ROLE OF INTRAVENOUS LIPID EMULSION ON CARDIOVASCULAR TOXICITY INDUCED BY COMBINED AMITRIPTYLINE AND CITALOPRAM OVERDOSES IN ADULT MALE ALBINO RATS

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ABSTRACT

Toxicity from antidepressant agents is considered a common phenomenon. The aim of this study was to estimate the role of intravenous lipid emulsion (ILE) as compared to sodium bicarbonate (Na bicarbonate) as a main line or as an adjunctive therapy for treatment of cardiovascular toxicity induced by concurrent single oral administration of amitriptyline and citalopram in rats. The intoxicated rats were equally divided into three groups. Group1 received a bolus dose of 2mEq/kg Na bicarbonate then by infusion of 0.25ml/kg/min. Group 2 received a bolus dose of 1.5ml /kg of 20% ILE followed by infusion of 0.25 ml/kg/min and increased stepwise to 12.4 ml/kg. Group 3 received Na bicarbonate + ILE by the same pattern and doses. All therapies were injected for 60 min. Mean arterial blood pressure (MAP), heart rate (HR) and electrocardiogram for QRS duration were assessed across all intervals with comparison of pH recordings before and after therapies. The results showed significant improvement of MAP and QRS prolongation after the iv bolus dose, along infusion period and even after 10 min of the follow up. HR was not changed in all groups while pH showed significant improvement after the end of therapies administration in all groups. No significant differences were found between Na bicarbonate and ILE groups while there was a highly significant improvement in Na bicarbonate + ILE group as compared to the other groups. In conclusion, ILE can be used alone or as an adjunctive therapy with Na bicarbonate which is preferred to reverse the cardiovascular toxicity induced by combined antidepressant agents in adult rats.

Keywords: Intravenous lipid emulsion, sodium bicarbonate, amitriptyline, citalopram, cardiovascular, toxicity

INTRODUCTION

Major depression is a common debilitating disorder affecting 10%–15% of the population per year (**Ward and Irazoqui, 2010).** Drug therapy combination is considered a type of treatment that many psychiatrists have been increasingly utilizing during the past decade. Selective serotonin reuptake inhibitors (SSRI) usually combined with tricyclic antidepressants (TCA) for treatment of major depression **(Al-Harbi, 2012).**

Due to increased risk of suicidal attempts in young adults 18 to 24 years of age by antidepressant medications, the Food and Drug Administration (FDA) ordered all antidepressant medications to carry an expanded black-box warning (**American Association of Suicidology, 2014).**

Despite of presence of newer antidepressant agents with low toxicity profiles, TCA ingestion is still high and continue to be a leading cause of death. Amitriptyline (AMT) is tertiary amines,

lipophilic TCA, with sedative effects. The fatalities of AMT have increased because of the low level of toxic and fatal concentrations that cause fatal dysrhythrmia **(Baeck et al., 2000).**

The toxic effects of AMT are mainly due to inhibition of norepinephrine reuptake at nerve terminals, direct α adrenergic block, membrane stabilizing or quinidine-like effect on the myocardium and anticholinergic action. These actions are leading causes to cardiovascular effects and anti-cholinergic effects **(Kerr et al., 2001).**

The cardiovascular toxicity is a leading cause of morbidity and occasional mortality in amitriptyline over dose intoxicated patients. The commonest feature is hypotension which is resulted from combination of reduced myocardial contractility and decreased systemic vascular resistance and is considered the most difficult sign to treat. Another characteristic feature is arrhythmias that result from atrio-ventricular conduction delays, blockade of cardiac sodium channels, which increases the duration of the cardiac action potential and refractory period **(Kaplan et al., 2008)**

Citalopram is a highly lipophilic, rapidly absorbed SSRI which is approved by the FDA in 1988 for the treatment of major depression and also it is widely prescribed worldwide **(Rocha et al., 2007).**

In general, SSRIs have been shown to be safer in overdose than TCA and the rate of suicide from antidepressant intoxication decreased after their introduction **(Muzyk et al., 2010).** However, citalopram is considered to have the most potential ability for cardiac and neurologic toxicity among the SSRI **(Tarabar et al., 2008).** Serotonin syndrome may also occur following its overdose **(Grenha et al., 2013).**

The currently available lines of treatment are decontamination, respiratory and circulatory support and Na bicarbonate as specific antidotal therapy. Refractory cases of circulatory collapse have responded to prolonged cardiopulmonary resuscitation **(Citak et al., 2002).**

The benefit of Na bicarbonate in cases of TCA overdose is probably due to both an increase in serum pH and extracellular sodium. Alkalization favors the neutral form of the drug and reducing the amount of active cyclic antidepressants. The high sodium load increases the electrochemical gradient across cardiac cell membranes, potentially attenuating the TCA-induced blockade of sodium channels. Citalopram may produce similar ECG and clinical manifestations with favorable response to similarly administered IV sodium bicarbonate (**Mirrakhimov et al., 2017**).

