

SUMMARY OF DATA FOR CHEMICAL SELECTION

Hydergine^{®1}

8067-24-1

BASIS OF NOMINATION TO THE CSWG

Hydergine was identified from a review of substances being promoted as nootropics or "smart drugs" for cognition enhancement in well persons of all ages. Hydergine is also a prescription drug for the treatment of senility and cerebrovascular insufficiency.

Hydergine is an ergot alkaloid. Ergot alkaloids have a wide field of therapeutic application, and their biological activities are strongly dependent on their structural conformation. Despite their widespread use, little information on the carcinogenic or mutagenic potential of hydergine or closely related ergot alkaloids was found in the available literature. Information on the genotoxicity of hydergine was mixed and not completely consistent with the results reported for the closely related compound, ergotamine.

SELECTION STATUS

ACTION BY CSWG: 12/16/99

Studies requested:

Standard battery of genotoxicity tests including Ames *Salmonella* and micronucleus assays

Priority: The CSWG does not assign priority to genotoxicity testing

Rationale/Remarks:

An ergot alkaloid prescription drug recently promoted for use as a "smart drug" for healthy individuals seeking cognition enhancement

Mixed results regarding genotoxicity; no information on carcinogenicity

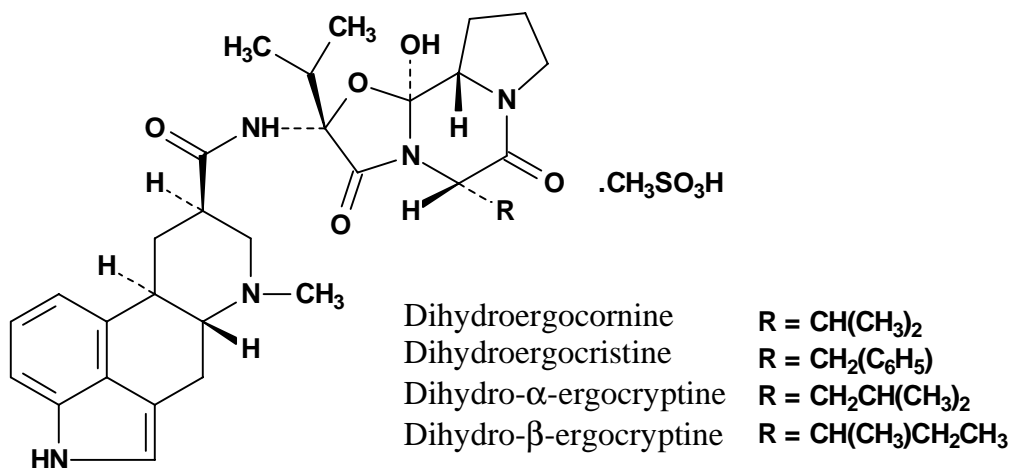
Ergot alkaloids have a wide range of effects influenced by small changes in structure which affect receptor site binding

¹Hydergine[®] is a registered trademark of Sandoz Pharmaceuticals; the drug will be referred to as "hydergine" for the purpose of this presentation.

CHEMICAL IDENTIFICATION

<u>CAS Registry Number:</u>	8067-24-1
<u>Chemical Abstracts Service Name:</u>	Ergotoxine, dihydromonomethanesulfonate (salt) (9Cl); hydergine (8Cl)
<u>Synonyms and Trade Names:</u>	Co-dergocrine mesylate; dihydroergotoxine mesilate; dihydroergotoxine mesylate; dihydroergotoxine methanesulfonate; ergoloid mesylates; Circanol; Hydergin; Ischelium; Redergin; Trigot
<u>Structural Class:</u>	Hydrogenated ergot alkaloids; peptide alkaloid

Structure, Molecular Formula and Molecular Weight:



Hydergine is a mixture of the methanesulfonate salts of three hydrogenated alkaloids, dihydroergocristine, dihydroergocornine, and dihydroergocryptine in an approximate weight ratio of 1:1:1.

