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Antibacterial Effect of N-Naphtylen Diamine Platinum (II) Choloride as Novel Compound

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Abstract: The present study synthesized N-Naphtylen Diamine Platinum (II) Chloride (NDPC) as a novel compound and tested ability of it regarding inhibition of cell division in some bacteria. Present results indicate that NDPC could act as antimitotic compound. It was inhibited growth of some microorganism as experimental organisms. The most antimitotic effect was seen in *pseudomonas aeurginosa* that treated by 15 mg mL^{-1}. Application of NDPC in all concentrations also was inhibited division and growth of other bacterial cells. Although *Escherichia coli* is less sensitive to NDPC than others, but also inhibition of growth is significant in *E. coli*.

Key words: Cis-platinum, cancer, antimitotic, antibacterial

INTRODUCTION

Platinum based compounds have antitumor effects. The interest in platinum-based antitumor drugs has origin in the 1960s, with the serendipitous discovery by Rosenberg of the inhibition of cell division by Pt complexes (Rosenberg and Van-Camp, 1979). *Cis*-Diammine dichloro- platinum (II) and *cis*-diammine-tetrachloroplatinum (IV) were identified as the Pt compounds responsible for the phenomena (Rosenberg 1967; 1971; Andrews *et al*., 1988; Sersa *et al*., 2000; Sacchi *et al*., 2006). Deducing that Pt compounds would have uses in cancer treatment. Rosenberg and co-workers performed experiments with Sarcoma 180 and Leukemia L 1210 bearing mice (Rosenberg and Van-Camp, 1979). This eventually led to cis-diammine dichloroplatinum (II) (Cis-platin (I) entering phase I clinical trials in 1971 (Andrews *et al*., 1988). Approval of cisplatin for the treatment of testicular and ovarian cancer was given in 1978. Today, Cis-platin is one of the three most widely utilized antitumor drugs in the world and has annual sales of approximately $500 million (U.S.). (Sersa *et al*., 2000) .It is highly effective in treating testicular and ovarian cancers and it contributes to the treatment of oropharyngeal carcinoma, bronchogenic carcinoma, cervical carcinoma, lymphoma, osteosarcoma, melanoma, bladder carcinoma and neuroblastoma (Sersa *et al*., 2000).

Despite its success, Cis-platin has several disadvantages that include severe toxicity such as nephrotoxicity, neurotoxicity and emetogensis. The toxic side effects of cisplatin limit the dose that can be given to patients; typical doses are 100 mg day^{-1} for up to five consecutive days (Sacchi *et al*., 2006). A number of protecting or rescue agents such as means, WR-2721, diethyldithiocarbamate and thiosulfate have also been used to control cisplatin toxicity; however, the exact role of these agents is not well understood and they are as of yet not routinely used in Pt chemotherapy (Reedijk, 1996).

Cisplatin is used in the treatment of a number of cancers, but its applicability is still limited to a relatively narrow range of tumors. Some tumors have natural resistance to cisplatin, while others develop resistance after the initial treatment, Cisplatin also has limited solubility in aqueous solution and is administered intravenously, another inconvenience to outpatient treatment. These drawbacks coupled with cisplatin toxicity have been the impetus for the development of an improved Pt antitumor drug (Yamamato *et al*., 2003).

All anti tumor drugs have inhibitory effect against bacterial culture. There is considerable evidence also that during the last ten years the pace of development of new antimicrobial drugs has slowed down while the prevalence of resistance (especially multiple) has increased astronomically (Hugo and Russel, 1984). The increase in number of antibiotic resistant bacteria is no longer matched by expansion I arsenal of agents available to treat infections.

Prior to examination of anti-tumoral effect of N-Naphtylen Diamine Platinum (II) Chloride (NDPC), we decide to exanimate its antibacterial effect. The aim of this research is to examination ability of N-Naphtylen Diamine Platinum (II) Choloride (NDPC) as a new synthesized

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complex, on the cell division in certain bacteria. This complex had been synthesized by our prior research. Synthesizing data has been confirmed by Iran Ministry of Research and High Education and recorded as No 3/11-2105.