During the last two decades, intravenous lipid emulsion (ILE) or lipid rescue has been developed to treat many poisonings **(Jamaty et al., 2010).**

The first human ILE use for overdose/poisoning was reported in 2006 in the management of acute local anesthetic toxicity (**Ciechanowicz and Patil, 2012)**, especially in restoring cardiac and hemodynamic stability. Since then, several studies evaluating the efficacy of lipid emulsions in treating toxicity from different fat-soluble drugs and xenobiotic such as calcium channel blockers **(Tebbutt et al., 2006)**, beta blockers **(Rothschild et al., 2010)**, organophosphates **(Moshiri et al., 2013)**, antipsychotics **(Moshiri et al., 2014)** and cocaine **(Arora et al., 2013)** had been done**.**

As amitriptyline and citalopram are most common combined therapeutics used in treatment of depression and known as lipophilic drugs. Therefore, the aim of our study is to evaluate the role of intravenous lipid emulsion as the main line of treatment compared to Na bicarbonate or as an adjunctive treatment with it for treatment of cardiovascular toxicity induced by administration of these combined drugs in adult albino rats.

MATERIAL & METHODS

Drugs

Amitriptyline (AMT) 50 mg (rounded white color tablets), citalopram hydrobromide 40 mg (oval, biconvex, white color, film coated tablets) were purchased from Egyptian company for drug trading (EGYDRUG), Zagazig, Egypt. Tablets were dissolved in distilled water that prepared into two separated solution sets. Each animal received 1 ml from each solution set.

Sodium bicarbonate (Na bicarbonate) 8.4% vial (50 ml for intravenous injection, pharmaceutical solutions industry, Jeddah, Saudi Arabia) was purchased from local drugstore, Zagazig, Egypt.

Intravenous lipid emulsion (ILE) (Smoflipid 20%, pH: 8, osmolality: 380 mosm/kg H2O, Fresenius Kabi Austria Gmbh, Graz, Austria) was obtained from the Egyptian group for import and export, Egypt. The lipid solution contained 60 gram refined soya –bean oil, 60 gram triglyceride, 50 gram refined olive oil, 30 gram fish oil, 163-225mg α tocopherol, 25gram anhydrous glycerol, 12 gram egg lecithin, 0.3 gram sodium oleate and water.

Experimental animals

Twenty one male adult albino rats (weight 300-330 g) were obtained from the Animal House of the Faculty of Medicine, Zagazig University, Egypt. The animals were maintained on rat chow and water ad libitum in the Breeding Animal House of the Faculty of Medicine, Zagazig University, Egypt. The animals were housed in filter-top plastic cages at a temperature-(25 °C) with a 12 hour light-dark cycle. All ethically approved conditions used for animal housing & handling were considered. All rats received human care in compliance with the guidelines of the Medical Research Ethics Committee of Zagazig University and met with those acquired by applicable international laws and regulations **(Institute of Laboratory Animal Resources, 1996)**. The experiments on animals were performed in department of physiology, faculty of medicine Zagazig University, Egypt.

Experimental design

The overnight fasted animals were anesthetized with urethane (1200 mg/kg) intraperitoneally, the tracheostomy is performed using a small piece of tracheal intubation tube for spontaneous breathing. The esophagus was cannulated by nasogastric cannula (eight-Gauge) for administration of AMT and citalopram. The right common carotid artery cannulated with polyethylene tube (with an internal diameter (ID) of 0.5 mm and an outer diameter (OD) of 0.9 mm PE50) provided with a 26 Gauge × 1/2 inch needle containing heparinized saline (0.5 IU/ml) for blood pressure measurement, electrocardiogram recording and blood sampling (for detection of arterial pH). The left external jugular vein and left femoral vein were cannulated with polyethylene tube (with an internal diameter (ID) of 0.5 and 0.7 mm and an outer diameter (OD) of 0.9 and 1.2 mm PE50, PE60,

respectively) both were provided with a 26 Gauge × 1/2 inch needle for Na bicarbonate and/or ILE administration, respectively. The body temperature was kept around 37°C by using desk lamp during the work.

Each animal left for stabilization for 15 min after cannulation then the baseline measurements of the experiment were recorded. All animals received single oral dose of 20mg/kg of AMT **(Baeck et al., 2000)** concurrently with 100mg/kg of citalopram **(Lullmann-Rauch and Nassberger, 1983),** dissolved in distilled water through nasogastric cannula with continuous recording of hemodynamic parameters and ECG while arterial pH was recorded once the target MAP was reached and 10 min after termination of experiment.

After 20-30min, MAP recorded reduction by ≤ 50 % indicating toxicity which was the target MPA, blood samples were taken and the intoxicated animals were treated by Na bicarbonate and/or ILE. The intoxicated animals were equally divided into three groups (seven rats/ group).

Group1 (Na bicarbonate):Once the target MAP was reached, the animals received Na bicarbonate in iv bolus dose of 2mEq/kg delivered during a 2-minute period **(Harvey and Cave, 2007)** then by iv infusion in a dose of 0.25ml/kg/min for 60 min.

