The Antitumour Activity of Some Platinum(II) Complexes of Amino Acids

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Speer and collaborators [1] reported that some bis[amino acid]platinum(II) complexes did not show promise as antitumour agents. Wappes, Schönenberger, Bissinger and Beck [2] have recently examined several *cis*-dichlorobis[α-amino acid ester]-platinum(II) complexes as potential antitumour agents. The complex containing glycine *tert*-butyl ester ligands inhibited the incorporation of [^{3}H]-thymidine into MDA-MB 231 cells and into ADJ/PC6 plasmacytoma cells *in vitro*. However, this complex did not influence tumour growth of ADJ/PC6 plasmacytoma *in vivo*. We reported [3, 4] that mixtures of glycine with potassium tetrachloroplatinate-(II), of *L*-serine with potassium tetrachloroplatinate-(II) and of *L*-glutamine with potassium tetrachloroplatinate(II) show antitumour activity in the P388 lymphocytic leukaemia test-system. A variety of platinum(II) complexes of glycine are known [5–8], and it is likely that a number of these complexes are present in solution when a mixture of glycine and potassium tetrachloroplatinate(II) is dissolved in water. It has also been shown [9] that *L*-glutamine can react with potassium tetrachloroplatinate(II) to yield a platinum blue compound. The purpose of this communication is to report that some amino acid complexes of platinum(II), in which the molar ratios of amino acid to metal are 1:1, show antitumour activity in rodent test-systems.

Potassium *cis*-dichloroglycinatoplatinum(II) was prepared according to Erickson and collaborators [5], and the method for preparing caesium *cis*-dichloro-*L*-serinatoplatinum(II) is given in the experimental section of this paper. Antitumour testing of these compounds was carried out by the National Cancer Institute (NCI) in Bethesda, Maryland, U.S.A. The definition and description of the test procedures used by NCI and the criteria for activity have been recorded by Geran and collaborators [10]. Results of anticancer testing in the P388 lymphocytic leukaemia mouse test-system are shown in Table I. According to the NCI evaluation, a compound is judged active if it produces an increase in lifespan greater than 25%. From the data given in Table I, it can be seen that both compounds are active. Caesium *cis*-dichloro-*L*-serinatoplatinum(II) has also been tested in the MBG5 subrenal capsule MX-1 mammary carcinoma Xenograph test-system, and the results are

TABLE I. Antitumour Testing of Some 1:1 Amino Acid Platinum(II) Complexes in the P388 Lymphocytic Leukaemia Mouse Test-result.

Substance tested	Dose level per injection (mg/kg)	Increase in lifespan %
Potassium *cis*-dichloroglycinato-platinum(II)	50 [a,c]	4
	25 [a,c]	71
	12.5 [a,c]	49
	6.25 [a,c]	31
	25 [b,c]	85
	12.5 [b,c]	48
	6.25 [b,c]	32
	3.15 [b,c]	29
Caesium *cis*-dichloro-*L*-serinatoplatinum(II)	50 [a,d]	53
	25 [a,d]	22
	12.5 [a,d]	13
	6.25 [a,d]	19
	50 [b,d]	42
	25 [b,d]	27
	12.5 [b,d]	25
	6.25 [b,d]	25

Substances were dissolved in water and administered intraperitoneally. [a]Female mice used. [b]Male mice used. [c]A total of nine injections were given. [d]A total of five injections were given.

TABLE II. Antitumour Testing of a 1:1 Amino Acid Platinum(II) Complex in the MBG5 Subrenal Capsule MX-1 Mammary Carcinoma Xenograph Mouse Test-system.

Substance tested	Dose per injection (mg/kg)	Tumour regression %
Caesium *cis*-dichloro-*L*-serinatoplatinum(II)	75 [a,c]	89
	37.5 [a,c]	43
	100 [b,c]	84
	50 [b,c]	0
	25 [b,c]	0
	12.5 [b,c]	8

The substance was dissolved in water and administered intraperitoneally. [a]Female mice used. [b]Male mice used. [c]A total of three injections were given.

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given in Table II. According to the NCI evaluation, a compound is judged active if it produces tumour regression greater than or equal to 80%. On the basis of the results shown in Table II, caesium *cis*-dichloro-*L*-serinatoplatinum(II) is active in the MBG5 test-system.

The well-known anticancer agent, *cis*-diammine-dichloplatinum(II) (cisplatin) shows an increase in lifespan of about 180% in the P388 test-system. Cisplatin is, therefore, considerably more active than the amino acid complexes described above. However, the data recorded in Table I are in agreement with our previously published results with mixtures [3, 4]. Unfortunately, we have been unable to prepare a pure 1:1 platinum(II) complex of *L*-glutamine.

By contrast with the activity shown by caesium *cis*-dichloro-*L*-serinatoplatinum(II) the NCI found the analogous palladium(II) complex, caesium *cis*-dichloro-*L*-serinatopalladium(II) [11], to be inactive in the P388 test-system. We reported that bis(*L*-glutaminato)copper(II) shows significant cytotoxicity in the KB cell-culture test-system [12]. Treshchalina and coworkers [13] investigated several mixed coordination compounds of copper(II) with amino acids as potential antineoplastic agents. All the substances showed antitumour activity in an adenocarcinoma of the mammary gland (strain AK-755) test-system and also in a cancer of the cervix of the uterus (strain RShM-5) test-system. The compound which contained *L*-serine and glycine ligands was judged to be the most effective of the copper(II) chelates [13].

Experimental

Caesium cis-*dichloro*-L-*serinatoplatinum(II)*

A mixture of *L*-serine (2.1 g) and potassium tetrachloroplatinate(II) (4.2 g) in water (60 cm^3) was heated 5 h on a boiling waterbath. Absolute ethanol (300 cm^3) was added to the filtered reaction mixture, and the yellow precipitate (2.0 g) was filtered off. The product was reprecipitated from water (10 cm^3) with ethanol (40 cm^3). A dark yellow caesium salt (1.8 g) precipitated on adding excess caesium chloride to a solution of the potassium salt (1.8 g) in water (10 cm^3). The caesium complex was purified by recrystallization from water (yield 1.1 g). *Anal.* Found: C, 7.34; H, 1.33; Cl, 14.3; N, 2.99. Calcd. for $C_3H_6Cl_2NO_3Pt$ Cs: C, 7.16; H, 1.20; Cl, 14.1; N, 2.78%.

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