

CARDIOTOXICITY OF PALLADIUM COMPOUNDS

KARDIOTOKSIČNOST JEDINJENJA PALADIJUMA

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Summary: Previous studies have shown that palladium has toxic effects on the kidney and liver, leads to deterioration of the general condition of animals, and could cause allergy in animals and humans. Considering the limited data about the influence of palladium on the cardiovascular system, the aim of our study was to evaluate the effects of palladium on the heart from available published data, and to compare the toxicity of inorganic and organic palladium compounds. Relevant studies for our review were identified from PubMed and Scopus databases. The search terms included »palladium«, »palladium compound«, »cardiotoxicity«, »toxicity«, »heart«, »myocardium«, »oxidative stress« and »myocardial enzyme«, as well as combinations of these terms. There were only two published studies with the primary purpose to investigate the effect of palladium on the cardiovascular system, while others registered the side-effects of palladium compounds on the heart. Palladium could cause arrhythmias, a drop in blood pressure, decrease of the heart rate, as well as death of experimental animals. Based on the presented data it seems that palladium does not express significant cardiac toxicity when it is bound in an organic compound. Further investigation of the effects of palladium on the heart is necessary for a clear picture of the nature and extent of its cardiac toxicity.

Key words: palladium, palladium compound, toxicity, cardiotoxicity, oxidative damage

Kratak sadržaj: Prethodne studije su pokazale da paladijum ispoljava toksično dejstvo na bubrege i jetru, dovodi do poremećaja opšteg stanja životinje i može izazvati alergiju kod životinja i ljudi. Uzimajući u obzir ograničeni broj podataka o uticaju paladijuma na kardiovaskularni sistem, cilj ove studije bio je da se proceni efekat paladijuma na srce na osnovu dostupnih podataka i uporedi toksičnost neorganskih i organskih jedinjenja paladijuma. Relevantne studije za ovaj pregled identifikovane su iz baza podataka »PubMed« i »Scopus«. Termini za pretragu su obuhvatili »palladium«, »palladium compound«, »cardiotoxicity«, »toxicity«, »heart«, »myocardium«, »oxidative stress« i »myocardial enzyme«, kao i kombinacije ovih termina. Postoje samo dve objavljene studije čiji je primarni cilj bio ispitivanje efekta paladijuma na kardiovaskularni sistem, dok su u ostalim registrovani propratni efekti jedinjenja paladijuma na srce. Paladijum može izazvati aritmiju, pad krvnog pritiska, smanjenje srčane frekvence, kao i smrt eksperimentalnih životinja. Na osnovu iznetih podataka čini se da paladijum ne pokazuje značajnu kardiotoksičnost kada je vezan u formi organskog jedinjenja. Potrebna su dalja istraživanja efekata paladijuma na srce da bi se dobila jasna slika o prirodi i obimu njegove kardiotoksičnosti.

Cljučne reči: paladijum, jedinjenja paladijuma, toksičnost, kardiotoksičnost, oksidativno oštećenje

Introduction

Palladium (Pd) is a lustrous, silvery-white, heavy metal belonging to the platinum group of elements (PGMs). The presence of palladium and other PGMs in the Earth's crust is small (<1 µg/kg) (1). It is obtained as a by-product of nickel, copper and other base metals refining. Numerous unsuccessful attempts at using different palladium compounds for treating tuberculosis (2), gout, obesity (3) and dermatological diseases (2) were made in the past.

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Nowadays, Pd¹⁰³ is used in oncology, in brachytherapy for prostate cancer (4–6) and ocular melanoma (7–9). The latest research indicated that some palladium complexes were effective in the treatment of non-small-cell lung cancer (10), breast cancer (11, 12) and ovarian cancer (13).

Little is known about the toxicity of palladium and its compounds. Previous studies conducted on rats and rabbits have shown that palladium has toxic effects on the kidney (14, 15), liver (16, 17), produces deterioration of the general condition of experimental animals (2, 18) and could cause allergy in animals (14, 19–21) and humans (22–26). Clinical signs of acute poisoning include death, tonic and clonic convulsions, ataxia, tiptoe gait, reduced intake of food and water, weakness and abdominal distension in animals (2, 18). Also, PdCl₂ caused testicular necrosis and destruction of all spermatozoa in mice (27) while its teratogenicity was not proven (28). On the other hand, studies of acute and chronic toxicity in rats and rabbits did not show specific histopathological or other toxic effects of palladium on the heart (29–31).

Considering the limited data about the influence of palladium on the cardiovascular system, the aim of our study was to evaluate the effects of palladium on the heart from available published data, and to compare the toxicity of inorganic and organic palladium compounds.

