PYRIDOXINE (VITAMIN B_6) TOXICITY LITERATURE REVIEW

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FOREWORD

This literature review was performed at the suggestion of the Biomedical Laboratory of the Aerospace Medical Research Laboratories, Toxic Hazards Branch, Physiology Division, Wright-Patterson Air Force Base, Ohio, and in partial fulfillment of the Phase III requirements for residency in Aviation Medicine. Sponsors for this portion of the work were Dr. Anthony Thomas and Dr. Kenneth Back, Toxic Hazards Branch.

This technical report has been reviewed and is approved.

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ABSTRACT

The literature from 1940 through June 1963 was surveyed to summarize the data from pyridoxine toxicity studies in animals and to ascertain the highest doses of pyridoxine (vitamin B_6 analogs) that have been administered to human subjects as a therapeutic measure with no clinical evidence of toxicity. Analysis of the data indicated that doses of 25 mg/kg pyridoxine hydrochloride should be well tolerated as a therapeutic measure when required. In particular, pyridoxine hydrochloride can be used when required in the specific treatment of a clinical entity such as acute UDMH intoxication.

SECTION I

INTRODUCTION

The increased use of 1,1-dimethylhydrazine (UDMH) as a missile propellant in recent years has necessitated numerous toxicological and pharmacological studies of this compound to obtain information needed for diagnosis and treatment in the event of accidental UDMH exposure in man (refs 2, 3, 4, 16, 17, 24, 25, 26, 36). These studies have also been useful in setting safe threshold limit values, and in establishing proper propellant handling procedures.

Several of these investigations have shown that treatment with certain vitamin B_6 analogs in high doses will prevent convulsions and death in various laboratory animals exposed to known lethal concentrations of UDMH (refs 3, 8, 16, 24). The exact mechanism of this protection is not completely understood, but is believed to be primarily related to the function of pyridoxine as a co-enzyme for glutamic acid decarboxylase (GAD) and gamma aminobutyric acid transaminase (GABAT), in the gamma aminobutyric acid (GABA) shunt of the tricarboxylic acid cycle within the central nervous system (refs 8, 16).

The dose of pyridoxine required to successfully treat animals exposed to high concentrations of UDMH, as well as the suggested emergency treatment dose for severely exposed humans (ref 3), is much higher than the dose normally used in clinical practice. The purpose of this study is to briefly summarize pyridoxine toxicity studies in animals and to review the reported clinical uses of pyridoxine in high and/or prolonged doses in man, with regard to its possible toxic effects.

SECTION II

ANIMAL TOXICITY STUDIES

Few pyridoxine toxicity studies in animals have been reported in the literature (refs 3, 34, 35, 37). The results of these studies are summarized in tables I and II.

TABLE I

SUMMARY OF ACUTE TOXICITY STUDIES
OF
PYRIDOXINE IN LABORATORY ANIMALS

Animal	Investigator & Date	Compound Tested	Route of Administration	LD_{50} Dose mg/kg	Death Time from Dose*
Rats	Unna 1940	Pyridoxine Hydrochloride	Subcutaneous	3700	36-72 hr
	Unna 1940	"	Oral	5500-6000	36-72 hr
	Weigand 1940	"	iv	657	5 min
Mice	Weigand 1940	Pyridoxine Hydrochloride	iv	545	5 min
	Back 1963	Pyridoxamine dihydrochloride	ip	2100	24 hr

*Convulsions occurred before death under each condition.

TABLE II

SUMMARY OF CHRONIC TOXICITY STUDIES
OF
PYRIDOXINE IN LABORATORY ANIMALS

Animal	Investigator & Date	Compound Tested	Route of Administration	Dosage mg/kg/day	Duration* Days
Rats	Unna 1940	Pyridoxine hydrochloride	Oral	20	80
Mice	Weigand 1940	"	iv	100	14
Dogs	Unna 1940	"	Oral	20	80
Monkeys	Unna 1940	"	Oral	10	39
Monkeys	Unna 1940	"	Subcutaneous	10	106

*No clinical or pathological changes occurred subsequent to administration.

