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ANTICOCCIDIAL ACTIVITY OF 2-SULFAMOYL-4,4-DIAMINODIPHENYLSULFONE, SULFADIAZINE, PYRIMETHAMINE AND CLINDAMYCIN IN CATS INFECTED WITH *TOXOPLASMA GONDII*

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Introduction

Cats infected with *Toxoplasma gondii* can shed millions of oocysts after ingesting cysts from intermediate hosts. The oocysts are resistant to ordinary environmental influences and can infect many mammals and birds (4, 9). Due to public health significance of *T. gondii* oocysts there is a need for drugs that will prevent the shedding of oocysts by cats.

2-Sulfamoyl-4,4-diaminodiphenylsulfone (SDDS) is known to be antitoxoplasmic during acute toxoplasmosis in mice (10), rabbits (7), and pigs (13). Clindamycin is a recently discovered antibiotic with antitoxoplasmic activity in mice (1, 8) and rabbits (14). Efficacy of SDDS and clindamycin against feline toxoplasmosis is reported in this paper and compared with two well known antitoxoplasmic drugs, sulfadiazine (SD) and pyrimethamine (PR).

Materials and Methods

Cats and their Maintenance

Specific-pathogen-free (SPF) cats were used. They were 62–159 days old and had been raised by their mothers in a closed colony derived from germfree cats (11). All cats were free of *Toxoplasma* antibody as determined by the Sabin-Feldman dye test. Cats were housed individually in stainless steel, steam sterilized cages, and were given dry food and water *ad libitum*.

Strain of Toxoplasma

White laboratory mice were fed *T. gondii* oocysts of the M-7741 strain (3). Mice were killed 30 or more days after inoculation and their brains homogenized in physiological saline using alundum (mesh 90). The resultant suspension was passed through a layer of gauze and five to six tenfold dilutions were inoculated intraperitoneally into two mice for each dilution to determine the number of infectious *Toxoplasma* present in the inoculum. The inoculum was homogenous and usually contained 10^4 to 10^5 *T. gondii*. Cats were inoculated orally through a syringe.

Drugs

A powdered form of SDDS, SD and PR was used. Daily dosages of these drugs were suspended in 5% aqueous gum arabic because all three drugs are insoluble in water. For parenteral inoculation, SDDS was suspended in propylene glycol in experiment 4 in concentration of 200 mg of SDDS in each ml of propylene glycol or dimethylsulfoxide (DMSO), in experiment 5 in concentration of 250 mg of SDDS in 1 ml of DMSO. Clindamycin phosphate (Upjohn, Kalamazoo, Michigan) was given intramuscularly in experiment 6. Dosage of drugs is expressed as mg/kg of body weight of the cat/day. Cats were administered drugs either once between 9:00 and 10:00 a.m. or in two divided doses at six hour intervals daily for five to 12 days starting two days before or three to four days post-inoculation with *Toxoplasma* (DPIT).

Method of Drug Evaluation in Cats

Six experiments were performed using *Toxoplasma* infected cats. In each experiment six or seven littermates or age-matched cats were used. Different dosages of drugs were administered to five or six cats and one cat was not drugged and served as control. In the first experiment the drugs were administered two days before inoculating with *Toxoplasma*

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TABLE I

EFFICACY OF SDDS AND SD THERAPY IN *Toxoplasma* INFECTED CATS.

(EXPERIMENT 1)

Cat. No.	1	2	3	4	5	6
Drug and Level[a] (mg/kg/day)	SDDS 10	SDDS 20	SDDS 40	SDDS 80	SD 60	None
Oocyst Shedding Days shed[b]	5–10	5–9	6–8	7–8	6	5–10
Total no. shed	43,000	122,000	40,000	11,000	11,000	1,196,000
Antibody Titer 28 DPIT	64	128	512	128	128	128
Isolation in Mice	Pos.	Pos.	Pos.	Neg.	Pos.	Pos.
Hemograms 0, 12 DPIT			NORMAL ALL CATS			
% Weight Gain DPIT						
12	10	10	11	20	23	11
28	36	28	28	60	43	37

[a]Drug administered twice daily starting two days before inoculation through tenth day after inoculation with *Toxoplasma*. Cats were 87 to 89 days old on day 0.
[b]First and last day oocysts shed after ingesting *Toxoplasma*.

