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Review Article

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An Update on Sodium Diethyldithiocarbamate Trihydrate

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Abstract Sodium diethyldithiocarbamate is found in trihydrate form (SDDCT) as fine yellowish-white solid crystals. SDDCT is a chelating agent that primarily used in the analytical determination of copper, nickel and many other metals. It has been identified as metabolite of disulfiram, whose primary role is in the treatment of chronic arsenic poisoning. The toxicity of SDDCT in rats was reported after i.p. administration of 1500mg/kg was as safe in experimental animal. SDDCT has tendency to inhibit the nephrotoxicity induced by cisplatin in mice and also its effect over the organ distribution and excretion of cadmium. SDDCT induces the GSH oxidation process by increasing the concentration of oxyhemoglobin and also reported as excellent effect on neurotransmitters. Application of SDDCT as the spin trap in conjugation with Fe^{2+} to detect NO in brain, kidney, liver, and other tissues. Superoxide dismutase plays biological role as defense mechanism and get decrease in brain, liver and blood on administration of 1.5 g of DDCT/kg i.p. The effect of Tetramethylthiuram disulfide (TMTDS), Dimethyldithiocarbamate (DMDTC) was studies in male rat at a dose of 1g/kg as hepatic microsomal drug. Industrial or agricultural exposure of these compounds may impair hepatic metabolism and therefore enhance pharmacological activity of drug exposed individually.

Keyword: Sodium diethyldithiocarbamate trihydrate, Disulfiram, SDDCT, Oxyhemoglobin, SOD, GSH

Introduction

Sodium diethyldithiocarbamate trihydrate (SDDCT) is the main metabolite of disulfiram (aldehyde dehydrogenase inhibitor), act as chelating agent and highly used to mobilize toxic metals from the humans tissues and experimental animals [1]. Disulfiram highly accomplished in the management of drug addiction that acts by interfering with the dopamine neurotransmitter [2]. It has the inhibitory effect Dopa Beta Hydroxylase (DBH), a copper-containingmonooxygenase enzyme which has the ability to converts dopamine (DA) into noradrenaline (NA), therefore regulating non adrenaline (NA) production [3]. Therefore it was shown that the effects on DBH, the activity of tyrosine hydroxylase (TH) in guinea pig brain was also inhibited after injections of disulfiram or dithiocarb [4]. SDDCT is known by several chemical name i.e. dithiocarb trihydrate, dithiocarb sodium trihydrate and Imuthiol. The molecular formula is $C_5H_{16}NNaO_3S_2$ and molecular weight is 225.297g/mol [5]. Solubility was detected as 20mg springily soluble in 1 ml of water produced clear colorless solution. The self -life of SDDCT is reported as 4 years [6].

The solution of dithiocarb for parenteral injection generally prepared by adding 10ml of the sterile solution of phosphate buffer (0.5g NaH_2PO_4 in 100ml) to 1g powered of dithiocarb containing in sterile ampule [7]. SDDCT-Cu play the critical role as a proteasome inhibitor in cancer cells [8]. The action is achieved by inhibiting the induction of macrophage nitric oxide synthase. The protective effect of SDDCT has also focused on the inhibition of SOD and cytochrome oxidase activities [9].

SDDTC has been shown to prevent nephrotoxicity induced by *cisplatin* without inhibition of tumor response in the rat. SDDCT at the dose of 25–300 mg/kg inhibits DDP-induced nephrotoxicity and bone marrow toxicity in mice, rats, and beagle dog's and also shows antiemetic effect in the dog [10]. SDDTC was evaluated for its efficacy in promoting organ mobilization and excretion of metallothionein bound cadmium (Cd) in mice. Diethyldithiocarbamate was highly effective in mobilizing Cd from kidney and spleen, but less effective in removing it from Liver. DDTC moderately enhanced Cd levels in lungs, heart and testes and increase brain level to over 500 percent of control values [11].