MATERIALS AND METHODS

Material preparation: N-Naphtylen Diamine Platinum (II) Chloride (NDPC) used in this study was synthesed in powder form, in our chemistry laboratory at 2004. Powder solved in distilled water and different solutions in series of 5, 10 and 15 mg mL^{-1} were prepared.

Test organisms: The standard strains of following microorganism were used as test organism. *pseudomonas aeruginosa* (PTCC 1074), *Escherichia coli* (PTCC 1330), *Bacillus cereus* (PTCC 1349), *Basilus subtilis* (PTCC 1672), *Corynebacterium pyogene* (Lio), *Staphylococcous aureus* (Lio) and *Stereptococcus faecalis* (Lio). Some of that microorganism obtained from Persian Type Culture Collection (PTCC), Tehran, Iran and others locally isolated (Lio). For use in experiments, the organisms were sub-cultured in nutrient broth and nutrient agar (Oxiod Ltd.) while diagnostic sensitivity test agar (DST) (Oxoid Ltd.) was used in antibiotic sensitivity testing.

Sensitivity testing: Sensitivity testes were doing in our cell and molecular laboratory during 2005-2006 years. For bioassayes, suspension of approximately 1.5×10^{8} cells mL^{-1} in sterile normal saline was prepared as described by Forbes *et al.* (1990). The sensitivity testing was determined using agar-well diffusion method (Russell and Furr, 1977; Irobi *et al.*, 1996). The Minimum Inhibitory Concentration (MIC) of synthesized complex was also determined using a two-fold dilutions method (Russell and Furr, 1977). The bacterial isolates were first grown in nutrient broth for 18h before use. The incolum suspensions were standardized and then tested against the effect of the NDPC at concentrations of 5, 10 and 15 mg mL^{-1} each in DST medium. The plates were later incubated at 37°C ± 0.5°C for 24 h after which they were observed for zones of inhibition (Table 1). The effects were compared with that of the standard antibiotic streptomycin at a concentration of 1 mg mL^{-1} (Khan and Omosto, 2003).

RESULTS

In this study the results of the investigations show that the N-Naphtylen Diamine Platinum (II) Chloride possesses antimicrobial activities against some of the tested organisms at concentrations of 5, 10 and 15 mg mL^{-1} (Table 1). Results indicate that in all group that treated by N-Naphtylen Diamine Platinum (II) Choloride, cell division was inhibited that is accordance with prior reports about other platinum based compounds. The most antibacterial effect were seen in *Pseudomonas aeruginosa* and *Staphylococcous aureus* g roups that treated by 15 mg mL^{-1} but antibacterial effect is significantly high in other groups of *Staphylococcous aureus* that were treated by 5 and 10 mg mL^{-1}. Results indicate that different solution of NDPC could affected growth and division in all bacterial cells as a tested organism in this study. But it seems that *Pseudomonas aeruginosa* is more sensitive than other microorganisms to antibacterial compound. According to our results *Pseudomonas aeruginosa* and *Staphylococcous aureus* are more sufficient for antimitotic studies by using N-Naphtylen Diamine Platinum (II) Chloride.

The Minimum Inhibitory Concentration (MIC) of synthesized complex was also determined using the method of Russell and Furr (1977). Results indicate that the Minimum Inhibitory Concentration (MIC) of N-Naphtylen Diamine Platinum (II) Chloride (NDPC) against the tested organism varied between 0.0213 and 0.625 mg mL^{-1}. The standard streptomycin had MIC values varying between 0.0313 and 0.560 mg mL^{-1}. The results indicate that standard antibiotic streptomycin has similar activity to N-Naphtylen Diamine Platinum (II) Chloride as shown in Table 2.

