

Cisplatin induced arrhythmia; electrolyte imbalance or disturbance of the SA node?

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Abstract

Since its approval in 1979 cisplatin has become one of the most extensively used chemotherapeutics in the clinic and although cell resistance and toxicity hinder its efficacy it continues to be a gold standard regimen. Cisplatin's side effects primarily include nephrotoxicity, gastrointestinal toxicity, neurotoxicity and ototoxicity. Cardiotoxicity is generally not defined as a side effect of cisplatin. However, over the past decade there has been a surge in the amount of clinical cases reporting a vast array of cardio-toxic events occurring during or shortly after cisplatin infusion, these range from angina to cardiac ischemia and chronic heart failure. This review intends to discuss the clinical cardiac manifestations of cisplatin specifically tachycardia and bradycardia which can be lethal and the possible mechanisms of action.

Keywords: Cisplatin; cardiotoxicity; arrhythmia; platinum; chemotherapy.

1. Introduction

The chemotherapeutic drug cisplatin (*cis*-diamminedichloroplatinum II) is one of the most extensively used drugs in the treatment of cancer. It was the first metal-based drug to enter clinical trials in 1972 and first to be used in the clinic in 1979 (Wheate et al., 2010). Cisplatin is now a gold standard drug in the treatment of testicular cancer in which it has a 90% cure rate and is used in the treatment of head and neck, cervical, breast, lung, ovarian, gastric, and bladder cancers amongst many more (Wheate et al., 2010, ; Kelland., 2007; Jamieson et al., 1999; Dasari et al., 2014)

Cisplatin exerts its anti-tumour activity through its alkylating properties. Once it enters the cytoplasm of a cell, where the chloride concentration is much lower than that of the blood (~20 mM vs ~ 100 mM), it spontaneously and sequentially replaces its chloride ligands with water molecules (Wheate et al., 2010). This results in the formation of a positively charged bis-aquated platinum complex that is now able to bind to DNA (Dasari et al., 2014; Siddik, 2003). Cisplatin predominantly forms intrastrand adducts between two adjacent guanines followed by an adjacent guanine and adenine. These adducts cause the DNA helix to bend by up to 60% towards the major groove and unwind by 23° therefore inhibiting further DNA replication and transcription and ultimately leading to cell death (Wheate et al., 2010; Dasari et al., 2014; Siddik, 2003).

The success of cisplatin in the clinic is hindered by two major limitations: the development of cisplatin resistant cancer cells and cisplatin's toxic side effects. When cells become resistant to cisplatin, the dose of cisplatin administered to the patient is increased, which in turn increases the level of its toxic side effects (Siddik, 2003). Cisplatin is primarily associated with nephrotoxicity; its dose limiting side effect, neurotoxicity and ototoxicity (Wheate et al., 2010; Jamieson et al., 1999). Other common side effects include: severe nausea, vomiting, gastrotoxicity and myelosuppression (Wheate et al., 2010; Jamieson et al., 1999).

Cardiotoxicity is generally not defined as a common side effect of cisplatin. However, over the past decade there has been a surge in the amount of clinical cases reporting a vast array of cardio-toxic events occurring during or shortly after cisplatin infusion (Patane, 2014; El-Awady et al., 2011). These include silent and symptomatic arrhythmias, angina, myocarditis, pericarditis, diastolic disturbances, cardiac ischemia, acute myocardial infarction, thromboembolic events, and chronic heart failure (CHF). The mechanisms of

action of cisplatin's cardiotoxic activity is still unknown and yet to be identified (Patane, 2014; El-Awady et al., 2011).

It is highly important to note that cisplatin infusion is routinely not administered under cardiac monitoring compared to other drugs (such as the anthracyclines) and thus cisplatin induced cardiotoxicity particularly those that occur silently may go undetected and thus the cardiotoxic effects of cisplatin may well be overlooked and underreported. Furthermore, platinum can be found in the plasma of patients twenty years after completion of chemotherapy which can lead to long term side effects or toxicity that develops years after completion of chemotherapy (Gerl, 2000). Therefore the cardiotoxic manifestations of cisplatin is an important issue that needs to be addressed and understood.

2. Cisplatin and Arrhythmia

Arrhythmia is cisplatin's most commonly reported cardiotoxic event occurring in the form of tachycardia; supraventricular tachycardia, ventricular arrhythmia, atrial fibrillation (AF), bradycardia; sinus bradycardia, bundle branch block and complete atrioventricular block with most occurring silently and in some cases being lethal (Connobio et al., 1986; Raja et al., 2013). Tachycardia is the most frequent type of arrhythmia to occur with cisplatin administration followed by bradycardia.