Metabolic Pathway

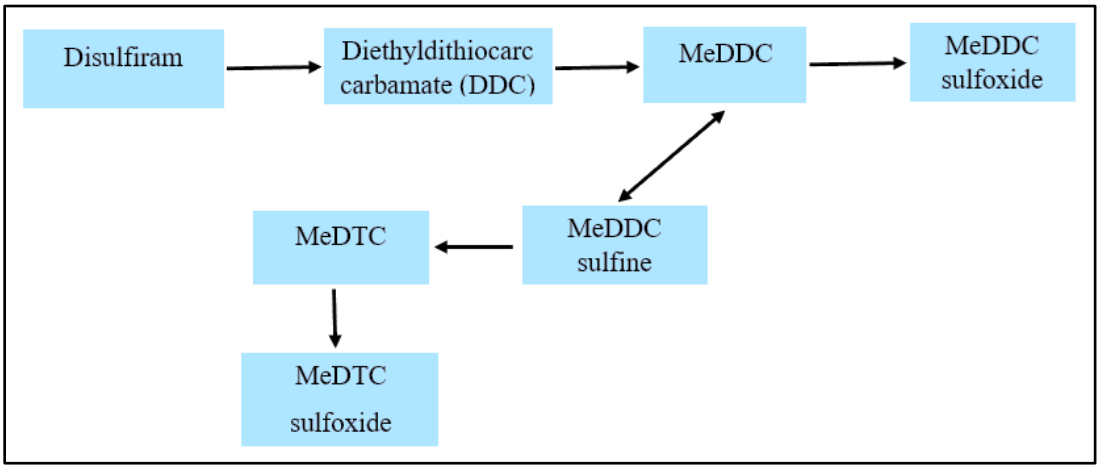

Figure 1: Schematic diagram for metabolic pathway and activation of disulfiram to prepare MeDTC

The alcohol deterrent disulfiram is rapidly reduced in to N, N-diethydithiocarbamate, which is methylated to form S-methyl N,N,-diethydithiocarbamate (MeDDC). MeDDC is oxidized primarily to the intermediate metabolite MeDDC sulfine, which is ultimately converted to S-methyl N, N- diethydithiocarbamate sulfoxide, the proposed active metabolite of disulfiram and a small amount of MeDDC sulfoxide obtained as final products (figure 1) [12].

Mechanism of Action

Inhibition of SOD

Superoxide dismutase (SOD) is a ubiquitously distributed copper-zinc enzyme play primary biological role as the defense mechanism against endogenously generated superoxide radicals. Incubation of pure superoxide dismutase in brain or liver with 10^{-3} m SDDCT for 1.5 hours resulted in total loss of superoxide dismutase activity. When 1.5g/kg of SDDCT were injected in mice, the superoxide dismutase activity decrease within 3 hours by 86% in blood, 71% in liver, 48% in brain respectively. *In vitro* study observe that the superoxide dismutase was preincubated for 1 and half hours at 37°C with 10^{-3} m DDC. The inhibitory effect on the rate of autoxidation of 6- hydroxyl dopamine was lost. On the other hand the dose of SDDCT 1.5g/kg used equivalently to the concentration of $9x10^{-3}$ mif DDC were uniformly distributed in all tissue [13].

Depletion of GSH

The increase concentration of oxyhemoglobin may increase rate of glutathione (GSH) oxidation by SDDCT. Treatment of oxyhemoglobin with N-ethyl-maleiminde(NEM) to alkylate the sulfhydryl group which did not inhibit the activity of hemoglobin due to Deoxyhemoglobin, cyanmethenoglobin and carboxyhemoglobin derivative failed to initiate GSH oxidation. Methemoglobin catalyzed the reaction, slower rate (18-24%) than an equivalent amount of oxyhemoglobin. Addition of ferric or ferrous chloride salt to a mixture of GSH and DDCT solution produced yellow color, indicating DDCT have chelating iron properties. Methylated DDCT did not oxidize GSH even in presence of oxyhemoglobin. [14]

Effect on Neurotransmitters

The metal-chelating capacity of SDDCT and the affinity for sulfhydryl groups due to which it is biologically highly active [15-16]. SDDCT treatment caused a decrease in the dopamine content along with fall in the levels of other catecholamine related molecules, such as L-DOPA (L-3,4-Dihydroxyphenylalanine), DR2, TH (tyrosine hydroxylase) enzyme, which is the rate-limiting step in catecholamine biosynthesis [17], and DBH (dopamine beta-hydroxylase). These alterations are dependable with the well-established reduction of dopamine levels in the entire rodent brain or selected regions following both acute and chronic treatment with high doses of disulfiram and SDDCT [18-22]. The increase in dopamine (DA) together with a decline in noradrenaline (NA) following disulfiram treatment. Moreover, the reduction of DBH is related to the dopamine decrease, then NA levels is also been affected [23-24].

