ASSESSMENT OF THE PROTECTIVE ROLE OF SODIUM THIOSULFATE AND ACETAZOLAMIDE ON CISPLATIN TOXICITY IN ALBINO RATS

Thesis

Submitted for partial fulfillment of the M.D. Degree in Clinical Toxicology

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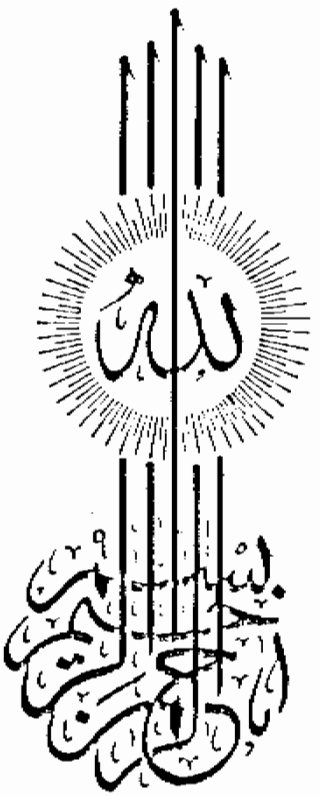

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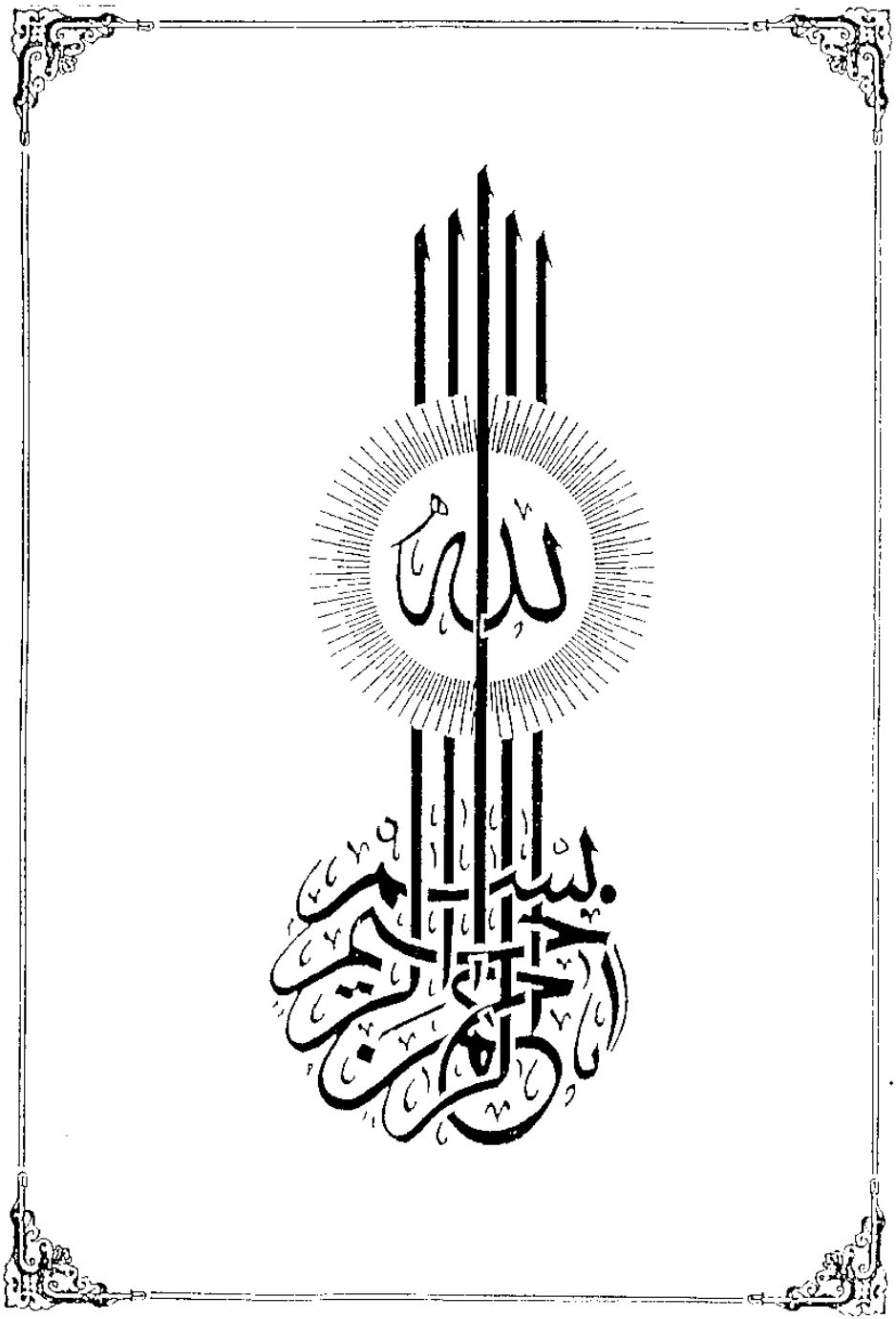

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INTRODUCTION

Chemotherapeutic agents include a wide range of compounds which act by various mechanisms *(Sewester et al., 1993)*. Considerable advances have occurred in recent years in the knowledge of the mechanism of action of many antitumour agents with various attempts to prevent or to minimize their toxicity on normal tissues *(Calabresi and Chabner, 1991)*.