$\text{C}_{31}\text{H}_{41}\text{N}_5\text{O}_5 \cdot \text{CH}_4\text{O}_3\text{S}$ (dihydroergocornine mesylate)	Mol. wt.: 659.81
$\text{C}_{35}\text{H}_{41}\text{N}_5\text{O}_5 \cdot \text{CH}_4\text{O}_3\text{S}$ (dihydroergocristine mesylate)	: 707.85
$\text{C}_{32}\text{H}_{43}\text{N}_5\text{O}_5 \cdot \text{CH}_4\text{O}_3\text{S}$ (dihydro- α -ergocryptine mesylate)	: 673.84
$\text{C}_{32}\text{H}_{43}\text{N}_5\text{O}_5 \cdot \text{CH}_4\text{O}_3\text{S}$ (dihydro- β -ergocryptine mesylate)	: 673.84

Chemical and Physical Properties:

<u>Description:</u>	White to off-white powder; practically odorless (Gennaro, 1995; McEvoy, 1997)
<u>Solubility:</u>	Slightly soluble in water (1g in 50 mL); soluble in alcohol; sparingly soluble in acetone (Gennaro, 1995; McEvoy, 1997)
<u>Stability:</u>	Unstable in the presence of light, moisture, or temperatures above 30°C (McEvoy, 1997)

Technical Products and Impurities: The USP grade of hydergine contains not less than 97% and not more than 103% of the alkaloid methanesulfonate mixture, calculated on the anhydrous basis, and not less than 30.3% and not more than 36.3% of the methanesulfonate salt of each of the individual alkaloids. Dihydroergocristine mesylate exists as a mixture of *alpha*- and *beta*-isomers. The ratio of *alpha* to *beta* isomers is not less than 1.5:1.0 and not more than 2.5:1.0 (USP, 1999).

Hydergine is available by prescription as 1 mg liquid-filled capsules (with parabens and propylene glycol), 1 mg tablets, and as 1 mg/ml solutions (with alcohol 28.5% and propylene glycol). For sublingual administration, 0.5 and 1 mg tablets are also offered (PDR Generics; 1996; McEvoy, 1997).

Hydergine is also available without a prescription through foreign-based mail order businesses and Internet suppliers; 1.5, 4.5, and 5 mg tablets are offered (Hutchison, 1999; Mail & Guardian Smart Drugs, 1999; Nubrain Store, 1999; Smart Nutrition, 1999; US-drugstore.com, 1999).

EXPOSURE INFORMATION

Production and Producers: Hydergine is prepared by catalytic hydrogenation of the several alkaloids isolated from ergot, *Claviceps purpurea*, a parasitic fungus on the rye plant. The salt mixture is prepared by reaction with methanesulfonic acid (Gennaro, 1995).

Hydergine was discovered in 1950 at Sandoz laboratories by Dr. Albert Hoffman, the discoverer of LSD (Hutchison, 1999; Smart Nutrition, 1999). In addition to the hydergine brand name supplier, Sandoz Pharmaceuticals, the PDR Generics (1996) lists 15 makers of generic ergoloid mesylates.

According to recent chemical catalogs and directories, hydergine is manufactured and/or distributed by B.I Chemicals, Inc., Boehringer Ingelheim, and SST Corp. (Rodnan, 1998; Tilton, 1998; Hunter, 1999).

No data were reported for hydergine by the US International Trade Commission (USITC) in the ten most recent volumes of *Synthetic Organic Chemicals, US Production and Sales* for the years 1984-1993. This source is no longer published. No quantitative information on annual production was found in the other available literature.

In 1991, Sandoz Pharmaceuticals had global sales of hydergine of \$199.5 million, a 5 percent rise from 1990 (Anon., 1992).

Hydergine is not listed in the EPA's Toxic Substances Control Act Inventory.

Use Pattern: In the US, the Food and Drug Administration (FDA) has approved hydergine for the treatment of senility and cerebrovascular insufficiency. However, physicians in many other countries prescribe hydergine to healthy people to increase intelligence and memory. Hydergine may provide some symptomatic relief in some elderly patients with signs and symptoms of senility, such as dizziness, confusion, unsociability, mental depression, or lack

of self-care, which are of unknown etiology but are often attributed to cerebrovascular insufficiency, cerebral arteriosclerosis, and/or progressive changes in the brain (McEvoy, 1997; Smart Nutrition, 1999).