Group 2 (ILE) :Once the target MAP was reached, the animals received the iv bolus of 1.5ml /kg of 20% ILE delivered during a 2-minute period followed by iv infusion of 0.25 ml / kg /min and increased stepwise to 12.4 ml/kg for 60 min (**Patocha et al., 2005; Harvey and Cave, 2007; Yurtlu et al., 2016).** The dosing regimen was adopted in line with the protocol of **(Varney et al., 2014).**

Group3 (Na bicarbonate + ILE): Once the target MAP was reached, the animals received the iv bolus of 2mEq/kg of Na bicarbonate delivered during a 2-minute period then by iv infusion in a dose of 0.25ml/kg/min in left external jugular vein and iv bolus of 1.5ml /kg of 20% ILE delivered during a 2-minute period followed by IV infusion of 0.25 ml / kg /min and increased stepwise to 12.4 ml/kg for 60 min in the left femoral vein.

All animals were continuously observed and hemodynamic parameters were monitored during the whole time of experiment and for 10 minutes after termination of administration of therapies. No death was recorded during the experiment.

Hemodynamic assessments

Mean arterial pressure (MAP), heart rate (HR) and electrocardiogram (ECG) for QRS duration that represented the cardiovascular parameters, were recorded via pressure transducer (MLT844 physiological pressure transducer with clip-on BP domes (AD Instruments Pty Ltd, Australia). Acquisition system (Power Lab 4/20 Data Acquisition System, AD Instruments, Australia).

The baseline hemodynamic recordings were evaluated for each group as (time 1). The target hemodynamic recordings were evaluated for each group as (time 2). The bolus dose hemodynamic recordings of each therapy for each group were evaluated as (time 3) then every 10 minutes of infusion for MAP, HR and QRS recordings in each group were evaluated as follow: at 10 min as time 4, 20 min as time 5, 30 min as time 6, 40 min as time 7, 50 min as time 8 and 60 min as time 9. Finally the recordings were evaluated 10 min after

termination of administration of all therapies for each group.

Arterial pH was recorded at time 1, time 2 and time 10 by blood gas analyzer. The experiment animals were killed by an intravenous bolus injection of 3 ml (300 mg/ml) pentobarbitone **(Harvey and cave, 2007)**.

Statistical analysis:

Results were expressed as mean ± standard deviation (SD). Two way repeated-measures ANOVA was used to evaluate the differences between variables where data were normal (Kolmogorov–Smirnov test),the assumptions of sphericity were violated (Mauchly's test) and the Greenhouse–Geisser correction was applied. Pairwise comparison for time, group and group versus time were evaluated. Bonferroni test was used to compare the difference between the experimental groups. Significance difference for all tests was set at $P < 0.05$ using SPSS software (v.16; SPSS).

RESULTS

The results of the present study revealed that, there were no statistically significant differences in the baseline values (time 1) of MAP, HR, QRS duration and pH between all studied groups ($P > 0.05$, figs 1-4) (table1).

Effects of combined single oral toxic dose of amitriptyline (AMT) and citalopram on MAP, HR, QRS and pH (time 2):

The combined antidepressant agents caused significant reduction of ≤ 50 % MAP and pH values after 20-30 min of therapies administrations indicating target toxicity (time 2) in all groups ($P \leq 0.001$ and $P \leq 0.05$, respectively, figs 1,4) while HR showed significant increase in all groups ($P \leq 0.05$, Figure 2) and QRS duration showed significant prolongation in all studied groups ($P \leq 0.001$, fig 3) compared to the baseline values (table 1).

Effects of iv bolus administration of Na bicarbonate, ILE and both therapies (time 3):

Mean arterial pressure and QRS duration showed significant improvement after iv bolus administration of therapies in all groups (time 3) as compared to toxicity values ($P \leq 0.001$).

There were no significant differences between Na bicarbonate and ILE groups in MAP measurements (58.2 ±1.6 mmHg, 59.2 ± 1.9 mmHg, $P > 0.05$, respectively) and QRS duration (21.8 ± 0.7 sec/min, 22 ± 0.8 sec/min, $P> 0.05$, respectively) (the same rate of change), while there was highly significant improvement of MAP measurement in Na bicarbonate + ILE group (60 ±1.3 mmHg, $P \leq 0.001$) and QRS duration (19.1± 0.9 sec/min, $P \leq 0.001$) as compared to the other groups (figs1,3).

Heart rate showed no significant changes as compared to toxicity values in all studied groups (332 ± 17.5 beats/ min, 331± 17.5 beats /min and 335 ± 8.5 beats/min $P > 0.05$) (fig 2).

Effects of iv infusion of Na bicarbonate, ILE and both therapies (time 4- time 9):

Mean arterial pressure results showed highly significant increase during iv infusion at 10 min to 60 min (time 4 to time 9) in gradual manner in all groups ($P \leq 0.001$). MAP developed increment at 10 min of infusion (time 4) in Na bicarbonate, ILE and Na bicarbonate + ILE groups (59.6±1.7 mmHg, 59.9 ± 1.8 mmHg and 62 ±1.3mmHg, respectively) reaching the maximum level at 60 min (time 9) in Na bicarbonate, ILE and Na bicarbonate +ILE (76.14 ± 0.9 mmHg,

76.9 ± 0.9 mmHg and 85.2 ± 1.4 mmHg, respectively).

There were no significant differences between Na bicarbonate and ILE groups across all time intervals ($P > 0.05$) (the same rate of improvement), while there was highly significant increment of MAP in Na bicarbonate + ILE group across all time intervals as compared to toxicity values from one hand and the other groups from the other hand ($P \leq 0.001$) (fig 1).