2.1. Tachycardia

Tachycardia which can also be referred to as tachyarrhythmia is defined as a heart rate that exceeds the normal resting range of 60 – 100 beats per minute (for an adult) (Menard et al., 1991). In the clinical cases identified in which tachycardia was reported, the majority of patients were receiving a combination of intravenous cisplatin and etoposide to treat various cancers (Raja et al., 2013; Tassinari et al., 1997; Yavas et al., 2008; Fassio et al., 1986). In some cases, tachycardia (130 – 230 bpm) was reported to have developed within a few minutes of cisplatin infusion in the first cycle of chemotherapy as well as in each consecutive cycle, while in others it developed on other days in the first, second or sixth cycle (Raja et al., 2013; Tassinari et al., 1997; Yavas et al., 2008; Fassio et al., 1986). All patients had no underlying cardiac illness and tachycardia was identified only as a result of patient's complaints of chest pain, dyspnea and palpitations that resulted in electrocardiogram's (ECG) and electrolyte serum values evaluated. During the tachycardia episodes patient's blood samples were collected and their urea, creatine, sodium (Na), potassium (K), calcium (Ca), chloride (Cl) and magnesium (Mg) electrolyte

concentrations analysed. Results found that the only significant change in some cases was the level of Mg in which it was reduced to 1.2 – 1.6 mg/dl (normal range of 1.7-2.2 mg/dl.) and in a few cases a reduction of both Mg and K levels were described (Tassinari et al., 1997; Yavas et al., 2008; Fassio et al., 1986). In a report by Tassinari *et al*, a 68 year old patient receiving intravenous 100 mg/m² cisplatin plus 100 mg/m² etoposide for the treatment of stage III B non-small cell lung cancer (NSCLC) complained of palpitations immediately after cisplatin infusion on day one of the first cycle (Tassinari et al., 1997). ECG showed rapid AF with a ventricular rate of 160-200 bpm [14]. Blood analysis showed no significant changes in serum electrolyte levels (Tassinari et al., 1997). A reduction of the patient's cardiac rate to 110 bpm was achieved with intravenous propafenone and return to sinus rhythm was achieved after 48 hours (Tassinari et al., 1997). The patient refused to continue chemotherapy (Tassinari et al., 1997). In another case, a 66 year old patient whom was formerly treated with five courses of 100 mg/m² cisplatin plus 100 mg/m² etoposide also for the treatment of NSCLC complained of palpitations and difficulty in breathing after cisplatin infusion on day one of the sixth cycle (Yavas et al., 2008) ECG showed rapid AF with a ventricular rate of 210 bpm, the patient's serum urea, K, Ca and Cl levels were normal whereas serum Mg levels were reduced to 1.2 mg/dl (Yavas et al., 2008). Return to sinus rhythm was achieved after 48 hours with intravenous propafenone plus intravenous magnesium sulphate (Yavas et al., 2008). Bashir *et al* reported a 26 years old patient that developed chronic hypomagnesaemia and hypokalaemia following cisplatin treatment, the patient suffered a brief asystolic episode for 15-20 sec in which normal sinus rhythm returned spontaneously without any intervention (Bashir et al., 2007). In another case reported by Pastorino *et al*, a 37 year old patient receiving combination treatment of 20 mg/m² cisplatin, 100 mg/m² etoposide, and 30 mg of bleomycin for the treatment of testicular cancer developed AF after cisplatin infusion and before etoposide infusion (Pastorino et al., 2016). Low Mg serum levels was found to be the only parameter below the normal level despite receiving diluted Mg in saline pre-treatment (Pastorino et al., 2016).

2.1.1. Hypomagnesaemia Induced by Cisplatin and its Role in Cardiotoxicity

Hypomagnesaemia (Mg serum levels less than 1.7 mg/dl) is a well-known complication of cisplatin treatment (Lager and Daugaard, 1999; Glaudemans et al., 2010; Daugaard and Abildgaard, 1989). Studies have shown that cisplatin induces hypomagnesaemia through its nephrotoxic properties by direct injury to the mechanisms of Mg reabsorption specifically in the renal distal convoluted tubule (DCT). The DCT plays an essential role in maintaining systemic Mg concentration. It is the final determinant of plasma Mg levels

as the more distal nephron segments are impermeable to Mg (Glaudemans et al., 2010; Daugaard and Abildgaard, 1989; Bell et al., 1985). The main mechanism in which cisplatin causes injury is still unknown but believed to include disturbances at the melastatin receptor, the voltage gated K channel and epidermal growth factor protein (Daugaard and Abildgaard, 1989; Bell et al., 1985). The reported incidence of patients developing hypomagnesaemia at some point during cisplatin treatment varies between 40-100% dependant on the course schedule and dosage (Lager and Daugaard, 1999). Buckley *et al* reported that the incidence of hypomagnesaemia in patients receiving 50 mg/m² of cisplatin was found to increase from 41% after the first course of treatment to 100% in patients receiving six courses of chemotherapy (Buckley et al., 1984). Bell *et al* studied patients receiving different regimens of cisplatin and found that all patients developed hypomagnesaemia after four courses of chemotherapy irrespective of the dosage taken (50-100 mg/m²) (Bell et al., 1985).