Material and Methods

Relevant studies for our review were identified from PubMed and Scopus databases (since 1975). The search terms included »palladium«, »palladium compound«, »cardiotoxicity«, »toxicity«, »heart«, »myocardium«, »oxidative stress« and »myocardial enzyme«, as well as combinations of these terms. We found 331 published papers which contained these terms. References from relevant original scientific research studies and literature reviews written in English and non-English languages were included. Unpublished and unsystematic studies were omitted.

Results

The number of studies which investigated the impact of palladium on the cardiovascular system is relatively small (Table I). Moreover, there are only two studies which were primarily designed to investigate this effect (32, 33), while two others only observed the side-effects of palladium compounds on the heart. In the first study, after intravenous administration of palladium to unanesthetized rats in the form of inorganic compounds (Pd(NO₃)₂, PdCl₂, (NH₄)₂PdCl₄, K₂PdCl₄ and PdSO₄), arrhythmias and decrease in blood pressure were observed, and some

of the animals died (32). In addition, Pd(NO₃)₂, PdCl₂ and PdSO₄ were three times more toxic than the bivalent compounds ((NH₄)₂PdCl₄ and K₂PdCl₄). In the second study, palladium (PdCl₂) caused a drop in diastolic (DLVP) and mean blood pressure (MBP) and decrease in the heart rate (HR) (33). On the contrary, the organic compound of palladium (*trans*-dichlorobis(triethanolamine-N)palladium(II) complex (*trans*-[PdCl₂(TEA)₂]) produced a limited decrease in the heart rate (33). In accordance with this finding, it appears that palladium does not express significant cardiac toxicity when it is bound in an organic compound. There are two more studies which observed rapid death of animals when PdCl₂ was given intravenously (2, 18). The mechanism of this toxic effect was not described, and the authors offered only speculations about the possible palladium-induced damage and disturbance of the heart.

On the other hand, some findings suggested that palladium α-lipoic acid (an organic form of palladium which is an ingredient of the food supplement »POLY-MVA«) has a protective effect on the heart, and might be useful in the prevention of cardiovascular and neurodegenerative diseases associated with aging (34, 35). In fact, the palladium complex significantly increased the activity of the main antioxidative mitochondrial enzymes in the myocardial cells of aged rats: the Krebs cycle enzymes (ICDH, α-KGDH, SDH and MDH), mitochondrial complexes I, III, and IV (34), catalase (CAT) and glutathione peroxidase (GPx); the level of reduced glutathione (GSH) (35) was also increased. Moreover, the antioxidant potential of the palladium α-lipoic acid complex was five times higher than that of alpha-lipoic acid itself (35).

The antioxidative effect of an organic palladium compound has been shown in another study, where *trans*-[PdCl₂(TEA)₂] decreased the index of TBARS (thiobarbituric acid reactive substances) (36). On the contrary, PdCl₂ did not affect significantly either NO, H₂O₂, O₂⁻ or TBARS. These findings further suggest that organic palladium compounds are less toxic than the inorganic ones.

Discussion

Studies of the distribution of palladium compounds in the tissues of rats, rabbits and dogs after intravenous or intratracheal administration indicated the highest percentage of retention in the kidneys and liver (8–21% of applied dosage), lymphatic nodes, adrenal glands, lungs and bones (37–40). Also, the retention period in some of the organs was up to 104 days long (37, 38). LD₅₀ of inorganic palladium compounds for rats, mice and rabbits ranged from 3 mg/kg to 4900 mg/kg (16, 38, 41). Oral administration of Pd showed the lowest toxicity compared to others due to the lowest bioavailability. The most toxic compound was palladium(II) chloride (PdCl₂), while

Table I Toxic effects of palladium on the cardiovascular system.