TABLE II

EFFICACY OF SDDS, SD AND PR THERAPY IN *Toxoplasma* INFECTED CATS.

(EXPERIMENT 2)

Cat. No.	7	8	9	10	11	12
Drug and Level[a] (mg/kg/day)	SDDS 160	SDDS 320	SDDS, PR 160, 1	SD 120	SD, PR 120, 1	None
Oocyst Shedding Days shed	5–6	None shed	5–6, 16–20	4–7	4–6, 17–21	4–10
Total shed	20,000		70,000, 546,000	40,000	30,000, 195,000	4,000,000
Antibody Titer 30 DPIT	64	64	<2	16	16	4096
Isolation in Mice	Pos.	Neg.	Pos.	Pos.	Neg.	Pos.
Hemograms DPIT						
0	Normal	Normal	Normal	Normal	Normal	Normal
10	Normal	Normal	Leukopenic	Normal	Leukopenic	Normal
% Weight Gain or Loss DPIT						
10	2	18	12	15	18	7
18	3	19	5	22	4[b]	22
28	15	47	15	40	18	40

[a]Drugs administered twice daily fourth through ninth DPIT. Cats were 86 to 89 days old on day 0.
[b]Weight loss. Other values are weight gain.

(Table I) and three to four days after inoculation with *Toxoplasma* in the rest of the experiments (Tables II to VI).

Efficacy of drugs against feline toxoplasmosis was judged by a) comparing the duration of oocyst shedding and the number of oocysts shed, b) hematological and clinical data, c) attempts to isolate *T. gondii* from feline tissues and d) determination of antibody titers to *T. gondii* in cats (experiments 1–3). The pharmacokinetics of SDDS and SD were determined after intravenous injections of 50 mg/kg body weight in groups of two cats each. Blood was withdrawn at one-half, one, three, five, eight and 24 hours for analysis by the method of Bratton and Marshall (2). Blood samples were taken at two, four, six, eight or 18 hours in an oral dose-response study or at two, six or 24

TABLE III

EFFICACY OF SDDS AND SD THERAPY IN *Toxoplasma* INFECTED CATS.

(EXPERIMENT 3)

Cat. No.	13	14	15	16	17	18
Drug and Level[a] (mg/kg/day)	SDDS 200	SDDS 250	SDDS 300	SDDS 350	SD 240	None
Oocyst Shedding						
Days shed	5–8, 15–18	5–7, 16	5–9	None	5–6	5–9
Total shed	810,000, 130,000	520,000, 10,000	1,020,000		250,000	2,876,000
Antibody Titer 30 DPIT	512	<2	<2	<2	ND[b]	128
Isolation in Mice	Pos.	Neg.	Neg.	Pos.	ND	Pos.
Hemograms 0, 4, 11 DPIT	NORMAL ALL CATS					
% Weight Gain DPIT						
16	15	9	12	18	ND	22
30	26	23	23	22	ND	33

[a]Drug administered twice daily fourth through the tenth DPIT. Cats were 117 to 119 days old on day 0.
[b]ND = No data.

TABLE IV

EFFICACY OF ORAL *vs* SUBCUTANEOUS INOCULATION OF SDDS IN *Toxoplasma* INFECTED CATS.

(EXPERIMENT 4)

Cat. No.	19	20	21	22	23	24
Drug and Level[a]	SDDS	SDDS	SDDS	SDDS	SDDS	None
(mg/kg/day)	350	350	500	500	500	
Route	S.C.[b]	Oral	S.C.	Oral	Oral	
Dosing	Once	Twice	Once	Once	Once	
Serum SDDS μg/ml						
2 hr	9	19	21	9	21	0
6 hr	9	31	17	31	42	0
24 hr	21	18	23	9	22	0
Oocyst Shedding						
Days shed	4–10[c]	4–8	5–8	4–7	4–9	4–10[c]
Total shed	83,100,000	3,430,000	1,030,000	620,000	1,240,000	199,200,000
Isolation in Mice	Pos.	Neg.	Neg.	Pos.	Neg.	Pos.
Hemograms 0, 10 DPIT	NORMAL ALL CATS					

[a]Drug administered daily from fourth through ninth DPIT. Cats were 115 to 120 days old on day 0. They were killed on tenth DPIT.
[b]SDDS suspended in propylene glycol in concentration of 200 mg/ml before subcutaneous inoculation into cats.
[c]Shedding oocysts at the time of death.

hours during the efficacy study to provide evidence of oral absorption.

