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ACUTE TOXICITY STUDY OF NEW DAPSONE SCHIFF BASE DERIVATIVE IN LABORATORY RATS

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Keywords; Dapsone**,** Albino rats**,** leprosy**.**

ABSTRACT

Dapsone (4,4-diaminodiphenylsulphon) is one of the types of sulfa drugs as an anti bacterial and is used particularly in the treatment of leprosy . The aim of present study to investigate *in vivo* toxic effect and find acute toxic doses (LD50) of new dapsone Schiff base derivative compound (4-{[4(ethylideneamino)phenyl] sulfonyl} aniline, was evaluated in this study. The experiment was performed on 10-14-week old male and female albino rats (225± 25 g) at the time of treatment. Its acute toxic dose being 0.58 g.

INTRODUCTION

Toxicity test examine toxic effects when a chemical is absorbed into the body, via mouth, skin, lungs. The most common test of acute (short-term) toxicity is the LD50 test. Many different substances are tested in this way, including all drugs, agricultural, chemicals cleaners, some cosmetics and their ingredents. LD50 means if we administer any dose of drug to animal group for experimental purpose for the estimation of therapeutic effectiveness of that drug, if 50% of animal get died then it means that particular dose of drug is lethal dose 50 (LD50). The smaller the LD50 value, the more toxic is chemical[(1)] .

A special interest has been given to dapson derivatives, since they were found useful in the diagnosis of certain infections[(2)] and to have anti-bacterial effects. The crude substance of the new derivatives compounds is yellowish powder with melting point of 247-250 ^{0} C, well dissolved in dimethyl sulfoxide (DMSO) and carbon tetrachloride. Sulfa antibacterial were first used in the 1930, S, and they revolutionized medicine [(3)]. After a few years, bacteria started to develop resistance to the drugs and eventually

penicillin replaced them as a first-line treatment. While antibiotics resistance remains a problem for this class of antibiotics, is still commonly used to treat a variety of bacterial infections [4]. Dapson drug (4,4-diaminodiphenylsulphon), has been proved to be a powerful antibacterial agent[5]. Dapson is the most widely used drugs in the treatment of leprosy and it inhibits foliate synthesis of M-Leprae[6].

Schiff-base is associated with antibacterial, antifungal and anti-tubercular activities and have diverse biological activities [7-9]. The present work includes modification of dapson drug by synthesis, characterization and pharmaceutical study of dapson- Schiff base derivative. .

However information regarding the toxicity of this new compound is lacking. The present study is therefore, intended at evaluating the acute toxic effect of this compound in laboratory animals.

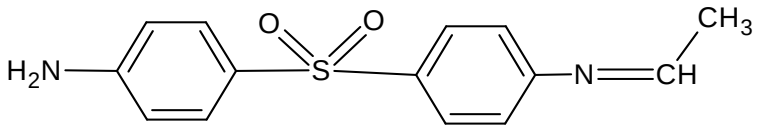
MATERIAL AND METHODS

Rats from both sex used to measure the acute toxicity of new dapson derivative with mean body weight of (225±25 g.),10-14-week old albino rats were used. The number of animals used for each was not less than 8 rats. The new drug was dissolved in dimethylsulfoxide (DMSO), and prepared in seven concentrations, the highest was 0.5 g/ml and given orally. A dose of (٢ ml) containing approximately 1 g/rat. A group of animals drenched with same volume of solvent was used as a control.

Synthesis of the drug candidate:

10 mmol (0.44g) of acetaldehyde in 25 ml ethanol was added to 10 mmol (2.48g) of hot ethanolic solution of 4,4-diaminodiphenylsulphon (dapson),two drops of conc. H_2SO_4 was added and resulting solution was refluxed for 4h and then lift overnight in refrigerator, the solid product obtained was filtered and washed with acetone and the final product was recrystallized by using chloroform: ethanol 8:2 to yield yellow-brown crystals.

