Pharmacodynamic Effects of the Diformyl Derivative of Diaminodiphenyl Sulfone (DDS)[1, 2]

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The proceedings of a "Symposium on Sulfones" have been published as a supplement to THE JOURNAL (35 (1967) 563-642, Part 2). In this symposium, the metabolism, drug resistance and efficacy of the use of sulfones were reviewed. Powell *et al.* ([9]) reviewed the antimalarial and hemolytic properties of diaminodiphenyl sulfone. They pointed out also that the sulfones may prove of increasing antimalarial value, especially for the prevention or treatment of infections caused by strains of *Plasmodium falciparum* that are resistant to chloroquine.

The diformyl derivative (DFD) of diaminodiphenyl sulfone is another antimalarial agent being considered to overcome the resistant strains ([1, 4]). In contrast to its parent compound, DFD has the following special advantages: (a) In mice infected with *Plasmodium berghei*, the suppressive dose 50 for DFD is one-half that of diaminodiphenyl sulfone. (b) In mice, the lethal dose 50 for DFD has proved to be about 4/7th that of diaminodiphenyl sulfone, and, therefore, the therapeutic index for DFD was four times that of the parent compound.

DFD appears to be a unique compound. Most known derivatives of diaminodiphenyl sulfone are converted to the parent compound and the required dose of the derivative for the treatment of leprosy is larger than the dose of diaminodiphenyl sulfone. DFD, however, is more potent than diaminodiphenyl sulfone in the suppression of malaria in mice. It is, therefore, reasonable to suspect that DFD is a sulfone that is not converted to the diaminodiphenyl sulfone, if appropriate experiments can be designed to exclude the possibility that DFD is slowly excreted from the body. The experiments reported below are intended to exclude such a possibility and to characterize the pharmacologic actions of DFD in the hope that the future application of DFD can be extended to include the treatment not only of malaria but also of leprosy. The chemical structures of both compounds are given in Figure 1.

MATERIALS AND METHODS

Unanesthetized rabbits. Three groups of rabbits were used on separate days. Diaminodiphenyl sulfone (DFD) was suspended in 0.5 per cent methocel and administered orally. Blood samples were collected by intracardiac puncture one hour before, one hour after, 18 hours after, and 42 hours after drug administration. The blood was analyzed for plasma hemoglobin ([5]), blood methemoglobin ([5]), blood sulfhemoglobin ([5]) and sulfone levels ([6]).

Unanesthetized rats. Nine mature rats were separated in individual metabolism cages for collection of urine. They were fasted on the day before and on the day of the experiment. The sulfone, suspended in 0.5 per cent methocel was administered subcutaneously. Urine was collected hourly for 24 hours. The collected urine was an-

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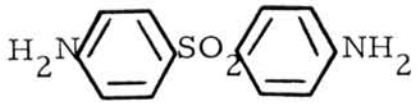
[4]A sample of this sulfone can be obtained by writing to: Dr. Melvin H. Heiffer, Chief, Department of Pharmacology, Division of Medicinal Chemistry, Walter Reed Army Medical Center, Washington, D. C. 20012.

Diaminodiphenyl sulfone



DFD of diformyl derivative of diaminodiphenyl sulfone (Walter Reed Compound No. 6798)

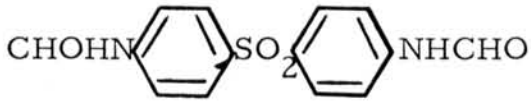


FIG. 1. Formula for the diformyl derivative of diaminodiphenyl sulfone, showing its relation to the parent compound.

alyzed for sulfone levels ([6]). Immature four-week-old rats were used in groups of four, to investigate the goitrogenic activity of the sulfones ([8]). Either thiouracil or a sulfone was administered subcutaneously, daily for nine days. On the tenth day, the rats were sacrificed, and the thyroids were dissected and weighed.

