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Evaluating the effects of rifampin in the prevention of neurogenic symptoms and cardiac arrhythmias caused by the systemic toxicity of lidocaine in rats

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Abstract

Lidocaine toxicity is caused by unintended intravascular injection or overdose. Lidocaine is metabolized in the liver by the CYP3A4 isoenzyme. The objective was to investigate if the administration of rifampin could accelerate animal recovery and reduce the symptoms of lidocaine toxicity by induction of the CYP3A4. Thirty-six male rats were divided into control and treatment groups, each containing three subgroups. The treatment group received oral rifampin suspension daily for 1 week. In all rats, 2.00% lidocaine was injected intravenously. The first subgroup was monitored for neurological symptoms. In the second subgroup, data were recorded after the electrode was placed in the right hippocampus. Electrocardiograms were taken from the third subgroup. CYP3A4 was measured using an ELISA kit. Neurological recovery was seen after 22 and 15 min in the control and treatment groups, respectively. Rifampin also caused a significant reduction in amplitude and number of field action potentials compared to the control group. Numerous cardiac arrhythmias were observed in the control group. The mean level of CYP3A4 in the treatment group was significantly higher than in the control group. In conclusion, oral rifampin could increase the synthesis of CYP3A4, therefore, the animal recovery from lidocaine toxicity was accelerated.

Introduction

Lidocaine is an amide-based local anesthetic that is also used as an antiarrhythmic drug. High levels of systemic lidocaine intake exert adverse effects on the central nervous system (CNS) and cardiovascular system (CVS). These negative effects occur by interrupting the conduction of cardiac and nerve signals which is caused by preventing the entry of sodium ions into sodium channels. Therefore, it increases the depolarization threshold and neutralizes the action potential.[1] Lidocaine toxicity is usually caused by either unintended intravascular injection or its overdose administration.[2] This toxicity is dose-dependent so that increased plasma concentration intensifies toxicity manifestations. The early signs of toxicity are usually neurological and in severe cases lead to seizures and coma. Cardiovascular toxicity usually begins as tachycardia and hypertension but turns into bradycardia and hypotension as toxicity progresses. Other complications include ventricular arrhythmias and cardiac arrest which may be seen in some patients.[3]

Currently, there are some methods to manage lidocaine toxicity. Oxygenation, seizures control by benzodiazepines or succinylcholine, maintaining tissue perfusion, and use of vasopressor and antiarrhythmic drugs such as epinephrine and amiodarone are the available options. However, these are not always successful.[4] Lipid emulsion therapy is another proposed treatment for recovery of cardiovascular collapse caused by local anesthetic systemic toxicity. However, this therapy is more suitable for highly soluble local anesthetics (particularly bupivacaine). On the other hand, lipid emulsion did not affect the symptoms caused by the CNS toxicity of lidocaine.[5]

Approximately one-third of lidocaine has been shown to accumulate in the rat liver 15 min after systemic injection.[6] About 95.00% of lidocaine entered into the body is metabolized in the liver.[3] The CYP3A4 isoenzyme metabolizes lidocaine in the liver. This isoenzyme is categorized as P450 enzymes and is more involved in drug metabolism in humans than any other liver enzyme. Lidocaine is converted by this enzyme to mono-

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ethylglycine xylidide (MEGX) and thereafter glycine xylidine (GX) in a sequential oxidative N-dealkylation process.[7] Although MEGX is an active metabolite of lidocaine and has similar pharmacological properties, it is less potent, so that it can produce only about 80.00 to 90.00% of the cardiac and neurological properties of lidocaine. The clearance of this metabolite is approximately 2.30 to 2.80 hr which is slightly lower than lidocaine itself.[6] Many drugs block the activity of the isoenzyme CYP3A4 including antibiotics such as erythromycin, antifungals, antidepressants and calcium channel blockers, therefore, their use can increase the risk of lidocaine toxicity.[7]