These data imply that pyridoxine toxicity, either acute or chronic, is relatively low in the species studied. Extrapolation of these findings to the clinical use of pyridoxine in humans suggests that a wide margin of safety exists between normal therapeutic doses and doses high enough to cause signs and symptoms of pyridoxine toxicity.

SECTION III

CLINICAL EXPERIENCE WITH MAN

Common Use and Dosage

Aside from its inclusion in small amounts in multivitamin preparations and its use in vitamin B_6 deficiencies, pyridoxine has been used in the treatment of many disorders for which no specific therapy is available, and in which the indications for pyridoxine are not well established. These include disorders such as the nausea and vomiting associated with pregnancy, motion sickness, post-anesthesia, and post-irradiation; acute alcoholic intoxication and delirium tremens; various dermatoses; anemias of certain types; and a variety of neuromuscular and neurological conditions.

The vitamin B_6 analog used almost exclusively in clinical practice is pyridoxine hydrochloride, since it is the form normally available to physicians. The usual adult doses range from 25 to 100 mg (occasionally up to 250 mg) daily, given either orally or parenterally. For a man weighing 70 kg, this is a dose range of 0.35 to 3.5 mg/kg/day.

Recommend Use in Acute UDMH Intoxication

To date, no human exposures to UDMH severe enough to cause convulsions have been reported, and pyridoxine in high doses has never been used for the treatment of acute UDMH toxicity in humans. Back, Pinkerton, and Thomas (ref 3) have recently recommended that an initial dose of pyridoxine hydrochloride of 25 mg/kg (25% given iv and 75% im) be administered parenterally at the first sign of significant UDMH toxicity (usually nausea or vomiting or both). They suggest a second dose of 25 mg/kg if convulsions occur and are at all severe or persistent.

Reported Clinical Use In High and/or Prolonged Doses

The literature from 1940 through June 1963 was surveyed. Twenty-four papers (11 U.S. and 13 foreign) were found in which were reported pyridoxine doses and/or duration of treatment to a degree sufficient to warrant inclusion in this review.

Only abstracts of the foreign papers were reviewed (these are noted in the list of references). Many of the U.S. papers reviewed in complete form did not contain all of the desired data, ie, numbers of subjects, ages, weights, sex, exact pyridoxine dose, routes, frequency and duration of administration, or methods used in evaluating possible toxic effects of pyridoxine. The purpose of the majority of articles reviewed was to evaluate the effectiveness of pyridoxine in various disorders, and not to study possible toxic side effects of the drug. Most of the 651 subjects reported in the 24 articles had active disease processes giving rise to a variety of symptoms, and positive physical examination and laboratory findings, all of which would complicate the detection of pyridoxine toxic effects were they to occur.

To aid in comparing the findings in these articles, the data were used to compute the milligram dose of pyridoxine per kilogram of body weight for each

study. The data available for these computations varied among the articles in completeness and specificity. The criteria used to calculate these mg/kg doses are given in table III. Accuracy of the computed mg/kg doses is believed to be reasonably reliable. The significant findings, including the calculated mg/kg doses, are given in table IV.

As shown in table IV, some subjects received large doses of pyridoxine in terms of usual clinical doses. However, harmful or toxic effects from the drug were not reported in any of the studies.

To determine the numbers of subjects receiving the drug, in single or total daily doses, at various dose levels, and by various routes, the data from the 24 studies were used as shown in table V. This information is helpful in regard to the relative safety of giving pyridoxine in high doses over a short period of time. The numbers of subjects are given cumulatively.

TABLE III

CRITERIA AND DATA USED TO COMPUTE PYRIDOXINE mg/kg
DOSES IN THE STUDIES REVIEWED

Dose of Pyridoxine (single or total daily dose)		Weight of Subjects		Age of Subjects				Criteria for mg/kg Computation	
					Known children				
Exact	Dose Range	Known	Unknown	Known Adults	Age Known ± 2 yr	Age Range Known > 2 yr	Age Un-known	No.	Factors Used in Calculation
X		X						I	Known dose and weight.
X			X	X				II	Known dose and "standard" 70 kg adult.
X			X		X			III	Known dose and average weight for closest year of age.
	X	X or	X	X or	X			IV	Known dose range and: (1) known weight; (2) 70 kg adult; or (3) average weight for closest year of age.
X or	X		X			X or	X	V	Known dose or dose range and arbitrarily selected, representative stated weight.