Anesthetized cats. Six cats were used. Each one was anesthetized with a combination of diethylbarbituric acid (60 mgm./kgm.) and urethane (240 mgm./kgm.) intraperitoneally. The trachea was cannulated and the carotid artery catheterized for measurement of aortic blood pressure. Contraction of the nictitating membrane was recorded by a strain gauge tied to the free border of the membrane. The corresponding contraction of the tongue in response to stimulation of the hypoglossal nerve was recorded by a second strain gauge. In some cats a balloon was inserted into the ileum to measure intestinal motility.

Anesthetized dogs. Six anesthetized dogs were used and each one received an infusion of either DFD dissolved in dimethylsulfoxide or of dimethylsulfoxide alone. Blood pressure was measured by a catheter inserted into one femoral artery and attached to a transducer. Pulmonary resistance and compliance were calculated from measurements of tracheal air flow, tidal volume and transpulmonary pressure reported elsewhere ([2]). Briefly, an endotracheal tube was connected directly to a mesh screen Fleisch pneumotachograph and the pressure difference across the screen was measured by a differential pressure transducer (Sanborn model 270). The signal from the transducer corresponded to air flow and was in turn integrated and recorded as tidal volume. Both flow and volume were recorded on a Sanborn Polyviso record. The pressure difference between the trachea and intrapleural space was measured by a second differential transducer (Sanborn 268B) and recorded on a third channel of the Polyviso. To measure pulmonary resistance, the flow and pressure signals were displayed simultaneously on both axes of the oscilloscope screen to show a P-V loop. Subsequently an amount of pressure proportional to volume was subtracted so that the loop was closed at zero flow. The slope of the line thus obtained corresponded to pulmonary resistance. The values for compliance were obtained similarly by displaying the P-V signals and subtracting pressure due to resistance, or by calculation from the subtracted pressure when closing the resistance loop. The loops were photographed from the screen.

RESULTS

Blood Levels in the Rabbit

Oral administration and blood sulfone. The first group of six rabbits was used to investigate the blood levels of sulfone after a single oral administration of either DFD or diaminodiphenyl sulfone (Table 1). The first two rabbits (Nos. 1 and 2) were used

TABLE 1. *Oral administration of diaminodiphenyl sulfone and DDS suspended in methocel in rabbits.*

Rabbit No. Weight (kgm.)	Drug (dose) Samples collected	Blood sulfone (mgm./100 ml.) net Δ		Methemoglobin (gm./100 ml.) net Δ		Sulfhemoglobin (gm./100 ml.) net Δ	
1 (1.80)	Before methocel (18 ml.)	0.02		0		0.21	
	18 hours later	0.05	+0.03	0	0	0.23	+0.02
	42 hours later	0.06	+0.04	0	0	0.42	+0.21
2 (1.75)	Before methocel (17 ml.)	0.07		0.03		0.21	
	18 hours later	0.07	0	0.03	0	0.29	+0.08
	42 hours later	0.07	0	0.03	0	0.21	0
3 (1.65)	Before diaminodiphenyl sulfone (100 mgm./kgm.)	0.02		0		0.26	
	18 hours later	0.18	+0.16	0	0	0.27	+0.01
	42 hours later	0.06	+0.04	0	0	0.32	+0.06
4 (1.85)	Before diaminodiphenyl sulfone (100 mgm./kgm.)	0.08		0.07		0.29	
	18 hours later	0.40	+0.32	0.07	0	0.25	−0.04
	42 hours later	0.05	−0.03	0.07	0	0.26	−0.03
5 (1.58)	Before diaminodiphenyl sulfone (100 mgm./kgm.)	0.02		—		—	
	18 hours later	0.21	+0.19	—		—	
	42 hours later	0.03	+0.01	—		—	
6 (1.72)	Before diaminodiphenyl sulfone (100 mgm./kgm.)	0.03		—		—	
	18 hours later	0.26	+0.23	—		—	
	42 hours later	0.06	+0.03	—		—	

TABLE 2. *Oral administration of diaminodiphenyl sulfone and DFD suspended in methocel in rabbits.*