Enzyme induction in pharmacology means an increase in the amount or activity of drug-metabolizing enzymes due to exposure to a chemical regardless of its mechanism.[8] Some drugs such as rifampin, carbamazepine, phenytoin and phenobarbitone can induce the synthesis of the CYP3A4 isoenzyme.[9] Rifampin is one of the basic antibiotics for the treatment of tuberculosis approved by the U.S. Food and Drug Administration in 1971.[10] *In vitro* studies have shown that rifampin can increase lidocaine metabolism in human hepatocytes.[11] When rifampin is administered concomitantly, the clearance of drugs metabolized by CYP2B6, CYP2C8, and CYP2C9 isoenzymes increases 2.30 to 3.80 times. Interestingly, the clearance of drugs metabolized by CYP3A4 isoenzyme is further increased to 10.00 times, thus, rifampin induces the CYP3A4 isoenzyme more than other P450 enzymes.[12] However, no report has been published to investigate the role of P450 inducers including rifampin in increasing lidocaine metabolism in cases of lidocaine toxicity. Considering that rifampin induces liver enzymes involved in lidocaine metabolism, more importantly isoenzyme CYP3A4, we hypothesized that administration of this antibiotic could reduce the symptoms of lidocaine toxicity or eliminate these symptoms more quickly by accelerating lidocaine metabolism.

Materials and Methods

Animals. This study was evaluated and approved by the Regional Research Ethics Committee of the University of Tabriz, Iran (approval ID: IR.TABRIZU.REC.1399.048, date: 2020-10-4). In addition, the research was in accordance with the Guide for the Care and Use of Laboratory Animals (NRC 2011) and associated guidelines. Thirty-six 2-month-old male Sprague-Dawley rats (*Rattus norvegicus domestica*) were entered into this study after consulting with a statistics expert. The animals were kept in separate cages in an environment with a 12 hr light/dark cycle with controlled temperature and humidity conditions. They were allowed to adapt to the laboratory environment for a period of 1 week. The animals had access to the semi-synthetic pellets and tap water *ad libitum*. In all stages of the work, additional stress was avoided to the rats and only one intravenous (IV) injection was performed in each rat. They were randomly divided into two equal groups (n = 18) including control (C) and treatment (T). Each experimental group was further subdivided into three subgroups (n = 6) for evaluating the mental status of unconscious and conscious rats along with cardiac arrhythmias.

Experimental procedures. Rifampin (Rifampin-Hakim, Hakim Co. Tehran, Iran) powder in the form of an oral capsule was dissolved in normal saline (3.00% suspension). The rats of the treatment group received daily oral rifampin suspension at a dose of 30.00 mg kg^{-1} for one week using a standard gavage tube.[13] The control group received the same volume of normal saline by intragastric gavage. The person who gavaged the animals was different from who recorded the neurologic and cardiac data. On the day of the experiment, the rats of the first subgroup in both C and T groups were placed in a holder and their tails were disinfected with alcohol. After placing the tail in warm water (30.00 - 35.00 ˚C) for 1 min to dilate the veins, 18.00 mg kg^{-1} of epinephrine-free 2.00% lidocaine HCl (Pasteur Institute, Karaj, Iran) was injected intravenously using a 23 G needle and insulin syringe. The dose of lidocaine (18.00 mg kg^{-1}) was chosen based on our pilot study. The higher doses of lidocaine caused rapid death in rats, therefore, it could not be used in this study. The time of injection was considered as time 0. They were removed from the holder after injection and monitored for neurological symptoms including whisker tremors as the main symptom as well as ataxia, restlessness, depression and death for 40 min. Observing any of these symptoms was considered a positive response to intoxication. The second subgroup rats were intraperitoneally anesthetized by 80.00 mg kg^{-1} of 10.00% ketamine HCl (Alfasan, Woerden, The Netherlands) and 5.00 mg kg^{-1} of 2.00% xylazine (Alfasan) combination.[14] The hair on their skull was removed and the area was prepared aseptically. The head was fixed in a stereotaxic apparatus (Stoelting, Wood Dale, USA). A 1.50 to 2.00 cm long incision was made on the scalp. After determining the Bregma point using the coordinates according to Watson's plan, a tiny hole was made in the skull by a dental drill and the recording tungsten bipolar electrode was placed in the stratum corneum layer of the right Cornu Ammonis 1 (CA1) region of the hippocampus. The coordinates for the electrode tip were as the following: Anterior-posterior (AP): –2.76 mm, medial-lateral (ML): –1.40 mm, and dorsal-ventral (DV): 3.00 mm (Fig. 1).[15] The data were recorded using an appropriate device (RubyMind; eLab electrophysiology workstation, Shenzhen, China) and software (eTrace Analyzer; ScienceBeam, Shenzhen, China). The IV lidocaine injection was carried out as mentioned before, 10 min after recording. Because the

