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Cisplatin, a platinum-containing antineoplastic drug: perspectives on analytical chemistry and prevention of ototoxicity

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ABSTRACT

The platinum-containing drug cisplatin plays a key role in the curative and palliative treatment of many solid malignancies. Unfortunately, the treatment can lead to sensorineural hearing loss, which limits the use of the drug. High single and cumulative dose levels are risk factors, but there is a large interindividual variability in the susceptibility to the ototoxic effects. The mechanisms behind the ototoxicity have not been fully elucidated, but one hallmark is oxidative stress. Moreover, the ototoxicity is dependent on the exposure of cisplatin and/or its biotransformation product MHC in the perilymphatic compartment of the cochlea. The aim of the research presented in this thesis was to contribute to the development of treatment strategies against cisplatin-induced ototoxicity.

Sulfur-containing nucleophiles are attractive candidate compounds against cisplatin-induced hearing loss since they are prone to chemically interact with cisplatin and MHC and could potentially reduce the exposure of these platinum species in the cochlea. A second possible mechanism may be relief of oxidative stress. The aim of the *in vitro* study described in Paper I was to investigate how quickly the concentrations of cisplatin and MHC can be reduced in the presence of five sulfur-containing nucleophiles. The results showed that thiosulfate was a promising candidate for future studies *in vivo*, since it reacted fast with cisplatin and, in particular, with MHC. This conclusion was further supported by the fact that thiosulfate is an endogenous ion, is well tolerated, and has been used clinically for decades against e.g. cyanide poisoning.

Systemic administration of thiosulfate has earlier been investigated in several *in vitro* and *in vivo* studies against cisplatin-induced ototoxicity. However, it has been unknown whether thiosulfate at all reaches the cochlea. In the study described in Paper II, it was demonstrated that the distribution of thiosulfate to the perilymphatic compartment was quick and extensive after an i.v. bolus injection in guinea pigs. Unfortunately, this way of administration of thiosulfate in connection with systemic cisplatin delivery is risky, since it may lead to decreased antitumoral effects due to inactivation of cisplatin and MHC not only in the cochlea but also in tumor tissues. In the studies on which Paper III is based, it was found that the ototoxicity in cisplatin-treated guinea pigs was reduced by a local administration strategy employing a thiosulfate-containing hyaluronan gel administered into the middle ear cavity three hours prior to the systemic cisplatin injection.

When quantifying cisplatin, unselective methods are almost always used, which may confound the results. In the final study, on which Paper IV is based, a sensitive, robust, and fast method using liquid chromatography and UV detection for the selective analysis of cisplatin in blood was developed. This method will be a valuable instrument in future studies exploring the role of pharmacokinetic parameters of cisplatin for the ototoxic effects.

Keywords: cisplatin, liquid chromatography, local administration, ototoxicity, perilymph, thiosulfate

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