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Research Article

Evaluation of cardiotoxicity of a new antitumor compound, anthrafuran, a derivative of anthracycline antibiotics

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Abstract

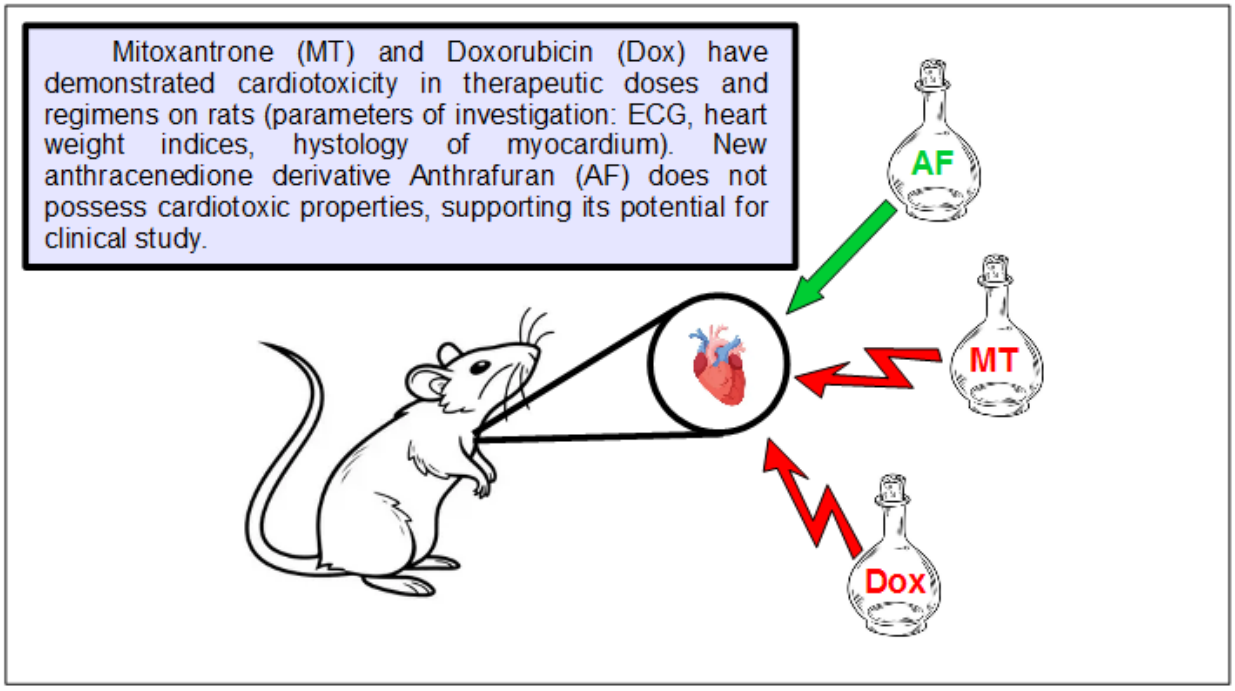
Introduction: Anthracyclines and anthracenedione derivatives are a group of anticancer drugs that are widely used in clinical practice. Their application is frequently limited by cardiotoxic effects. **The aim of this study** was to evaluate the cardiotoxicity of the new anthracenedione derivative Anthrafuran (AF) in comparison with Doxorubicin (Dox) and Mitoxantrone (MT).

Materials and Methods: The study was conducted on 50 adult female Wistar rats. AF, MT, and Dox were administered in therapeutic doses and regimens for this animal species (AF: 20 mg/kg x 3/48 per os; MT: 1 mg/kg x 3/96 i.v.; Dox: 2.5 mg/kg x 3/72 i.v.). Electrocardiographic (ECG) parameters and heart weight index were determined; histological evaluation of the myocardium was performed on days 1 and 30 post-treatment.