Cisplatin is one of the most widely used drugs in oncology, and it is an important cytotoxic agent in the treatment of a variety of human neoplasms *(Haskell, 1990)*.

The usefulness of cisplatin chemotherapy is often limited by toxic reactions, of which its nephrotoxicity is well known as the most common dose limiting factor *(Gourley et al., 1992)*.

There is a clinically important need to develop procedures that enhance the therapeutic efficacy of cisplatin and to prevent or at least ameliorate its toxicity without inhibition of antitumour effect *(Murthy et al., 1987)*.

In response to this need, we will examine the usefulness of a treatment regimen that combines cisplatin with a sulfur-containing compound sodium thiosulfate and diuretic acetazolamide, based on the hypothesis that both sodium thiosulfate and acetazolamide will counteract the chemical mechanism of cisplatin toxicity without interfering with DNA cross-linking mechanism which produces the antitumour effect of cisplatin *(Bodenner et al, 1986 and Jones et al, 1991)*.

Sodium thiosulfate (STS) is a sulfur - containing metal - chelating agent which is proved clinically as an antidote for cyanide poisoning *(Drisbach and Robertson, 1987)*.

Acetazolamide "ACZ" is a carbonic anhydrase inhibitor with a sulfonamide grouping that has been used to reduce elevated intraocular pressure in chronic simple glucoma and caused a diuresis of sodium bicarbonate ***(Melmon et al., 1992)***.

THE AIM OF THE WORK

The aim of this work is to assess the protective effect of sodium thiosulfate and acetazolamide on cisplatin toxicity and which one is the ideal protective agent.

Review of Literature

REVIEW OF CISPLATIN

Historical Review

The antitumour activity of the platinum complexes was discovered as the result of observation by ***Rosenberg and coworkers in 1965*** during the study of the effects of electric current on growing bacteria ***(Rosenberg et al., 1965)***. When alternating current was delivered through platinum electrodes to a growing bacterial culture, the bacterial cells stopped dividing and grew into long filaments. The same result was seen when an attempt was made to grow the bacteria in fresh media that had previously been subjected to an electric current ***(Rosenberg et al., 1969)***. Since filamentous growth was known to occur in bacteria subjected to alkylating agents or radiation, Rosenberg suspected that an active substance may have entered the medium, possibly through the release of soluble platinum compounds from the electrodes.

It was found that platinum was released by electrolysis as hexachloroplatinate which, in the presence of ammonium salts and light, generated the platinum complex, cis-Diamminedichloroplatinum II (CDDP) (cis Pt (II) $(NH_3)_2Cl_2$), which is now known as the anticancer drug, cisplatin ***(Reed and Kohn, 1990)***.

Considerable progress has been made to understand the use of this new class of chemotherapeutic drugs of platinum coordination complexes, which are proving to be of increasing value in the treatment of a variety of solid tumours ***(Leh and Wolf, 1976)***.

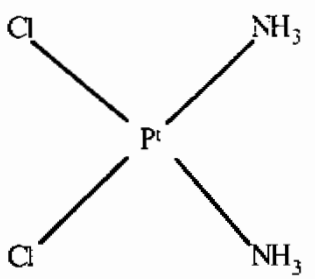
Cisplatin was found to be the most active of these substances in experimental tumour systems and has proven to be of clinical value since 1971 ***(Leh and Wolf, 1976)***. It has broad activity as an antineoplastic agent especially in the treatment of epithelial malignancies and has become the primary building block for regimens that cure patients with testicular carcinoma ***(Rozencweig et al., 1977)***. It also produces high

response rates in patients with small cell carcinoma of the lung, bladder cancer, and ovarian cancer *(Zwelling and Kohn, 1982)*.

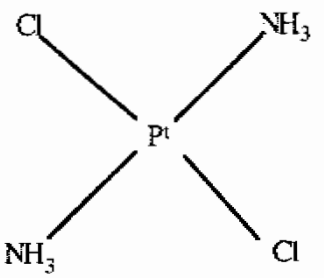
The radiosensitizing effect of cisplatin when used together with radiation on experimental tumours was first demonstrated by ***Wodinsky and Colleagues in 1974.*** Further work by ***Douple and Richmond in 1978*** on Escherichia coli bacteria and Chinese hamster cells, showed that cisplatin sensitizes cells to the cytotoxic effects of radiation therapy. Now cisplatin is used as a potential radiation sensitizing agent *(Rotman and Aziz, 1992)*.

Chemistry

Cisplatin (Cis-Diamminedichloroplatinum (II)) (CDDP) is an inorganic water-soluble platinum-containing complex with a molecular weight of 300 *(Hoskins et al., 1992)*. It is formed by a central atom of platinum surrounded by chloride and ammonia atoms in the cis position in the horizontal plane *(Haskell, 1990)* and the (II) indicate the valence of platinum. The cis isomer is more active than the trans compound *(Cassartt and Daull's, 1986)*.