Rabbit No. Weight (kgm.)	Drug (dose) Samples collected	Blood sulfone (mgm./100 ml.)	net Δ	Methemoglobin (gm./100 ml.)	net Δ	Sulfhemoglobin (gm./100 ml.)	net Δ
7 (1.95)	Before methocel (19.5 ml.)	0.04		0.12		0.18	
	1 hour later	0.08	+0.04	0.21	+0.09	0.21	+0.03
	18 hours later	0.04	0	0.54	+0.42	0.21	+0.03
	42 hours later	0.03	−0.01	—		—	
8 (1.85)	Before methocel (19.5 ml.)	0.11		0.03		0.25	
	1 hour later	0.08	−0.03	0.03	0	0.19	−0.06
	18 hours later	0.06	−0.05	0.03	0	0.24	−0.01
	42 hours later	0.04	−0.07	0.03	0	—	
9 (1.82)	Before diaminodiphenyl sulfone (500 mgm./kgm.)	0.05		—		—	
	1 hour later	0.70	+0.65	—		—	
	18 hours later	0.42	+0.38	—		—	
	42 hours later	0.38	+0.33	—		—	
10 (1.75)	Before diaminodiphenyl sulfone (500 mgm./kgm.)	0.08		—		—	
	1 hour later	0.70	+0.62	—		—	
	18 hours later	0.53	+0.45	—		—	
	42 hours later	0.48	+0.40	—		—	
11 (1.60)	Before DFD (500 mgm./kgm.)	0.10		0.14		—	
	1 hour later	0.26	+0.16	0.14	0	—	
	18 hours later	0.61	+0.51	0.12	−0.02	—	
	42 hours later	0.50	+0.40	—		—	
12 (1.80)	Before DFD (500 mgm./kgm.)	0.14		0.20		—	
	1 hour later	0.27	+0.13	0.20	0	—	
	18 hours later	0.48	+0.34	0.20	0	—	
	42 hours later	0.42	+0.18	0.20	0	—	

as controls, receiving only the suspending agent, 0.5 per cent methocel. The variations in blood levels were within the error of the analysis for sulfone. The next pair of rabbits (Nos. 3 and 4) received diaminodiphenyl sulfone, 100 mgm./kgm., and blood samples were collected 18 and 42 hours later. The peak levels, appearing 18 hours later, were elevations of +0.16 and +0.32 mgm./100 ml. over the controls for each of the two rabbits. The remaining pair (Nos. 5 and 6) received 100 mgm./kgm. DFD orally, and the corresponding levels 18 hours later were +0.19 and +0.23 mgm./kgm. respectively. In all four rabbits the sulfone levels 42 hours later were back at control.

The second group of six rabbits was devoted to the administration of DFD, 500 mgm./kgm. orally, contrasted with diaminodiphenyl sulfone, 500 mgm./kgm., and the control administration of methocel only (Table 2). The peak blood levels, one hour after administration, were essentially higher for the rabbits receiving diaminodiphenyl sulfone. However, the levels 42 hours later were essentially the same for the rabbits receiving either sulfone.

Parenteral administration. The last three rabbits received DFD exclusively but administered in three different ways, orally, intraperitoneally, and intramuscularly (Table 3). The sulfone levels in the blood collected at various times were essentially the same, indicating that the various routes of administration did not influence the level of blood sulfones.

Methemoglobin and sulfhemoglobin levels. In some of the rabbits included in Tables 1 to 3 abnormal forms of hemoglobin in the blood were determined. None of the rabbits showed an elevation of either sulfhemoglobin or methemoglobin, as noted on comparison with control levels prior to the administration of the sulfone.

Urinary Excretion and Goitrogenic Activity in Rats

Urinary excretion of sulfones. The next study involved nine mature rats that received either DFD or diaminodiphenyl sulfone, 100 mgm./kgm. subcutaneously (Table 4). The day before the injection, and on the day of the injection, each rat received water, 5 per cent of body weight, by stomach tube. Among three rats that received DFD, the hourly urinary volume was increased in one but decreased in the other two. In spite of the varied change in volume, the pH of the urine was consistently increased and contained detectable amounts of sulfone. Three rats receiving diaminodiphenyl sulfone all showed a decrease in urine volume, but a fall in urinary pH in two and a detectable increase in sulfone level in all. These results do not indicate any serious loss of renal function following a dose of 100 mgm./kgm. There was no indication that DFD is excreted at a faster rate than diaminodiphenyl sulfone.

