An Overview on Cardio-Protective Compound Dexrazoxane

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Abstract  Heart plays a vital role in the human life survival. Now a days the global burden of heart problems is very high. There is very high mortality rate. So in this review we aimed to explore the cardioprotective drug dexrazoxane. Now, dexrazoxane has received approval for two different uses: avoiding tissue damage after anthracycline extravasation and preventing cardiotoxicity during anthracycline-based chemotherapy. Regardless of existing cardiac risk factors, the medication seems to provide cardiac protection. Dexrazoxane is a bisdioxopiperazine with iron-chelating, chemoprotective, cardioprotective, and antineoplastic properties, according to the prior study. So this study suggests that the dexrazoxane will play very important role in the treatment of cardiac problems.

Keywords-  Dexrazoxane, Anthracycline, Cardiotoxicity, Cardiovascular Disease, Chemotherapy, Doxorubicin

Introduction

Dexrazoxane is a drug used to manage and treat extravasation damage and cardiotoxicity brought on by anthracyclines. (Eneh and Lekkala 2021) It belongs to the group of drugs called cardio protectants.(Štěrba, Popelová et al. 2013) Dexrazoxane, a helpful medication in the treatment of cardiotoxicity and anthracycline extravasation that results in tissue damage, is examined in this study's indications, mode of action, contraindications, adverse event profile, and other essential components. This will be essential for the interprofessional members' therapy of patients with anthracycline-induced cardiotoxicity, extravasation injuries, and related illnesses (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions).(Kreidieh, Moukadem et al. 2016)

Dexrazoxane which is a bisdioxopiperazine contains iron-chelating, cardioprotective, chemoprotective, and antineoplastic properties. Dexrazoxane chelates iron by preventing the production of anthracycline-iron complexes that can cause free radicals, which may minimise the oxidative damage caused by these complexes to soft tissues like the heart.(Rochette, Guenancia et al. 2015) After hydrolysis, this active form of dexrazoxane resembles
ethylenediaminetetraacetic acid (EDTA). Additionally, this substance prevents topoisomerase II from catalysing reactions, which may slow the growth of tumour cells.(Langer 2014)

Uses:

Dexrazoxane, an FDA-approved cardioprotective drug, has been used successfully to lessen cardiac toxicity in cancer chemotherapy patients who received anthracycline-based drugs (such as doxorubicin, daunorubicin, or epirubicin), particularly those with advanced breast cancer, adult patients with soft tissue sarcomas, or patients with small-cell lung cancer. It is administered intravenously together with the appropriate anthracycline to lower the prevalence of cardiomyopathy and congestive heart failure.(Langer 2014, Kreidieh, Moukadem et al. 2016)

FDA-approved signs:

1. Reduced incidence and severity of cardiac dysfunction associated with anthracycline usage.(Bloom, Hamo et al. 2016)

2. Tissue damage brought on by anthracyclines that leak from the vein while being injected can also be treated with dexrazoxane.(Eneh and Lekkala 2021)

FDA-unapproved indication:

Dexrazoxane's possible significance as a helpful neuroprotectant for treating Parkinson's disease patients' neurodegeneration is still being studied as of this writing.(Hellmann and Rhomberg 2010)

Mechanism of Action:

It is well established that anthracyclines can increase cytotoxicity in a number of ways, including by intercalating into nuclear DNA, generating reactive oxygen species, and inducing cell death by apoptosis.(Tacar, Sriamornsak et al. 2013, Shin, Song et al. 2020)

Dexrazoxane appears to minimise the cardiotoxicity brought on by anthracyclines by fusing with both free and bound iron, so decreasing the formation of anthracycline-iron complexes and, ultimately, the production of reactive oxygen species, which are harmful to the surrounding cardiac tissue.(McGowan, Chung et al. 2017, Renu, Abilash et al. 2018)

