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Mutagenic Activity of Antileprosy Drugs and Their Derivatives[1]

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The first report in 1973 that dapsone (4, 4′-diaminodiphenyl sulfone, DDS) was weakly carcinogenic in male rats ([3]) was subsequently confirmed by reports from the National Cancer Institute ([4]) and the International Agency for Cancer Research ([12]). The principal tumors found in these studies were mesenchymal tumors of the abdominal organs—mainly in the spleen. These reports have caused concern that DDS may present a risk to patients receiving antileprosy therapy with this drug ([7]) even though the doses that induced tumors in the rats ranged from 42 mg to 300 mg per kg per day for the lifetime of the animals; whereas the usual maximum dose of DDS for man is 100 mg per day or about 1 mg to 2 mg per kg per day.

Stimulated by the original report in 1973 and before the confirmatory studies were available, we initiated studies using the short-term presumptive test for carcinogenicity of Ames because this screening system for mutagenic activity had proved to be a reliable indicator of carcinogenic activity in rodents for about 90% of the 300 compounds tested ([19]).

We tested DDS and all available metabolites, potential metabolites, and derivatives of DDS and also other drugs employed in leprosy chemotherapy using all five of the recommended test strains of *Salmonella typhimurium* with and without metabolic activation by rat liver microsomal enzymes. The drugs tested, besides dapsone and its derivatives, were clofazimine, ethionamide, prothionamide, prothionamide-S-oxide [the major metabolite of prothionamide ([18])], and rifampin (The Figure).

Furthermore, after finding that 4, 4′-diaminodiphenyl sulfide (DDSD) and 4, 4′-diaminodiphenyl sulfoxide (DDSO) exhibited mutagenic activity in the Ames screen and following the report by the National Cancer Institute that DDSD was strongly carcinogenic in mice and rats ([6]), we examined pharmaceutical preparations of DDS and urine from patients receiving DDS therapeutically for the presence of DDSD and DDSO. Finally, urine concentrates from volunteers taking DDS were also examined for mutagenic activity using the most sensitive *S. typhimurium* strains TA98 and TA100.

MATERIALS AND METHODS

Chemicals. The following antileprosy drugs (The Figure) were assayed for mutagenicity: clofazimine was a gift from Dr. L. Levy, Hadassah Medical School, Hebrew University, Jerusalem, Israel; ethionamide was supplied by the Pasteur Institute, Paris, France; prothionamide was a gift from May and Baker, Ltd., Dagenham, England; prothionamide-S-oxide was synthesized as reported previously ([18]); rifampin was obtained from CIBA Pharmaceutical Products, Inc., Summit, New Jersey, U.S.A.; DDS was supplied by Merck & Co., Rahway, New Jersey, U.S.A., and we purified it by recrystallization from 95% ethanol. Also tested for mutagenicity were seven derivatives of DDS shown in Table 1: MADDS, DADDS, and AHADS were synthesized by Dr. W. Colwell, SRI International, Menlo Park, California, U.S.A.; $(HA)_2DS$ and $(HAAc_2)_2$ DS were provided by Dr. T. Maren, University of Florida, Gainesville, Florida, U.S.A.; DDSO was synthesized by a published procedure ([17]); and DDSD was supplied by K & K Laboratories, Plainview,

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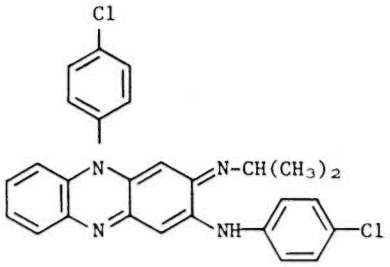
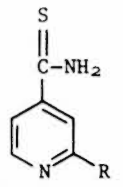
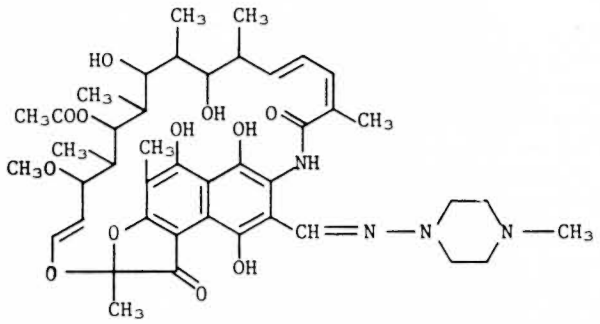


CLOFAZIMINE



ETHIONAMIDE
($R=C_2H_5-$)

PROTHIONAMIDE
($R=C_3H_7-$)



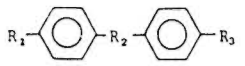
RIFAMPIN

THE FIGURE. Structures of the antileprosy drugs clofazimine, ethionamide, prothionamide, and rifampin.