animals were generally anesthetized and did not normally show apparent nervous symptoms, the seizure-like activity was induced by the intraperitoneal injection of 80.00 mg kg^{-1} pentylenetetrazole (PTZ; Sigma-Aldrich, Saint Louis, USA) 10 min after lidocaine administration. Diazepam at a dose of 10.00 mg kg^{-1} was injected after 10 min to suppress PTZ-induced epileptic activity (Fig. 2).[16]

Fig. 1. Immobilization of a rat head in a stereotaxic device and attachment of a tungsten dipole electrode in the stratum corneum of the right CA1 region of the hippocampus after scalp incision and piercing the skull with a dental drill.

The third subgroup of animals was anesthetized as described above and three leads of electrocardiogram (ECG) were connected. The ends of the electrode wires were stripped and hooked and attached subcutaneously to the right and left hands and left leg.[17] The ground electrode was also placed in its right position. The electrodes were connected to the same device used for mental status recording and ECG was taken 10 min before lidocaine administration. The ECG recording was continued after the lidocaine injection until the symptoms subside. Heart rate and any arrhythmias were noticed. Blood samples (1.00 mL) were taken from the heart of anesthetized rats of the third subgroup at the end of the experiment. All rats were euthanized by over injection of intraperitoneal 150 mg of sodium thiopental (VUAB Pharma Inc., Roztoky, Czech Republic).[18]

Enzyme assay. The blood samples were allowed to coagulate. They were then centrifuged for 5 min at 1,500 rpm to obtain serum. The serums were stored at –70.00 ˚C refrigerator until enzyme assay. Isoenzyme CYP3A4 was measured using Rat CYP3A4/Cytochrome P450 3A4 ELISA kit (LifeSpan BioSciences Inc., Seattle, USA). This assay was based on the sandwich ELISA principle. Briefly, standards or samples were added to the wells of the microtiter plate pre-coated with a target-specific capture antibody according to the instructions. The target antigen binds to the capture antibody. A horse-radish peroxidase (HRP)-conjugated detection antibody was then added which binds to the captured antigen. Unbound antigen and detection antibody was washed away. A3,3',5,5' tetramethyl-benzidine (TMB) substrate was then added which reacts with the HRP enzyme resulting in color development. A sulfuric acid (LifeSpan BioSciences Inc.) stop solution was added to terminate the color development reaction and then the optical density (OD) of the well was measured at a wavelength of 450 ± 2.00 nm using Hiperion microplate reader (model: MPR4+; Medizin-technik GmbH & Co. KG, Roedermark, Germany). An OD standard curve was generated using known antigen concentrations, the OD of an unknown sample was then compared to the standard curve in order to determine its antigen concentration.

Statistical analysis. The results related to behavioral changes in the first subgroup and cardiac arrhythmias in the third subgroup were reported descriptively. Statistical analyses were performed using Minitab software (version 16.2.0; Minitab Inc., State College, USA). The number and range of action potentials were analyzed using the two-sample *t*-test. The normal distribution of the data related to changes in heart rate was examined based on the Shapiro-Wilk test. Heart rate changes were analyzed by two-way analysis of variance (ANOVA) with repeated measures. The Bonferroni post hoc test was also used to determine the differences between the groups. The normality of the distribution of enzyme levels was investigated using the Shapiro-Wilk test and the assumption of the equal variance was made using the Levene's test. Enzyme levels were analyzed using the two-sample *t*-test method. The results were reported as Mean ± SEM. The differences were considered significant when $p < 0.05$.

