INTRODUCTION

Cisplatin, *cis*-Diamminedichloroplatinum (II), is a platinum-containing antineoplastic agent. The drug is an inorganic complex that contains a platinum atom surrounded in a plane by 2 chloride atoms and 2 ammonia molecules in the *cis* position (Figure 1). Its molecular weight is 300.09 and its solubility is 1 mg/ml in water and in 0.9% sodium chloride solution (McEvoy, 1989; Riley and Sternson, 1985).

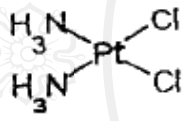

Figure 1. Cisplatin structural formulae

Dried form of cisplatin is stable to light and air at room temperature, but to degrade as platinum metal at 270°C (Riley and Strenson, 1985). In aqueous solution, cisplatin undergoes reversible substitution of its ligands with water to form at least 5 products in accordance with the scheme depicted in Figure 2. The substitution mechanism involves equilibria that depend on the chloride ion concentration and solution pH (Riley and Strenson, 1985; Reynold, 1989; Macka et al., 1994; Conners et al., 1985).

It has been found that greater than 90% of the drug solution remained after 24 hours at room temperature, in 0.45% saline, isotonic saline with 5 % dextrose, and lactated Ringer's solution (Hincal et al., 1979).

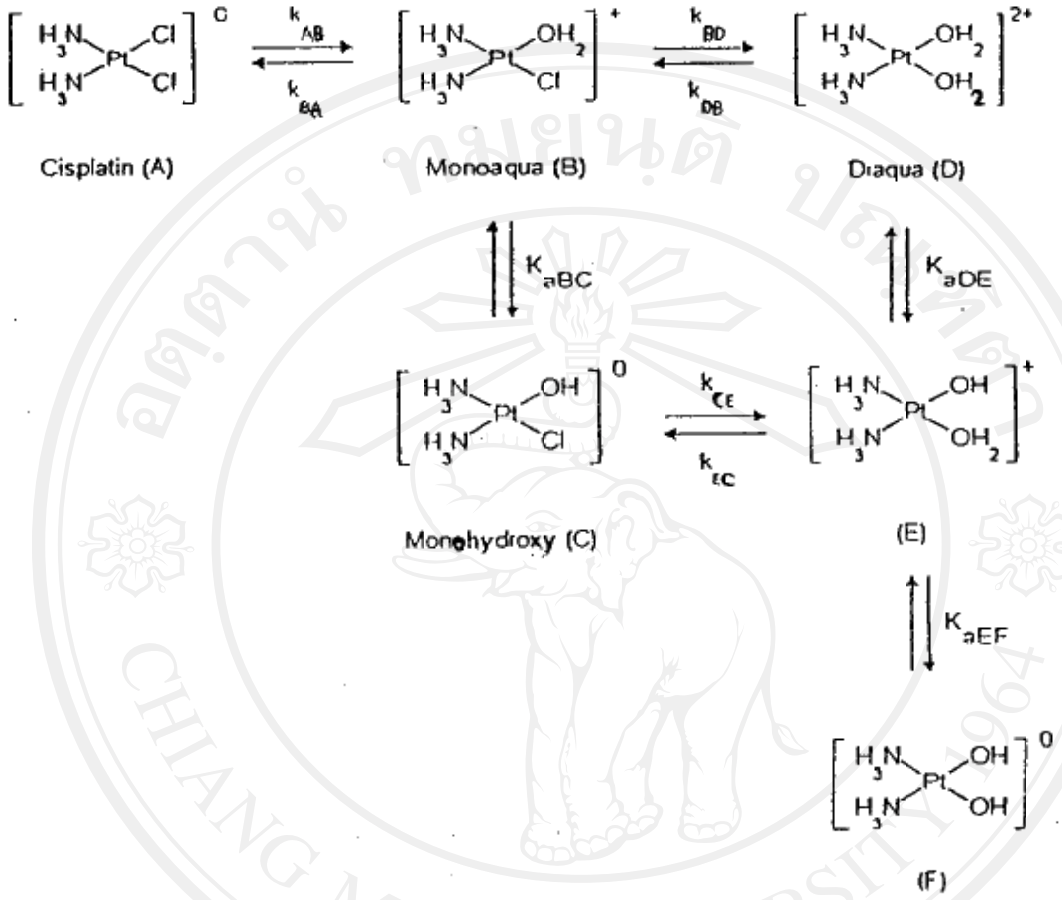

Figure 2. Hydrolysis of cisplatin

It has been reported that cisplatin in 0.9 % sodium chloride solution (NSS) for injection has 3 % loss in less than one hour and remains stable at this equilibrium value for 24 hours at room temperature (Greene et al., 1979). The amino ligand-exchange reaction with chloride is promoted by light and ultrasound. Aqueous cisplatin solutions containing chloride must be protected from any light of wavelength below 500 nm and from sonication (Macka et al., 1994). The main degradation products are amine trichloroplatinate (II). Sonication leads to rapid decomposition of cisplatin forming of several unknown compounds. Degradation of cisplatin was found to be a first-order reaction (Jumbhekors, 1994).