New York, U.S.A.; Aroclor 1254, which was used for induction of rodent liver post-mitochondrial metabolic activation system (S9), was received from Monsanto Company, St. Louis, Missouri, U.S.A.; chemicals used as positive controls in mutagenesis tests were sodium azide (Difco Laboratories, Detroit, Michigan, U.S.A.); 9-aminoacridine (Pfaltz & Bauer, Inc., Stamford, Connecticut, U.S.A.); 2-nitrofluorene and 2-anthramine (Aldrich Chemical Co., Milwaukee, Wisconsin, U.S.A.); and 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (also called AF-2). High-purity reagents used for high-performance, liquid chromatographic procedures (HPLC) were ethylene dichloride (Burdick & Jackson Laboratories, Muskegon, Michigan, U.S.A.); dimethyl sulfoxide (DMSO) (MCB Manufacturing Chemists, Inc., Gibbstown, New Jersey, U.S.A.); thiodiglycol (Pierce Chemical Co., Rockford, Illinois, U.S.A.); and water, purified through a Super-Q water purification system by Millipore Corporation, Bedford, Massachusetts, U.S.A. All other chemicals were of reagent grade.

Mutagenesis assay. The full panel of *S. typhimurium* strains recommended for mutagenesis testing, i.e., TA1535, TA1537, TA1538, TA98, and TA100, were obtained from Dr. B. N. Ames, University of California, Berkeley, California, U.S.A. The plate incorporation method of the *Salmonella*/mammalian-microsome mutagenicity test of Ames, *et al.* (1) was followed to assay all chemical compounds for mutagenic activity. All compounds were dissolved in dimethyl sulfoxide (DMSO). The S9 batches were prepared from liver following induction with Aroclor 1254 by the method of Ames, *et al.* (1); also S9 preparations from livers of hamsters and mice were used in addition to S9 from rats in some experiments. Sterility was confirmed for all S9 batches. Where it was required, 0.50 ml of S9 (10% S9 fraction: 90% cofactors in buffer) were added per plate. We modified the standard method in some tests by using a

TABLE 1. *Chemical structures of DDS and derivatives studied.*



Compound	R_1	R_2	R_3	Abbreviation
4, 4′-Diaminodiphenyl sulfone	NH_2	SO_2	NH_2	DDS
4-Amino-4′-acetamidodiphenyl sulfone	NH_2	SO_2	NHAc[a]	MADDS
4, 4′-Diacetamidodiphenyl sulfone	NHAc	SO_2	NHAc	DADDS
4-Amino-4′-hydroxyaminodiphenyl sulfone	NH_2	SO_2	NHOH	AHADS
4, 4′-Bis(hydroxyamino)diphenyl sulfone	NHOH	SO_2	NHOH	$(HA)_2DS$
4, 4′-Bis(N,O,-diacetylhydroxyamino)diphenyl sulfone	NAcOAc	SO_2	NAcOAc	$(HAAc_2)_2DS$
4, 4′-Diaminodiphenyl sulfoxide	NH_2	SO	NH_2	DDSO
4, 4′-Diaminodiphenyl sulfide	NH_2	S	NH_2	DDSD

[a] Ac = $(-COCH_3)$.

20 min preincubation of bacteria and S9 with the compound being tested before adding the top agar overlay and pouring onto the test plate.

Adult male rats (two strains), hamsters, and mice (Simonsen Labs, Gilroy, California, U.S.A.) were used for S9 preparation by pooling livers from the following numbers of animals for each rodent strain: 15 Sprague-Dawley or Fischer 344 rats (200–250 g); 30 Syrian hamsters (100 g); and 100 $B6C3F_1$ mice (30 g). All animals were housed in quarantine rooms and fed Purina Lab Chow and water *ad libitum* until 12 hr before sacrifice.