No specific evidence clearly establishes the mechanism by which hydergine produces mental effects. Hydergine has some peripheral α -adrenergic blocking action but has little or no vasoconstrictor activity and no oxytocic activity. The drug causes peripheral vasodilation mainly through central nervous system depression of vasomotor activity and may cause slight decreases in blood pressure and heart rate. While some studies indicate that hydergine may improve cerebral blood flow and EEG tracings, other studies indicate that the drug does not significantly alter blood flow. It has been postulated that hydergine may increase oxygen utilization in the brain via stabilization of ganglion cell metabolism (PDR Generics, 1996; McEvoy, 1997).

There is only limited clinical evidence to support the efficacy of hydergine in the treatment of patients with compromised cognitive functions. The effects in patients with Alzheimer's have been modest and benefits have been associated with behavioral rather than cognitive measures. The beneficial effects of hydergine treatment for vascular dementia seem to be stronger than those seen in the treatment of Alzheimer's. Because of the history of poor efficacy in Alzheimer's, the FDA has been pressured to remove hydergine from the market (Zaczek & Chorvat, 1995).

The recommended dosage for hydergine in the US is 1 mg three times daily. In Europe and Japan, up to 12 mg of hydergine daily have been used without serious adverse effects and there has been speculation that US dose levels of the drug are insufficient to produce significant cognition enhancement (Thompson *et al.*, 1990; Hutchison, 1999).

Hydergine is being promoted on the Internet as one of the "smart drugs" or nootropics, substances which are claimed to enhance brain function. It is purported to improve

intelligence, memory, and recall and to counteract aging (Hutchison, 1999; Mail & Guardian Smart Drugs, 1999; Nubrain, 1999; Smart Nutrition, 1999).

Human Exposure: The greatest potential for human exposure to hydergine is through its use as a prescription drug to treat elderly patients with symptoms of senile dementia. In 1984, hydergine was the 11th most widely prescribed drug in the world. However, exposure of healthy individuals may increase through its use as a “smart drug.” In 1991, before the Internet promotion of today, there were an estimated 100,000 users of “smart drugs” in the US (Thompson *et al.*, 1990; Anon., 1991).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 82 workers, including 14 female employees, were potentially exposed to hydergine in the workplace (NLM, 1999).

Environmental Occurrence: Hydergine is derived from ergot, a naturally occurring rye fungus. No additional information on the natural or environmental occurrence of hydergine was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by the NIOSH or OSHA for occupational exposure to or workplace allowable levels of hydergine. Hydergine was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) have been made.

Hydergine is approved by the FDA for use in treating elderly patients with symptoms of senile dementia (PDR Generics, 1996).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to hydergine and cancer risk in humans were identified in the available literature.

Hydergine has been well tolerated in patients with age-related cognitive decline with few participants in controlled studies developing adverse reactions to therapy. Gastrointestinal disturbances (nausea, gastric upset, anorexia, abdominal pain, and vomiting) were the most frequently reported adverse effects. Dizziness, headache, nasal stuffiness, precordial discomfort, drowsiness, sleep disorders, and restlessness occurred in less than 3 percent of participants in nonblind studies (Wadworth & Chrisp, 1992).

Hydergine was also well tolerated in healthy elderly patients and no side effects or drug-related changes were seen in standard laboratory test values after hydergine administration for over 5 years (Huber *et al.*, 1986). In 6- to 14-year old children, nasal stuffiness was the most frequently reported side effect following hydergine treatment for 12 weeks to assess the drug's effectiveness in improving cognitive function and behavior in children with learning difficulties (Tareen *et al.*, 1988).

Animal Data: Information on the acute toxicity of hydergine is presented in Table 1.

Table 1. Acute toxicity data for hydergine

Route	Species	LD ₅₀ (mg/kg)
Oral	Rat	>1000
	Rabbit	>1000
Intraperitoneal	Rat	500
	Mouse	350
Subcutaneous	Rat	>2000
	Mouse	>4000
Intravenous	Rat	86
	Mouse	180
	Rabbit	>1000

Source: NLM, 1999

No 2-year carcinogenicity studies of hydrgine in animals were identified in the available literature.