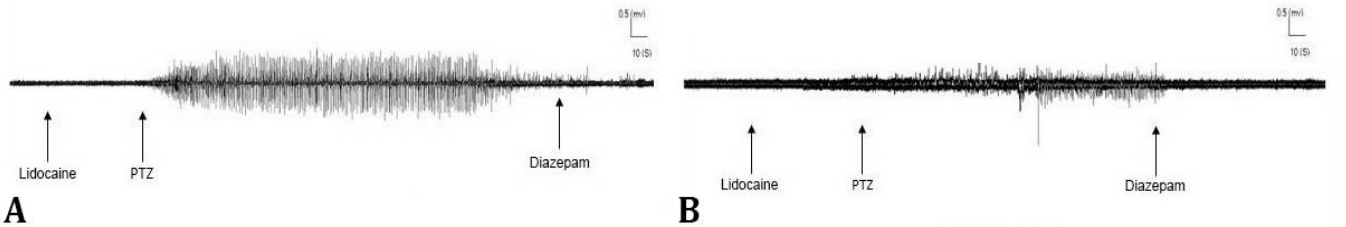

Fig. 2. Effects of lidocaine injection on pentylenetetrazole-induced seizure activity recorded in the CA1 hippocampus of male rats. Lidocaine: Hippocampal activity following intravenous injection of 18.00 mg kg^{-1} lidocaine. PTZ: Convulsive activity induced by intraperitoneal injection of 80.00 mg kg^{-1} pentylenetetrazole. Diazepam: Intraperitoneal injection of 10.00 mg kg^{-1} of diazepam, which suppresses seizure activity. **A)** Control group, **B)** Treatment group.

Results

Neurological symptoms. The animals in the first subgroup of the control group fell into the corner of the cage and began to have convulsive movements, severe tremors and shaking of their tails immediately after the lidocaine injection. These convulsive movements lasted about 2 - 3 min after which the animals entered the resting phase. There was a relative return of consciousness and effort to walk, imbalance and severe staggering from the 4th or 5th min. Jaw muscle tremors were seen at this time, some lasting up to the 16th min. The imbalance was seen in them until the 15th min. Abdominal breathing and intense movements in the abdominal muscles were observed at 20th or 21st min. Grooming was seen from 20th to 27th min after which most of them were able to move normally. In rats of the treatment group, convulsive movements began immediately after injection. The limb movements were intense and lasted for 3 min. From the 4th min onwards, they tried to walk which was accompanied by an imbalance. The animals were groomed, completely normal, and walked in balance from the 14th or 16th min. In general, in the behavioral evaluation of neurological symptoms caused by lidocaine toxicity, the seizure was seen in the control group immediately after lidocaine injection. After a short period of rest, they tried to walk, however, symptoms such as abdominal muscle tremors, respiratory depression, deep abdominal breathing, jaw muscle tremors and circle movements were obvious. This group recovered after about 22 min. The rifampin treatment group also developed severe seizure symptoms after the lidocaine injection and showed severe convulsive movements. They then entered a resting phase, however, this group recovered after about 6 min. In addition, the return of balance while walking occurred earlier in this group and they performed the first grooming about 15 min after the injection and were able to walk without staggering in about the 17th min. In animals in the second subgroup, rifampin significantly reduced the amplitude (Fig. 3) and number (Fig. 4) of field action potentials compared to the control group ($p < 0.001$).

Cardiac arrhythmias. In the third subgroup of rats in the control group, sinus arrhythmia, sinus block, atrioventricular block grade 2, atrioventricular block grade 3 and atrial fibrillation was observed in most animals and complete cardiac arrest in some. In general, the QRS wave height was decreased. Rats developed bradycardia and the heart rate was dropped sharply.

Rifampin-treated rats had sinus arrhythmias for a few seconds and in one animal, atrioventricular block grade 1 was observed 10 min after lidocaine injection which was returned to normal up to the 20th min. In this group, none of the rats suffered cardiac arrest and a decrease in wave height at the beginning of the injection was seen in a small number of cases. Sinus arrhythmias and atrioventricular block grade 1 did not progress and returned to normal. Therefore, the rate of cardiac arrhythmias in the treatment group was much lower than the control group. In the statistical analysis of heart rate over time, the effect of treatment, time and the interaction between the two were all significant. Comparing the times, in both groups immediately after lidocaine injection, the heart rate was decreased significantly which was more in the control group ($p < 0.01$). Ten min later, the heart rate in the treatment group remained in the same range ($p > 0.01$), however, in the control group, there was still a significant decrease ($p < 0.01$).