To ensure the validity of mutagenesis test results, we routinely confirmed the nutritional requirements and biochemical characteristics of the *S. typhimurium* strains as recommended by Ames, *et al.* ([1]). Diagnostic chemicals used routinely for confirming the reversion properties of the strains without metabolic activation were: sodium azide (1.0 μg/plate with strain TA1535); 9-aminoacridine (100 μg/plate with strain TA1537); 2-nitrofluorene (10 μg/plate with strain TA1538); and AF-2 (0.10 μg/plate with strains TA98 and TA100). To confirm reversion in the presence but not in the absence of metabolic activation, 2.5 μg/plate of 2-anthramine with and without S9 were tested on all five *S. typhimurium* strains. The numbers of spontaneous revertants observed (Tables 2, 3, and 4) were in agreement with the findings of Ames, *et al.* ([1]). In all tests, our criterion for mutagenic activity was a dose-related increase in number of revertants to a level of at least twofold greater than the number of spontaneous revertants.

Collection and concentration of urine for mutagenesis assay. Two nonsmoking, male human volunteers, known to excrete mutagen-free urine in other studies ([21]), were given 50 mg DDS (Winthrop Laboratories, New York, New York, U.S.A.) orally and urine was collected during 0–12, 12–24, 24–36, and 36–48 hr. Urine aliquots (100 ml) were treated by the XAD-2 resin column method ([28]) to yield 200-fold concentrates in DMSO. Aliquots of 5, 10, 30, and 75 μl of each urine concentrate were tested for mutagenic activity using strains TA98 and TA100 with and without rat liver S9. Preincubation was not employed in these tests.

Search for DDSO and DDSD in pharmaceutical preparations of DDS and in urine. To examine for the presence of DDSO and DDSD in pharmaceutical preparations of DDS, we triturated tablets of DDS (25-mg tablets, Winthrop Laboratories; 100-mg tablets, Ayerst Laboratories, New York, New York, U.S.A.) in ethanol. After centrifugation, an aliquot of the clear supernatant liqud was evaporated to dryness and the residue dissolved in the mobile phase for HPLC.

We also examined 24 hr urine collections from six volunteers receiving a single oral dose of 50 mg of DDS (Winthrop Laboratories) and from nine patients receiving daily oral doses of 100 mg of DDS (Ayerst Laboratories) for the presence of DDSO and DDSD. Urine specimens (10 ml) were alkalinized (pH 12–13) and extracted with 25 ml of ethylene dichloride. After separation of the organic phase by centrifugation, we re-extracted it with 5.0 ml of 2.0 N HCl. The acid phase was separated, made alkaline with 1.1 ml of 10 N NaOH, and ex-

TABLE 2. *Mutagenicity of antileprosy drugs in* Salmonella *strains.*

Compound	Rat S9	Micrograms compound/plate	Revertants/plate[a]				
			TA1535	TA1537	TA1538	TA98	TA100
Negative controls	−	0	16	7	10	13	116
	+	0	13	8	23	20	120
Clofazimine	−	5 to 1000	10	−2	3	9	7
	+	5 to 1000	1	−1	8	10	17
Ethionamide	−	5 to 1000	19	0	5	8	19
	+	5 to 1000	0	3	5	5	21
Prothionamide	−	5 to 1000	14	3	5	10	18
	+	5 to 1000	3	2	−1	10	22
Prothionamide-S-oxide	−	5 to 1000	−1	1	3	3	31
	+	5 to 1000	6	−2	2	3	40
Rifampin	−	0.001 to 1.0	3	1	3	6	16
	+	0.001 to 1.0	9	−1	7	4	17

[a] For antileprosy drugs, values are the differences between the highest number of revertants observed at any concentration of drug and the negative controls.

tracted with 1.0 ml of ethylene dichloride. This organic extract was evaporated to dryness, and the residue was dissolved in the mobile phase for HPLC.

This procedure was applied to untreated urine aliquots and to additional urine specimens that were hydrolyzed in 1.9 N HCl containing 0.90 mM $Na_2S_2O_3$ at 90–100°C for 60 min.