TABLE IV

REPORTED USES OF PYRIDOXINE HYDROCHLORIDE IN HIGH DOSES IN 651 HUMAN SUBJECTS

Reference	Subjects: Description	Subjects: No.	Pyridoxine Hydrochloride Usage: Purpose	Dose or Dose Range (mg)	Route* (P,O, or ?)	Duration** (days, S or ?)	mg/kg Dose (single or daily total***): Calculated	mg/kg Dose (single or daily total***): Criteria
14	Adult diabetics M&F	144	B_6 deficiency test	1000	P	S	14.3	II
14	" " "	94	B_6 deficiency therapy	500-1000	?	?	7.15-14.3	IV(2)
18	" " "	27	Xanthuremic acid excretion study	500- 600	O	5	7.15- 8.6	IV(2)
22	Children w/anemias or 1-2 yr	28	Therapy	80- 100	O&P	14-21	8.0- 9.0	IV(3)
22	Dystrophies 0-1 yr	76	"	40- 80	O&P	14-21	6.0-10.0	IV(3)
12	INH poisoning-25 mo. M, 13.0 kg	1	"	200	P(½iv, ½im)	S	15.4	I
12	21 mo. F, 11.4 kg	1	"	100	P(iv)	S	8.8	I
27	Adult M w/anemia	1	"	1000	O	30	14.3	II
29	Convulsions-3½mo,6.7 kg	1	"	100	P(im)	S	15.0	I
20	Hemiconvulsive & hemiplegic children, ? ages	4	"	300- 400	O&P	?	8.5-11.5 (35 kg)	V
21	Adults w/delirium tremens	14	Therapy/study	0-1000	?	?	0 -14.3	IV(2)
10	Adults w/acute alcoholism	20	Therapy	500	P(iv)	7	7.15	II
13	Adult nursing mothers-? number	1+	B_6 enrichment of milk	500-1000	O	?	7.15-14.3	IV(2)
33	Children w/encephalopathies - ? ages	19	Therapy	300	P	30	8.5 (35 kg)	V
15	Phenylketonuric pts-ages: 8-13 yrs	5	Therapy	150	?	28	3.0 - 5.4	III
15	15-41 yrs	5	Therapy	150	?	28	2.1 - 2.6	IV(2)
32	Children w/pertussis encephalitis-? ages	3	Therapy	300	?	30	20.0 (15 kg)	V
9	Adults-17 normals, 5 hepatic pts	22	Glutamic acid metabolism study	500	?	10	7.15	II
1	Adults, M, acute alcoholism	35	Therapy	1000	?	?	14.3	II
30	Adults, M, 2 normals, wts: both 71.5 kg	2	B_6 therapy study	500	P(iv)	S	7.0	I
30	Adults, M, 6 alcoholics wts: 54.0 kg	1	B_6 therapy study	500	P(iv)	S	9.3	I
30	" 64.0 kg	1	" "	500	P(iv)	S	7.8	I
30	" 64.0 kg	1	" "	1000	P(iv)	S	15.6	I
30	" 74.0 kg	1	" "	1000	P(iv)	S	13.5	I
30	" 76.9 kg	1	" "	1000	P(iv)	S	13.0	I
30	" 63.0 kg	1	" "	2000	P(iv)	S	31.7	I
19	Adult, M, alcoholic	1	Therapy	1000	P(iv)	S	14.3	II
11	Adults, w/Parkinson's disease	20	Therapy	600-1400	O&P	?	8.6 -20.0	IV(2)
5	Adult tbc pts on INH	21	Prevention and Therapy, INH neuritis	150- 450	?	70	2.1 - 6.4	IV(2)
28	Adults w/dermatoses	11	Therapy	300	P	28	4.3	II
28	Adults w/dermatoses	6	Therapy	600	P	28	8.6	II
28	Adults w/dermatoses	6	Therapy	600-1000	P	21	8.6 -14.3	IV(2)
23	Infants w/erythroderma - ? ages	46	Therapy	30-50	P	3-21	5.0 - 8.0 (6 kg)	V
7	Adult nursing mothers-? number	1+	Milk secretion stimulation	200- 900	?	?	3.6 - 7.15	IV(2)
6	13 adult normals: ? number adult pts w/ diabetes or myopathies	14+	Study on B_6 effect on blood sugar	20- 800	P(iv)	S	0.3 -11.4	IV(2)
31	Adults w/Parkinsonism	16	Therapy	250- 500	P(iv & im)	?	3.6 - 7.15	IV(2)
	Total subjects	651						