Yield;80% , M.P.= 247-250 ^{0}C. ^{1}H NMR(DMSO-d_6); δ 2.51(d,3H-CH_3); 6.7-6.88(m,4H-Ar-H); 7.48-7.51(m,4H,Ar-H). Below The chemical structure of the new derivative of dapson compound.



4-{[4-(ethylideneamino)phenyl]sulfonyl}aniline

STATISTICAL ANALYSIS:

The dose- effect data were fitted into LANGMUIR equation[10].

$$E = \frac{C.E\ max}{C50+C}$$

Using least square-nonlinear model. E max and C50 were generated by the computer and referred to the maximal effect produced and the dose which kills 50% of the animal respectively. E refers to the required effect and C to the dose which produces that effect. Deaths were calculated during 24 hours period after drenching the drug.

RESULTS

The new compound of daps one appears to be safe with low toxicity. It's LD50, calculated by Langmuir equation[10] . Is 0.58 gm /kg of body weight, and the safe dose was less than 0.098 gm /kg. The animals show signs of convulsion before dying.

Table (1): lethal effects of different concentration of the new dapsone Schiff base derivative compound.

Conc. of comp.gm./2ml	Dose/kg. Bwt,gm./kg.Bwt	% of death
0.125	0.500	0
0.250	1000	0
0.500	2000	10%
0.625	2500	25%
0.750	3000	50%
0.875	3500	80 %
1.000	4000	100%

DISCUSSION

The laboratory mouse can be used in bioassays, toxic test and screening of new compound. Among chemicals, there is a wide spectrum of doses needed to produce deleterious effect or death. Some chemicals will produce death in microgram doses and are commonly of as being poisonous like botulin's toxin (0.00001 mg/kg) and dioxin (TCDD) (0.001 mg/kg)[11].

In present study, we determined the LD50 of dapsone Schiff-base by oral route, the toxicity of this substance by other routes, such as i/p, inhalational, and skin contact because of its use in medicine, should also be studied in future. This new sulfa compound has no therapeutic application, so far and we are interested mainly in its toxic effect, and we did not study its potential pharmacological uses. But we hear that some researcher has pilot study attended to see its effect on different microorganisms *in vitro*[15]. The obtained data showed that the new dapsone derivatives cause high toxicity than dapsone marketed drug with LD50 = 1g/kg in rars.

Sulfa compound, in general, have been reported to cause death of microorganism, since sulfa is known to have an affinity for the especially leprosy[12]. Moreover some derivatives used against fungus[13], other researcher show for some derivatives has anti leshmanial activities[14], other derivatives has potential antimicrobial and anti-cancer actions, recently some reporter show cytotoxic action for dapson derivatives[16].

The mechanism of toxicity of this new sulfa compound may be different from the above cited mechanisms. Further studies are under way in our laboratory to investigate this possibility.

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دراسة السمية المميتة لمشتق جديد من مشتقات الدابسون في الجرذان المختبرية

حسن طعمة ، وصفي المسعودي ،جلاء الاحمد

فرع الفسلجة والادويه ،كلية الطب البيطري ، جامعة البصرة ،البصرة ،العراق

الخلاصة

عقار الدابسون (٤,٤-ثنائي امينوثنائيفنيل سلفون) هو احد ادوية السلفا ويستخدم كمضاد بكتيري وبشكل اساسي في معالجة مرض الجذام.

أن الهدف من الدراسة الحالية كان لتقييم ولتقصي السمية والجرعة السمية المميتة لمشتق جديد من مشتقات الدابسون، حيث قيمت هذة الامور في الدراسة الحالية . أجريت الدراسة على الجرذان البيضاء من الذكور والاناث وبعمر ١٠-١٤ اسبوع ووزن (25 ± ٢٢٥)غرام. وكانت السمية الحادة المميتة ٠.٥٨ غرام /كغم .

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