Normalization of QRS Segment, Blood Pressure and Heartbeat in an Experimental Model of Amitriptyline Intoxication in Rats Following Hyperbaric Oxygenation Therapy

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ABSTRACT
Tricyclic antidepressants are responsible for the majority of cases of intoxication due to psychoactive medications. Such intoxication results in an alteration of cardiovascular function. Sodium bicarbonate (\(\text{HCO}_3\)) is the current treatment of choice, although, we propose Hyperbaric Oxygenation (HBO) therapy as an alternative treatment, since it is known to be an effective adjuvant therapy in the treatment of cardiovascular disease. However, the use and utility of this therapy has not been fully clarified. To evaluate hyperbaric oxygenation therapy as a collaborating agent in the treatment of amitriptyline intoxication, allowing recovery in a lesser period of time of the cardiovascular parameters under study, as compared to the sodium bicarbonate treatment. Male Wistar rats were intoxicated with amitriptyline and hyperbaric oxygen therapy or sodium bicarbonate were administered as a treatment. Blood pressure measures were taken and an electrocardiogram was performed to determine the heartbeat and the length of the QRS interval. After amitriptyline intoxication and first treatment with either HCO3 or HBO, heartbeat returned to normal and the length of the QRS segment was shortened. The latter parameter returned to normal after the second treatment with either SB or HBO. Whereas, HBO therapy normalized blood pressure after the first treatment, this result was found only after the second treatment with SB. The HBO therapy proved better than SB treatment for improving blood pressure.

Key words: Hyperbaric oxygen therapy, amitriptyline intoxication, QRS segment, blood pressure, heartbeat

INTRODUCTION

Tricyclic Antidepressants (TCAs) are a group of drugs used mainly for treating depression, neurological pain, migraine, enuresis and attention deficit hyperactivity disorder. Amitriptyline, the most widely used TCA, is associated with cardiac and neurological toxicity. Reports on its toxic effects on the heart include abnormalities in the rhythm and electrical activity, an extended QRS, ventricular arrhythmia (such as ventricular tachycardia), ventricular fibrillation, Torsades des points and myocardial infarction (the latter is less common but far more serious than the other conditions) (Kiyano et al., 2006; Chamsi-Pasha and Barnes, 1988).

Electrocardiograms play a fundamental role in diagnosis, treatment and prognosis of morbi-mortality associated with intoxication by TCAs (Caravati and Bossart, 1991; Liebelt et al., 1995). Findings from this test that have been successfully employed as indicators of the severity of intoxication by TCAs are sinus tachycardia, a QRS greater than 100 ms, a right axis deviation (130-270 degrees) and/or
Experimental groups: Five groups of animals were formed (n = 6 in each sub-group): Group 1 was the control group without treatment, group 2 received amitriptyline, group 3 received HCO₃, 2 h after the amitriptyline treatment, group 4 was given hyperbaric oxygen therapy after the amitriptyline treatment and group 5 was treated with HCO₃ and HBO simultaneously. All amitriptyline treatments were administered by intraperitoneal via at 50 mg kg⁻¹ (Kalkan et al., 2010; Thorstrand et al., 1976).

In group 1 animals (no treatment), blood pressure measures were taken and ECG with 6 derivations was performed. The length of the QRS interval and the heartbeat were determined from the latter test.

Group 2 animals were divided into two sub-groups, 2A and 2B. Blood pressure measures were taken and ECG was performed for the rats of group 2A immediately after the amitriptyline treatment and 3 h later and the same measurements were made for the animals of group 2B only once, 9 h after intoxication.

In group 3 animals, a venodissection was performed one hour after intoxication on the jugular vein to introduce a central catheter, by which HCO₃ was administered at 2 m Eq kg⁻¹ (IV) diluted in a 5% glucose solution at a ratio of 1:5. This group was divided into two sub-groups (n = 6), 3A and 3B. Blood pressure measures were taken and ECG was performed for group 3A rats 2 h after the HCO₃ treatment. Group 3B rats were subject to a second HCO₃ treatment (at the same dose) 8 h after intoxication and 2 h later blood pressure measures were taken and ECG was performed.

Group 4 animals underwent hyperbaric oxygen therapy (HBO, at 2 atm for 1 h, with 15 min pressurization and 15 min depressurization), 1 h after intoxication. This group was divided into 2 sub-groups (n = 6), 4A and 4B. In both sub-groups, blood pressure measures were taken and ECG was performed immediately after HBO therapy and 2 h later. Group 4B rats were subject to a second HBO session, 8 h after intoxication, immediately after which blood pressure measures were taken and ECG was performed.

Animals in group 5 were treated with both HCO₃ and HBO simultaneously and were divided in 2 sub-groups, 5A and 5B (n = 6). Animals in group 5A were subject to an ECG and blood pressure measurements 2 h after treatments and animals in group 5B were subject to blood pressure measurements and ECG, 8 h after intoxication.

Drugs: Amitriptyline chlorohydrate (Research Biochemical International) was dissolved in 0.5cc of injectable water for intraperitoneal administration. An injectable solution of HCO₃ was prepared at 1 m Eq mL⁻¹ (8.4 g r/100 mL; Pharmakin lab) which was diluted at a ratio of 1:5 with a 5% glucose solution for intravenous administration through the central venous catheter. Pentobarbital sodium (Sanfer, at 50 mg mL⁻¹) was administered by intraperitoneal via.
Data analysis and statistics: Data represent Means±SE. Each experimental condition had an “n” value of 6 rats. Comparisons between groups and among treatments were performed using an ANOVA and Bonferroni post-test for individual differences. Differences were considered statistically significant where, p<0.05.

