Platinum Coordination Complexes in Cancer Chemotherapy

PAPERS FROM THE THIRD INTERNATIONAL SYMPOSIUM

By M. J. Cleare

Group Research Centre, Johnson Matthey & Co Limited

The symposium which took place at the Wadley Institutes of Molecular Medicine in Dallas, Texas, embraced a wide range of scientific disciplines from platinum metal chemistry through to clinical practice and was attended by over one hundred and fifty delegates of equally diverse backgrounds. The first two days of the meeting were largely concerned with the more fundamental aspects of platinum compounds and their biological activity, while the final day was devoted to reports of clinical efficacy and protocols.

The introductory lecture by M. J. Cleare of Johnson Matthey Research Centre discussed the basic chemistry of platinum (II) complexes and related this to their biological and anti-tumour activity. Later M. L. Tobe of University College, London, covered more specific aspects of structure-activity relationships for a series of Pt(II) and Pt(IV) amine complexes of type *cis*-$[PtA_2Cl_2]$ and *cis*-$[PtA_2Cl_4]$ (A=organic amine). Good anti-tumour activity and selectivity was observed in animal tests with certain alkyl, alicyclic and heterocyclic amines, but aqueous solubility was too low to make them of clinical value. However, he reported that incorporation of *trans* hydrophilic hydroxo groups in Pt(IV) complexes of type *cis*-$[Pt(A)_2(OH)_2Cl_2]$ improved the solubility and in some cases maintained the activity as well.

A number of new compounds based on amine systems with anionic groups other than chloride were described by researchers from the Wadley Institute. The compound which attracted most attention was $[Pt(A)SO_4]$ (A=1,2 diamino cyclohexane, active against a number of tumour systems, soluble, and having relatively low toxicity.

The chemical structure of blue platinum pyrimidine compounds, known as Platinum Blues, which have interesting biological properties, was discussed in several papers by B. Lippert, Michigan State University; S. J. Lippard et al, Columbia University, New York; and A. J. Thomson, University of East Anglia. Although these are recognised as cationic polymers of mixed or non-integral valency, their precise structure remains unknown. X-ray crystallography studies were presented on possible Platinum Blue precursors isolated from the starting material for their preparation, *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$. These are hydroxo bridged dimers and trimers, for example $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ (C. J. L. Lock et al, McMaster University, Hamilton, Ontario; J. A. Stanko et al, University of South Florida). Dr. McAlister of Michigan State University discussed the electron microscopy staining properties of these compounds. It appears that contrary to original reports, cell surface staining is encountered with all cells and is not selective for tumour cells. The nature of this staining remains unclear although studies reported by S. K. Aggarwal of Michigan

State University indicated that it may still be a useful staining technique.

X-ray crystallographic studies on complexes between platinum and various nucleoside and necleotides were presented by R. Bau et al, University of Southern California and confirmed the preferred base binding sites as the N7 of guanine (G) and N of cytidine (C) although some phosphate binding was also involved. The modes of binding of Pt compounds to DNA were the subject of many *in vitro* studies all indicating heavy G–C involvement. Evidence for binding at O6 of guanine to make a chelate ring with N7 was not forthcoming in physicochemical studies. Intercalation studies reported by I. A. G. Roos of the University of Adelaide support the concept of intra strand linking of DNA. Previous studies have demonstrated that interstrand cross linking is unlikely to be the major lesion leading to cell death.

An interesting new development concerns the ability of platinum compounds to sensitise cells to irradiation (R. C. Richmond et al, U.S. Army Natick Laboratories; A. H. W. Nias, Glasgow Institute of Radiotherapeutics). Of particular note is the ability to sensitise both in the presence and absence of oxygen. This could be important as anoxic cells in tumour masses are always difficult to kill by irradiation.

The distribution of ^{195m}Pt labelled *cis*-$[Pt(NH_3)_2Cl_2]$ in rats was reported by W. Wolf et al, University of Southern California. Two blood phases were observed, one very fast ($T_{\frac{1}{2}}$<30 minutes) and the second slow ($T_{\frac{1}{2}}$ approximately 19 days). An important storage compartment for the slow phase appears to be the skin which contains more than 20 per cent of the injected dose at 30 minutes and still houses 11 per cent after 72 hours. Other organs retaining more than 1 per cent of the injected dose at 12 hours were the liver (3.5 per cent), kidneys (2.8 per cent), muscle (5.1 per cent) and bone (5.1 per cent).

Evidence concerning the nature of the renal damage produced by *cis*-$[Pt(NH_3)_2Cl_2]$ was presented by T. F. Slater of Brunel University. The drug binds strongly at the membrane of the proximal tubule of the kidney and unlike other membrane binding this cannot be reversed by the use of cysteamine. This may explain why the kidney suffers the dose limiting toxicity.