Fecal Examination and Oocyst Determination

Feces from each cat were collected daily in litter and the litter was changed daily. Feces were moistened with water and floated in a sucrose solution of 1.15 specific gravity in 50 ml centrifuge tubes at 2000 revolutions per minute (rpm). After removing a drop of the supernatant from the top for microscopic examination, 5 ml of the supernatant was mixed with 45 ml of water and centrifuged at 2000 rpm for ten minutes. After discarding the supernatant, the sediment was suspended in 10 ml of 2% H_2SO_4 and the number of oocysts were counted in 0.4 μl of oocyst suspension in a hemocytometer. The total number of oocysts

TABLE V

EFFICACY OF ORAL *vs* SUBCUTANEOUS INOCULATION OF SDDS IN *Toxoplasma* INFECTED CATS.

(EXPERIMENT 5)

Cat. No.	25	26	27	28	29	30
Drug and Level[a]	SDDS	SDDS	SDDS	SDDS	SDDS	
(mg/kg/day)	500	500	350	500	500	None
Route	S.C.[b]	S.C.[b]	Oral	Oral	Oral	
Dosing	Once	Once	Twice	Once	Once	
Serum SDDS μg/ml						
7 hr	11	8	6	1	0	0
25 hr	22	31	10	6	6	0
Oocyst Shedding						
Days shed	5–9	5–11[c]	4–11[c]	5–10	5–8	5–10
Total shed	19,070,000	1,020,000	15,620,000	9,250,000	420,000	16,250,000
Isolation in Mice	Pos.	Neg.	Neg.	Pos.	Pos.	Pos.

[a]Drug administered daily from fourth through tenth DPIT. Cats were 149 to 159 days old on day 0.
[b]SDDS dissolved in DMSO in concentrations of 250 mg/ml for subcutaneous inoculation.
[c]Shedding oocysts at the time of death.

TABLE VI

EFFICACY OF SDDS AND CLINDAMYCIN THERAPY IN *Toxoplasma* INFECTED CATS.

(EXPERIMENT 6)

Cat. No.	31	32	33	34	35	36	37
Drug and Level[a]	SDDS	SDDS	SDDS	SDDS	Clindamycin		None
(mg/kg/day)	350	500	500	1000	100	250	
Route	Oral	Oral	Oral	Oral	Intramuscular		
Oocyst Shedding							
Days shed	3–10[b]	3–6	3–6	4–7	5–6	5–9	5–10[b]
Total shed	441,800,000	9,100,000	1,350,000	6,625,000	20,000	50,000	940,000
Isolation in Mice	Neg.	Neg.	Pos.	Pos.	Neg.	Neg.	Pos.
Hemograms 0, 10 DPIT	NORMAL ALL CATS						

[a]Drug administered twice daily from third to ninth DPIT. Cats were 62 to 65 days old on day 0. They were killed on the tenth DPIT.
[b]Shedding oocysts at the time of death.

present in the entire daily fecal sample was obtained by multiplying the number of oocysts in 0.4 μl of fecal suspension by 25,000. Thus, the lower threshold of countable oocysts was 25,000 in the daily sample. A cat was presumed to be shedding 10,000 oocysts daily if several oocysts were detected microscopically but were absent in 0.4 μl of fecal suspension and 1,000 if only one to five oocysts were found in the microscopic examination and none in the hemocytometer chamber.

All fecal samples were inoculated in mice and the mice examined for *Toxoplasma* infectivity as described (3).

Clinical Data

Cats were weighed before, during and at the termination of the experiments. Their hemograms (hemoglobulin, PCV, total protein, total leukocytic differential, and sometimes platelets) were determined one to three times during the experiment.