Short-Term Test: The genotoxicity of hydrgine has been assessed in several assays. The drug was positive in the mouse dominant lethal test; sister chromatid exchange (SCE) and micronucleus assays were negative; and the results of chromosomal aberration (CA) assays were mixed. Details of these tests are shown in Table 2.

Table 2. Genotoxicity of hydrgine

Test system/Species, cell line	Dose, route	End point/Results	Reference
Dominant lethal/mouse	25; 50; 100 mg/kg ip once	<i>Mutation</i>	Roberts & Rand (1978)
		+ (high dose)	
Mouse, erythrocytes Chinese hamster, erythrocytes	50; 100; 200 mg/kg ip twice 100; 200 mg/kg ip twice	<i>Micronuclei induction</i>	Matter (1976) Matter (1976)
		- -	
Mouse, bone marrow Chinese hamster, bone marrow Human, lymphocytes Human, lymphocytes Human, lymphocytes	25; 50; 100 mg/kg ip twice 100; 200; 300 mg/kg ip twice 1.5 mg 3/day orally for 12 weeks 0.1; 0.25; 0.5 µg/ml <i>in vitro</i> 0.1; 0.25; 0.5 µg/ml <i>in vitro</i>	<i>Chromosomal aberrations</i>	Roberts & Rand (1977a) Matter (1976) Tsuchimoto & Stalder (1976) Roberts & Rand (1977b) Tsuchimoto <i>et al.</i> (1979)
		+ (mid & high dose)	
		-	
		-	
		-	

Test system/Species, cell line	Dose, route	End point/Results	Reference
Human, lymphocytes	0.1; 0.5 μ g/ml <i>in vitro</i>	<i>Sister chromatid exchange</i>	Tsuchimoto <i>et al.</i> (1979)
		-	

Metabolism: Hydergine is rapidly but incompletely absorbed from the gastrointestinal tract resulting in low concentrations in body fluids. Although the metabolic fate is not completely known, hydergine undergoes first-pass metabolism in the liver and less than 50 percent of a dose reaches the systemic circulation unchanged. The elimination from blood is biphasic with half-lives of 1.5-4 hours and 13-15 hours. Biotransformation studies on the individual components of the drug have shown that it is metabolized mainly *via* oxidation and cleavage of proline in the peptide portion of the molecule. Hydergine is also cleaved at the amide bond, yielding dihydrolysergic acid amide; several hydroxylation products of dihydro- β -ergocryptine have also been identified (Eckert *et al.*, 1978; Schran *et al.*, 1988; Wadworth & Chrisp, 1992; McEvoy, 1997).

The pharmacokinetics of tritium-labeled hydergine was studied following administration to 6 subjects in a randomized cross-over design as single oral (1 mg) and intravenous (iv) (0.3 mg) doses. Approximately 25 percent of the administered oral dose was absorbed. The maximum plasma concentration in ng-equivalents/ml, standardized to a 1 mg oral dose, was 0.50 which was achieved in 2.3 hours. Two percent of an oral dose and 8.5 percent of an intravenous (iv) dose were excreted in the urine (Aellig & Nüesch, 1977).

Schran and coworkers (1988) studied the pharmacokinetics and bioavailability of hydergine in volunteers following single administration of various dose levels (3-9 mg) and dosage forms (oral tablet, sublingual tablet, and solution) under different dosing conditions (fasted or with meals). Male and female subjects showed a similar rate and extent of hydergine bioavailability after treatment. All dosage forms were rapidly absorbed with peak plasma levels of 60-80 pg/ml per mg of administered dose achieved after 0.6 to 1.3 hours.

Administration of hydergine with food did not affect the extent of absorption but lowered the absorption rate.

Hydergine has been detected in the granular layer of the cortex, cerebellum, basal ganglion, and neuronal cells of the reticular formation of cat brain. Animal studies suggest that approximately 60 percent of cerebral hydergine is localized in the synaptic structures (Wadworth & Chrisp, 1992).

