PROPHYLACTIC EFFECT OF SDDS (2-SULFAMOYL-4,4’-DIAMINODIPHENYL SULFON) ORALLY ADMINISTERED AGAINST EXPERIMENTAL TOXOPLASMOsis IN PIGS

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In their previous report, the authors described the therapeutic effect of 2-sulfamoyl-4,4’-diaminodiphenyl sulfon (SDDS) on experimental toxoplasmosis of pigs, making it clear that the drug had a very strong suppressive effect against the development of clinical signs and parasitemia when administered to pigs simultaneously with the inoculation of toxoplasmas, and that it had also an eminent therapeutic effect when administered to infected pigs within one day after the onset of fever attack. The minimal effective dose was proved to be 30 mg/kg given daily for 7 days.

Later, OHSHIMA et al. conducted a similar experiment and reported that the minimal effective dose was 10 mg/kg given daily for 7 days.

After that, the present authors performed a further experiment with this drug given by the oral route against Toxoplasma infection in pigs.

MATERIALS AND METHODS

1. Experimental pigs
A total of 12 apparently healthy pigs 40 days old weighing about 10 kg were employed. All of them were negative for the dye test (1:4 or below) as shown in Table 1. In the experiment, they were divided into 6 groups (A, B, C, D, E, and F) of two each. Groups D and F were set up as control ones consisting of non-medicaded pigs.

2. Method of drug administration
Pigs were administered orally with white powder containing 2% SDDS by and mixed with a commercial pig feed throughout the experimental period. The net dose of the drug given per pig of each group was as follows: 1.25 mg (group E), 2.5 mg (group A), 5.0 mg (group B), and 10.0 mg (group C) per kg of body weight per day. Administration of the drug was started 7 days before the inoculation of toxoplasmas and continued to the end of the experiment. The body weight was checked every 10 days.

3. Experimental inoculation
On the 8th day of the drug administration, all the pigs were inoculated with toxoplasmas by the intraperitoneal or peroral route, as indicated in Fig. 1.

The pigs (Nos. 5 and 6) of group E (1.25 mg) and those (Nos. 11 and 12) of group F (non-medicaded control) were challenged by the peroral route with two mice

### Table 1. Design of the Experiment

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Sex</th>
<th>Experimental pigs</th>
<th>Body weight (kg)</th>
<th>Dye-test titer</th>
<th>Dose of SDDS (mg/kg/day)</th>
<th>Inoculation route†</th>
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<tbody>
<tr>
<td>A</td>
<td>1</td>
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<td>8.4**</td>
<td>10.4**</td>
<td>1: 16*</td>
<td>1: 4**</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
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<td>♀</td>
<td>8.6</td>
<td>10.9</td>
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<td>B</td>
<td>3</td>
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<td>10.8</td>
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<td>♀</td>
<td>9.0</td>
<td>10.8</td>
<td>1: 16</td>
<td>1: 4</td>
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<tr>
<td>C</td>
<td>9</td>
<td>♀</td>
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<td>10.2</td>
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<tr>
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<tr>
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<td>♂</td>
<td>8.8</td>
<td>11.4</td>
<td>1: 16</td>
<td>1: 4</td>
<td></td>
</tr>
<tr>
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<td>5</td>
<td>♀</td>
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<td>8.8</td>
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<td>1: 4(−)</td>
<td></td>
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<tr>
<td>F</td>
<td>11</td>
<td>♀</td>
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<td>10.0</td>
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<td>1: 4(−)</td>
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<td>12</td>
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<td>8.0</td>
<td>10.2</td>
<td>1: 4(−)</td>
<td>1: 4(−)</td>
<td></td>
</tr>
</tbody>
</table>

* At the beginning of administration of the drug (SDDS).
** At the time of inoculation.
† I. P.: intraperitoneal, P. O.: peroral.

### Fig. 1. Methods of Artificial Inoculation

- **Peroral route**
  - Strain T.T. 5x10⁶ organisms
  - Two infected mice
  - Administration of SDDS
  - 0, 4, 10 days: 60-62 days

- **Intraperitoneal route**
  - Strain T.T. 5x10⁶ organisms
  - Strain HG 2x10⁷ organisms
  - Administration of SDDS
  - 0, 28 days: 67-74 days

- Conjunctival route

Infected with the TT strain which had been isolated from an acute fatal swine case. Because of the mild clinical manifestation of the pigs of both groups, additional inoculation was carried out by the peroral route (with two infected mice) 4 days later, and further inoculation was made by the conjunctival route (with 5x10⁶ organisms) 10 days after the first inoculation.