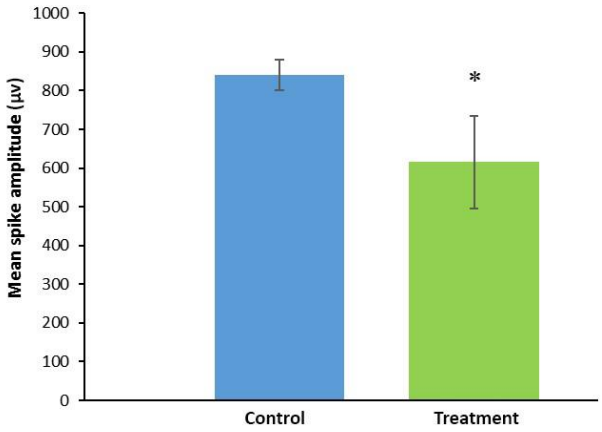

Fig. 3. Effects of oral administration of rifampin (30.00 mg kg^{-1}) for 1 week in the treatment group on the range of field action potentials (mean ± SEM) due to intraperitoneal injection of pentylenetetrazole (80.00 mg kg^{-1}) following intravenous injection of lidocaine (18.00 mg kg^{-1}) in anesthetized male rats with a combination of ketamine and xylazine in comparison with the control group.
The asterisk indicates a significant difference ($p < 0.001$).

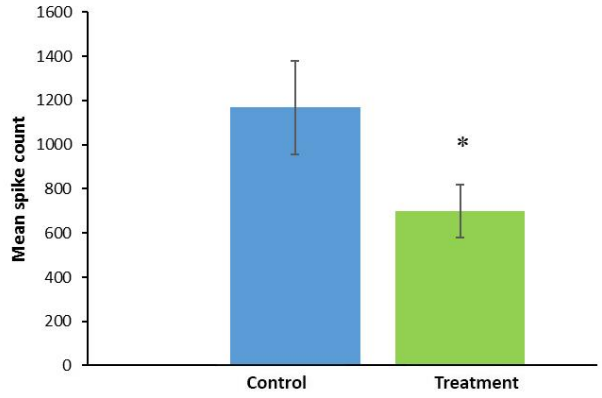

Fig. 4. Effects of oral administration of rifampin (30.00 mg kg^{-1}) for 1 week in the treatment group on the number of field action potentials (mean ± SEM) due to intraperitoneal injection of pentylenetetrazole (80.00 mg kg^{-1}) following intravenous injection of lidocaine (18.00 mg kg^{-1}) in anesthetized male rats with a combination of ketamine and xylazine in comparison with the control group.
The asterisk indicates a significant difference ($p < 0.001$).

Twenty min later, the heart rate in the treatment group was increased and approached the normal range before injection. However, in the control group, there was still a significant decrease in heart rate ($p < 0.01$). In terms of comparison between groups, except for the time before injection when the heart rate of both groups was in the same range ($p > 0.01$), the difference between the two groups was significant at other times ($p < 0.01$), (Fig. 5).

Enzyme levels. Cytochrome P450 isoenzyme CYP3A4 levels (8.52 ± 1.90, and 14.88 ± 1.50 ng mL^{-1} in C and T groups, respectively) had a significant difference between the two groups ($p < 0.05$) indicating rifampin induced the hepatic enzyme production in the liver responsible for lidocaine metabolism (Fig. 6).

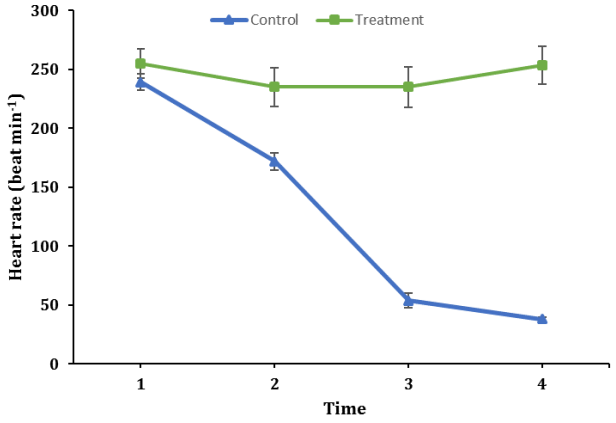

Fig. 5. Changes in heart rate (mean ± SEM) over time in rats of control (▲; blue line) and treatment (■; green line) groups. Time 1: Before lidocaine injection, Time 2: Immediately after intravenous injection of lidocaine at a dose of 18.00 mg kg-1, Time 3: 10 min after lidocaine injection, Time 4: 20 min after lidocaine injection. The effect of treatment, time and interaction between the two are all significant ($p < 0.01$).