| Pd form | Experimental model/animal | Route | Dose ^a | Clinical signs and effects | Reference |
|---|---------------------------|---------------------------------|--|---|---------------------------|
| PdSO ₄ | unanesthetized rat (n=41) | Intravenous: bolus 0.5 ml | 0.4 ± 0.2 | Cardiac arrhythmias with concomitant decrease in blood pressure; abnormal ECG patterns, death of the animal. | Wiester MJ (1975) |
| Pd(NO ₃) ₂ | unanesthetized rat (n=9) | Intravenous: bolus 0.5 ml | 0.4 ± 0.2 | Cardiac arrhythmias with concomitant decrease in blood pressure; abnormal ECG patterns, death of the animal. | Wiester MJ (1975) |
| (NH ₄) ₂ PdCl ₄ | unanesthetized rat (n=21) | Intravenous: bolus 0.5 ml | 1.2 ± 0.3 | Cardiac arrhythmias with concomitant decrease in blood pressure; abnormal ECG patterns, death of the animal. | Wiester MJ (1975) |
| K ₂ PdCl ₄ | unanesthetized rat (n=8) | Intravenous: bolus 0.5 ml | 1.2 ± 0.3 | Cardiac arrhythmias with concomitant decrease in blood pressure; abnormal ECG patterns, death of the animal. | Wiester MJ (1975) |
| PdCl ₂ | unanesthetized rat (n=6) | Intravenous: bolus 0.5 ml | 0.4 ± 0.2 | Cardiac arrhythmias with concomitant decrease in blood pressure; abnormal ECG patterns, death of the animal. | Wiester MJ (1975) |
| PdCl ₂ | isolated rat heart (n=6) | Langendorff perfusion technique | 5.6 × 10 ⁻⁸ – 5.6 × 10 ^{-4b} | There was no effect on oxidative status (NO, TBARS, O ₂ ⁻ , H ₂ O ₂) on the isolated rat heart. | Živković V. et al. (2011) |
| PdCl ₂ | isolated rat heart (n=6) | Langendorff perfusion technique | 5.6 × 10 ⁻⁸ – 5.6 × 10 ^{-4b} | Decrease in DLVP, MBP and HR, without effects on dP/dt max and SLVP. | Perić T. et al. (2012) |
| Palladium α-lipoic acid complex (POLY-MVA) | rat (n=6) | Oral | 0.05 ^c | Administration of POLY-MVA significantly improved the antioxidant status in the heart mitochondria of aged rats. The Krebs cycle enzymes activities (ICDH, α-KGDH, SDH and MDH) and activities of complexes I, III, and IV significantly increased, compared to the aged control group. | Sudheesh NP et al. (2009) |
| Palladium α-lipoic acid complex (POLY-MVA) | rat (n=6) | Oral | 0.05 ^c | Administration of POLY-MVA significantly improved the antioxidant status in the heart mitochondria of aged rats (except Mn SOD activity). The activities of CAT, GPx and GSH increased in the POLY-MVA treated group, compared to the aged control group. | Sudheesh NP et al. (2010) |
| trans-[PdCl ₂ (TEA) ₂] | isolated rat heart (n=6) | Langendorff perfusion technique | 2.1 × 10 ⁻⁸ – 2.1 × 10 ^{-4b} | Decrease of TBARS, without effects on NO, O ₂ ⁻ and H ₂ O ₂ . | Živković V. et al. (2011) |
| trans-[PdCl ₂ (TEA) ₂] | isolated rat heart (n=6) | Langendorff perfusion technique | 2.1 × 10 ⁻⁸ – 2.1 × 10 ^{-4b} | Decrease of HR, without effects on dP/dt max, SLVP, DLVP and MBP. | Perić T. et al. (2012) |

^aThe mean dose of palladium, which caused mild effects, in mg/kg body weight, unless otherwise specified.

^bIncreasing concentrations of the heart perfusion for compound in M/l.

^cThe concentration of applied compound in ml/kg (which is equivalent to 0.38 mg α-lipoic acid complex/kg).

the least toxic compound was palladium(II) oxide (PdO) (42).

The mechanism of palladium toxicity is not understood yet. Some of the results suggest an association with changes of the membrane potential in myocardial cells (32). Recent research has shown that Pd(II) complexes have an affinity for binding with numerous ion channel proteins and enzymes, leading to disturbances in membrane potential and arrhythmias, decreased entry of calcium in cells, and decreased myocardial contractility (33). It seems that palladium interferes with thiol (SH) groups of membrane Na^+/K^+ ATPase (43, 44), Ca^{2+} Mg^{2+} dependent ATPase of the sarcoplasmic reticulum (45–47), and of some other important enzymes. Inhibition of these proteins could cause a disturbance of cardiac functioning.

Previous studies of palladium have indicated that its inorganic compounds in most cases have prooxidative effects (48, 49), emphasizing reactions with superoxide anion (O_2^-) and H_2O_2 . Reactive oxygen species-mediated DNA damage (50) and inhibition of DNA (51–54) and RNA synthesis (55) are important toxic effects of the palladium ion. Moreover, inhibition

of the main energetic enzyme in the cell, creatine kinase (CK) (29, 30), might reduce the amount of free energy in myocardial cells, which decreases the activity of Ca^{2+} ATPase and limits the calcium-binding capacity (56). It appears that palladium inhibits enzymes by binding with SH groups (29), or by substituting Fe^{2+} (57). Also, available data indicate that palladium inhibits some other cell enzymes: lactate dehydrogenase (LDH) (58), alkaline phosphatase (30, 59), aldolase, carbonic anhydrase (30), etc. These cytotoxic effects of the palladium ion could explain the depressant effect of palladium compounds on the heart.

Based on the presented data it is not certain whether organic palladium compounds are less toxic than the inorganic ones. Further investigation of the effects of palladium on the heart is necessary to get a clear picture of the nature and extent of its cardiac toxicity.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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