Toxoplasma Infectivity of Cats

Cats were killed between ten and 30 DPIT and pooled suspensions of their brain, heart, mesenteric lymph nodes, lungs, liver, spleen, and skeletal muscles (hereafter referred to as tissues) were inoculated intraperitoneally into six mice. Mice were examined for *Toxoplasma* infectivity, as previously described (3). Briefly, smears of internal organs of the mice that died were examined for evidence of *Toxoplasma* infection. Survivors were bled and killed 21 days after inoculation and their brains were examined for *Toxoplasma* cysts. Mice were con-

TABLE VII
SERUM CONCENTRATION OF SDDS DURING DOSE RESPONSE STUDIES IN NORMAL CATS

Route	Time (hr)	Dose mg/kg 200	250	300	350
			SDDS μg/ml		
Oral	2	2	3	—	9
	4	22	23	36	27
	6	28	30	42	36
	8	26	28	38	38
	18	21	26	26	22
Subcutaneous			Dose 500 mg/kg		
	2	21			
	6	17			
	24	23			

sidered not infected if cysts and antibody to *T. gondii* were not demonstrable 21 days after inoculation with feline tissues.

Serological Testing for T. gondii

Cats were bled before feeding *Toxoplasma* and at necropsy.

Feline and murine sera were tested for Sabin-Feldman dye test antibodies to *Toxoplasma* as previously described (6). Titers are expressed as reciprocal values.

Histological Examination

Internal organs of cats that died were fixed in 10% formalin. Paraffin-embedded sections were examined microscopically after staining with haematoxylin and eosin.

RESULTS

2-Sulfamoyl-4,4-diaminodiphenylsulfone

Cats administered SDDS generally shed fewer oocysts than the controls (Tables I–V) except in experiment 6 where SDDS medicated cats shed more oocysts than the control cat. It was not possible to stop oocyst shedding consistently by administering SDDS after the cats started shedding oocysts. Three cats administered 160, 200 and 250 mg SDDS/kg of body weight reshed oocysts between 15 and 21 DPIT. However, *Toxoplasma* was not recovered in mice from the tissues of 11 of 21 cats that were administered the drug two to four DPIT (Tables II to VI).

SDDS was well tolerated by cats as judged by weight gain, hematological and clinical data. The half-life after intravenous injection of SDDS in two cats was 2.8 and 3.3 hours. The apparent volume of distribution in these cats was approximately 1.25 l/kg and 1.13 l/kg. Serum SDDS levels obtained during dose-response studies with SDDS are shown in Table VII. SDDS was slowly absorbed as indicated by the persistent blood concentration after oral administration. In no experiment, even when given subcutaneously at a dosage of 500 mg/kg, did the serum levels exceed 42 μg/ml and dissection of the injection site revealed significant quantities of unabsorbed SDDS 24 hours after injection.

Sulfadiazine

All three cats given 60 or 120 or 240 mg of SD shed fewer oocysts as compared to control cats (Tables I to III). One cat given 240 mg/kg body weight of SD became depressed on the ninth DPIT and died the following day. Necropsy revealed degeneration of epithelial cells lining the proximal tubules of both kidneys and pulmonary edema but no inflammatory cells. The other organs were normal. These changes are consistent with sulfadiazine toxicity. The serum concentration of sulfadiazine in this cat at four, six, and eight hours were 427, 560, and 452 μg/ml respectively. The intravenous half-life of SD was 2.5 and 3.5 hours after an intravenous dosage of 50 mg/kg. The apparent volume of distribution was 555 ml/kg in one cat and 406 ml/kg in the other.

Pyrimethamine

Both cats given PR reshed *Toxoplasma* oocysts ten and 11 days after the cessation of the drug (Table II). Cats given PR in conjunction with SD or SDDS had leukopenia on the sixth day (WBC 4610, seg. neutrophils 2535, bands 329, lymphocytes 876, eosinophils 645, basophils 184, monocytes 46, platelets 472,000 in cat 9 given SDDS + PR, and WBC 4730, seg. neutrophils 1088, bands 189, lymphocytes 3122, eosinophils 94, monocytes 189, platelets 110,000 in cat 11 given SD + PR) of drug therapy. However, the blood picture became normal within two days after PR was discontinued on the sixth day.

Clindamycin

Two cats administered clindamycin shed two and five times fewer oocysts than the control. *T. gondii* was not isolated from the tissues of these cats (Table VI).

Oocysts from cats given SDDS, SD, PR or clindamycin sporulated normally and were infectious to mice.