Bisdioxopiperazine is a class of chemicals that includes dexrazoxane. Dexrazoxane is ring contained and hydrophilic in contrast to its homolog ethylenediaminetetraacetic acid (EDTA), which chelates iron. But it diffuses into cells more easily than EDTA does. Dexrazoxane passes through chemical transformation to become a substance that resembles EDTA, a strong iron chelator. More iron is removed from the anthracycline during this process, which is likely to contribute to the cardiomyopathy associated with anthracyclines.(Jirkovská, Karabanovich et al. 2021)
In addition to acting as a DNA topoisomerase II inhibitor, dexrazoxane also targets DNA topoisomerase II anti-cancer drugs by preventing the development of the topoisomerase II cleavage complex and the rapid degradation of topoisomerase II beta. (such as the anthracyclines). (Bailly 2012)

However, unlike anthracyclines, dexrazoxane does not cause damaging breaks in DNA's double strands. (Goodenow, Emmanuel et al. 2020)

Dexrazoxane was also reported to promote cell survival and impose cardiac function protection by reducing cardiomyocyte necroptosis and apoptosis concurrently after treatment with doxorubicin via suppression of the p38MAPK/NF-B pathways. (Bing and Li 2016)

Administration:

Typically, a 15-minute intravenous infusion is used to provide the medication. It is not advised to use it as a push.

The dosage ratio for dexrazoxane and doxorubicin should be 10 to 1 (for instance, 500 mg/m2 of dexrazoxane to 50 mg/m2 of doxorubicin). Doxorubicin ought to be given after dexrazoxane. It is recommended to provide doxorubicin 30 minutes after the infusion of dexrazoxane is complete. (Kropp, Roti Roti et al. 2015)

15 minutes before doxorubicin, provide an intravenous infusion of a diluted dexrazoxane in lactated ringer's solution. Usually, doxorubicin is administered 30 minutes after dexrazoxane. Dexrazoxane should not be combined with non-anthracycline chemotherapy. (Kropp, Roti Roti et al. 2015)

Within six hours of extravasation, 1,000 mg/minute IV is the recommended dosage and rate for extravasation prophylaxis. This treatment is followed by doses of 1,000 mg/minute and 500 mg/minute after two and three days, respectively. (Eneh and Lekkala 2021)

People with renal or hepatic impairment receive medication in a different way. (Luks and Swenson 2008)

Dosage for people with impaired kidney function:

Dexrazoxane dosage for patients with moderate to severe renal impairment must be halved, resulting in a dexrazoxane to doxorubicin ratio of 5 to 1. (Kane, McGuinn Jr et al. 2008)

Dosing in Hepatic Impairment:

In order to maintain the 10 to 1 ratio while lowering the dose of doxorubicin in a patient with hyperbilirubinemia, a lower dose of dexrazoxane must be administered to this group of patients.

Only patients who have had dosages of epirubicin >550 mg/m2 or doxorubicin >300 mg/m2 and are still receiving anthracycline...
therapy are advised to utilise dexrazoxane. (Kane, McGuinn Jr et al. 2008)

Adverse Effects:

Similar to the side-effect profile of anthracyclines, dexrazoxane frequently results in dose-limiting myelotoxicity (neutropenia, leukopenia, granulocytopenia, and thrombocytopenia). The side effects of anthracycline chemotherapy and those brought on by the usage of dexrazoxane can therefore be difficult to discern from one another. In addition to these side effects, dexrazoxane should be administered through a large vein due to reactions at the injection site, such as pain, and superficial phlebitis. Other side effects include hair loss, mucositis, inconsistent increases in liver enzymes (alanine aminotransferase/aspartate aminotransferase), nausea, vomiting, increased renal excretion of iron and zinc, and mucositis. Research on mice also revealed damage to the foetus and male infertility. (Eneh and Lekkala 2021)

Recently, there have been concerns about the potential long-term effects of dexrazoxane in patients receiving doses meant to prevent cardiotoxicity, particularly in young patients. In two randomised studies, researchers discovered that, despite being very rare, the incidence of new primary malignancies (myelodysplastic syndrome and acute myeloid leukaemia) was three times greater in the dexrazoxane-treated patient group compared to the control group. (Kollárová-Brázdová, Jirkovská et al. 2020)

Warnings:

If either the mother or the father take this medication, dexrazoxane could harm the unborn child or result in birth problems.