Metabolites of Disulfiram

Dithiocarb involved in the metabolism of disulfiram (also known as Antabuse) after administration in to animals Dithiocarb (also known as SDDCT) was completely distributed in blood, organ tissues, urine, bile, and feces. During the metabolic pathway the Antabuse and SDDCT endures oxidation to form free salt, ethereal sulfates and metal complexes as well as counter to form diethylamine and carbon disulfide (figure 2) [7].

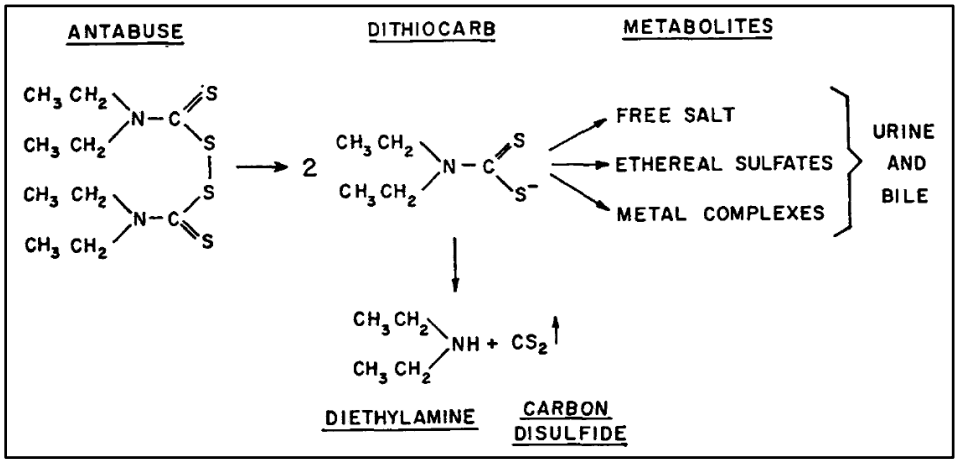

Figure 2: Chemical interaction and conversion of disulfiram into dithiocarb as active compound

Properties of Dithiocarb

Appearance of SDDCT is white crystalline solid having melting point of 90 to 92°C which is soluble in water, methanol, ethanol, and acetone and insoluble in ether and benzene, Stability of SDDCT is at room temperature and unstable in acid solutions. The lethal dose (LD_{50}) in case of Mice and rats when given orally and parentally (i.p.) is 1.5 g/kg b.w. A 10% aqueous solution of dithiocarb yields a pH value of 11.6 at room temperature, this solution may be buffered with monosodium phosphate to 7.4. The mixture becomes turbid when pH concentrations is lower than 7.4, and decomposes, developing an odor of H_2S (figure 3) [7].

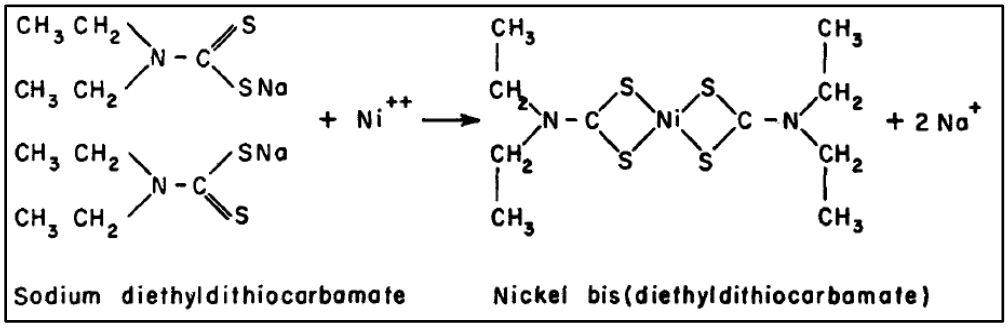

Figure 3: Chelating of nickel by dithiocarb

Pharmacodynamics of SDDCT

SDDCT completely inhibit the SOD activity of cytosolic Cu, Zn at 10^{-5} M concentration because superoxide dismutase catalyzes the conversion of superoxide anion radical to molecular oxygen and hydrogen peroxide. Gamma-glutamyl transpeptidase (GGT) is one of the most important enzymes for the uptake of precursor molecules from the extracellular fluid and for the intracellular synthesis of glutathione, which is a crucial factor in the stability of bronchiole-alveolar fluid. The alteration of GGT indicates impaired glutathione synthesis of type II pneumocytes. Glutathione peroxidase (GSH-Px) a selenium-containing enzyme protects the cells from oxidative damage by converting H_2O_2, lipid peroxides, or other peroxides (-ROOH) to H_2O_2 or unreactive hydroxyl fatty acids. The increase in the activity of GSH-Px might be attributed to a defense mechanism to protect the cell against lipid peroxidation. Glutathione reductase (GSH-Rd) converts oxidized glutathione to glutathione in presence of NADPH provided by glucose-6- phosphate. The activity of GSH-Px showed a significant increase of tissue repair processes even after the environmental interference [25].