The pigs of groups A (Nos. 1 and 2), B (Nos. 3 and 4), C (Nos. 9 and 10), and D (Nos. 7 and 8) were challenged by the intraperitoneal route with the TT strain (5x10⁶ organisms). One additional inoculation was conducted on the 28th day after the first inoculation with the HG strain (2x10⁷ organisms) which had been used in the previous report⁴.

4. Parasitemia in pigs

On the 2nd, 4th, 7th, and 14th day after the first inoculation, 5 ml of blood collected from the jugular vein of each inoculated pig was injected into 5 mice (1 ml each) by the intraperitoneal route.
The pig group which had been challenged by the intraperitoneal route was again examined for the occurrence of parasitemia by the method described above on the 4th and 9th day after the 2nd inoculation with the HG strain.

Onset of parasitemia in an inoculated mouse was decided either by death of the mouse due to toxoplasmosis or by detection of Toxoplasma cysts in the mouse brain or cytoplasm-modifying antibody in the pool of sera collected from this and other mice which had survived for more than 30 days after inoculation.

5. Recovery of toxoplasmas from pigs

All the pigs were sacrificed during a period from the 62nd to 74th day after the initial challenge with toxoplasmas. Organ materials were collected from them and submitted to the detection of toxoplasmas.

The methods used were almost the same as those described in the previous report by the authors4).

6. Serological observation

The pigs were examined for antibody response by the dye test and hemagglutination (HA) test generally every 10 days during the experimental period. The dye test was carried out by the original technique described by Sabin and Feldman with a slight modification by Hasegawa et al., no heparin being used. The HA test was performed by the procedures originally mentioned by Chordi et al.1)

RESULTS

1. Clinical symptoms and parasitemia

a. Pig groups E and F challenged by the peroral route: AsA indicated in Chart 1, a rise of body temperature was observed in the two pigs of group F, but not in the pigs of group E which had already been fed SDDS, except pig No. 5 which showed a temperature of 40.7°C on the 49th day after inoculation.

The pigs manifested none of the other clinical signs, such as depression, anorexia, cyanosis and diarrhea.

Parasitemia was observed only in the control pigs (group F) on the 7th day (pig No. 12) and the 14th day (Nos. 11 and 12), as shown in Table 2.

b. Pig groups (A, B, C, and D) challenged by the intraperitoneal route: Febrile responses below 41°C were observed in the control pigs (group D) on the 2nd to 7th day after inoculation. A very slight rise of body temperature was also noticed in one pig of group B which had been fed 5.0 mg of the drug per kg of body weight per day. No other pigs suffered from any fever attack throughout the experimental period, as indicated in Chart 2. No clinical manifestations other than pyrexia were observed in any of the pigs.

Parasitemia occurred to the control pigs (group D) on the 2nd day (pig No. 8), and the 4th and 7th day (Nos. 7 and 8) after inoculation, and to pig No. 10 of group C which had been fed 10 mg of the drug per kg of body weight per day, on the 2nd day, as indicated in Table 2.

2. Antibody responses

a. Groups of peroral inoculation (groups E and F): The two control pigs showed such high dye-test titers as 1:256 throughout the experimental period. The pigs of group E which had received the medication of 1.25 mg/kg/day, however, revealed slight responses and their dye-test titers gradually decreased to 1:4, as shown in Chart 3.

Moreover, their HA-test titers showed a similar tendency to that of their dye-test titers. In the pigs treated with the drug, the titers showed a slight transient increase.
Table 2. Parasitemia in Experimental Pigs

<table>
<thead>
<tr>
<th>Group</th>
<th>Inoc. route</th>
<th>Dose of SDDS (mg/kg/day)</th>
<th>Pig No.</th>
<th>Days after the 1st inoculation</th>
<th>Days after the 2nd inoc.</th>
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<td></td>
<td></td>
<td>2</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>
| A     |            | 2.5                      | 1       | ○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○○ ○
and dropped gradually to 1:4 or below.

In one control pig, however, a titer higher than 1:64 persisted, as seen in Chart 4.

b. Groups of intraperitoneal inoculation (groups A, B, C, and D).

Dye test: After the first challenge, few pigs presented high antibody responses
while many pigs showed such considerably high titers as 1:64 ~ 1:256 after the second inoculation with the organisms. After that, the two control pigs and two pigs (Nos. 1 and 3) of group A and B respectively, maintained a rather high titer (1:64).

On the contrary, the pigs of group C (10 mg/kg/day) and one pig each of the other groups (pig No. 2 of group A and pig No. 4 of group B) showed a gradual decrease in titer, as illustrated in Chart 5.