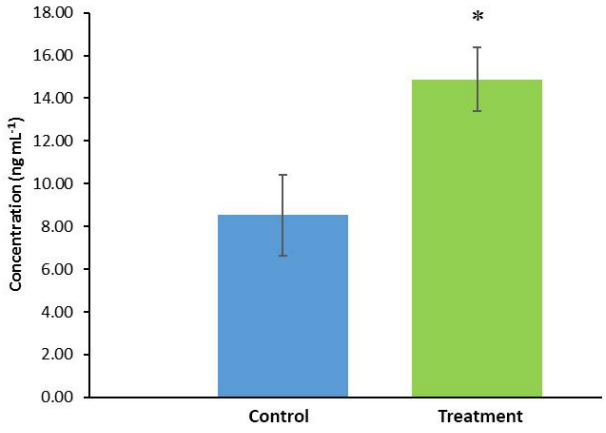

Fig. 6. CYP3A4 isoenzyme levels (mean ± SEM) in control and treatment groups. Enzyme levels in the two groups are statistically significant ($p < 0.05$).

Discussion

Systemic intoxication due to local anesthesia is rare but can be fatal with seizures, arrhythmias and cardiovascular collapse. The site of administration and the dose of local anesthetic are independent risk factors for systemic intoxication;[19] thus, miscalculation of dosing, injection into blood vessels, or repeated administration of therapeutic doses are major causes of systemic intoxication.[20,21] Lidocaine prevents the action potential by binding to sodium channels. The main target organs are the CNS and the CVS. Because the CNS is more sensitive to electrophysiological changes than CVS, neurological symptoms such as dizziness, tinnitus and numbness around the mouth usually precede cardiovascular manifestations. The usual clinical manifestations require a transient apparent stimulus followed by depression. Although the stimulus phase generally precedes the depression phase, the former may be very short or even absent.[22] Aburawi and Souid showed lidocaine causes cardiac toxicity in rat cardiomyocytes by inhibiting myocardial cellular respiration. They described the clinical manifestations of QRS prolongation, hypotension, shock and dysrhythmia.[23]

The diagnosis of lidocaine toxicity is usually clinical because serum levels are not readily available and do not change treatment guidelines if present. Therapeutic levels of lidocaine in plasma can be as high as 5.50 µg mL^{-1}, while plasma levels of 8.00 - 12.00 µg mL^{-1} or higher are associated with central and cardiovascular toxicity.[24] In a study in mice, the relative potency (ED_{50}) of intravenous lidocaine using the up-and-down method was determined 19.50 mg kg^{-1} for neurological symptoms (seizures, ataxia, absence of balance reflex, and death) and 21.20 mg kg^{-1} to cause cardiac symptoms.[25] In other studies, the dose required for seizures in sheep, cats, horses and dogs has been reported from 5.80 to 11.70 mg kg^{-1} and in birds 30.50 mg kg^{-1}.[2] We choose the dose of 18.00 mg kg^{-1} of epinephrine-free 2.00% lidocaine based on a pilot study since the clinical symptoms of nervous and cardiac organs were apparent with this dose, without causing very early death of rats.

Slight to moderate overdose in humans leads to clinical signs of dizziness, change of direction, excitement, speech changes, nystagmus, hypertension, increased heart rate and respiration, and loss of consciousness. Moderate to severe overdose leads to general tonic-clonic seizures, followed by CNS depression and cardiovascular depression including blood pressure, heart rate and respiration, lack of concentration, drowsiness and loss of consciousness.[22] In this study, seizure symptoms were observed in the control group immediately after injection and then a short period of CNS depression was developed. The animals then experienced symptoms such as abdominal muscle spasms, respiratory depression, deep abdominal breathing, jaw muscle tremors and spinning around. Thus,

according to the symptoms, it could be said that moderate to severe overdose was occurred in them.