Discussion

Two types of drugs should be looked for in the prevention of shedding of *Toxoplasma* oocysts by cats: 1) that which could be used prophylactically in cat food on a long term basis, 2) that which can minimize or stop oocyst shedding after oocysts have been demonstrated in feline feces. Neither of these objectives are completely fulfilled by SDDS, although oocyst shedding was reduced when administered prophylactically. The reasons for the variable efficacy of SDDS against *T. gondii* oocysts are unexplained. Measurement of serum concentration indicates the drug is poorly absorbed and bioavailability due to poor dissolution of the insoluble drug is one apparent variable. SDDS appears to be partially effective against tachyzoites because *T. gondii* was not isolated from the tissues of 11 of 21 cats administered SDDS three or four DPIT.

Sulfadiazine and pyrimethamine are still the most widely used drugs for the treatment of toxoplasmosis in man. A combination of 120 mg/kg body weight of SD and 1 mg/kg body weight of PR was reported to have reduced oocyst shedding in *Toxoplasma* infected cats (5). In a recently reported study oocyst excretion was inhibited in three of four cats treated intramuscularly with 2 mg/kg body weight PR and 100 mg/kg body weight SD, but not in four cats treated with one-half that dose (12). In the present investigation SD and PR did not eliminate oocysts from cats even in toxic doses. These results suggest that the treatment with SDDS or SD or SD + PR cannot be relied upon in the prevention of excretion of *Toxoplasma* oocysts. The preliminary experiments reported in this study suggest that clindamycin might be an effective drug against feline toxoplasmosis and further research is needed in this area.

Summary

Efficacy of 2-sulfamoyl-4,4-diaminodiphenylsulfone (SDDS), sulfadiazine (SD), pyrimethamine (PR) and clindamycin was tested against feline toxoplasmosis. The criteria used in evaluating the effects of drugs were the duration and the number of oocysts shed, clinical and hematological data and isolation of *T. gondii* from tissues of cats orally inoculated with *Toxoplasma* cysts. Cats administered 160 to 1000 mg/kg body weight of SDDS three to four days after feeding *Toxoplasma* generally shed fewer oocysts than the control cats but did not completely eliminate oocysts after the cat started shedding oocysts. SDDS was well tolerated by cats as judged by weight gain, hematological and clinical data. *Toxoplasma* was not isolated from 11 of 21 cats administered SDDS three or four days postinoculation with *Toxoplasma*. The half-life of SDDS after intravenous injection in two cats not inoculated with *Toxoplasma* was 2.8 and 3.3 hours. After oral administration of 500 mg/kg of SDDS to cats peak serum SDDS levels were lower than 42 μg/ml indicating poor intestinal absorption.

Three cats administered 60 or 120 or 240 mg of SD shed fewer oocysts as compared to control cats. One cat given 240 mg/kg body weight of SD died on the tenth day due to sulfadiazine toxicity. The serum concentration of SD in this cat was 427, 560 and 452 μg/ml at four, six and eight hours respectively. The half-life of SD was 2.5 and 3.5 hours after an intravenous dosage of 50 mg/kg in two cats not inoculated with *Toxoplasma*.

Pyrimethamine 1 mg/kg given in conjunction with SDDS or SD was unpalatable and apparently caused leukopenia in cats. The two cats administered 100 or 250 mg/kg of clindamycin shed ten to 50 times fewer oocysts than the control cats. *Toxoplasma* was not isolated from the tissues of 2 cats administered clindamycin.

Résumé

Cette expérience visait à déterminer l'efficacité du 2-sulfamoyl-4,4-diaminodiphénylsulfone (SDDS), de la sulfadiazine, de la pyriméthamine et de la clindamycine, pour traiter la toxoplasmose féline. On utilisa à cette fin les critères suivants: la durée d'élimination d'oocystes et leur nombre, les données cliniques et hématologiques, ainsi que l'isolement de *Toxoplasma gondii* des tissus des chats auquels on avait administré ce parasite, par la voie orale.

En général, les sujets qui reçurent de 160 à 1,000 mg/kg de SDDS, de trois à quatre jours après l'ingestion des toxoplasmes, éliminèrent moins d'oocystes que les témoins; ils ne se débarrassèrent toutefois pas complètement des oocystes, après avoir commencé à en éliminer; par ailleurs, ils tolérèrent bien ce médicament, d'après leur gain de poids et les données cliniques et hématologiques. On n'isola pas de

toxoplasmes, chez 11 des 21 chats auxquels on avait administré du SDDS, trois ou quatre jours après leur avoir fait ingérer ce parasite. La demi-vie du SDDS, inoculé par la voie intraveineuse à deux chats témoins, atteignit 2.8 et 3.3 heures. Après l'administration orale de 500 mg/kg de SDDS aux chats, la concentration sérique la plus élevée de ce médicament s'avéra inférieure à 42 μg/ml, indice d'une piètre absorption intestinale.