*Route of Administration: P = parenteral
O = oral
? = not reported in the study

**Duration of treatment: Days listed in whole numbers, S = single dose
? = not reported in study

***Criteria: Refer to Table III for criteria used in computing mg/kg dosages.

TABLE V

CUMULATIVE NUMBERS OF SUBJECTS RECEIVING PYRIDOXINE (SINGLE OR TOTAL DAILY DOSES) AS mg/kg DOSE LEVELS AND BY VARIOUS ROUTES OF ADMINISTRATION

Dose mg/kg* Levels (single or total daily dose)	Cumulative Numbers of Subjects						
	All Subjects	Route of Administration					
		Unknown	Oral	Parenteral			
				Total	iv	im	Unknown
30 +	1	-	-	1	1	-	-
20 +	4	3	-	1	1	-	-
15 +	7	3	-	4	3	1	-
13 +	190	38	1	151	6	1	144
11 +	191	38	1	152	7	1	144
9 +	191	38	1	152	7	1	144
7 +	442	154	55	233	31	1	201
5 +	564	154	93	317	31	1	285
3 +	597	160	93	344	39	9	296
1 +	623	186	93	344	39	9	296
< 1	651	200	93	358	53	9	296

*mg/kg dose levels as computed in table IV.

The relative safety of giving pyridoxine at various dose levels is probably a lesser problem than short-term high dose safety. However, the data obtained in this review have been examined in terms of duration of treatment, various dose levels, and numbers of subjects. This cumulative information is given in table VI.

TABLE VI

CUMULATIVE NUMBERS OF SUBJECTS RECEIVING PYRIDOXINE
BY DURATION OF TREATMENT AT VARIOUS mg/kg DOSAGE LEVELS

Dose mg/kg* Levels (single or total daily dose)	Cumulative Numbers of Subjects							
	All Subjects	Duration of Treatment (in days)						
		<1	1-4	5-9	10-19	20-29	30+	Unknown
30+	1	1	-	-	-	-	-	-
20+	4	1	-	-	-	-	3	-
15+++	7	4	-	-	-	-	3	-
13+	190	151	-	-	-	-	4	35
11+	191	152	-	-	-	-	4	35
9+	191	152	-	-	-	-	4	35
7+	442	156	-	47	50	12	23	154
5+	564	156	46	47	126	12	23	154
3+	597	156	46	47	126	28	23	171
1+	623	156	46	47	126	33	44	171
<1	651	170	46	47	126	33	44	185

*mg/kg dosage levels as computed in table IV.

SECTION IV

CONCLUSION

A review of pyridoxine toxicity studies in animals suggests that both acute and chronic toxicity are relatively low in the species studied. This implies the existence of a very wide margin of safety between normal therapeutic doses and doses high enough to cause signs and symptoms of pyridoxine toxicity.

Analysis of the data on the clinical use of pyridoxine at high and/or prolonged doses suggests that pyridoxine toxicity, both acute and chronic, is low for man. It seems reasonable to believe that pyridoxine hydrochloride can be used safely in doses much higher than the usual clinical doses when required in the specific treatment of a clinical entity such as acute UDMH intoxication.

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13. ABSTRACT

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