin, streptomycin and mycerin were used intramuscularly with simultaneous administration of sulfodimezin perorally.

As one can see from Table 2, combination of sulfodimezin with monomycetin, tetracylcin, bicyllin, streptomycin, mycerin and levomycetin, in the conditions of our experiment, proved to be ineffective, since the survival of animals, treated with sulfodimezin alone, is much higher (85%) than when treated with the combined method. Moreover, the combined therapy with antibiotics and sulfodimezin gives a better therapeutical effect than the therapy with the antibiotics alone.

Whereas the use of chlortetracyclin, under similar experimental conditions, in combination with sulfodimezin,

gave excellent therapeutical effect, reflected not alone in high percentage of survival of animals (90%), but in marked prolongation of life in case of dead mice which had been treated, as compared to the controls (more than twice).

Table 2

Results of treatment of experimental melioidosis with antibiotics + in combination with sulfodimezine

Drug	Number of mice in experiment	Dead	Survived	Average life span of dead mice (in days)
Monomycin + sulfodimezin				
Tetracylcin + sulfodimezin				
Oxytetracylcin + sulfodimezin				
Bicyllin + sulfodimezin				
Streptomycin + sulfpdimezin		table not retyped, see p. 1015		
Mycerin + sulfodimezin				
Chlortetracylin + sulfodimezin				
Levomycetin + sulfodimezin				
Control				

Conclusions

1. Of the nine (9) tested durgs, the greatest therapeutical effect in the treatment of melioidosis was obtained with levomycetin, sulfodimezin and chlortetracylcin; 75% to 90% of white mice, treated with these substances, remain alive.

2. Tetracyclin and oxytetracyclin, even though they do have some therapeutical effect, have much weaker effect than levomycetin, sulfodimezin and chlortetracyclin.

3. Monomycin, bicyllin, streptomycin and mycerin, under same experimental conditions, have weak therapeutical effect and in practice their use should be considered unsuitable.

(continued)

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4. ~~Treatment of infected animals with melioidosis~~ Sulfodimezin therapy, combined with monomycetin, tetracyclin, oxytetracylcin, bicyllin, streptomycin, mycerin and levomycetin, in treatment of animals, infected with melioidosis, under the conditions of our experiments, should be considered as irrational.

5. The combined administration of sulfodimezin with chlortetracyclin guarranttees a high percentage of survival of animals (50%) and a considerable ~~increase~~ prolongation of the average life span of the dead mice.

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For Mr. Joseph

Mr. Joseaph: please note, some of these new drugs are not listed in dictionaries, and I do not know how to figure out their spelling; the Russians use phonetic transcriptions of what they imagine the English should be. -twb

Translated by Tatiana Boldyreff

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