Pharmacokinetics of SDDCT

The clinical pharmacokinetics of SDDTC reported after administration of 200 mg/m^2/hr (n=8) and 400 mg/m^2/hr (n=7) DDTC as 4-hour intravenous infusions to normal male healthy volunteers. Diethyldithiocarbamate concentration at steady-state were observed disproportionally for lower dose (27.0±7.6 microM) and higher dose (74.8±19.3 microM), whereas total body clearance reported for low dose (23.83±8.23 mL/min/kg) and higher dose (15.48±2.72 mL/min/kg). The volume of distribution in the terminal phase was estimated to be 3.67±1.15 mmol /min/kg. The terminal elimination half-life was observed for low dose (3.74±1.10 minutes) and high dose (6.08±1.07 minutes). The metabolism for DDTC was estimated as 124.3±19.9 microM, and the small amount of unchanged form was detected in the urine [26].

A preclinical study reported that the administration of dithiocarb in adult male Wistar rats at a dose of 25mg/kg b.w. was observed as the plasma levels reached up to 2mg/L within 3 hours. One hour after dosing, the S-glucuronide conjugate was 96.1%, inorganic sulfate 3.9% and carbon disulfide 7% detected in non-protein bound radiolabel within 15 minutes and also in the plasma (1561 nmoles/ml) and in liver (3211 nmoles/g). The half-life of dithiocarb was determined as 26 minutes whereas a small amount detected as unchanged in the urine of rats on receiving 25mg/kg i.p. injection [27-29].

Therapeutic Properties

SDDCT is used to manage following conditions such as;

- It act like chelating agent in metal poisoning Ni, Cd, Th, Cu, Zn, Hg, Co, Pb.
- Treatment in specific disorders like-Hepatolenticular degradation, Systemic lupus erythematosus.
- Act asantidote in poisoning from polyhalogen compounds, $CHCl_3$, CCl_4, $BrClF_3$
- In Tumors and as an adjunct in cisplatin therapy, Protective against radiation sensitization, Inhibition of fungal infection [30]
- Used in thallium poisoning, SDDCT given orally has been found more effective than dimercaprol in rising urinary excretion of thallium [31]
- Industrial or agricultural exposure of these compounds may impair hepatic metabolism and therefore enhance pharmacological activity of drug taken by exposed individuals [32]
- Used as inhibitor in progression to Acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC) [33]
- Sodium diethyldithiocarbamate, enhances over a large range of doses macrophage listericidal capacity and T cell activities in terms of increased IgG-antibody forming spleen cells and delayed hypersensitivity levels [34]
- It is a useful tool to analyze the toxicity affecting neurotransmitter systems and areas usually involved in psychiatric diseases [35].

Conclusion

The SDDCT is chelating agent obtained from the metabolite of disulfiram. Disulfiram having primary role towards alcohol aversion therapy. In case of metabolic pathway of disulfiram the end product obtained is MeDDC sulfoxide. SDDCT in the form of yellowish-white solid crystals, does not show the toxic level at a dose of 1500mg/kg in experimental animals. SDDCT play an important role by inhibiting enzyme SOD whose primary role is as defense mechanism against endogenously generated superoxide radicals. It also increases the GSH oxidation process by increase in the concentration of oxyhemoglobin. SDDCT has affinity to decrease level of biogenic monoamines in adult mouse brain by affecting the dopamine as well as showing kits effect over catecholamine molecules. The chelation of nickel takes place by dithiocarb. The formation of diethylamine, carbon disulfide along with the metabolites formation also take place by the metabolism of dithiocarb and disulfiram. It has vast therapeutic properties as chelating agent, in thallium poisoning, in tumor and as an antidote in poisoning from polyhalogen compounds. It is too useful in case of psychiatric diseases by affecting neurotransmitter systems.

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Conflict of Interest

The author declares no potential conflict of interest concerning the authorship, or publication of this review article.

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