The residues from either extracts of the pharmaceutical preparations or the urine samples were chromatographed on a 3.2 × 250 mm column packed with 5-μm Lichrosorb SI-60 silica (Altex Scientific, Inc., Berkeley, California, U.S.A.) using ethylene dichloride : DMSO : water : thiodiglycol (988: 5:5:2.5, v/v) as the mobile phase. Detection was by absorption at 280 nm and quantitation was by automatic integration of the peak areas. Retention times for DDSD, DDS, MADDS (a major metabolite of DDS), and DDSO were 5, 12, 21, and 26 min, respectively, with base-line resolution. Limits of sensitivities were 5 ng for DDSO and 1 ng for DDSD by these methods.

RESULTS

Mutagenicity of antileprosy compounds and derivatives

Tests of clofazimine, ethionamide, prothionamide, and prothionamide-S-oxide using 5, 10, 50, 100, 500, and 1000 μg per plate using all five test strains with and without S9 from Sprague-Dawley rats yielded no evidence of mutagenicity. Table 2 lists only the highest net number of revertants found in these tests. Because rifampin exhibits marked toxicity for *S. typhimurium,* we tested this compound at levels ranging from 0.001 μg to 1.0 μg per plate. As shown in the last line of Table 2, we also found rifampin to be nonmutagenic under any test conditions.

Tests of DDS and its N-acetylated and N-hydroxylated derivatives of up to 1000 μg or 5000 μg per plate for the five strains with and without S9 from Sprague-Dawley rats also yielded negative results as shown in Table 3. Again, only the highest net number of revertants observed at any of the levels of compound are shown. These tests were repeated using a 20 min preincubation with and without S9 from Sprague-Dawley rats. Again, no mutagenic activity of these compounds with any of the five strains of bacteria was detected (results not shown). Subsequently, 10, 50, 100, 500, 1000, and 5000 μg DDS were tested using 20 min preincubation, all five test strains, and S9 from Sprague-Dawley and Fischer 344 rats, Syrian hamsters, and B6C3F_1 mice. Again, no mutagenic activity was detected under any test condition (results not shown).

In contrast with the above negative results, Table 4 shows that the sulfoxide analog of DDS, DDSO, was mutagenic for strains TA1538 (at ≥100 μg) and TA100 (at ≥50 μg) in the presence of S9. It was inactive under all conditions without met-

TABLE 3. *Mutagenicity of DDS and derivatives in* Salmonella *strains.*

Compound	Rat S9	Micrograms compound/plate	Revertants/plate[a]				
			TA1535	TA1537	TA1538	TA98	TA100
Negative controls	−	0	22	6	11	26	140
	+	0	10	5	15	28	123
DDS	−	10 to 5000	3	1	−4	−12	−47
	+	10 to 5000	3	3	8	−5	−16
MADDS	−	5 to 5000	6	7	5	2	11
	+	5 to 5000	5	5	16	9	8
DADDS	−	5 to 5000	10	8	6	−2	6
	+	5 to 5000	5	8	16	13	13
AHADS	−	5 to 1000	0	6	10	−9	−9
	+	5 to 1000	3	6	15	5	47
$(HA)_2DS$	−	5 to 1000	−2	1	18	−8	31
	+	5 to 1000	5	3	14	3	22
$(HAAc_2)_2DS$	−	5 to 1000	−1	3	4	−1	−8
	+	5 to 1000	3	7	6	11	12

[a] For DDS and derivatives, values are the differences between the highest number of revertants observed at any concentration of drug and the negative controls.

abolic activation. Clearly, DDSO exhibited mutagenic activity. As shown, the sulfide analog of DDS, DDSD, was weakly active in the absence of metabolic activation for strain TA100 (≥ 100 μg) but inactive for the other strains. However, DDSD exhibited substantial activities with added S9 for strain TA1538 (≥ 100 μg), for strain TA98 (≥ 10 μg), and for strain TA100 (≥ 5 μg). The maximum increases over the negative control values in the presence of S9 were 1100% for DDSO (at 1000 μg) and for DDSD (at 500 μg) with strain TA100. These comparative increases suggest that DDSD was about twice as active as was DDSO.