Types of container, i.e. glass bottles, polyvinyl chloride bags, polyethylene and polypropylene containers, had no effect on cisplatin decomposition (Pujul et al., 1993).

Cisplatin can undergo nucleophilic substitution by strong nucleophiles in aqueous solution, indicating that the drug should not be formulated in the presence of such species. For example, bisulphite or metabisulphite has been shown to react rapidly with cisplatin, suggesting that its inclusion as an antioxidant in formulations containing cisplatin is not recommended. Cisplatin is stable in the presence of mannitol, dextrose, benzyl alcohol, and paraben. The stability of cisplatin in solution is not adversely affected by the presence of up to 5 % mannitol. However, cisplatin-mannitol complexes might formed after several days; so advanced preparation and storage of such admixtures should be avoided (Riley and Sternson,1985; McEvoy, 1989; Connors et al., 1986; Reynolds, 1994).

Cisplatin solution should generally not be diluted in sodium bicarbonate or other alkaline solutions because of enhanced decomposition of cisplatin. Formation of bright gold precipitate has occurred after admixture of 5% sodium bicarbonate and cisplatin solution. This was confirmed by Hincal et al. (1979) who showed that the addition of 5 % W/V sodium bicarbonate (pH 7.5) increase the rate of degradation of cisplatin and lowers the concentration present at equilibrium. Cisplatin may react covalently with sodium thiosulfate to form a pharmacologically inactive compound (Riley and Sternson, 1985; Connors et al., 1986; Reynolds, 1994).

Cisplatin solutions should not be prepared or administered with needle or IV administration sets containing aluminium parts that might come in contact with the drug. Aluminium displaces platinum from the cisplatin molecule, causing the formation of black precipitate and loss of potency approximately 30% in 3 hours. This reaction occurs, when metallic aluminum was placed in contact with a 1 mg/ml solution of cisplatin. Microscopic examination revealed a black precipitate, accompanied by the evolution of gas bubbles, in 5 to 10 minutes. The black precipitate became visually apparent within 30 to 60 minutes. This precipitate contained platinum, aluminum, and oxygen. Stainless steel needles and plated brass nubs do not react with cisplatin within 24 hours (Trissel et al., 1983; Conner et al., 1986)

Recently cisplatin for injection commercially available in 2 forms, lyophilized powder for injection and ready to use solution of cisplatin. Cisplatin powder for injection occur as a white lyophilized and contains sodium chloride, mannitol, and hydrochloric acid to adjust pH. The drug is reconstituted with a

volume of sterile water for injection sufficient to give a 0.5 mg/ml and 1 mg/ml final concentration. The solution is clear, colorless, pH 3.7-6.0, an osmolality of about 285-286 mOsm/Kg and a sodium chloride concentration of 0.9%. Commercial formulation of cisplatin contains; no preservative and the reconstituted solutions have a shelf-life of eight hours at room temperature. Unopened vials are stable for 2 years at 27°C (McEvoy, 1995).

Cisplatin is used for the treatment of metastatic testicular tumor; metastatic ovarian tumor, advanced bladder carcinoma, and a wide variety of other neoplasm. The drug is often used as a component of combination chemotherapeutic regimens because of its relative lack of hematologic toxicity (Dollery et al., 1993; Renolds, 1994; Bernie et al., 1994).

The major toxicity caused by cisplatin is dose-related, cumulative impairment of renal tubular function. Otoxicity caused by cisplatin is manifested by tinnitus and hearing loss in high frequency range. Marked nausea and vomiting occur in almost all patients. Electrolyte disturbance, particularly hypo-magnesaemia, hypocalcemia, hyperuricaemia is also seen. Bone marrow depression may be severe with higher doses of cisplatin, Anaemia is commonly seen. Anaphylactoid reactions and cardiac abnormalities have occurred (Dollery et al., 1993; Renolds, 1994; Bernie et al., 1994). As with other antineoplatic agents, the long term health risks to those with chronic occupational exposure to cisplatin are uncertain. The guidelines promulgated by the Council on Scientific Affairs of American Medical Association should be given careful consideration when using this agent (Dollery et al., 1993).

The exact mechanisms of action of cisplatin has not been conclusively determined, but the drug has biochemical properties similar to those of bifunctional alkylating agents. Cisplatin appears to be cycle-phase nonspecific. Cisplatin binds to DNA and inhibits DNA synthesis; protein and RNA synthesis are also inhibited but less extensively. Cisplatin also has immunosuppresive, radiosensitizing and antimicrobial properties (Reynolds, 1994; Benie et al., 1994; McEvoy, 1995).

