

Recent Developments in Platinum Chemotherapeutic Drugs

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Since the discovery of the antitumor properties of *cis*-diaminedichloro-platinum(II) by Rosenberg^{1,2} in 1965, cisplatin has become one of the most frequently used chemotherapeutic drugs.³ The mechanism of action of cisplatin has been intensively studied.

Cisplatin undergoes hydrolysis in cells to form monoquo- and diaquo- compounds which bind to DNA at the N7 residues on purine nucleotides.^{4,5} Adjacent intrastrand guanine nucleotides have shown the most specificity for cisplatin binding. Other cisplatin-DNA adducts are such as 1,2-d(ApG), 1,3-d(GpNpG), and interstrand adducts occur with less frequency.⁶

Recently, a crystal structure of a 12 base pair strand of B-DNA bound to cis-DDP has been solved. Bending angles of 39° and 55°, previously observed by gel electrophoresis, have been obtained from the crystal parameters. Additionally, unwinding (~12-19°) of the DNA strand has been observed.⁷ Cisplatin bound DNA adopts a hybrid structure between that of A-DNA and B-DNA with minor groove widening and tilting of the nucleotides observed in the complexed DNA.



Figure 1. Unit cell of cisplatin damaged DNA⁷

In 1990, two unidentified proteins (26 and 81 kD) were found to bind to the cisplatin-DNA adducts. Bruhn et al.⁸ identified these proteins as "structure specific recognition protein one" (SSRP1) and "high mobility group one" (HMG1) proteins. Recently discovered, normal function of these proteins within the cell is currently unknown. Amino acid sequence comparison between SSRP1 and HMG1 reveals a 47% homology between a region known as the HMG-box on the SSRP1 and on HMG1. Other proteins with HMG-boxes such as Ixr1 have been found. HMG1 binds specifically to cisplatin damaged DNA at the site of the adduct, shielding the adduct from the normal DNA repair pathways and increasing the bending of the DNA.⁹⁻¹¹ Ixr1 confers increased sensitivity of the cells to cisplatin.¹²⁻¹³

Lesions on the DNA are responsible for the cytotoxicity of cisplatin. Cells repair DNA lesions through the nucleotide excision pathway. 1,2-d(GpG) adducts (the major adduct of cisplatin-DNA complexes) are repaired much slower than other Pt-DNA adducts. Shielding of the damage site by HMG-box proteins may account for this decreased rate of repair, or modification of the DNA strand (bending) may block repair.¹¹

Side effects of cisplatin include nephrotoxicity, neurotoxicity, ototoxicity and nausea. Additionally, cisplatin must be given intravenously, requiring outpatient service. Synthesis of new drugs which possess reduced side effects and easier routes of delivery is of current interest. Three such complexes carboplatin (approved for drug use by the FDA), JM216 (in phase II clinical trials), and JM221 show promise as alternatives to cisplatin.

Carboplatin [*cis*-diamine(cyclobutane-1,1-dicarboxylato)platinum(II)], is a second generation platinum drug which shows increased solubility to cisplatin. Chromatography studies show ~33% 1,2-d(GpG) drug-DNA adduct in vivo.¹³ Dosage studies show carboplatin binding to be 17.5 times less effective than cisplatin. NMR studies of carboplatin show similar binding methodology to that of cisplatin. Kinetic studies of carboplatin binding indicate that cisplatin binds 25 times faster than carboplatin.¹⁴ Despite cisplatin advantages, carboplatin is a viable option due to decreased side effects as well as equivalent cytotoxicity as compared to cisplatin.

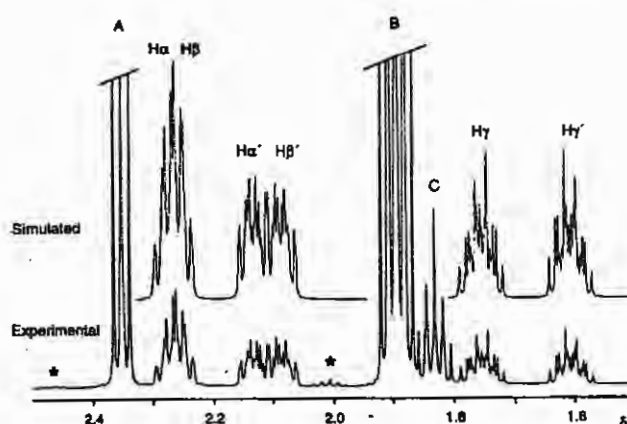


Figure 2. ^1H NMR of carboplatin-5'-GMP-N7 adduct¹⁴

JM216¹⁵ and JM221¹⁶ are platinum(IV) complexes. These complexes are relatively inert and have the ability to survive the gastrointestinal tract. As these complexes get absorbed into the bloodstream, ascorbic acid and thiols reduce the platinum(IV) octahedral metal center to a square planar platinum(II) metabolite.¹⁷⁻¹⁹ This metabolite shows comparable reactivity to that of cisplatin with a reduction in side effects.²⁰⁻²² These properties make both of the above compounds ideal candidates as oral chemotherapeutic drugs.

References

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