RESULTS

Blood pressure increased from 120-170.6 mm Hg in rats intoxicated with amitriptyline (Fig. 1a), this happens within the first 3 h after intoxication. The first HBO treatment almost normalized the blood pressure (130 mm Hg), whereas HCO₃ required two treatments. Interestingly, we observe that upon administration of both treatments simultaneously in intoxicated rats, the results achieved are similar to those observed in the group that received HBO treatment only (Fig. 1a and b).

On the other hand, we can observe that amitriptyline intoxication induces bradycardia, from 269.1-383.8 L min⁻¹ in the control group. Both the HCO₃ and HBO therapies (Fig. 2a and b) reduced the effect of amitriptyline after the first treatment and normalized the heartbeat after the second treatment.

Interestingly, amitriptyline treatment made QRS to last longer (from 32.6-41.6 ms) (Fig. 3a and b) and the effect remained along the 9 h experiment. Both HCO₃ and HBO reduced QRS length after the first (37.5 ms SB and 31.6 ms HBO) and second treatments (34.1 ms HCO₃ and 31.6 ms HBO). On the other hand, we can observe the results achieved when administering both treatments at the same time. The results observed are similar to those achieved in group 3, which received HBO only where, blood pressure is normalized after the first HBO session and both heartbeat and the length of the QRS segment start to normalize since, the first session reach normal values until 8 h after the initial HBO treatment.

Figure 4a control and b intoxicated, shows ECG of an animal in the control group and one of the intoxicated animals group where, changes in heartbeat and length of the QRS segment of the intoxicated group can bee observed.
Fig. 3(a-b): QRS length in control and intoxicated rats with amitriptyline, (a) 180 and (b) 540 min with HCO₃, HBO, HCO₃/HBO treatment

Fig. 4(a-b): Electrocardiogram representing a rat in the (a) Control rat and (b) Intoxicated rat

**DISCUSSION**

A lethal dose of 25-75 mg kg⁻¹ has been reported (Kalkan et al., 2010; Thorstrand et al., 1976; Gill and Bell, 2004). In this study, we used 50 mg kg⁻¹ of body weight, administered by intraperitoneal via, with a result of myocardial toxicity.

Amitriptyline intoxication may induce abnormalities in conduction, as well as severe ventricular arrhythmias and modification of blood pressure. Some authors have mentioned that the most important effect of intoxication with TCAs is the inhibition of fast sodium channels which in turn delays phase 0 of depolarization in the His and Purkinje bundles of neural fibers and the ventricular myocardium. This effect appears on the electrocardiogram as an extension of the QRS intervals (Singh et al., 2002; Glauser, 2000; Sasyniuk et al., 1986). On the other hand, bradycardia, hypotension and hypertension have been reported, depending on the dose. The current results are consistent with these reports, as we found bradycardia, an increase in blood pressure and lengthening of the QRS segment.

The HCO₃ treatment is used to counteract intoxication with TCAs by alkalinizing the medium. In this way, it antagonizes the interaction between amitriptyline and the inactivated channels, thus allowing recovery of the electrical activity of the heart (Tilney, 2011), favoring a shortening of the QRS segment and normalizing blood pressure and heartbeat.

HBO therapy has been used for carbon monoxide (Tilney, 2011; Weaver et al., 2002) and other types of intoxication (Youngster et al., 2010; Taslipinar et al., 2013). However, the mechanism of the beneficial effect has not been established. We propose that the mechanism of action is that by increasing the concentration of oxygen in the organism, this treatment improves antioxidant defenses and thus increases the production of ATP and nitric oxide while, at the same time decreases intracellular calcium levels. Therefore, the ionic transmembrane gradient of K⁺, Na⁺ and Cl⁻ is modified, which avoids cytotoxicity and favors recovery of normal parameters in the heart (Castillo et al., 1996; Choi and Rothman, 1990; Moro et al., 2005).

In this study, after the first HBO treatment there was a shortening of the QRS segment and a normalization of heartbeat, effects that are also found after the first treatment with HCO₃. After the second treatment with either of these two therapies, the length of the QRS segment returned to normal. However, the normalization of blood pressure observed after the first treatment with HBO was found until after the second treatment with HCO₃. Interestingly, we observe that when
administering both treatments to a group of intoxicated rats, the results achieved were similar to those observed in the group of intoxicated animals treated with HBO only which suggests that these two treatments do not potentiate or inhibit each other.

**CONCLUSION**

Amitriptyline intoxication in our experimental model in rats resulted in the extension of the QRS segment, bradycardia and a blood pressure increase starting on the first hours after intoxication. With HBO, we obtained a normalization of blood pressure in the 1st 3 h after exposure to this therapy. Similar results were obtained with HBO/HCO₃ administered simultaneously; however, with administration of HCO₃, blood pressure was normalized only after 8 h. The QRS segment and heartbeat were normalized in a similar period of time with the three treatments.

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**REFERENCES**