Contraindications:

Dexrazoxane is categorised as a Category D medication by the FDA. (Blanusa, Varnai et al. 2005)

In a research on pregnant mice and rabbits, dexrazoxane administration led to toxicities in embryos and their mothers, as well as embryonal deformation, even at doses substantially lower than those clinically approved for use in humans. (Gianni, Herman et al. 2008)

Based on its impact on repeated dose toxicological research, dexrazoxane consumption may potentially result in infertility in males. (Vejpongs and Yeh 2014)

Monitoring:

There are currently no dexrazoxane monitoring standards in existence. However, this medicine causes the liver to produce more proteins than usual. Elevated liver function tests (LFT), such as high alkaline phosphatase and aspartate aminotransferase, can be used to detect this. Continuous liver enzyme monitoring may be necessary after dexrazoxane administration with the knowledge that the combination of dexrazoxane and doxorubicin would increase hepatic protein production more
than dexrazoxane alone would. (Herman and Ferrans 1998)

Toxicity:

Dexrazoxane experiments have not yielded any information on toxicity, and there is no published information on an antidote for reversal.

It is advised to use good supportive care while managing suspected overdoses. These interventions target areas including fluid management, nutritional requirement preservation, infection therapy, and control.

Conclusion

To avoid cardiac damage in patients getting chemotherapy based on anthracyclines, dexrazoxane is a helpful drug. It must be demonstrated whether it protects patients who received chemotherapy based on anthracyclines during infancy or adolescence from developing late-onset heart impairment. Further clinical experience is required to identify the appropriate treatment plan, show that it is a cost-effective option, and show that it does not adversely affect clinical outcome.
**Brief summary/Discussion**

| Mode of action | • Probably a prodrug that undergoes intracellular metabolization to produce a potent iron-chelating agent.  
  • It suppresses the development of the iron-doxorubicin complex and iron-mediated hydroxyl radicals that cause oxidative damage to cell membranes and proteins by chelating iron through its metabolites.  
  • Moreover, it might function by catalytically inhibiting topoisomerase II, which would counteract the effects of anthracyclines on DNA damage and cell proliferation. |
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<td>Properties of pharmacokinetics and metabolism</td>
<td>• Dexrazoxane is rapidly converted to the iron-chelating, rings-opened form ADR-925 after intravenous injection.</td>
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| Clinical and preclinical effectiveness | • Extremely effective at preventing mice models of anthracycline-induced subcutaneous lesions.  
  • Four case studies involving a total of five individuals who had doxorubicin or epirubicin extravasation have reported successful results.  
  • Clinical trials in Phase II/III are currently being conducted but have not yet been reported on. |
| Tolerability and Safety | • Dexrazoxane's safety and tolerability have been thoroughly proven in extensive clinical trials when used as a cardioprotective drug, so treating extravasation shouldn't be any different.  
  • Some cytotoxic medications' myelosuppressive effects may be marginally enhanced by dexrazoxane.. |
| Medication interactions | • According to data that indicates it interferes with 5-fluorouracil-doxorubicin-cyclophosphamide therapy, dexrazoxane is only recommended for patients in the USA who have already had a total doxorubicin dose of 300 mg/m2. |
| Administration and dosage | • No clinically ideal dose or schedule for treating anthracycline extravasation has been identified, but three patients have responded well to the intravenous dexrazoxane dosage schedule of 1000 mg/m2 on day 1, 1000 mg/m2 after 24 h on day 2, and 500 mg/m2 on day 3. This dosage schedule is currently being used in multicenter trials. |
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