The major discussion of cellular repair membrane was given by J. J. Roberts of the Chester Beatty Institute, Pollards Wood, who presented evidence from tissue culture studies to suggest that platinations of DNA can be circumvented by a post replication repair process. This repair protects cells from the cytotoxic and chromosome damaging effects of *cis*-Pt(II) and is caffeine sensitive since post treatment incubation in caffeine enhances these effects. Failure of the repair process to occur within a finite time leads to irreversible cell damage. The differing abilities of cells to perform the process rapidly may account for differing sensitivities to *cis*-Pt(II).

Clinical Trials with *cis*-$[Pt(NH_3)_2Cl_2]$

There was little doubt that the interest of clinicians in this drug has changed considerably since the 2nd International Symposium at Oxford in 1973. In reviewing the clinical situation I. Krakoff of the Sloan Kettering Memorial Institute indicated that the drug was now established as being useful for certain tumour types namely genito-urinary, head and neck, and held promise for several others. It would undoubtedly become an accepted chemotherapeutic drug. He also called for the apparently more promising second generation drugs to be brought along more quickly.

D. D. Von Hoff of the National Cancer Institute stated that the N.C.I. sponsorship of *cis*-Pt (II) started in 1971 but that a sharp increase in the interest of clinicians in this drug was noted in May 1976. In August 1976 twenty-five thousand 10 mg vials were supplied and two hundred and seven

investigations are currently in progress.

Several clinicians indicated means by which the nephrotoxicity could be significantly limited. E. Cvitkovic and his colleague also of the Sloan Kettering Memorial Institute, New York, have hydrated patients prior to treatment and administered mannitol (a diuretic) to promote urine flow, along with the *cis*–Pt(II). This technique allows much higher doses to be given and greatly improved therapeutic results are being obtained. There are indications that the higher dose therapy will cause a wider range of tumours to respond. C. Merrin of Roswell Park, Buffalo, reported that they had found a dose schedule comprising multiple small doses to be equally effective in this respect.

Reports on *cis*–Pt(II) given in combination with other chemotherapy agents were particularly encouraging and this represents another way of overcoming the toxicity. Results for testicular cancer involving *cis*–Pt (II) with Bleomycin and Vinblastine reported by L. H. Einhorn of Indiana University Medical Centre, were outstanding although true judgement must await a larger sample of patients. E. Wiltshaw of the Royal Marsden Hospital, London, stated that *cis*–Pt (II) was as good as any other single agent in the therapy of ovarian tumours and initial results indicated that in combination a considerable improvement was obtained.

Clinical Trials with Newer Platinum Compounds

The only report of clinical trials on other Pt compounds came from the Wadley Institutes of Molecular Medicine where trials on [Pt A(malonate)] (A=1,2 diaminocyclohexane) are in progress. Some responses have been observed but the results are of too preliminary a nature to draw conclusions as yet. Clinical testing of platinum uracil blue and *cis*–[PtA_2Cl_2] (A=cyclopentylamine) has been discontinued. Clinical trials on [PtA(sulphate)] (A=1,2 aminocyclohexane) will start shortly.

Exhaust Gas Sensors Aid Emission Control

ZIRCONIA DEVICES UTILISE PLATINUM ELECTRODES

The purification of automobile exhaust gases by platinum group catalysts can be most consistently achieved when the engine is operated with an exactly stoichiometric air/fuel ratio. One way of achieving this state is by monitoring the oxygen content of the exhaust gas and using the information to control the input of air to the engine. This requires an instrument which can reliably detect the variations in oxygen concentration.

Exhaust sensors consisting of a ceramic tube of stabilised zirconia closed at one end and having porous platinum electrodes on both the inner and the outer surfaces have been developed for this purpose. The sensor is inserted in the exhaust system so that the exhaust gases flow over the outer platinum anode while the platinum cathode on the inner surface is open to atmosphere. As the sensor is heated by the engine exhaust the ceramic becomes conducting to oxygen ions and, as the partial pressure of the oxygen on the two sides of the device is different, an electrical potential is generated between the two electrodes. A change in voltage occurs whenever the composition of the exhaust changes, for example from 'rich' to 'lean' or vice versa. This signal is a measure of the air/fuel ratio and can be used, via a closed loop circuit, to control any departure from stoichiometry.

While the sensor voltage can be calculated from the appropriate thermodynamic relationship, actual sensor behaviour can differ from this ideal, and such departures are detrimental to the performance of the systems they control. In a recent article W. J. Fleming of General Motors Corporation, Research Laboratories (*J. Electrochem. Soc.*, 1977, **124**, (1), 21–28) describes work to derive a physical model of a non-ideal sensor. The physical processes involved in the function of zirconia exhaust gas sensors are examined and a theory to account for the departure from ideal behaviour is presented.