QRS duration results, QRS prolongation showed highly significant reduction during iv infusion at 10 min to 60 min (time 4- time 9) in gradual manner in all groups as compared to toxicity values ($P \leq 0.001$). QRS duration recorded reduction at 10 min of infusion (time 4) in Na bicarbonate, ILE and Na bicarbonate +ILE groups(19.9± 0.8 sec/min, 21.1± 0.9 sec/min and 16.6±0.7sec/min, respectively) reaching the maximum level of reduction at 60 min (time 9) in Na bicarbonate, ILE and Na bicarbonate +ILE groups (12.6± 0.1 sec/min, 11.8 ± 0.2 sec/min and 11.6 ± 0.1 sec/min, respectively).

There were highly significant differences between Na bicarbonate and ILE groups at time 4,5,6 and 7 ($P \leq 0.001$) then at time 8 and 9 the statistical results recorded no significant differences ($P > 0.05$) between both of two groups (the same rate of improvement). However, in Na bicarbonate + ILE group, there was highly significant differences as compared to toxicity values from one hand and the other groups from the other hand (the best results of reduction of QRS duration that approximate the base line values was evaluated at 60 min (time 9) ($P \leq 0.001$) (fig 3).

Heart rate results showed no significant changes along iv infusion time intervals in all studied groups as compared to toxicity values ($P > 0.05$) and high significant changes as compared to baseline values ($P \leq 0.001$) (fig 2) .

Follow up results after the end of administration of Na bicarbonate, ILE and both therapies (time 10):

Mean arterial pressure, HR and QRS duration results after the end of administration (time 10)showed no significant differences as compared to the results of time 9 ($P > 0.05$) and highly significant differences as compared to toxicity values ($P \leq 0.001$ table 1).

There were no significant differences between Na bicarbonate and ILE groups after the end of administration (time 10)($P > 0.05$) (the same rate of change), while there was highly significant differences in Na bicarbonate + ILE group as compared to other groups ($P \leq 0.001$, figs1,2 and 3, respectively).

pH results, showed highly significant differences after the end of administration of all therapies (time 10) as compared to toxicity values (time 2) in all studied groups ($P \leq 0.001$ table 1). There was no significant differences in pH results among all studied groups at time 10 ($P > 0.05$, fig 4).

Table (1): Mean arterial pressure (MAP), Heart rate, QRS duration and pH measurements comparisons at different time intervals between the studied groups.

Group / Measurement		Group 1 Na bicarbonate mean ± SD	Group 2 ILE mean ± SD	Group 3 Na bicarbonate + ILE mean ± SD
Mean arterial pressure (mm/Hg)	**Time 1**	92 ± 0.97	91.4 ± 1.3	90.2 ± 1.5
	Time 2	*45.2 ± 0.59	*44.6 ± 0.88	*43.8± 0.93
	Time 10	**76 ± 0.9	**77.8 ± 0.8	**85 ± 1.3
Heart rate (beat/ min)	**Time 1**	311 ± 8.7	312 ± 7.6	314 ± 8.1
	Time 2	*330 ± 18.9	*331 ± 17.7	*332 ± 12.5
	Time 10	*322 ± 8.3	*323 ± 5.1	*320 ± 6
QRS duration (sec/min)	**Time 1**	12 ± 0.54	11.7 ± 0.53	11. 5 ± 0.43
	Time 2	*24.8 ± 1.7	*25.6 ±1.8	*26.1 ± 2.2
	Time 10	**12.6 ± 0.12	**11.8 ± 0.3	**11.3 ± 0.12
pH	**Time 1**	7.38 ± 0.01	7.36 ± 0.02	7.37 ± 0.01
	Time 2	*7.20 ± 0.05	*7.25 ± 0.03	*7.27 ± 0.02
	Time 10	**7.35 ± 0.01	**7.33 ± 0.02	**7.34 ± 0.01

Results are expressed as mean ± SD (Number = 7 rats/group).
ILE: Intravenous lipid emulsion
Time 1: post-operative baseline measurement.
Time 2: target toxicity.
Time 10: 10 min after the end of all therapies administration.
*** Significantly different compared to baseline values (p < 0.001).**
**** Significantly different compared toxicity values (p < 0.001).**

