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A NOTE ON THE ACUTE TOXICITY OF SUBSTITUTED AMIDE SOLVENTS

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ABSTRACT

The acute toxicities of the solvents, dimethylacetamide, tetramethylpimelamide, tetramethylsuberamide, tetramethylazelamide, and tetramethylsebacamide were compared by the administration of single doses of each intraperitoneally to groups of mice. The LD_{50} values calculated are dimethylacetamide 3467 mg/kg, tetramethylpimelamide 2239 mg/kg, tetramethylsuberamide 1479 mg/kg, tetramethylazelamide 447 mg/kg, and tetramethylsebacamide 400 mg/kg. The increase in toxicity with an increase in chain length might in part be explained by an enhanced lipid solubility and increased penetration into the central nervous system. The series of N, N, N', N'-tetramethyl-substituted dicarboxylic acid amide solvents studied appear to be more toxic than dimethylacetamide which is currently being used commercially to enhance solubility.

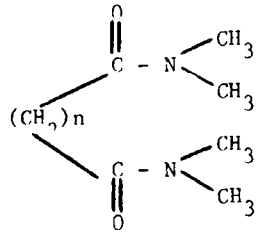
INTRODUCTION

The formulation of drugs with limited water solubility into acceptable dosage forms for oral, parenteral, and topical administration can be a formidable challenge. Nonaqueous solvents are frequently combined with water even in parenteral products to dissolve a poorly soluble drug[1]. The solvent selected must be non-toxic and devoid of pharmacological activity.

N, N-dimethylacetamide has been used in the preparation of drug products containing sparingly soluble drugs[2]. The solubilities of tetracycline and oxytetracycline have been increased in non-aqueous systems by the use of N, N-dimethylacetamide[3] and other amides[4]. In view of the demonstration of these amides to solubilize slightly

soluble drugs, e.g., glutethimide, reserpine, griseofulvin, higher homologs of N, N, N', N'-tetramethyl-substituted dicarboxylic acid amides were studied and reported to be good solubilizers for glutethimide[5]. The general structure of these amides is shown below:

pimelamide: n=5
suberamide: n=6
azelamide: n=7
sebacamide: n=8



While studies on the solvent properties of the substituted amides have been published,[5-8] the literature is sparse in regard to the pharmacologic and toxicologic properties of these solvents. Dimethylacetamide, dimethylformamide and dimethylsulfoxide have been shown to increase myocardial contractility in isolated atria presumably via their ability to stimulate microsomal Ca^{2+} transport and to inhibit Na^{+}, K^{+} - dependent ATPase activity[9]. Once toxicologic information is available, studies to elucidate the pharmacologic profile of these amide solvents should be undertaken. Therefore, the purpose of this study was to compare the acute toxicity of the four N, N, N', N'-tetramethyl-substituted dicarboxylic acid amides with that of N, N-dimethylacetamide and ascertain whether they warrant further consideration as solubilizing agents in oral and parenteral dosage forms.

EXPERIMENTAL

The acute toxicities of the solvents, dimethylacetamide, tetramethylpimelamide, tetramethylsuberamide, tetramethylazelamide, and tetramethylsebacamide were compared by the administration of single doses of each intraperitoneally to groups of ten male Swiss-Webster mice weighing 22-28 grams at each 0.05 log-dose interval (exception suberamide 0.1 log-dose interval). Preliminary dose range finding experiments were conducted with groups of four mice at 0.6 and 0.2 log-dose intervals.

Statistical calculations of the LD_{50} were made by the Cornfield-Mantel adaptation of Karber's method[10], based on cumulative mortality during a 28-day postinjection observation period.

The amides were administered as 10% (w/w) solutions in distilled water in order to accurately measure the volumes of solvents injected at the dose ranges used. The densities of the solutions were assumed to be 1 g/ml since they were previously reported to range from 0.99 g/ml to 1.03 g/ml[8]. The solutions were measured rather than weighed and the doses were calculated for the amide content of the solution. The pH of the 10% (w/w) solutions of the amide solvents ranged from 3.5 to 4.7.

The synthesis and purification of the tetramethyl-substituted amides have been reported previously[5]. The N, N-dimethylacetamide was obtained commercially as a reagent grade solvent[1].

RESULTS AND DISCUSSION

The acute toxicity data amides are listed in Table 1. The LD_{50} values were 3467 mg/kg for dimethylacetamide which compares favorably with that reported by Davis and Jenner (3236 mg/kg)[11], 2239 mg/kg for pimelamide, 1479 mg/kg for suberamide, 447 mg/kg for azelamide, and approximately 400 mg/kg for sebacamide. In the initial dose range finding experiments with sebacamide all the mice injected with the lowest dose of a 10% (w/w) aqueous solution of the amide died. When a 5% (w/w) aqueous solution of sebacamide was injected in these preliminary experiments, the LD_{50} was approximated (400 mg/kg) and therefore, is not shown in Table 1.

The amides at every dose produced an initial central nervous system depression as evidenced by a reduction in observed motor activity. Hind leg paralysis was observed in some mice. Animals injected with high doses of the amides generally died within 5 to 60 minutes postinjection. In these mice clonic and tonic seizures followed the initial depressive phase. Similar observations have been reported in the literature in toxicity studies for N, N-dimethyl-formamide[11].

TABLE 1. - ACUTE TOXICITY OF FOUR SUBSTITUTED AMIDE SOLVENTS WHEN ADMINISTERED INTRAPERITONEALLY TO MICE[a]

AZELAMIDE		PIMELAMIDE		SUBERAMIDE		DIMETHYLACETAMIDE	
Dose (Mg/Kg)	Mortality	Dose (Mg/Kg)	Mortality	Dose (Mg/Kg)	Mortality	Dose (Mg/Kg)	Mortality
398	2/10	1995	1/10	1000	0/10	3162	3/10
447	3/10	2239	4/10	1259	4/10	3548	5/10
501	8/10	2512	10/10	1585	6/10	3981	9/10
562	10/10	2818	10/10	1995	8/10	4467	10/10
LD_{50} Mg/Kg	447		2239		1479		3467
LD_{50}:95% confidence limits (Mg/Kg)	417-479		2081-2409		1288-1698		3222-3730

[a]Calculations by the Spearman-Karber method as adapted by Cornfield-Mantel, based on cumulative mortality during a 28-day post-treatment observation period.

The acute toxicity of the amide solvents studied increases as the carbon chain increases in length. This increase in toxicity with an increase in chain length might in part be explained by an enhanced lipid solubility and increased penetration into the central nervous system.

SUMMARY AND CONCLUSIONS

A series of four N, N, N', N'-tetramethyl-substituted dicarboxylic acid amides appear to be more toxic than dimethylacetamide which is currently being used commercially to solubilize some slightly water soluble drugs.

While the amides have been shown to be effective as solubilizing agents for hydrophobic drugs, on the basis of this study it does not appear that further consideration of these agents in oral and parenterally administered drug products is warranted.

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FOOTNOTE

[1] Fisher Scientific, Lot 766228, Fairlawn, New Jersey.