Les chats qui reçurent respectivement 60, 120 ou 240 mg de sulfadiazine éliminèrent moins d'oocystes que les témoins. Un de ceux auxquels on avait administré 240 mg/kg de sulfadiazine succomba à une intoxication attribuable à ce médicament, dix jours plus tard. La teneur du sérum en sulfadiazine s'éleva respectivement à 427, 560 et 452 μg/ml, au bout de quatre, six et huit heures. Sa demi-vie atteignit 2.5 et 3.5 heures, chez deux chats témoins qui en avaient reçu une injection intraveineuse de 500 mg/kg.

L'addition de 1 mg/kg de pyriméthamine au SDDS ou à la sulfadiazine produisit des mélanges au goût désagréable et provoqua de la leucopénie chez les chats qui en reçurent. Les deux sujets auxquels on avait administré 100 ou 250 mg/kg de clindamycine éliminèrent dix à 50 fois moins d'oocystes que les témoins et on n'isola pas de toxoplasmes de leurs tissus.

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References

1. Araujo, F. G. and J. S. Remington. Effect of clindamycin on acute and chronic toxoplasmosis in mice. Antimicrob. Ag. Chemother. 5: 647–651. 1974.
2. Bratton, C. G. and E. K. Marshall. A new coupling component for sulfanilamide determinations. J. biol. Chem. 128: 537–551. 1939.
3. Dubey, J. P. and J. K. Frenkel. Experimental *Toxoplasma* infection in mice with strains producing oocysts. J. Parasit. 59: 505–512. 1973.
4. Dubey, J. P., N. L. Miller and J. K. Frenkel. Characterization of the new fecal form of *Toxoplasma gondii*. J. Parasit. 56: 447–456. 1970.
5. Frenkel, J. K. Toxoplasmosis in cats and mice. Feline Practice 5: 28–41. 1975.
6. Frenkel, J. K. and L. Jacobs. Ocular toxoplasmosis. Archs Opthtal. 59: 260–279. 1958.
7. Gill, H. S. and O. Prakash. Chemotherapy of experimental *Toxoplasma gondii* (RH strain) infection. Indian J. med. Res. 59: 1197–1202. 1970.
8. McMaster, P. R. B., K. G. Powers, J. F. Finerty and M. N. Lunde. The effect of two chlorinated lincomycin analogues against acute toxoplasmosis in mice. Am. J. trop. Med. Hyg. 22: 14–17. 1973.
9. Miller, N. L., J. K. Frenkel and J. P. Dubey. Oral infections with toxoplasma cysts and oocysts in felines, other mammals and in birds. J. Parasit. 58: 928–937. 1972.
10. Ohshima, S., H. Tanaka and Y. Inami. The chemotherapeutic effect of 2-sulfamoyl-4,4′-diaminodiphenylsulfone (SDDS) on acute experimental toxoplasmosis in mice. Jap. J. Parasit. 16: 331–338. 1967.
11. Rohovsky, M. W., R. A. Griesemer and L. G. Wolfe. The germfree cat. Lab. Anim. Care 16: 52–59. 1966.
12. Sheffield, H. G. and M. L. Melton. Effects of pyrimethamine and sulfadiazine on the intestinal development of *Toxoplasma gondii* in cats. Am. J. trop. Med. Hyg. 25: 379–383. 1976.
13. Shimizu, K., H. Goto, T. Shirahata, T. Yoshida and Y. Inami. Prophylactic effects of SDDS (2-sulfamoyl-4,4′-diaminodiphenylsulfone) orally administered against experimental toxoplasmosis in pigs. Jap. J. vet. Sci. 32: 159–167. 1970.
14. Tabbara, K. F., R. A. Nozik and G. R. O'Connor. Clindamycin effects on experimental ocular toxoplasmosis in the rabbit. Archs Ophthal. 92: 244–247. 1974.