Goitrogenic activity. The immature rats receiving thiouracil (10 or 100 mgm./kgm. daily for nine days showed an enlarged thyroid on comparison with untreated controls (Table 5). These effects were expressed as 100 per cent of goitrogenic activity for comparison with the administration of sulfone in 10 and 100 mgm./kgm. doses. Administration of diaminodiphenyl sulfone 10 mgm./kgm. daily, caused a 19 per cent goitrogenic action, but the 100 mgm./kgm. dose did not influence the thyroids. The thyroid effects of the DFD in both doses were negligible.

Acute Toxicity in Anesthetized Cats

Blood pressure and lethal dose. The lethal doses for the six cats are summarized in Table 6. The range of doses for diaminodiphenyl sulfone was 55 to 180 mgm./kgm., whereas the range for DFD was 255 to 350 mgm./kgm. The cats died of hypotension, which appeared after approximately half of the lethal dose had been injected intravenously.

Other effects in the cat. Both DFD and diaminodiphenyl sulfone also caused paralysis of the tongue as noted in response to stimulation of the hypoglossal nerve. This was explained as a curareform action, although antagonism by anticholinesterase was not tested. Intestinal motility was not depressed. However, the response of the nictitating membrane to epinephrine was potentiated and prolonged in duration (Fig. 2). The corresponding hypertensive

TABLE 3. *Oral and parenteral administration of DFD in rabbits.*

Rabbit No. Weight (kgm.)	Drug (dose) Samples collected	Blood sulfone (mgm./100 ml.) net Δ		Methemoglobin (gm./100 ml.) net Δ		Sulfhemoglobin (gm./100 ml.) net Δ	
13 (1.7)	Before DFD (500 mgm./kgm.) orally	0.08		0		0.33	
	1 hour later	0.25	+0.17	0	0	0.17	−0.16
	18 hours later	0.45	+0.37	0	0	0.31	−0.02
	42 hours later	0.18	+0.10	0	0	0.19	−0.14
14 (1.8)	Before DFD (500 mgm./kgm.) intramuscularly	0.12		0		0.26	
	1 hour later	0.42	+0.30	0	0	0.12	−0.14
	18 hours later	0.18	+0.06	0	0	0.27	+0.01
	42 hours later	0.17	+0.05	0	0	0.16	−0.10
15 (1.7)	Before DFD (500 mgm./kgm.) intraperitoneally	0.06		—		—	
	1 hour later	0.57	+0.51	—		—	
	18 hours later	0.20	+0.14	—		—	
	42 hours later	0.12	+0.06	—		—	

TABLE 4. *Urinary excretion following oral ingestion of DFD or diaminodiphenyl sulfone (DDS) in rats.*

Rat No. Weight (gm.)	Drug (dose)	Urinary pH		Urinary volume (ml./hr.)		Urinary sulfone (mgm./ml)		
		Before	+ 3 hr.	Before	+ 3 hr.	Before	+ 3 hr.	+ 24 hr.
1 (370)	control	7.0	6.0	2.1	3.1	.004	.004	.004
2 (390)	control	7.5	6.5	2.1	2.9	.003	.003	.006
3 (320)	control	7.0	7.0	5.0	4.1	.004	.004	.006
4 (370)	DFD (100 mgm./kgm.)	6.0	7.5	2.1	8.2	.004	.012	.004
5 (330)	DFD (100 mgm./kgm.)	5.5	7.0	4.8	1.8	.004	.006	.006
6 (310)	DFD (100 mgm./kgm.)	6.0	6.5	3.6	0.2	.004	.006	.006
7 (330)	DDS (100 mgm./kgm.)	7.0	5.0	1.3	0.6	.004	.012	.008
8 (290)	DDS (100 mgm./kgm.)	6.0	5.0	4.1	1.3	.004	.005	.005
9 (270)	DDS (100 mgm./kgm.)	6.5	7.5	3.8	2.9	.004	.006	—