Results: Dox intravenous injections in therapeutic doses caused a pronounced cardiotoxic effect. The signs of cardiac decompensation manifested as a significant decrease in heart rate (HR) (Dox 486±6, control 522±12.8), prolongation of the QT interval (Dox 0.06±0.002, control 0.048±0.001), an increase in weight index of the heart (Dox 0.41±0.03, control 0.36±0.006), and myocardial damage. Although the cardiotoxicity of MT was less pronounced, it nevertheless negatively affected both ECG parameters (HR 465±15, QT 0.056±0.002) and the structure of the heart muscle. The use of AF did not cause any pathological changes and had no effect on the heart weight index or ECG parameters (HR 498±7.3, QT 0.052±0.003, weight index of the heart 0.35±0.009).

Conclusion: Unlike Dox (2.5 mg/kg x 3/72 i.v.) and MT (1 mg/kg x 3/96 i.v.), the new anthracenedione derivative AF (20 mg/kg x 3/48 per os) in therapeutic doses does not possess cardiotoxic properties, supporting its potential for clinical study.

Graphical Abstract



Keywords

anthracenediones; anthrafuran; antitumor compound; cardiotoxicity; doxorubicin; mitoxantrone; rats

Introduction

Anthracyclines are a crucial group of anticancer drugs used for the treatment of various malignant diseases (Maurer and Clayton 2023). Insufficient selectivity of action of tumor cells often limits their use. For instance, hematotoxicity significantly impacts treatment tolerance. Manifestations of hepato-, nephro-, and gastrointestinal toxicity are also frequently observed side effects in anthracycline antibiotic therapy (Johnson and Keyes 2024). Among the long-term side effects of application of drugs from this class, it is necessary to note the syndrome of cognitive dysfunction (Lehmann et al. 2016; Bayles et al. 2023) and the occurrence of secondary malignant tumors (Ben-Aharon et al. 2015). However, the most important dose-limiting type of toxicity for anthracyclines is cardiotoxicity (Bhagat and Kleinerman 2020; Dempke et al. 2023). The mechanism of this phenomenon is still not entirely clear. According to one theory, the death of cardiomyocytes is facilitated by the formation of reactive oxygen and nitrogen species. There is also an opinion that the development of toxic cardiomyopathy is associated with mitochondrial dysfunction induced by topoisomerase Top2β (Murabito et al. 2020; Wallace et al. 2020). Cardioprotectors are used to reduce the cardiotoxicity of anthracyclines, particularly of doxorubicin (Dox) as the most widely used drug of this class in clinical practice. These include dexrazoxane and protosappanin A. The drug binds to free and bound iron, preventing the formation of complexes and reactive oxygen species that destroy normal tissues (Eneh and Lekkala 2023; Cui et al. 2024). The development of new Dox formulations changes its delivery to target organs; in some cases, it helps reduce its toxicity and increase selectivity of action. Currently, liposomes, nanoparticles, and micelles are actively being researched for this purpose (Aloss and Hamar 2023). Several attempts have been made to modify and improve the structure of anthracyclines to reduce their cardiotoxicity. A key success was the development of mitoxantrone (MT), which has antitumor efficacy close to that of Dox but has a narrower spectrum of action (Evison et al. 2016). Chemically, this analogue of anthracyclines is a synthetic derivative of anthracenedione (Bu et al. 2020; Mattioli et al. 2023). The mechanism of action of MT does not differ significantly from that of antitumor antibiotics of the anthracycline group. It

also inhibits topoisomerase-II, disrupting DNA reparation and replication (Kciuk et al. 2023). The novel synthetic derivative of anthracenedione – anthrafuran (AF) – was developed at the Gause Institute of New Antibiotics (Shchekotikhin et al. 2016). Though it is chemically close to anthracycline antibiotics, the modification of structure changes significantly in the therapeutic characteristics of the compound. Furthermore, it has high activity *in vitro* against human cancer cells of different origins, including high potency against Dox-resistant subline and outstanding antitumor efficacy *in vivo*. The route of administration has also been changed. It was found that AF is highly effective when administered orally (Shchekotikhin et al. 2020).

The aim of this work was evaluation of the cardiotoxicity of AF, as well as morphological and physiological changes in the myocardium in comparison with Dox and MT for therapeutic doses and regimens.

Materials and Methods

The experiments were performed in accordance with the European Convention for the Protection of Vertebrate Animals ETS No. 170 and the National standard of the Russian Federation "The Principles of Good Laboratory Practice" (August 1, 2015).