Studies of pharmaceutical preparations of DDS and urine collections from volunteers and patients

Examination of ethanolic extracts of recrystallized DDS or DDS tablets from Ayerst or Winthrop Laboratories yielded no detectable DDSO or DDSD. From the limits of sensitivity for detection and the amounts analyzed, we can calculate that these DDS preparations contained <0.01% contamination by these compounds. Thus, patients receiving 100 mg DDS per day of these DDS preparations would receive < 10 μg of either DDSO or DDSD.

Application of the same detection method to extracts of aliquots of urine from volunteers receiving a single oral dose of 50 mg DDS or from patients receiving daily oral doses of 100 mg DDS yielded no detectable DDSO or DDSD in any urine specimen (results not shown). These results indicate that <0.01% of the daily dose of 100 mg DDS was excreted as either DDSO or DDSD. Because major quantities of urinary metabolites of DDS and MADDS in man are acid-hydrolyzable ([10]) and because DDSO or DDSD, if formed, would probably be excreted as such conjugates, we re-examined urine samples from the patients after acid hydrolysis for the presence of DDSO and DDSD. As shown in Table 5, these urine samples contained less than 10 ng DDSO or DDSD per ml. Thus, the sum of these compounds and their potential conjugates did not exceed 0.01% to 0.02% of the daily dose of DDS administered.

In a further study, urine was collected at 12 hr intervals for a total of 48 hr from two volunteers following a single 50 mg oral dose of DDS. After concentration by the XAD-2 resin column method, each sample was tested for mutagenicity with TA98 and TA100 by the standard procedure with and without S9 from Sprague-Dawley rats. No mutagenic activity was detected when aliquots ranging from 5 μl to 75 μl of DMSO extracts (equivalent to 1 ml to 15 ml of urine) were tested. This study supports our earlier observations that DDSO and DDSD, the mutagenic analogs of DDS, were absent

TABLE 4. *Mutagenicity of DDSO and DDSD in* Salmonella *strains.*

Compound	Rat S9	Micrograms compound/plate	Revertants/plate[a]				
			TA1535	TA1537	TA1538	TA98	TA100
Negative controls	−	0	23	5	16	18	115
	+	0	16	5	23	32	128
DDSO	−	5 to 1000[b]	−1	6	3	−1	51
	+	5 to 10[b]	−5	1	0	0	0
	+	50	−3	−2	7	−2	255
	+	100	−2	5	40	−2	371
	+	500	2	8	83	12	664
	+	1000	1	1	76	25	1404
DDSD	−	5 to 50[b]	−6	4	0	13	53
	−	100	−7	−2	0	12	131
	−	500	−12	−1	−3	6	180
	−	1000	−13	−1	2	11	201
	+	5	−3	1	0	18	304
	+	10	8	3	4	37	475
	+	50	6	2	19	92	891
	+	100	14	1	29	204	1074
	+	500	10	2	47	227	1387
	+	1000	11	−2	26	177	1316

[a] Values represent averages of two experiments. For DDSO and DDSD, values are the differences between the numbers of revertants observed and the negative controls.

[b] The number of revertants listed are the differences between the highest number of revertants observed at any concentration of drug and the negative controls.

from the urine of subjects receiving DDS; it further suggests the absence of any mutagenic metabolites of DDS in the urine of humans receiving this drug.

DISCUSSION

The similarity of chemical structure between DDS and such strong rodent aromatic amine carcinogens as benzidine, 4, 4′-oxydianiline, 4, 4′-methylene-dianiline, and 2, 7-fluorenediamine ([13]) makes DDS unusual in its very weak carcinogenic activity for rats. Most arylamines are activated to proximate carcinogens by N-hydroxylation ([20]) but our studies have shown that neither AHADS, the mono-N-hydroxy derivative, $(HA)_2DS$, the di-N-hydroxy derivative, nor $(HAAc_2)_2DS$, a di-N-hydroxy derivative wherein the N-OH groups are protected by acetylation, are mutagenic under any conditions tested using the *S. typhimurium* strains (Table 3). Thus, these derivatives, along with DDS and its mono- and di-acetylated analogs, were not mutagenic under any test conditions we employed (Tables 3 and 4).