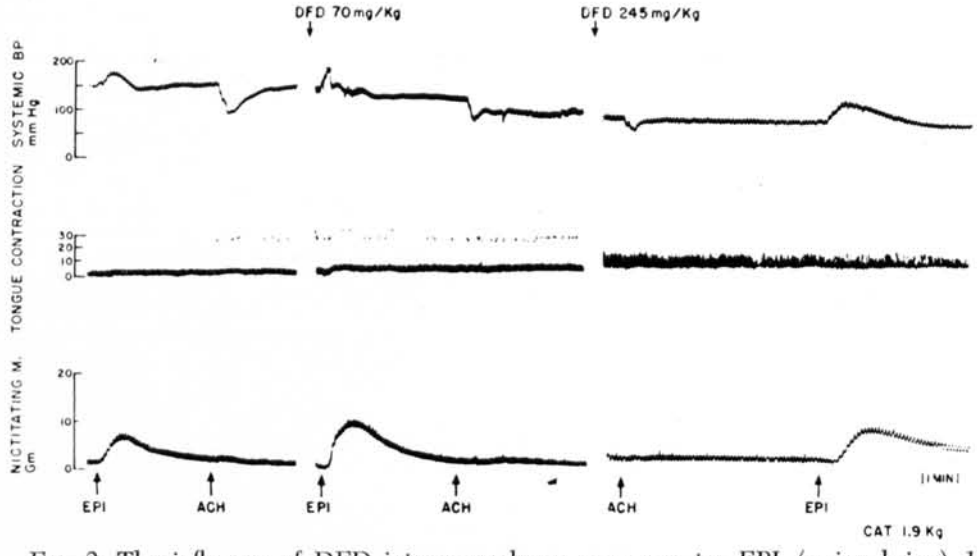


FIG. 2. The influence of DFD intravenously on responses to: EPI (epinephrine) 1 μgm./kgm.; and ACH (acetylcholine) 1 μgm./kgm. After 170 mgm./kgm. DFD, the contraction of the nictitating membrane produced by epinephrine was exaggerated. After injection of 245 mgm./kgm. the strength of contraction of the tongue was reduced. Cat 1.9 kgm. under dialurethane anesthesia with closed chest.

effect of epinephrine was also prolonged as a result of infusion of DFD. The depressor action of acetylcholine was not potentiated and appeared to be reduced in some cats but the reduction in responses may be an outcome of the low blood pressure resulting from the sulfone when acetylcholine was injected.

Acute Toxicity in Anesthetized Dogs

In a group of three anesthetized dogs DFD was infused intramuscularly at the rate of 1 mgm./kgm. (Table 7). The lethal doses for each of three dogs were as follows: 98, 114 and 117 mgm./kgm. As the infusion progressed, there was a fall in blood pressure, so that, at about 80 per cent of the lethal dose, the mean blood pressure fell to 56 per cent of that of the control. There was also tachycardia, which was marked (183%) when 20 per cent of lethal dose was infused. With larger doses the tachycardia was less severe. Pulmonary resistance gradually became elevated and

TABLE 5. *Goitrogenic activity in immature rats.*

Rat No.	Drug Daily dose (mgm./kgm.)	Mean weight gain + S. D. (gm./day)	Thyroid weight (mgm./100 gm. body weight)	Goitrogenic activity (%)
10 to 13	control	3.7 ± 0.7	9.5	—
14 to 17	Thiouracil (10)	3.7 ± 0.6	13.1	100
18 to 21	Thiouracil (100)	3.1 ± 0.7	18.5	100
22 to 25	Diaminodiphenyl sulfone (10)	3.1 ± 0.3	10.2	19
26 to 29	Diaminodiphenyl sulfone (100)	3.5 ± 0.5	9.7	2
30 to 33	DFD (10)	3.3 ± 0.5	9.2	8
34 to 37	DFD (100)	3.5 ± 0.5	9.7	2