Experimental animals

The study was conducted on 50 adult female Wistar rats obtained from the laboratory animal nursery of Scientific Center for Biomedical Technologies of the Federal Biomedical Agency (Moscow, Russia). The ethical aspects of animal experimentation were reviewed and approved by the local ethics committee of the Gause Institute of New Antibiotics, with protocol number 02/2024 dated September 16, 2024. The animals were caged in groups of five and acclimatized for 2 weeks. They were maintained under standard laboratory conditions and had free access to standard laboratory food and water throughout the experiment.

Experimental groups and chemicals

The rats (140-170 g) were randomized into five groups (3 experimental groups and 2 control groups) (n=10). Drugs, doses, and treatment regimens are presented in Table 1.

Table 1. Drugs, doses, and treatment regimens

Drug	Concentration, mg/mL	Solvent	Doses (mg/kg) and regimens
Doxorubicin(LLC VEROPHARM, Russia)	0.5	Saline	2.5×3/72
Mitoxantrone (Baxter, Germany)	0.3	Saline	1.0×3/96
Anthrafuran (oral dosage form)	15	5% glucose for injection	20×3/48

Dox and MT were administrated intravenously in tail vein, AF – orally with syringe, equipped with metal probe.

The doses and regimens of the drugs corresponded to therapeutic ones for rats and were chosen based on literature data (Fujimoto and Ogawa 1982; Steiniger et al. 2004; Treschalin et al. 2018). Anthrafuran was obtained from the Laboratory of Chemical Transformation of Antibiotics (Gause Institute of New Antibiotics, Russian Federation) in the form of a granular formulation for oral administration, with an active ingredient concentration of 50%.

In this study, females were selected as subjects due to their increased sensitivity to doxorubicin-induced toxicity (Schmetzer and Flörcken 2012).

It has previously been demonstrated that AF has a strong antitumor effect when administered orally (Shchekotikhin et al. 2020). For this reason, oral administration of anthrafuran is recommended for clinical use. Dox and MT are administered through intravenous infusion in the clinic. Therefore, in our experiment, we selected routes of administration that are consistent with the clinical setting.

Animals in the control groups received saline (isotonic NaCl solution) intravenously or a 5% glucose solution for injection orally in a volume equal to the volume of the administered drug.

Parameters of investigation

The condition and behavior of the animals were examined daily. The body weight was evaluated weekly. Electrocardiographic examination (second standard lead) was performed on days 8 and 30 post-treatment (electrocardiograph Zoomed iE300, China). Heart rate (HR), QT, RR, and QRS intervals were assessed.

Half of the animals from each group were euthanized on days 8 and 30 post-treatment. Heart weight was measured using laboratory scales Sartogosm SE 153-C (Sartogosm, Russia), and the relative organ weight (weight index – the ratio of organ weight to body weight, %) was calculated on the basis of body weight measurement prior to necropsy.

The heart was subjected to histological evaluation. It was fixed in 10% neutral formalin, embedded in paraffin with Tissue-Tek TEC 5 tissue embedder (Sakura, Japan), and cut using Accu-Cut SRM microtome (Sakura, Japan). The sections were stained with haematoxillin-eosin and analyzed with Nikon Eclipse 50i (Nikon, Japan) microscope.

Statistical analysis

The mean value and standard error were calculated for all quantitative data. All obtained cohorts were analyzed for normal distribution using the Shapiro-Wilk test in the StatPlus 2006 program. Statistical analysis was performed with one-way ANOVA in Statistica 8 program. The difference between the groups was considered significant at $p \leq 0.05$.

Results

Heart functions

The results of the electrocardiographic examination performed in a second standard lead on days 8 and 30 post-treatment are presented in Fig. 1. At both time points in the groups receiving Dox and MT, HR was significantly decreased compared to the control (Fig. 1A). By day 8, a significant decrease in the QT interval was observed in the group treated with MT, while by day 30 post-treatment the QT interval was significantly higher compared to that in the control. In the group receiving Dox, the QT interval increase was detected only on day 30 after administration (Fig. 1B). In the group treated with MT, a significant decrease in the QRS was noted by day 8, but by day 30 it did not differ from such in the control (Fig. 1C). The RR interval in all groups was similar to that in the control (Fig. 1D). Thus, in contrast to Dox and MT, the use of AF did not affect any of the studied ECG parameters.

