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Cisplatin

Updated: January 20, 2014.

OVERVIEW

Introduction

Cisplatin is the prototype platinum coordination complex classified as an alkylating agent and used intravenously in the treatment of several forms of cancer. Cisplatin has been associated with a low rate of serum enzyme elevations and with rare cases of clinically apparent, acute liver injury.

Background

Cisplatin (sis pla' tin) was the first chemotherapeutic agent of its subclass to be discovered. It is an inorganic, water soluble complex containing a central platinum atom surrounded by 2 chlorine atoms and ammonia moieties in the cis position in the horizontal plane. Cisplatin forms irreversible covalent links with DNA, causing cross linking of DNA chains as well as breaks in the DNA chain and missense mutations. The DNA injury triggers cell death and inhibits RNA and protein synthesis, particularly in rapidly dividing cells. Cisplatin has activity against multiple tumor types and was approved for use by the United States in 1978. Current indications include testicular, ovarian and bladder cancer. It is also used in combination with other agents in head and neck, breast, lung and colon cancer. Cisplatin is administered parenterally and is available in 50 and 100 mg vials in generic forms and under the brand name Platinol. The recommended dose varies by indication, tumor type, patient age and body weight. Common side effects include nausea, vomiting, bone marrow suppression, electrolyte imbalance, neuropathy, ototoxicity and nephrotoxicity. Cisplatin is mutagenic, teratogenic and carcinogenic and its use has been show to increase the risk of secondary malignancies, particularly leukemia.

Hepatotoxicity

The platinum compounds generally are not considered to be hepatotoxic, but cisplatin has been associated with a low rate of serum enzyme elevations during therapy. These elevations are usually mild, self limited and asymptomatic, rarely requiring dose modification. There have been only rare case reports of clinically apparent liver injury attributed to cisplatin. In one instance, steatosis and necrosis (steatohepatitis) was found by liver biopsy in a patient who developed liver enzyme elevations 4 weeks after starting a regimen of cisplatin. In another instance, hepatocellular liver injury was described. The number of cases of liver injury attributed to cisplatin have been too few to characterize the liver injury clinically. Autoimmune and immunoallergic features have not been described and cases have all been self limited.

Mechanism of Injury

The cause of hepatotoxicity from cisplatin is not known. There have been extremely few cases of cisplatin induced hepatotoxicity described and generally, the platinum cordination complexes have not been considered

to be hepatotoxic. Recently however, oxaliplatin when given in multiple courses has been linked to development of nodular regenerative hyperplasia and non-cirrhotic portal hypertension.

Outcome and Management

Liver injury from cisplatin is rare and when it does occur, the severity in published cases was generally mild and the outcome benign. There is likely to be cross sensitivity to liver toxicities of the various platinum coordination complexes and rechallenge should be avoided.

References to the hepatotoxicity of carboplatin, cisplatin and oxaliplatin are given after the Overview section on Platinum Coordination Complexes.

Drug Class: Antineoplastic Agents, Alkylating Agents, Platinum Coordination Complexes: Carboplatin, Oxaliplatin

CASE REPORT

Case 1. 47 year old man with acute liver toxicity following cisplatin therapy.

[Modified from: Cavalli F, Tschopp L, Sonntag RW, Zimmermann A. A case of liver toxicity following cis-dichlorodiammineplatinum (II) treatment. Cancer Treat Rep 1978; 62: 2125-6. PubMed Citation]

A 47 year old man with bladder carcinoma developed jaundice 4 weeks after a single infusion of cisplatin given as adjuvant chemotherapy. The patient had no history of liver disease, alcohol abuse, risk factors for viral hepatitis or previous drug allergies. On examination, he was jaundiced, but without fever, rash or lymphadenopathy. The serum bilirubin was minimally elevated at 2.2 mg/dL and AST 58 U/L with alkaline phosphatase twice the upper limit of the normal range. Tests for hepatitis B were normal as was imaging of the gall bladder. His serum bilirubin returned to normal and he received another dose of cisplatin but developed similar abnormalities, detected one month later. After the fifth course of cisplatin, serum bilirubin levels rose to 9.8 mg/mL, AST 144 U/L and alkaline phosphatase twice normal. A liver biopsy showed steatosis, hepatocellular ballooning necrosis and mild cholestasis. The liver test abnormalities quickly resolved and he remained asymptomatic and without evidence of recurrent carcinoma 6 months later.

Key Points

Medication:	Cisplatin
Pattern:	Cholestatic (R=~1.0)
Severity:	2+ (jaundice, not requiring hospitalization)
Latency:	2-4 weeks
Recovery:	4 weeks
Other medications:	Furosemide 40-80 mg intravenously with each infusion of cisplatin

Comment

A distinctly unusual form of drug induced liver injury marked by recurrent cholestasis without symptoms or severe injury, possibly due to an idiosyncrasy of cisplatin metabolism leading to cholestatic injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Cisplatin – Generic, Platinol®

DRUG CLASS

Antineoplastic Agents, Alkylating Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Cisplatin	15663-27-1	C12-H6-N2-Pt