TABLE 5. *Search for DDSO and DDSD in acid-hydrolyzed urine from patients.*[a]

Patient no.	DDSO		DDSD	
	ng/ml of urine	% of dose	ng/ml of urine	% of dose
1	<10	<0.01	<10	<0.01
2	<10	<0.01	<10	<0.01
3	<10	<0.01	<10	<0.01
4[b]	<10	<0.01	<10	<0.01
5	<10	<0.02	<10	<0.02
6	<10	<0.01	<10	<0.01
7	<10	<0.01	<10	<0.01
8[c]	<10	<0.02	<10	<0.02
9	—[d]	—[d]	<10	<0.01

[a] Samples were aliquots of 24 hr urine collections from patients receiving 100 mg DDS daily.

[b] 300 mg rifampin/day was also given.

[c] DDS dose was 50 mg/day.

[d] Not determined.

Evidence of N-hydroxylation of DDS and the possible formation of nitroso and azoxy analogs of DDS was found *in vitro* with rat microsomes ([8]), and observations in man also reported the formation of N-hydroxy metabolites of DDS ([14]). Using relatively non-specific colorimetric methods, Uehleke and Tabarelli ([27]) reported that N-hydroxy metabolites can comprise as much as 50% of the oral dose of 200 mg DDS to man. However, we found, using highly specific liquid chromatographic techniques, that AHADS in 24 hr urines accounted for only

4.2% (mean of 6; S.D. = 2.3) of the daily dose of 100 mg of DDS taken by leprosy patients ([11]). Substantially more AHADS was found after weak acid hydolysis of urine aliquots and reassay for AHADS. This mild treatment yielded a mean increase corresponding to 27.6% (S.D. = 13.6%) of the dose. Thus, N-hydroxylated DDS metabolites are important urinary metabolites of DDS in man although, in contrast with such derivatives of other arylamines, these derived from DDS exhibit no mutagenic activity in the Ames screen. It would appear that N-hydroxy compounds may not be the cause of tumors in rats receiving DDS.

A more likely suggestion is that the rat is capable of converting small amounts of the high DDS doses used in the carcinogenesis studies to the mutagenic DDSO or to the strongly mutagenic and carcinogenic DDSD (Table 4). Recently, other authors ([16]) have also reported that DDS is non-mutagenic and that DDSD is a strong mutagen of *S. typhimurium* strains TA98 and TA100. However, we are not aware of any reports at this time that DDS can be metabolically reduced to either DDSO or DDSD in the rat or any other species. Many years ago when DDSO was being considered as a therapeutic agent for leprosy chemotherapy, a comparative study of the urinary excretion of metabolites by man receiving DDS and DDSO was performed. The author ([9]) found that DDSO was converted to DDS but that DDS was not excreted as DDSO. It appears from this information that the fully oxidized sulfone form may be the end product of metabolism; whereas the reduced forms such as DDSD and DDSO may be preferentially oxidized to the sulfone.

Our search for the presence of DDSD and DDSO in pharmaceutical preparations of DDS and in urine, both in conjugated and unconjugated forms, yielded the conclusion that these compounds were not present in pharmaceutical preparations of DDS nor in urine from patients receiving 100 mg DDS daily. Also, using a technique that detects mutagens readily in urine concentrates from cigarette smokers ([21, 28]), we could not detect mutagenic activity in urine from volunteers taking DDS. Other workers ([2]) found that DDS caused chromosome damage in human lymphocytes at 4.0 μg/ml but not at 0.4 μg/ml.

A number of epidemiologic studies have examined cancer incidence in leprosy patients ([22, 24, 26]), and all concluded that leprosy patients do not exhibit statistically higher cancer incidence than do control populations. In only one study was drug therapy considered. These authors ([15]) analyzed their data in two time periods: prior to 1950, i.e., prior to sulfone or DDS therapy; and after 1950, when DDS therapy was used extensively. In the lepromatous and the tuberculoid groups of patients they found risk ratios of 1.6 and 1.4, respectively, for the period before 1950. After 1950, these ratios were 1.5 and 0.6 for the two types of disease. No ratio was significantly different from unity, however. Such results do not suggest patients receiving DDS routinely are at undue risk.