TABLE 6. *Summary of intravenous lethal doses in anesthetized cats.*

Cat No. Weight (kgm.)	Sulfone	Intravenous lethal dose	Additional observations
1 (2.9)	Diaminodiphenyl sulfone	55 mgm./kgm.	Fall in blood pressure and shock coincided with injection of acetylcholine 1 μgm./kg.
2 (2.3)	Diaminodiphenyl sulfone	180 mgm./kgm.	No depression of intestinal motility; paralysis of neuromuscular junction at 100% lethal dose.
3 (2.5)	Diaminodiphenyl sulfone	100 mgm./kgm.	Death by hypotension.
4 (1.9)	DFD	350 mgm./kgm.	(See Figure 1).
5 (2.0)	DFD	255 mgm./kgm.	No depression of intestinal motility; depression of tongue contraction proportionate to dose and paralysis at lethal dose.
6 (2.0)	DFD	300 mgm./kgm.	No depression of intestinal motility: death from hypotension.

TABLE 7. *Continuous infusion of DFD, 1 mgm./kgm./min. in anesthetized dogs.*

Measurements	Dog 1	Dog 2	Dog 3	Mean
Body weight (kgm.)	4.2	5.0	4.7	
Lethal dose (mgm./kgm.)	98	114	117	110
Aortic blood pressure:				
control (mm. Hg)	120	125	145	
% after 20% lethal dose	88	89	86	88
% after 40% lethal dose	79	100	65	81
% after 60% lethal dose	58	76	83	72
% after 80% lethal dose	63	48	58	56
Heart rate				
control (beats/min.)	64	70	45	
% after 20% lethal dose	130	140	280	183
% after 40% lethal dose	134	71	175	127
% after 60% lethal dose	79	142	189	137
% after 80% lethal dose	156	100	110	122
Pulmonary resistance				
control (cm. H_2O/LPS)	4.0	0.7	0.5	
% after 20% lethal dose	130	143	120	131
% after 40% lethal dose	140	186	110	145
% after 60% lethal dose	140	228	120	163
% after 80% lethal dose	211	257	130	199
Pulmonary compliance				
control (ml./cm. H_2O)	20	35	15	
% after 20% lethal dose	62	71	90	74
% after 40% lethal dose	62	63	100	75
% after 60% lethal dose	62	43	90	65
% after 80% lethal dose	40	28	80	49

pulmonary compliance was reduced as the infusion was continued, reaching highest and lowest levels respectively just before the animal died. None of these changes was induced by infusion of dimethylsulfoxide alone, the solvent used for the intravenous infusion of DFD. The only effect of DMSO alone was hemolysis of red blood cells.

DISCUSSION

The experiments reported above emphasize some similarities and differences between DFD and diaminodiphenyl sulfone. They are as follows:

Blood levels. Our experiments in the rabbit have failed to show any difference in levels of sulfone in the blood following the oral administration of either sulfone. Therefore, one can exclude the possibility that DFD remains in the blood for periods longer than does diaminodiphenyl sulfone. It also follows that the higher potency of DFD in the treatment of experimental malaria in the mouse, reported previously [1], cannot be explained by any difference in metabolism or excretion detectable by blood levels.

Urinary excretion. Our experiments in the rat failed to show that DFD is excreted less slowly, as compared with diaminodiphenyl sulfone. This is another item of information that supports the generalization stated elsewhere [1] that DFD is more potent than diaminodiphenyl sulfone in the treatment of experimental malaria and that the high potency cannot be explained by differences in excretion. There is added support to the suspicion that, unlike other sulfones, DFD is not converted to diaminodiphenyl sulfone in exerting its antimalarial activity, and it would be interesting to test this further in experimental leprosy.

Intravenous toxicity. In the anesthetized cat, the lethal doses intravenously for each are strikingly different, viz., 155 to 180 mgm./kgm. for diaminodiphenyl sulfone and 255 to 350 for DFD. This difference in toxicity was also encountered in mice reported elsewhere [1]. There is, therefore, additional support to our earlier conclusions that DFD is less toxic than its parent sulfone.