Other Biological Effects: Bechter and Schön (1988) used a whole-embryo culture system to assess the embryotoxicity and teratogenic potential of hydergine *in vitro*. The drug was tested in rat embryo cultures as a single component as well as in a drug mixture with clopamide and triamterene (HYCT). As a single component, hydergine was tested at concentrations of 0.074, 0.222 and 0.74 $\mu\text{g/ml}$, which were equivalent to its concentration in the mixture except for the highest concentration which was equivalent to 10 $\mu\text{g/ml}$ of mixture. When tested alone, hydergine did not cause any significant embryotoxicity. A relatively high number of embryos with anomalies was found in all groups including controls. One control group embryo and two mid-dose group embryos expressed neural tube anomalies. One embryo at the highest concentration had an abnormally enlarged heart. None of the increased incidences were statistically significant. Although none of the single components of the HYCT mixture produced significantly increased incidences of abnormalities, the high dose of HYCT produced a distinct general toxicity. All eight embryos tested exhibited morphologically abnormal features. The results suggested an additive effect for the three compounds.

Hydergine was reported to be non-teratogenic in animals; no information was available on the teratogenicity of the drug in humans (Schardein, 1976; Bechter & Schön, 1988).

Structure/Activity Relationships: Ergot alkaloids and related compounds are chemical entities containing the tetracyclic ergolene- or ergoline-ring system. These compounds can be divided into four main structural groups: clavine alkaloids, lysergic acids, simple lysergic acid-amides, and peptide alkaloids. The following peptide alkaloids, derivatives of D-lysergic acid, were chosen for SAR analysis: ergosine [561-94-4], ergostine [2854-38-8], ergotamine [113-15-5], and ergotoxine [8006-25-5] (Berde & Stürmer, 1978).

Ergot alkaloids have a wide field of therapeutic application including treatment of migraine and other vascular headaches, uterine atonia, orthostatic circulatory disturbances, senile cerebral insufficiency, and infertility due to hyperlactinemia. The biological activity of ergot alkaloids depends largely on their configuration. Some basic pharmacological actions occur at the following: 5-HT receptors, dopamine receptors, and adrenoreceptors. Pharmacological actions may also include depletion of noradrenaline from tissues. Extremely small changes in conformation can account for greater affinity to receptor sites or changes in agonist efficacy. These minor changes can have significant consequences to biological activity (Berde & Stürmer, 1978).

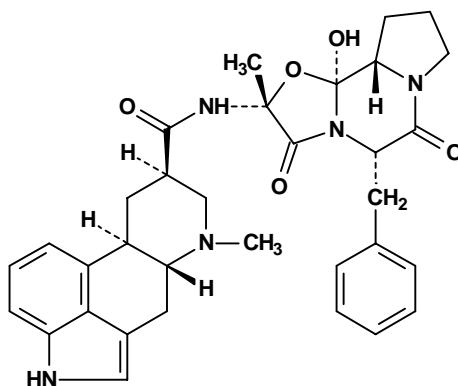
The basic skeleton of the ergot alkaloids selected for SAR analysis consists of a D-lysergic acid linked to a tricyclic peptide moiety by a peptide bond. In the ergotamine group, the peptide part consists of 3-amino acids, L-proline, L- α -hydroxyalanine, and a third amino acid. The third amino acid in ergotamine is L-phenylalanine and L-leucine is the third amino acid in ergosine and ergostine. Ergostine differs from ergosine by the addition of a single methyl group on the proline side chain (Berde & Stürmer, 1978).

Ergotoxine consists of ergocristine, ergocornine and ergokryptine and is very closely related to hydergine, which is a 1:1:1 mixture of dihydroergocristine, dihydroergocornine, and dihydroergocryptine (Berde & Stürmer, 1978).

No information on carcinogenicity was identified for any of the selected compounds.

Ergotamine, tested as the tartrate salt, was the only SAR chemical for which genotoxicity data was identified.

Ergotamine (structure shown below) was negative in the dominant lethal assay in mice (Roberts & Rand, 1978). Ergotamine induced chromosomal aberrations in human lymphocytes *in vitro*. It also induced chromosomal aberrations in mouse bone marrow cells *in vitro* but was considered negative in an *in vivo* chromosomal aberrations assay in guinea pigs (Matter, 1976; Robert & Rand, 1977a,b; 1978). Ergotamine was negative in *in vivo* micronucleus assays in mice and guinea pigs (Matter, 1976).



Ergotamine

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