Table 1: Antimicrobial activity, indicated by diameter of inhibition zones, of N-Naphtylen Diamine Platinum (II) Chloride against seven species of bacteria

	Zones of inhibition (mm)			
Microorganisms	Control	5 mg mL^{-1}	10 mg mL^{-1}	15 mg mL^{-1}
Bacilus cereus	0	14±1.80	17±2.40	22±2.70
Bacilus subtilis	0	18±2.60	20±3.10	21±3.40
Corynebacterium pyogene	0	15±1.90	20±2.10	24±2.70
Escherichia coli	0	11±1.20	16±1.90	20±2.10
Pseudomonas aeruginosa	0	16±0.90	22±2.30	24±3.20
Staphylococcous aureus	0	21±2.30	25±2.80	26±3.20
Stereptococcous faecalis	0	16±2.90	23±3.50	30±4.30

Each data represents the mean±SE of 5-8 experiments $p<0.05$

Table 2: The minimum inhibitory concentration (mg mL^{-1}) of -Naphtylen Diamine Platinum (II) Chloride and Streptomycin against the bacterial isolates

	MIC (mg mL^{-1})	
Microorganism	NDPC	Streptomycin
Bacilus cereus	0.032	0.0313
Bacilus subtilis	0.0125	0.0625
Corynebacterium pyogene	0.062	0.0313
Escherichia coli	0.01	0
Pseudomonas aeruginosa	0.0313	0.25
Staphylococcous aureus	0.063	0.5
Stereptococcous faecalis	0.25	0.0725

DISCUSSION

Since discovery of cisplatine as effective anticancer drug, new platinum with higher or equal antitumor activity but lower toxicity have been sought (Umpathy, 1989). Consequently, efforts were directed towards altering the pharmacokinetics of Cis-platinum and this was achieved by replacing the labile chloro ligands with other leaving groups and extending the stable amino ligands to a series of either cyclic or acyclic alkyl amines (Hacker *et al*., 1984). Our synthesized complex belonging to such second-generation platinum drugs that was examined regarding inhibition of cell division in this research.

Our results showed that N-Naphtylen Diamine Platinum (II) Chloride possesses antimicrobial activities against some of the tested organisms. On the base of our results N-Naphtylen Diamine Platinum (II) Chloride could inhibit cell division in the bacterial cells. This findings accordance with some prior reports about antimitotic and antitumor ability of other members of Cis-platinum complexes (Rosenberg *et al*., 1965; Rosenberg, 1967; *Andrews et al*., 1988; Sersa *et al*., 2000; Sacchi *et al*., 2006). But this is the first report about antibacterial and antimitotic ability of N-Naphtylen Diamine Platinum (II) Chloride as a novel synthesized complex.

All tested organisms were inhibited by treatment of N-Naphtylen Diamine Platinum (II) Chloride but results showed that *pseudomonas aeruginosa* is more sensitive than other ones, which is accordance with some reports about other antibacterial compounds (Digrak *et al*., 2001; Bonjar, 2004). We can conclude that *pseudomonas aeruginosa* is a more sufficient organisms for antibacterial tests of N-Naphtylen Diamine Platinum (II) Chloride.

According to many reports (Essawi, 2000; Cos *et al*., 2002), multiple resistances were to some bacteria hazards in the world. An alternative to combat the problem of microbial resistance as development of new antibacterial for substitution with infected ones. We suggest N-Naphtylen Diamine Platinum (II) Chloride as an alternative antibacterial against some resistant bacteria.

All Cis-platinum compounds have toxicity, for this reason we need new compound that have low toxicity (*Yamamato et al*., 2003). According to our results (Table 1) N-Naphtylen Diamine Platinum (II) Chloride is a good new antibacterial compound and also amitotic platinum base compound that inhibits strongly growth and cell division in bacterial cultures. Regarding this effect we suggest more experiments by using carcinogenic cultures and also *in situ* using in experimental animals that have different carcinogenic tumors. We are going to plane such researches in our new activities.

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