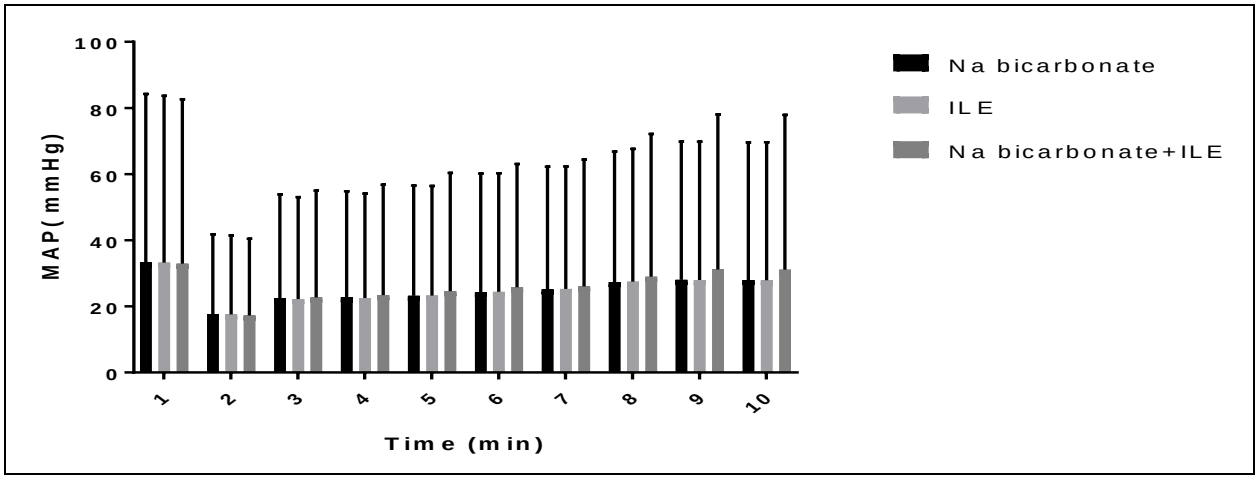

Figure (1): Mean arterial pressure changes in all studied groups versus time

Results are expressed as mean ± SD (Number = 7 rats/group).
ILE: Intravenous lipid emulsion.
Time 1: post operative baseline measurement. Time 2: target toxicity recordings.
Time 3:The bolus dose recordings. Time 4:10 min post infusion recordings.
Time 5: 20 min post infusion recordings. Time 6: 30 min post infusion recordings.
Time 7:40 min post infusion recordings. Time 8:50 min post infusion recordings.
Time 9: 60 min post infusion recordings. Time 10: 10 min after the end of all therapies administration.

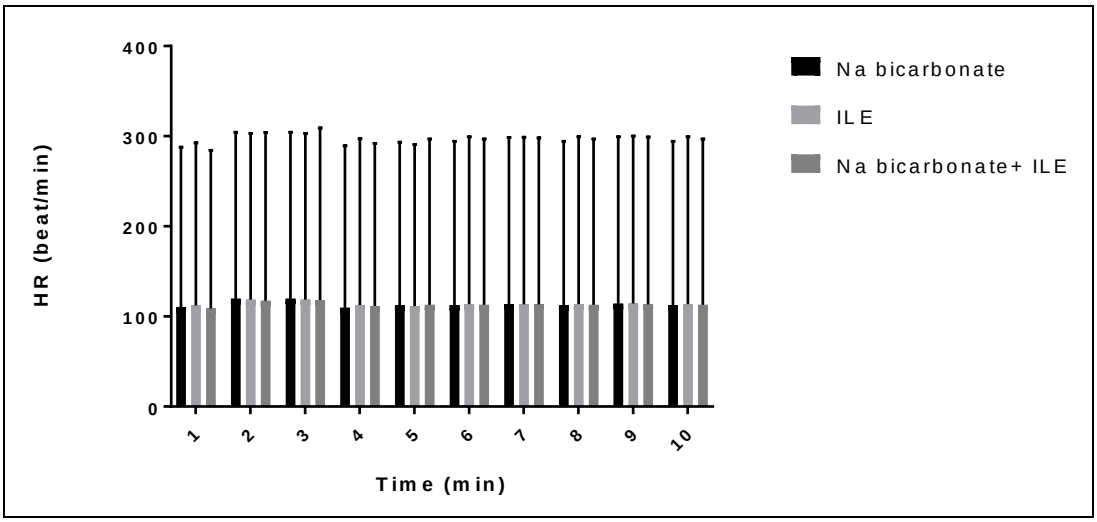

Figure (2): Heart rate changes in all studied groups versus time

Results are expressed as mean ± SD (Number = 7 rats/group).
ILE: Intravenous lipid emulsion.
Time 1: post operative baseline measurement. Time 2: target toxicity recordings.
Time 3:The bolus dose recordings. Time 4:10 min post infusion recordings.
Time 5: 20 min post infusion recordings. Time 6: 30 min post infusion recordings.
Time 7:40 min post infusion recordings. Time 8:50 min post infusion recordings.
Time 9: 60 min post infusion recordings. Time 10: 10 min after the end of all therapies administration.