Cardiovascular depression and bronchoconstriction. Both DFD and diaminodiphenyl sulfone caused hypotension in the cat. The cause of this effect was not investigated in our experiments. Our experiments in the dog indicate that DFD also increases pulmonary resistance and reduces pulmonary compliance. These are effects arising from lethal amounts of the sulfone. The mechanism for bronchoconstriction is unrelated to the potentiation of sympathomimetic activity seen in the cat, but may be a direct action of sulfone on the smooth muscle. Other investigators have reported spasm of smooth muscle and direct cardiac depression induced by sulfones [3, 4, 7].

Miscellaneous actions. Although the sulfones have been known to produce hemolysis in man [10–12], and in the rabbit, the oral administration of either sulfone failed to produce hemolysis or abnormal forms of hemoglobin. In the rat diaminodiphenyl sulfone in 10 mgm./kgm. dose caused enlargement of the thyroid, but DFD did not.

SUMMARY

Diaminodiphenyl sulfone and its diformyl derivative (DFD) were investigated in four animal species. The following differences and similarities were encountered: (a) Diaminodiphenyl sulfone had a smaller lethal intravenous dose than DFD in the anesthetized cat; (b) in the anesthetized dog, DFD caused bronchoconstriction and hypotension; (c) in the unanesthetized rabbit, the blood levels of sulfone following oral administration of either sulfone were not different; (d) in the rat, the excretion of DFD was not more rapid than the excretion of diaminodiphenyl sulfone. It is proposed that DFD is more effective than diaminodiphenyl sulfone as an antimalarial, but not because of a difference in excretion or metabolism of these sulfones. Additional studies are needed to prove that, unlike other sulfones, DFD is not converted to diaminodiphenyl sulfone in exerting a chemotherapeutic action. If studies in mice show that DFD is effective against *Mycobacterium leprae*, this drug should be tested also in leprosy in man.

RESUMEN

Diaminodifenil sulfona y su derivado diformyl (DFD) se estudiaron en cuatro especies animales. Se encontraron las siguientes diferencias y semejanzas: (a) Diaminodiphenyl sulfona tuvo una dosis letal indovenosa menor que DFD en el gato anestesiado; (b) en el perro anestesiado DFD produjo constricción de los bronquios e hipotensión; (c) en el conejo no anestesiado, los niveles de sulfona en la sangre luego de administrarla oralmente, no fueron diferentes en ningún tipo de sulfona; (d) en las ratas, la excreción de DFD no fué mas rápida que la excreción de diaminodiphenyl sulfona. Se indica que DFD es mas efectivo que la diaminodiphenyl sulfona como antimalárico, pero no a causa de la diferencia en la excreción o metabolismo de estas sulfonas. Nuevos estudios son necesarios para demostrar que, a diferencia de otras sulfonas, DFD no se convierte a diaminodiphenyl sulfona al ejercer una acción quimioterapeútica. Si los estudios en ratones demuestran que DFD es efectivo contra el *M. leprae*, esta droga debería ensayarse también en la lepra en el hombre.

RÉSUMÉ

Chez quatre espèces animales, on a étudié la diaminodiphenyl sulfone et son dérivé diformyl (DFD). On a observé les différences et similitudes reprises ci-après: (a) chez le chat anesthésié, la dose intra-veineuse léthale de diaminodiphenyl sulfone était plus faible que celle notée pour le DFD; (b) chez le chien anesthésié, le DFD a entraîné une broncho-constriction et de l'hypotension; (c) chez le lapin non anesthésié, les niveaux sanguins de sulfones à la suite de l'administration orale de l'une ou de l'autre sulfone n'étaient pas différents; (d) chez le rat, l'excrétion du DFD n'était pas plus rapide que l'excrétion de la diaminodiphényl sulfone. On suggère que le DFD est plus efficace que la diaminodiphényl sulfone comme anti-malarique; cette différence d'efficacité ne proviendrait cependant pas de différences dans l'excrétion ou dans le métabolisme de ces sulfones. Des études complémentaires sont nécessaires pour prouver que, contrairement aux autres sulfones, le DFD ne doit pas être transformé en diaminodiphényl sulfone pour exercer une action chimio-thérapeutique. Si des études menées chez la souris montrent que le DFD est efficace contre *M. leprae*, ce médicament devrait alors être également essayé dans la lèpre humaine.

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