HA test: All the pigs, except pig No. 3 of group B and pig No. 9 of group C, first indicated rather high antibody titers, such as 1:128 ~ 1:256, which are considered to have been derived from the maternal antibody, but showed no rise in titer after the first inoculation with five million organisms. Even in pigs which had shown low HA titers at first, antibody responses were scarcely observed and there was a gradual decrease in titer, as indicated in Chart 6.

Like the dye-test titers, HA titers exhibited a rise in these groups after the 2nd inoculation with the HG strain, although they dropped to less than 1:16 in all the control pigs, except one (1:32).

5. Autopsy findings

Of eight pigs which had received intraperitoneal inoculation with Toxoplasma, five pigs (the pigs of group A and one pig each of groups B, C, and D) were affected with mild peritonitis. Moreover, lymph nodes in every region were swollen slightly in all the pigs. It is not certain whether these changes were induced by toxoplasmas or not. The authors could not find any other abnormal macroscopical changes than those mentioned above.

4. Isolation of Toxoplasma organisms

The pigs of groups A, B, C, and D which had been challenged by the intraperitoneal route were examined on the 67th ~ 74th day after inoculation. The pigs
Table 3. Detection of Toxoplasmas from Organs of Experimental Pigs

<table>
<thead>
<tr>
<th>Group</th>
<th>Inoc. Pig route No.</th>
<th>Sex</th>
<th>Body weight (kg)</th>
<th>Termination</th>
<th>Dye test titer of autopsy</th>
<th>Liver</th>
<th>Spleen</th>
<th>Kidney</th>
<th>Pancreas</th>
<th>Lymph node</th>
<th>Intestine</th>
<th>Heart muscle</th>
<th>Intercostal muscle</th>
<th>Diaphragm</th>
<th>Brain</th>
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<tr>
<td>1</td>
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<td>10.4—41.0</td>
<td>28th day after the 2nd inoculation</td>
<td></td>
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<tr>
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<td>♀</td>
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<td></td>
<td>1: 4</td>
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<tr>
<td>3</td>
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<tr>
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<tr>
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<td>7</td>
<td>♀</td>
<td>10.6—41.0</td>
<td>39th day</td>
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<td>1: 64</td>
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<td>8</td>
<td>♂</td>
<td>11.4—42.0</td>
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<td>1: 64</td>
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<td>5</td>
<td>♀</td>
<td>8.8—27.0</td>
<td>50th day after the 3rd inoculation</td>
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<td>1: 4</td>
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<td>6</td>
<td>♀</td>
<td>10.0—39.0</td>
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<td>1: 4</td>
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<tr>
<td>11</td>
<td>♀</td>
<td>10.0—34.0</td>
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<td>1: 256</td>
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<td>12</td>
<td>♀</td>
<td>10.2—36.0</td>
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* At initial challenge.
** At autopsy.
*** The day after initial challenge.

of the orally challenged groups (E and F) were also examined on the 60th—62nd day. The results obtained are shown in Table 3.

Toxoplasmas were isolated from one pig each of the untreated control groups. They were detected in the muscle and brain. The other two control pigs (one pig each of groups E and F) gave no evidence of Toxoplasma infection even when examined by the dye test on serum from surviving mice which had received inoculation with swine materials. Those pigs which had been fed the drug gave low dye-test titers, such as 1:4—1:16, except two pigs, Nos. 1 and 3 (1:64), and no toxoplasmas were detected at all.

DISCUSSION

The TT strain, which was employed in this experiment, had been isolated from a case of acute fatal swine toxoplasmosis, like the HG strain which was used in the previous investigation. The TT strain, however, caused no severe clinical signs, except a fever attack and parasitemia, in non-medicated control pigs. Then, the HG strain was reinoculated in to the pigs of groups A, B, C, and D by the intraperitoneal route and in to the pigs of groups E and by the conjunctival route. None of the inoculated pigs, however, revealed any symptoms other than antibody responses. Toxoplasmas were demonstrated in only two of control pigs at autopsy.

From these results, it may be somewhat difficult to say that the present experiment was performed very satisfactorily, but the pigs which had been fed SDDS (except pig No. 10) did not reveal any clinical signs of infection or parasitemia at all. Accord-
ingly, the authors are confident that the prophylactic effect of SDDS against Toxoplasma infection could sufficiently be demonstrated.

The natural transmission route of swine toxoplasmosis is not clear. It is supposed that this disease may be transmitted by ingestion of infected materials. In the present experiment, this route was tested in some pigs. It was proved that pigs were protected from infection by administration with SDDS even in such a small dose as 1.25 mg/kg/day. Some pigs were challenged by the intraperitoneal route, which had been demonstrated in the previous report to be a very reliable route for the establishment of infection. In these pigs, the doses of medication were more than 2.5 mg/kg/day. These doses were also proved to protect the pigs from infection almost completely (except the development of slight parasitemia in pig No. 10).