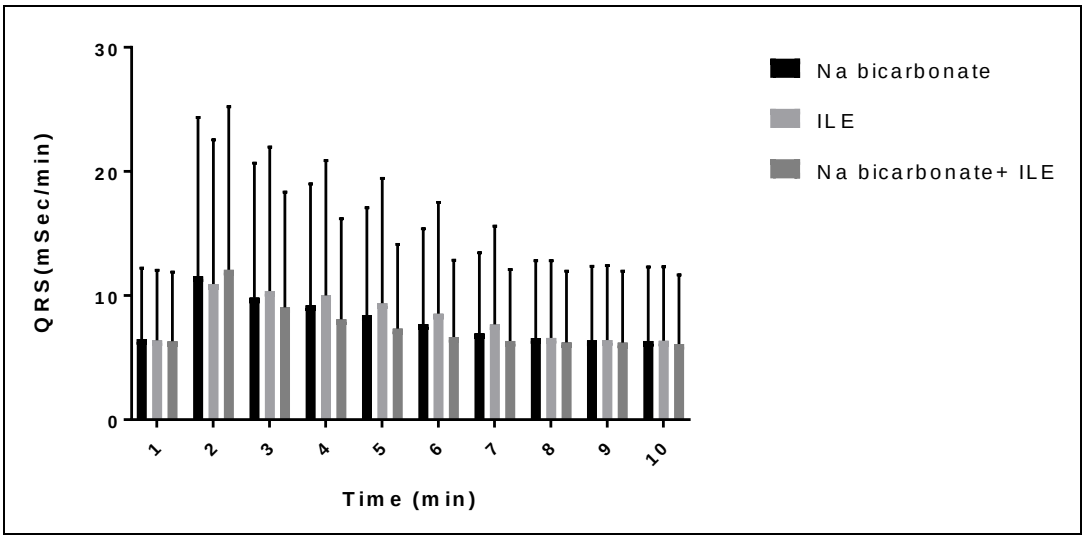

Figure (3): QRS duration changes in all studied groups versus time

Results are expressed as mean ± SD (Number = 7 rats/group).
ILE: Intravenous lipid emulsion.
Time 1: post operative baseline measurement. Time 2: target toxicity recordings.
Time 3:The bolus dose recordings. Time 4:10 min post infusion recordings.
Time 5: 20 min post infusion recordings. Time 6: 30 min post infusion recordings.
Time 7:40 min post infusion recordings. Time 8:50 min post infusion recordings.
Time 9: 60 min post infusion recordings. Time 10: 10 min after the end of all therapies administration.

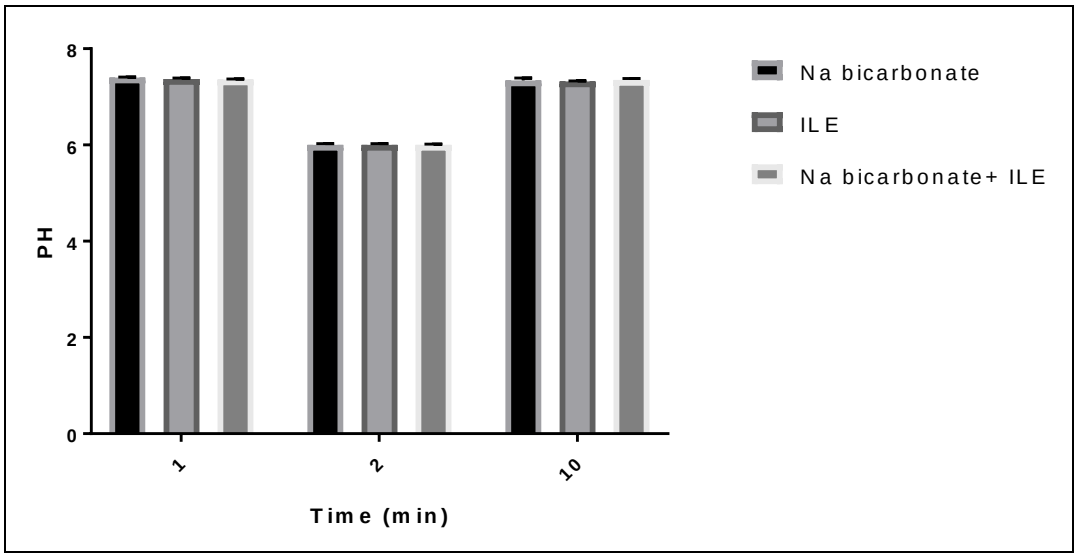

Figure (4): pH changes in all studied groups versus time

Results are expressed as mean ± SD (Number = 7 rats/group).
ILE: Intravenous lipid emulsion.
Time 1: post operative baseline measurement.
Time 2: target toxicity.
Time 10: 10 min after the end of all therapies administration.

DISCUSSION

Overdoses toxicity of therapeutics especially antidepressant agents in patients with depressive disorders are considered a major problem in our country. Overdoses poisoning by combined therapeutics is another phenomena. Besides presence of new trend as ILE in treatment of such toxicological cases. All these circumstances encouraged us for this work.

Intravenous lipid emulsion (ILE) is an emulsion of soybean oil, egg phospholipids and glycerin. It gives essential fatty acids such as linoleic acid, omega-6 fatty acid, alpha-linolenic acid (ALA) and omega-3 fatty acid. It was approved for human use since 1962 **(Foxall et al., 2007).** Now, ILE is considered as a novel method for treating drug toxicity especially lipophilic toxins **(Agarwala et al., 2014).**

Amitriptyline and citalopram are lipophilic drugs, with a large volume of distribution **(Baldessarini, 2006; Rocha et al., 2007).** They are combined for treating patients with major depression **(Rampello et al., 2004).**

The results of the present study showed significant improvement in MAP and QRS duration after iv bolus administration of therapies in all studied groups with no significant differences between Na bicarbonate and ILE groups, while there were highly significant improvements in Na bicarbonate + ILE group as compared to the other groups.