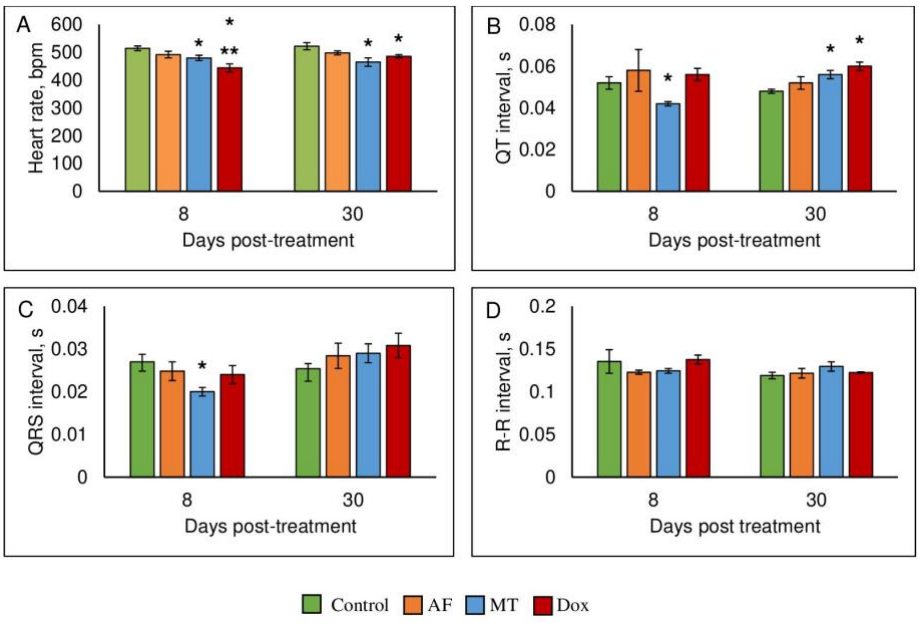


Figure 1. Electrocardiographic parameters of rats post-treatment with doxorubicin (Dox), mitoxantrone (MT), and anthrafuran (AF). ***Note:*** A – HR, B – QT interval, C – QRS interval, D – RR interval. *Values significantly different from control, $p \leq 0.05$.

Weight indices of heart

Administration of both Dox and MT led to an increase in the heart weight indices (HWI) of rats. However, under the influence of MT, this parameter was significantly higher on day 8, as well as on day 30 post-treatment, while after the treatment course with Dox, it increased only one month after the treatment. Meanwhile, the HWI of rats receiving AF did not differ from the value in the control group on either day 8 or day 30 of observation (Fig. 2).

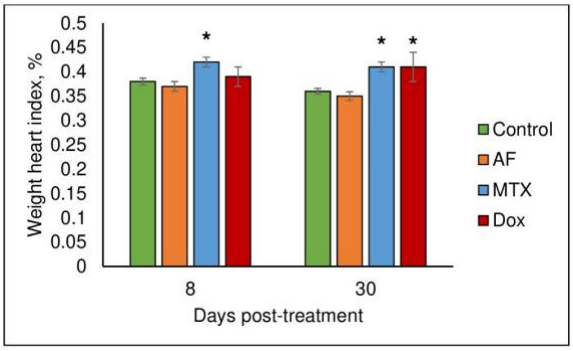


Figure 2. Heart weight indices in rats post-treatment with doxorubicin (Dox), mitoxantrone (MT), and anthrafuran (AF). ***Note:*** *Values significantly different from control, p≤0.05.

Pathomorphological evaluation of the myocardium

On day 8 after the treatment course with Dox, mild to moderate interstitial edema, primarily near blood vessels, and small foci of toxic cardiomyopathy within the edematous areas were found in the rat myocardium (Fig. 3G). By day 30 of the experiment, multiple extensive zones of myocardial edema appeared, along with foci of swollen muscle fibers showing signs of toxic cardiomyopathy, such as increased cytoplasmic eosinophilia and loss of cross-striation, as well as mild lymphoid infiltration in areas of edema and disorganization of myofibers (Fig. 3H).