From these results, the effective dose of SDDS was clarified as follows: 1.25 mg/kg/day against the oral infection and 2.5 mg/kg/day against the intraperitoneal infection. As to the toxicity of the drug, it has been reported that oral administration of 400 mg/kg/day for 30 days did not cause any changes in the rat. In the present experiment, no toxicity of the drug for pigs was demonstrated either, judging from the growth curves of pigs both in the medicated and in the non-medicated groups.

Accordingly, at least for the time being, it seems desirable for pigs to be fed a diet containing SDDS for the prevention of Toxoplasma infection. Further experiments should be carried out to determine a minimal effective dose of this drug and establish an effective method of administration.

**SUMMARY**

Prophylactic effect of 2-sulfamoyl-4,4′-diaminodiphenyl (SDDS) was studied against Toxoplasma infection in pigs.

1. Powder containing 2% SDDS was mixed with a commercial pig diet and administered daily to pigs divided into four groups. The net doses of SDDS given were 1.25 mg in group E, 2.5 mg in group A, 5.0 mg in group B, and 10.0 mg in group C per kg of body weight throughout the experimental period.

2. On the 8th day of medication, these pigs and untreated control ones (groups D and F) received inoculation with toxoplasmas by the intraperitoneal route (groups A, B, C, and D) or the oral route (groups E and F).

3. In a group which had been fed 1.25 mg/kg of SDS and had received inoculation with toxoplasmas by the peroral route, the pigs were completely protected from any fever attack and parasitemia.

4. Three groups of pigs withstood infection with toxoplasmas when they had received a daily medication with 2.5 mg, 5.0 mg, and 10.0 mg, respectively, and had been challenged by intraperitoneal inoculation with the organisms.

In contrast to this, the four pigs of the untreated control groups (D and F) suffered from fever attack and parasitemia. Toxoplasmas were isolated from the brain and muscle in 2 pigs of them.

5. From the results mentioned above, it may be concluded that an oral administration of SDDS protects pigs from Toxoplasma infection.

**ACKNOWLEDGMENTS**

The authors wish to express their cordial thanks to the staff members of the Department of Veterinary Pathology, Obihiro Zootechnical University, for their as-
SDDS Orally Administered against Experimental Toxoplasmosis in Pigs

stance in the pathological examination of the experimental pigs, and to Dr. K. Tsunoda, of the National Institute of Animal Health, for his kind supply of the HG strain.

REFERENCES


経口投与による SDDS の豚トキソプラズマ症
感染防御効果について

清水亀平次・後藤 仁・白橋敏一・吉田 隆
帯広畜産大学獣医学部家畜微生物学教室
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田辺製薬株式会社生研研究所
(昭和44年10月27日受付)

SDDS の50倍散を市贩の配合飼料に混じ、各群2匹の子豚に、薬剤全量それぞれ1.25mg, 2.5mg, 5.0mg, 10.0mg/kg/day を朝夕2回に分けて投与し続けた。薬剤投与後8日目に、トキソプラズマ原虫（自然感染豚より分離し、マウスにて繁殖実験を記載中）TT株の腹腔内感染（マウス腹腔内増殖型Passed株5×10⁶/pig）または経口感染（感染マウス2匹/pig）を実施した。その後、感染無投薬対照豚の発症が軽度であったので、経口感染例では、4日にふたたび感染マウス2匹/pig を飼育した。さらに10日後に被検豚感染（5×10⁶/pig）を行ない、腹腔内感染例では、28日に実施した。前報告で使用した HG株の再接種（2×10⁶/pig）を試みた。その結果、1.25mg/kg/day の投薬例でも、経口感染に対して抵抗を示し、発熱も、パラジテミアも完全に阻止された。一方、腹腔内感染豚では、2.5mg, 5.0mg, 10.0mg/kg/day 各群とも、完全に発病が阻止された。ただしパラジテミアは10.0mg/kg/day群の1例に1回観察されたが、その他の供試豚では、すべて陰性を示した。

試験薬計12例を、初回トキソプラズマ感染後60～74日の間に投与処し、体内外の器官、リンパ節、筋肉等における原虫の存在を検索した。その結果、投薬群は全例陰性であったのに比し、対照群の半数では、心筋、横隔膜、肋間筋または脳から、原虫が検出した。

以上の成績から、SDDS 抗原性の経口投与は、豚トキソプラズマ症感染防御にきわめて有効であることが認められた。

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