Cis



trans

Diamminedichloroplatinum (II)

$N_2Cl_2PtH_6$

Pharmacological Properties of Cisplatin

Cisplatin is available in the form of white powder in vials containing 10 mg *(Haskell, 1990)*.

Stability in Solution

Cisplatin is much more stable when reconstituted with sterile saline (0.9%) than with sterile water *(Reed and Kohn, 1990)*. Studies on the stability of cisplatin in aqueous solution indicated that when reconstituted with sodium chloride (NaCl 0.9%), it was stable for 24 hours at room temperature and lower NaCl concentrations resulted in greater rates of drug loss *(Pizzo and Poplack, 1993)*.

It was not necessary to prepare a solution immediately before use provided it was protected from light and stored between 15°C and 25°C. The solution should not be stored in the refrigerator but if stored, the concentration should be less than 600 ug per ml to prevent precipitation *(Reynolds et al., 1989)*.

Incompatibility

Cisplatin should not be administered to patients with materials containing aluminium as is occasionally found in some intravenous needles but may be administered with stainless steel needles. Cisplatin may react with aluminium to form metal precipitates, effectively lowering the concentration of the drug in solution and resulting in unexpected side effects from drug delivery *(Prestayko et al., 1979)*.

There was total loss of cisplatin in 30 minutes at room temperature when mixed with metoclopromide and sodium metabisulphite in concentrations equivalent to those that would be found on mixing with a commercial formulation *(Garren and Repta, 1985)*.

It has been reported that a chemical reaction occurs between cisplatin and sodium bisulfite. Such antioxidants might inactivate cisplatin before administration if they are present in intravenous fluid *(Hussain, 1980)*.

When cisplatin admixed with dextrose-containing solutions, by chromatographic analysis, it appeared to be relatively unstable, with decomposition evident by 2 hours *(Earhart, 1979)*, cisplatin can also form significant coloured complexes if directly admixed with mannitol and stored for 2 to 3 days *(Eshaque et al., 1979)*.

Pharmacokinetics of Cisplatin:

The clinical pharmacokinetics of cisplatin have been described by a number of investigators using either radiolabelled cisplatin, X-ray fluorescence technique or atomic absorption spectroscopy. *Bannister et al, (1977) & Corden et al, (1985)*.

Cisplatin is not effective when administered orally. After rapid intravenous administration of usual doses, cisplatin is widely distributed in the kidney, liver, and intestines, but there is poor penetration into the central nervous system or cerebrospinal fluid (CSF) *(Shelley et al., 1985)*.

Plasma clearance of total platinum is biphasic, with an initial half life ($T_{1/2}$) of 25 to 49 minutes and a terminal $T_{1/2}$ of 58 to 73 hours. The half life of the drug is longer in patients who receive high doses of cisplatin *(Wiemann and Calabresi, 1985)*.

Cisplatin is non enzymatically transformed to one or more inactive metabolites, and these are extensively bound to plasma proteins (90 percent) *(Pizzo and, Poplack, 1993)*. These metabolites also reach high concentrations in kidney, liver and intestines, and they may persist in these tissues for months after drug administration. The unbound, untransformed cytotoxic form of cisplatin has different pharmacokinetics. It is cleared more rapidly from plasma after intravenous administration, with an initial $T_{1/2}$ of 8 to 30 minutes and a terminal $T_{1/2}$ of 40 to 48 minutes *(Haskell, 1990)*.

Cisplatin is metabolized in the liver and there is evidence for an enterohepatic recirculation of the drug *(Stewart, 1983)*.

The principal route of excretion of cisplatin is the kidney, and renal function is the key determinant of safe use. Free cisplatin is cleared both by glomerular filtration and renal tubular secretion *(Weiner and Jacobs, 1983)*.

Only a small portion of the drug is excreted by the kidney during the first 6 hours. After 5 days up to 43% of the administered dose is recovered in the urine *(Calabresi and Chabner, 1991)*.

Biliary excretion accounts for less than 10% of total drug removed from the systemic circulation *(Shelley et al., 1985)*.

Cisplatin appears to cross the placenta, especially late in pregnancy and breast-feeding is not recommended due to potential risk to the infant *(De Vries et al, 1989)*.

Pharmacodynamics of Cisplatin

Cisplatin is an inorganic complex formed by an atom of platinum (II) surrounded by chlorine and ammonia atoms in the cis position of the horizontal plane.

Both neutrality of charge and the cis position are required for the platinum complex to exert its antitumour effects *(Haskell, 1990)*.

In plasma, which is a high - chloride environment, the cisplatin complex is thought to be unionized, thus allowing the passage of the drug into cells. Inside the cell, where the chloride concentration is low, water displaces the chloride ligands of the complex, forming positively charged platinum complexes that are highly reactive *(McEvoy, 1988)*. These complexes inhibit DNA synthesis to a much greater extent than RNA synthesis or protein synthesis. The most important form of binding appears to