During and after the end of iv infusion of the therapies, MAP and QRS duration showed highly significant improvement in all groups that appeared in gradual manner with no significant differences between Na bicarbonate and ILE groups across all time intervals, while there were highly significant improvements of MAP and QRS duration in Na bicarbonate + ILE infusion group across all time intervals

as compared to toxicity values and the other improving groups.

Follow up for 10 min after the end of therapies administration, results for MAP and QRS duration showed no significant differences in all studied groups as compared to the results of ending therapies infusion time and also high significant differences as compared to toxicity values.

No significant differences were observed between both of Na bicarbonate and ILE groups, while there were highly significant differences in Na bicarbonate + ILE group as compared to other groups. The results of pH showed highly significant differences as compared to toxicity values in all studied groups.

There were no animal studies conducted for the efficiency of ILE on mixed amitriptyline and citalopram overdoses, however, there were animal studies evaluated the role of ILE in the treatment of TCA toxicity. **Harvey and Cave (2007); Harvey et al. (2009)** in their studies about the effect of ILE on clomipramine toxicity as an example of TCA in rats and rabbits respectively, showed an improvement of hypotension and increased animals survival.

In comparison with sodium bicarbonates, the ILE administration in animals studies showed reduction in the mortality and increased the median survival better than sodium bicarbonates **(Harvey and Cave, 2014).**

Bania and Chu (2006) founded that ILE had been a superior treatment over both saline and sodium bicarbonate in improving MAP after administration of amitriptyline in rats.

However, other studies founded that ILE sequesters AMT in plasma, but had no significant effect on hemodynamic parameters**(Litonius et al., 2012; Heinonen, 2016).** In other rodent model of oral administered AMT, the survival was significantly lower with ILE treatment and blood AMT concentration was higher with ILE treatment**(Perichon et al., 2013) .**

In a swine model of intravenous AMI toxicity, ILE infusion was compared with infusion of hypertonic sodium bicarbonate. The median time from hypotension to death was prolonged with bicarbonate therapy**(Varney et al., 2014)** but neither treatments affected overall survival.

There were case reports of mixed amitriptyline and citalopram overdoses. In these cases, blood pressure and cardiac conduction times seemed to improve after lipid emulsion administration **(Scholten et al., 2012; Nair et al., 2013).**

Also, there were several case reports of administration of ILE as adjunctive therapy in treatment of AMT toxicity where the cardiovascular toxicity of AMT presented by wide QRS complex, hypotension and even cardiac arrest. These patients received the ordinary lines of treatment including sodium bicarbonate but, immediate improvement after ILE administration in the form of bolus dose followed by infusion had occurred **(Harvey and Cave, 2012; Levine et al., 2012; Odigwe et al., 2016; Baylis, 2017) .**

In some other patients, the improvement was seen more gradually within an hour or longer time (**Carr et al., 2009; Eren et al., 2014).** However, Only one patient seemed not to have benefit from lipid emulsion at all **(Kiberd and Minor, 2012).**

Kasnavieh et al. (2013) in their randomized controlled trial where they evaluated the role of ILE with

comparison to bicarbonate on cardiotoxicity and the complications of severe TCA toxicity. The authors founded that there was not any significant changes in outcomes regarding blood pressure, mortality and duration of hospitalization in patients receiving ILE.

As regard heart rate, the present study showed no significant changes as compared to toxicity values in all studied groups after iv bolus, iv infusions of the therapies and after 10 min of follow up.

In a case report of AMI overdose presented by ventricular tachycardia with wide QRS complex. The patient treated by traditional treatment with Na bicarbonate for 24 hours then start ILE for another 24 hours. On discharge, the patient had normal QRS complex but still had tachycardia **(Sabah et al., 2017).** In another case report of AMI overdose presented by wide complex tachycardia . Intravenous lipid emulsion reduced tachycardia after 39 hours **(Kiberd and Minor, 2012).**

The lipid emulsion therapy was recommended to be used as evidence based in TCA overdoses if other therapies failed while in SSRI toxicity the recommendations were neutral **(Gosselin et al., 2016).** This approach is supported by (**Baylis, 2017)** who consider lipid emulsion therapy in patients presenting with refractory cardiovascular collapse secondary to lipophilic drug toxicity with failure of the ordinary lines of treatment.

Most researchers attributed the role of ILE in the treatment of lipophilic drug toxicity to several mechanisms of action. The most widely accepted one, is "lipid sink" theory. This theory suggests that the rapid intravenous administration of lipid leads to movement of lipophilic drugs from the site of toxicity to bloodstream down the concentration gradient. Thus, the volume of distribution of a lipophilic drug was reduced with increasing its blood level leading to prevention of drug action in the target tissues **(Harvey et al., 2009)**.

However, **Harvey and Cave (2014)** suggested that the lipid sink alone cannot explain the action of ILE therapy because of its inefficacy with lipophilic agents as β blockers. Besides the previous findings that was reported increased TCA blood level with decreasing its volume of distribution without any significant effect on hemodynamic parameters**(Litonius et al., 2012; Perichon et al., 2013)**.