The clinical manifestations of Mg deficiency include neuromuscular abnormalities such as tremor and ataxia, psychiatric disturbances such as confusion and hallucinations, and cardiotoxicity such as ECG changes (including changes in QT intervals) and arrhythmias (Lager and Daugaard, 1999; Buckley et al., 1984; Afus and Agus, 2001; Douban et al., 1996). Reports of cardiotoxicity developing as a result of hypomagnesemia are not as common, however there is sufficient *in vivo* evidence to suggest a correlation. In a study conducted by Fiset *et al*, the correlation between hypomagnesaemia and cardiac death was studied in rats (Fiset et al., 1996). Results found that 80% of the hypomagnesaemia rats suffered -episodes of bradycardia and tachycardia compared to the control group in which 0% showed any cardiac adversity (Fiset et al., 1996). As well as this, 36% of rats in the hypomagneseamic group suffered sudden unexpected asystolic death compared to 0% in the control group (Fiset et al., 1996). In a study by Yusuf *et al*, tachycardia was the prime manifestation of Mg depletion in experimental animals followed by bradycardia (Afus et al., 2001). In a clinical study by Oladapo *et al*, the occurrence of arrhythmia in relation to Mg serum concentrations in CHF patients was studied (Douban et al., 1996). Results showed that in the CHF arm patients that suffered arrhythmias had a significantly lower serum Mg concentration compared to the CHF arm that did not suffer a form of arrhythmia (Douban et al., 1996). Furthermore, there are a number of clinical cases which report the association between magnesium deficiency and sudden cardiac death in humans (Efstratiadis et al., 2006). However in some cases there has been no clear cause and direct relation as there may have been other potential confounders (Efstratiadis et al., 2006).

There are only a few clinical cases published that link cisplatin induced hypomagnesemia with cardiac dysrhythmias as discussed above. However, it is important to note that the exact time taken for the development of hypomagnesemia was not investigated in any of the reported clinical cases. Furthermore, there is no mention that patient's Mg serum levels were within normal range before initiation of cisplatin therapy. Therefore it is difficult to suggest that hypomagnesemia is the sole reason to tachycardia, especially in cases in which tachycardia developed within minutes of cisplatin infusion as hypomagnesemia can take longer to develop.

Interestingly, in other cases, arrhythmia has been reported to develop with cisplatin infusion independent of serum electrolyte levels suggesting that another mechanism of action is in play (Yavas et al., 2008). In a study by Yavas *et al*, patients receiving 20-100 mg/m² of cisplatin plus etoposide for treatment of various cancers underwent intensive cardiac monitoring. Results showed that 67% of patients had asymptomatic supraventricular or ventricular arrhythmia during the infusion period with no changes to blood pressure or serum electrolyte values including that of Mg (Yavas et al., 2008). The only significant change found was an increase in the length of QT dispersion that indicated a delay in repolarization (Yavas et al., 2008). It was suggested that cisplatin may have induced arrhythmias in these cases by affecting cardiac sodium channels (Yavas et al., 2008). However, these two changes can occur independently; it is possible for QT lengthening to occur without increased dispersion and vice versa.

Evidently there is conflicting results as to whether hypomagnesemia alone is a cause of tachycardia. To answer this question it is important to investigate the correlation between the development of hypomagnesemia and occurrence of rhythm disturbances. Furthermore, the effect of Mg supplementation before or after cisplatin treatment on the occurrence of rhythm disturbances may also provide some critical answers. Currently there is no published data on this topic.