Cisplatin is administered intravenously. It is usually given as a single dose of 50 to 120 mg/m^2 body-surface, or a dose of 15 to 20 mg/m^2 daily for 5 days. Therapy is repeated every 3 or 4 weeks. In combination chemotherapy regimens, lower doses may be given, ranging from 20 mg/m^2 upwards every 3 to 4 weeks. To aid diuresis and protect the kidney, adequate hydration and use of osmotic diuretics such as mannitol to increase urine volume and thus decrease the urinary concentration of platinum, can reduce the incidence of nephrotoxicity (Dollery et al., 1993; Renolds, 1994; Bernie et al., 1994).

Cisplatin is not effective when administered orally. After infusion cisplatin and its platinum-containing products are rapidly and extensively bound to tissue and plasma proteins, including albumin, γ-globulin and transferrin. Binding to tissue and plasma protein appears to be essentially irreversible (Mc Evoy, 1995). Cisplatin is excreted primarily in the urine. Gromley et al. (1979) suggested that the free drug is actually secreted by the renal tubules. Following rapid IV injection or infusion of cisplatin, plasma concentrations of total platinum have generally been reported to decline in monophasic (Reece et al., 1987; Goel et al.,1990) with half-life 30-50 minutes, biphasic (Gromley et

al., 1979; Fracasso et al.,1987; Leone et al., 1981) with initial half-life 23-67 minutes, and triphasic (Himmelstein, 1981) with half-life 26 minutes, 1 hour and more than 24 hours. Some reports indicate that the non-protein bound platinum decline in monophasic manner (Gormley et al., 1979; Himmelstein et al., 1981) with half-life 3-5 minutes and exhibit biphasic (Bonetti et al., 1994) with half-live 12-30 minutes and 60 hours. Intact cisplatin was decline in monophasic (Himmelstein et al., 1981) with half-life 25 minutes. Prestayko et al. (1978) reported a prolonged terminal half-life for total platinum of 228 hours in a patient with acute renal failure. In a patient with impaired renal function, the peak plasma level of filterable or non-protein bound cisplatin was 4 to 10 times higher than that observed in patient with normal renal function, but the terminal half-life of the non-protein bound cisplatin was not prolonged in this patient. The volume of distribution of platinum in adults following IV administration of cisplatin has been reported to range from 20 to 80 liters (Dollery et al., 1993). The concomitant use of mannitol resulted in higher peak plasma concentrations and decreased urinary excretion of filterable platinum, but did not affect the terminal half-life (Dollery et al., 1993).

Cisplatin Analysis Method

The pharmacokinetics of cisplatin are complex and have been studied principally by using assays for elemental platinum or by using preparation of the drug containing radioactive platinum. Only a few studies have used analytical methods capable of measuring intact cisplatin. Published study on pharmacokinetics of cisplatin have varied widely in the doses administered, the

rate of administration, the use of IV hydration, and the concurrent use of diuretics (Gromley et al., 1979; Himmelstein et al., 1981; Vermorken et al., 1984; Bonetti et al., 1995).

Early pharrmacokinetic studies determined total platinum in plasma or urine by graphite furnace atomic absorption spectrophotometry (FAA). These determinations reflect total platinum content in plasma and plasma ultrafiltrate.

Andrews et al. (1984) studied development of a reverse phase HPLC method, that has improved selectivity to "total active Pt" species in plasma ultrafiltrate. Their method is an adaptation of HPLC techniques described by Bannister and Borch (1979) which determined Pt (II) species after complexation with sodium diethyldithiocarbamate (DDTC) (Andrews et al., 1984; Goel et al., 1990). Bannister et al. (1979) have previously demonstrated that DDTC reacts readily and quantitatively with the epoxide, dianhydrogalactitol, directly in blood plasma to form a stable product, which is significantly more hydrophobic than the parent and with pronounced UV absorbance at 254 nm (Bannister et al., 1979). The scheme of reaction of DDTC-cisplatin derivatization is shown in Figure 3.

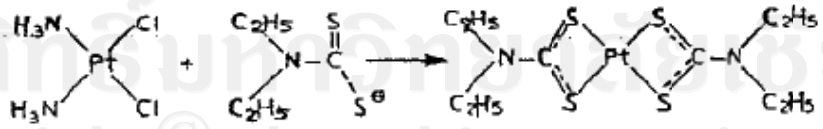

Figure 3. DDTC-cisplatin derivatization

The adduct (s) strongly absorbed UV light with wavelength maximum at 254 nm and 347 nm (Bannister et al., 1979).

At least 6 different brands of cisplatin for injection are commercial available in Thailand (e.g. Platinol®, Cisplatin®, Cisplatinum®). Platinol is an original product imported from Italy. The others are locally made in Thailand. Because of instability in aqueous solution and lack of sufficient pharmacokinetic information in Thai patients as well as the price of the original product is more than 4 times higher than the local ones. This thesis research aimed to study the stability of cisplatin solution for injection, and to investigate pharmacokinetic parameters of cisplatin in Thai patients during IV infusion. Three commercial, ready to use, cisplatin for injection were used and compared with each others.