Effects on CVS are also related to concentration so that low blood levels cause antiarrhythmic electrophysiological changes but high levels lead to longer conduction time and increased diastolic threshold. These can be seen on the ECG as an increase in deviation intervals with sinus bradycardia. Peripheral vasodilation, negative inotropic effects, decreased cardiac output and hypotension may also occur.[22] In control rats, different types of arrhythmias were observed in this study, including sinus arrhythmia, sinus block, grade 2 atrioventricular block, grade 3 atrioventricular block, atrial fibrillation and even complete cardiac arrest. In general, in the samples of control group, QRS wave height was decreased. Rats developed bradycardia and a sharp decrease in heart rate, all of which indicated cardiovascular depression due to lidocaine toxicity.

The induction of CYP3A4 has been shown to alter the pharmacokinetics of many drugs which is why laboratory methods for screening new chemicals and drugs as inducers of CYP3A4 have been developed.[26] The antibiotic rifampin (rifampicin) is one of the first drugs of choice for the treatment of tuberculosis. This drug can induce liver enzymes of CYP450.[27] Previously, the induction of lidocaine metabolism by cultured human hepatocytes was reported by rifampin.[11] In a study by Lou *et al*., the induction of CYP3A4 isoenzyme activity by rifampin in cultured human primary hepatocytes was observed to be 2 to 10-fold.[26] Although Lu and Li concluded that rifampin could not induce CYP3A enzymatically in cultured rat hepatocytes as opposed to human hepatocytes,[28] the results of our study contradict it. It should be noted that only three rats were used in Lu and Li's study and on the other hand, the type of cell culture may have played a role in their lack of response to rifampin. In this study, the mean level of CYP3A4 isoenzyme in rats in the treatment group receiving rifampin was significantly higher than the control group (14.88 ± 1.50 and 8.52 ± 1.90 ng mL^{-1}, respectively). Therefore, it could be claimed that rifampin induced the synthesis of this liver enzyme. Due to the fact that CYP3A4 isoenzyme is responsible for lidocaine metabolism, it is found that lidocaine metabolism was faster in the treatment group than the control group and this justified faster recovery of rats in the treatment group. It has been suggested that the onset of action of rifampin is gradual and that its clinical effects may not appear 2 - 3 weeks after the start of treatment.[29] Nevertheless, one week of oral administration of rifampin was able to show a positive effect in our study.

In this study, although the symptoms of lidocaine toxicity were also seen in the rifampin-treated group, rifampin was able to accelerate the neural recovery of the animal after lidocaine toxicity. Six min after receiving lidocaine, they recovered and no longer had seizures, jaw tremors and abdominal breathing symptoms. Complete recovery occurred in the first subgroup of the treatment group up to 17 min after intoxication, while this time was longer (22 min) for the control group. In other words, it seemed that lidocaine entering the body was metabolized faster in the treatment group and its effects were eliminated. Also, in the second subgroup, rifampin caused a significant reduction in amplitude and number of field action potentials compared to the control group. In the third subgroup, unlike the control group which had different types of cardiac arrhythmias, in the treatment group, except for sinus arrhythmias and grade 1 atrioventricular block, no significant arrhythmia was observed. In addition, none of the rats in the treatment group suffered cardiac arrest. Thus, the rate of cardiac arrhythmias in the treatment group was much lower than the control group, indicating the preventive effect of rifampin in cardiac manifestations of lidocaine toxicity.

Based on the findings of the present study, it could be concluded that oral rifampin could increase the metabolism of lidocaine by increasing the synthesis of CYP3A4 isoenzyme in the liver of rats, therefore, in cases of lidocaine toxicity, accelerate the recovery of the animal. Because lidocaine toxicity due to dose miscalculation or unwanted intravenous injection is always a potential risk, rifampin therapy can be considered alongside conventional treatments. However, this study was a preliminary study to evaluate the effectiveness of rifampin in enzyme induction and subsequent lidocaine metabolism. Therefore, more studies are needed to determine whether injecting this antibiotic can rapidly alter liver enzyme levels, because for this treatment to be used clinically, the speed of action of the drug in the induction of the enzyme is also important.

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Conflict of interest

The authors have no competing interests to declare.

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