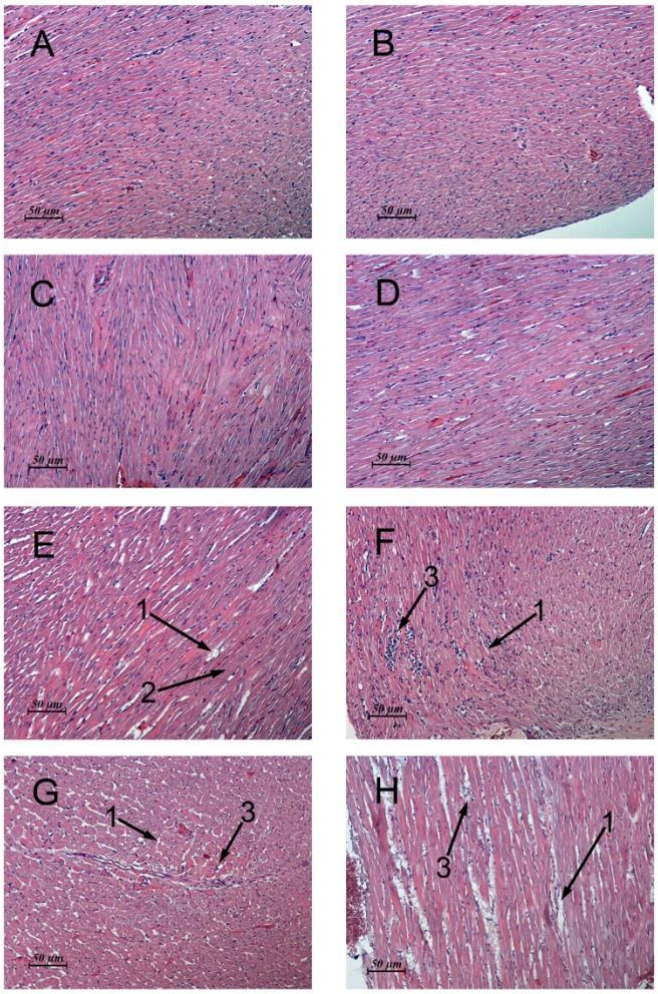


Figure 3. Rat myocardium, x10. ***Note:*** **A** – control (saline, per os); **B** – control (5% glucose for injection); **C** – AF 20 mg/kg x 3/48 per os, day 8 post-treatment; **D** – AF 20 mg/kg x 3/48 per os, day 30 post-treatment; **E** – MT 1 mg / kg x 3/96 i.v., day 8 post-treatment; **F** – MT 1 mg/ kg x 3/96 i.v., day 30 post-treatment; **G** – Dox 2.5 mg/ kg x 3/72 i.v., day 8 post-treatment; **H** – Dox 2.5 mg / kg x 3/72 i.v., day 30 post-treatment. 1 – moderate interstitial edema; 2 – foci of swollen muscle fibers with loss of cross-striation; 3 – foci of toxic cardiomyopathy.

On day 30 after MT treatment, small areas of toxic cardiomyopathy, small foci of myofiber disarray, infiltrated by lymphocytes and macrophages, appeared in the myocardium against the background of moderate interstitial edema (Fig. 3F). In striking contrast, no pathological changes were observed in the myocardium after administration of AF on both day 8 and day 30 post-treatment (compare control in Fig. 3A,B and AF in Fig. 3C,D).

Thus, a comparative study of pathomorphological changes in the myocardium of rats under the influence of anthrafuran, mitoxantrone, and doxorubicin showed that the use of these antitumor drugs at a therapeutic dose and in the optimal regimen established in experiments on rats and mice with transplanted tumors has a significantly different damaging effect on the myocardium that depends on the antitumor agent used and varies in intensity and timing of morphological manifestation. So, administration of MT and Dox resulted in mild changes in heart tissue as early as 8 days after the treatment course. A month after the treatment course, the damaging effect of Dox was more pronounced compared to MT, whereas no changes in myocardial structure were detected at either the first or second observation time points following AF administration.