Of the other antileprosy drugs we found to be non-mutagenic in the Ames screen (Table 2), only rifampin and ethionamide have been tested previously for mutagenic or carcinogenic activity. Rifampin was non-mutagenic in a number of test systems, carcinogenic only in female mice of one strain, and not carcinogenic in rats. Rifampin in combination with other drugs for the chemotherapy of tuberculosis patients did not increase the frequency of chromosome damage in leukocytes ([25]). Ethionamide was not carcinogenic in mice and rats in the standard bioassay of the National Cancer Institute ([5]).

SUMMARY

We tested the mutagenic activity of antileprosy drugs (clofazimine, ethionamide, prothionamide, prothionamide-S-oxide, rifampin, and dapsone and many of its derivatives) using the Ames *Salmonella*/microsome assay system. None of these, including N-acetylated and N-hydroxylated derivatives of dapsone, were found to be positive with or without metabolic activation in this test. However, the sulfoxide and sulfide analogs of dapsone were found to be mutagenic with metabolic activation. These two analogs could not be detected in pharmaceutical preparations of dapsone (<0.01%), nor could they be found (in either unconjugated or conjugated form) in urine from volunteers taking a single oral dose of 50 mg of dapsone or from patients receiving daily oral doses of 100 mg of dapsone. Also,

urine concentrates from volunteers taking 50 mg of dapsone did not exhibit mutagenic activity in the Ames screen. These results indicate that patients receiving antileprosy therapy with clofazimine, dapsone, ethionamide, prothionamide, and/or rifampin are not being exposed to mutagenic (and thereby possible carcinogenic) drugs.

RESUMEN

Se probó la actividad mutagénica de las drogas antileprosas clofazimina, etionamida, protionamida, sulfoxido de protionamida, rifampina, dapsona y varios de sus derivados, usando el sistema de ensayo de Ames con microsomas y *Salmonella*. Ninguna de ellas, incluyendo a los derivados N-acetilados y N-hidroxietilados de la dapsona, resultó positiva en la prueba de mutagenicidad aún después de su activación metabólica. Sin embargo, los derivados sulfóxido y sulfuro de la dapsona resultaron mutagénicos después de su activación metabólica. Estos dos análogos no se pudieron demostrar en las preparaciones farmacéuticas de dapsona (<0.01%) ni en la orina de voluntarios que tomaron una dosis única de 50 mg de dapsona, ni en la orina de pacientes tratados con dosis orales diarias de 100 mg de dapsona. Los concentrados de orina de los voluntarios que tomaron 50 mg de dapsona tampoco mostraron actividad mutagénica en el ensayo de Ames. Estos resultados indican que los pacientes en tratamiento con clofazimina, dapsona, etionamida, protionamida, o rifampina, no estan expuestos a drogas mutagénicas, potencialmente carcinogénicas.

RÉSUMÉ

On a étudié l'activité mutagénique d'une série de médicaments contre la lèpre (clofazimine, ethionamide, prothionamide, prothionamide-S-oxyde, rifampicine, dapsone et plusieurs de ses dérivés), en ayant recours au système d'évaluation de Ames qui fait appel aux *Salmonella* et aux microsomes. Aucun de ces médicaments, y compris les dérivés N-acetylés et N-hydroxylés de la dapsone, n'ont révélé une activité mutagénique, que ce soit avec ou sans activation métabolique au cours de l'épreuve. Néanmoins, les analogues sulfoxydés et sulfidés de la dapsone se sont révélés mutagéniques lorsqu'on avait recours à une activation métabolique. Il n'a pas été possible de détecter la présence de ces deux produits analogues, dans des préparations pharmaceutiques de dapsone (<0.01%); il n'a pas été davantage possible de les déceler, tant sous la forme conjuguée que non conjuguée, dans l'urine de volontaires auxquels on avait administré une dose orale unique de 50 mg de dapsone, ou dans l'urine de malades recevant des doses quotidiennes de 100 mg de dapsone par voie buccale. De même, des concentrés d'urine de volontaires recevant 50 mg de dapsone n'ont pas témoigné d'activité mutagénique dans l'épreuve de Ames. Ces résultats indiquent que les malades qui reçoivent une thérapeutique antilépreuse avec la clofazimine, la dapsone, l'éthionamide, la prothionamide, et/ou la rifamicine, ne sont pas exposés à des médicaments mutagéniques, et dès lors à des carcinogènes éventuels.

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