Others attributed the mechanism of ILE to increase the myocardial energy substrate delivery and the direct cardiotonic effect of ILE by which improving cardiac function **(Weinberg, 2012**) while, (**Pennec et al., 2010)** reported the effect of ILE on calcium ion channels through the higher levels of long-chain fatty acids leading to increased the level of cardiomyocyte calcium and with positive inotropic effect improving the heart contractility.

Recently, **Partownavid et al. (2012)** attributed the cardioprotective action of the long-chain fatty acids in ILE to Ca^{2+}-homeostasis and rescue signaling pathways that regulate the opening of the mitochondrial permeability transition pore (mPTP). The Ca^{2+}-homeostasis requires fatty acid metabolism leading to production of reactive oxygen species (ROS) by the mitochondria which, in turn, activates rescue pathways **(Lou et al., 2014).**

These direct ILE cardiac effects may be superior than the lipid sink theory as very high doses of lipid emulsion have caused a rise in arterial

blood pressure, heart rate and carotid blood flow were reported in studies on rats, possibly through inotropic and lusitropic mechanisms **(Fettiplace et al., 2014).**

CONCLUSION

From the former results, it can be concluded that ILE is efficient as Na bicarbonate in reversing cardiovascular toxicity especially the reduction of MAP and QRS prolongation induced by antidepressant agents besides, improving the pH recordings. While the concurrent use of Na bicarbonate + ILE showed better results than using ILE or Na bicarbonate alone indicating the effect of ILE, where it accelerated the improvement of MAP and QRS duration earlier in time during infusion.

Therefore, ILE may be used as a main line of treatment and also, can be used as an adjunctive therapy in treatment of combined AMT and citalopram induced cardiovascular toxicity in adult rats.

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الملخص العربى

دور المستحلب الدهنى الوريدى على تسمم القلب والاوعيه الدمويه الناتج عن الجرعات الزائدة لكلا من الأمتربتالين و السيتالوبرام على ذكور الجرذان البيضاء البالغه

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المقدمه: يعد التسمم بمضادات الاكتئاب ظاهره شائعه جدا بين مرضى الاكتئاب.

الهدف: تقييم دور المستحلب الدهنى الوريدى كعلاج اولى اوعلاج موازى لبيكربونات الصوديوم فى علاج تسمم القلب والاوعيه الدمويه الناتج عن اعطاء الجراذن جرعات زائدة متزامنه لمره واحدة من كلا من الأمتربتالين و السيتالوبرام.

المواد والطرق المستخدمة: تم تقسيم الجرذان بالتساوى بعد تعرضها للجرعات الزائده وظهور آثار التسمم عليها الى ثلاث مجموعات كالآتى: المجموعه الأولى: تم حقن الجرذان وريديا بجرعه ٢مل/كجم من بيكربونات الصوديوم دفعه واحدة ثم تبعها ٠,٢٥مل/كجم/ دقيقه بالضخ الوريدى، المجموعه الثانيه: تم حقن الجرذان بالمستحلب الدهنى الوريدى٢٠% بدايه بجرعه ١,٥مل/كجم كدفعه واحدة ثم تبعها ٠,٢٥ مل/كجم/ دقيقه بالضخ الوريدى وتم زيادتها بالتدريج حتى ١٢,٤مل/كجم، المجموعه الثالثه :تم حقن الجرذان كلا من بيكربونات الصوديوم و المستحلب الدهنى الوريدى٢٠ % بنفس الطريقه و الجرعات. تم إعطاء كلا من الجرذان بيكربونات الصوديوم والمستحلب الدهنى الوريدى لمدة ٦٠ دقيقه. تم قياس كلا من ضغط الدم الشريانى و معدل ضربات القلب وعمل رسم قلب كهربائى لكل جرذ خضع للتجربه قبل وبعد التجربه كما تمت المتابعه على مدى فتره التجربه كلها. كما تم مقارنه درجه حموضه او قلويه الدم قبل وبعد التجربه.

النتائج: لوحظ تحسن ذو دلاله احصائيه فى كلا من قياسات ضغط الدم ورسم القلب الكهربائى بعد دفعه الحقن الوريدى الاولى، واثناء الضخ الوريدى لكلا من بيكربونات الصوديوم والمستحلب الدهنى الوريدى وبعد ١٠ دقائق من انتهاء التجربه فى كل المجموعات بينما لم تتغير قياسات معدل ضربات القلب اثناء التجربه لكل الجرذان، كما اظهرت نتائج قياس حموضه او قلويه الدم تحسن بالمقارنه بقبل العلاج. من ناحيه أخرى لم نجد اختلاف احصائي بين نتائج المجموعه الاولى والثانيه فى كل القياسات (بيكربونات الصوديوم، والمستحلب الدهنى الوريدى) بينماوجد تحسن ملحوظ ذو دلاله احصائيه فى نتائج المجموعه الثالثه (بيكربونات الصوديوم+ والمستحلب الدهنى الوريدى) عند مقارنته بنتائج المجموعتين السابقتين.

الاستنتاج: يمكن استخدام المستحلب الدهنى الوريدى ٢٠% كعلاج اولى كما يمكن استخدامه كعلاج مساعد مع بيكربونات الصوديوم فى علاج الآثار المترتبه على التسمم بادويه الاكتئاب على القب والاوعيه الدمويه فى الجرذان البالغه.