2.2. Bradycardia

At the other end of the arrhythmic spectrum, cisplatin has also been reported to induce bradycardia (slow heart rate of below 60 bpm) (Kucharz et al., 2016). In the clinical cases identified bradycardia was reported to occur during or shortly after cisplatin infusion with no disturbances detected in patient's serum electrolyte concentrations or in blood pressure or other physical examinations. Furthermore, in the majority of cases reported bradycardia resolved on its own without any treatment. In a report by Kucharz *et al*, a 58

year old patient was found to suffer from recurring bradycardia after cisplatin infusion in each of the three cycles of chemotherapy (Kucharz et al., 2016). The patient was receiving 25 mg/m² cisplatin and 100 mg/m² etoposide and following the initial 48 h of the first cycle of chemotherapy exhibited resting dyspnea, chest discomfort and was found to be suffering from severe symptomatic bradycardia (Kucharz et al., 2016). The patient was found to have a heart rate reduction to 40 bpm and was treated with intravenous atropine which aided in raising the patient's heart rate to ~ 70 bpm (Kucharz et al., 2016). These episodes of bradycardia (~ 40 bpm) were observed again during the second and third treatment cycles (Kucharz et al., 2016). The patient was found to have no significant changes in serum electrolyte concentrations (Kucharz et al., 2016). In another case reported by Darling, a 15 year old patient receiving salvage combination treatment of cisplatin, bleomycin and methotrexate for the treatment of bony and distant lymph nodal metastases was incidentally found to have asymptomatic sinus bradycardia (heart rate of 38 bpm) post cisplatin hydration on the first day of chemotherapy (Darling, 2015). The patient exhibited no nausea or vomiting and physical examinations including blood pressure were within normal limits as were serum electrolyte levels (Darling, 2015). The patient's heart rate returned to normal after six hours without any intervention (Darling, 2015). On the following second day of treatment, the patient received cisplatin infusion at a slower cautious rate under intensive cardiac monitoring (Darling, 2015). The patient was found to exhibit asymptomatic bradycardia again after 30 minutes of cisplatin treatment with heart rate returning to normal after 24 h (Darling, 2015). The patient continued to suffer from asymptomatic bradycardia during and after cisplatin infusion on the following three days of chemotherapy (Darling, 2015). Cabuk *et al* also reported a patient that exhibited recurrent asymptomatic bradycardia (40 bpm) during cisplatin infusion (Cabuk et al., 2013). The patient's blood pressure and serum electrolyte levels were also within normal limits (Cabuk et al., 2013). In two other different cases reported by Schlaffer *et al* and Altundag *et al*, asymptomatic bradycardia was observed in patients receiving cisplatin chemotherapy and again there were no disturbances to the patient's serum electrolyte concentrations (Schlaeffler et al., 1983; Altundag and Kars, 2001).

The mechanism of action in which cisplatin induces bradycardia has still not been identified. However it has been hypothesised to occur as a result of disposition of cisplatin at the SA node which may cause disruption in the electrical conduction system of the heart (Kucharz et al., 2016; Darling, 2015; Cabuk et al., 2013).

2.2.1. Cisplatin and the SA Node

There is no published data in which the direct effect of cisplatin on the SA node has been studied. However, the inotropic effect of cisplatin on heart atria has been investigated (Oun et al., 2014). In this *ex vivo* electrophysiological study, both rat right and left atria were incubated with cisplatin and changes to the rate and force of atria contraction were recorded at specific intervals over a two hour period (Oun et al., 2014). Results showed that by the end of the two hours, cisplatin had significantly reduced the right atria's rate and force of contraction by 69% and 54% respectively (Oun et al., 2014). However, in the left atria, cisplatin induced no significant changes in the rate of contraction and had decreased the force of contraction by 55% (Oun et al., 2014). Furthermore, when cisplatin was encapsulated within a drug delivery system, cucurbit[7]uril, the cardiotoxic effect of cisplatin on the right atria was significantly reduced by 58% (Oun et al., 2014). Therefore, due to cisplatin's significant changes on the right atria which were absent on the left atria, the authors hypothesised that cisplatin may have induced these bradycardia events by acting on the SA node (Oun et al., 2014). However these results alone are not sufficient to confirm that cisplatin does interfere with the SA node and that this is the mode of action of cisplatin's bradycardia effects. Further investigation is essential, in particular it would be of interest to study the effect of cisplatin on the action of the spontaneous diastolic depolarization phase of the sinoatrial cells.

3. Conclusion

There is a number of clinical and lab-based data that strongly portray cisplatin as a cardiotoxic agent. Whether cisplatin induces its cardiotoxic activity directly on the heart or indirectly through its nephrotoxic properties is a matter that still needs to be identified. The significance of electrolyte imbalance induced by cisplatin, particularly that of Mg is regarded as an important factor to its cardiotoxic activity. However, the difficulty in measuring intracellular concentrations of Mg as well as the fact that serum Mg levels represents only <1% of total body Mg storage puts the theory to debate. Furthermore, it is possible that the intensive saline hydration and the use of mannitol during cisplatin treatment (to decrease the risk of nephrotoxicity) may play a part in decreasing Mg proximal reabsorption.

Due to the severity of its asymptomatic arrhythmic potential it is important that cisplatin infusion is administered under cardiac monitoring especially with patients suffering with cardiac problems or whom have a history of cardiac complications.

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