Discussion

The problem of anthracycline antibiotic cardiotoxicity remains relevant. A retrospective review of three clinical studies established that the risk of developing congestive heart failure with Dox at a cumulative dose of 550 mg/m² ranges from 7 to 26%, and this likelihood significantly increases with higher doses (Nysom et al. 1998; Vandecruys et al. 2012). This limits the duration of Dox courses even when successfully used, ultimately affecting treatment efficacy. Signs of heart failure are detected even 13 years after therapy in 30% of patients who received Dox at doses ranging from 180 to 240 mg/m² (van der Pal et al. 2010). Pathomorphological changes, such as myofibril loss and cardiomyocyte vacuolization, are found in biopsies from patients who received less than 240 mg/m² of Dox. All this indicates that even low doses of this antitumor drug cannot be considered safe, as they too can cause cardiac dysfunction (Chang et al. 2017). Despite the success of some new approaches to overcoming cardiotoxicity, the search for effective cardioprotectors, the development of delivery systems to enhance the selectivity of this cytotoxic antibiotic, and the development of new analogues still continues (Elberry et al. 2010). This paper presents the results of the study on the cardiotoxic properties of the new antitumor anthracenedione derivative AF. The therapeutic dose and optimal regimen for AF, which were used in the study, provided the maximum antitumor effect of this agent upon oral administration. Both comparator drugs (Dox and MT) administered at therapeutically equivalent doses and regimens led to significant functional and morphological changes in the myocardium. Our obtained data on decreased heart rate and increased QT interval are consistent with findings from other scientists who studied Dox cardiotoxicity in rats after a single intraperitoneal injection at a dose of 15 mg/kg (Zbinden and Beilstein 1982). The development of toxic cardiomyopathy is accompanied by an increase in the heart weight coefficient, as shown not only in our study but also in experiments on rats by independent studies. In our study, AF did not exhibit cardiotoxic effects in any of the investigated parameters. A previously conducted study on the chronic toxicity of AF in rats and rabbits showed that oral administration of the drug for 14 days at a single therapeutic dose five times (100 mg/kg) caused focal myocardial damage immediately after the course and atrophy of muscle fiber groups after 30 days (Pereverzeva et al. 2017; Treschalin et al. 2018). Thus, the development of heart failure can only be expected with significant overdoses of AF. The difference in cardiotoxic properties between the new anthracenedione derivative AF and reference drugs of this class could be explained by specific features of its mechanism of action, which also determine the specifics of its cardiotoxic potential. The mechanism of cardiotoxicity for Dox and MT is associated with the formation of a complex with topoisomerase Top2β – the isoform that is expressed in cardiomyocytes. The formation of this complex is considered a key mechanism of anthracycline cardiotoxicity (Vejpongsa and Yeh 2014). The MT-Top2β complex is less stable in comparison with Dox, which may explain the reduced cardiotoxicity of MT (Huang and Lin 2014).

AF has a somewhat different mechanism of action compared to such of MT and Dox. In addition to inhibiting Top I and II, anthrafurans affect the expression of Aur B and Pim protein kinases (Tikhomirov et al. 2018). This is likely associated with the insignificant cardiotoxic effects of the new anthracenedione derivative in doses close to therapeutic.

Conclusion

The study in rats of the cardiotoxicity of new anthracenedione anthrafuran in comparison with doxorubicin and mitoxantrone, administered at their optimal therapeutic doses and regimens, demonstrated that AF has no cardiotoxic effect. Dox, introduced i.v. at a dose of 2.5 mg/kg three

times every 72 hours, caused most pronounced cardiotoxic effect, expressed in significant decrease in HR, prolongation of the QT interval, increase in weight index of the heart, and myocardial damage. MT injected i.v. at a dose of 1 mg/kg three times every 92 hours, also decreased HR of rats and increased QT interval, as well as induced the injury of the heart muscle. AF does not possess cardiotoxic properties when administered per os at a dose of 20 mg/kg three times every 48 hours. These results highlighted the high chemotherapeutic potential of AF for further clinical investigation.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

The authors have no funding to report.

Ethics statement

The ethical aspects of animal experimentation were reviewed and approved by the local ethics committee of the Gause Institute of New Antibiotics, with Minutes number 02/2024 dated September 16, 2024.

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Data availability

All of the data that support the findings of this study are available in the main text.

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