Can empirical hypertonic saline or sodium bicarbonate treatment prevent the development of cardiotoxicity during serious amitriptyline poisoning?

Experimental research

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Abstract

Objective: The aim of this experimental study was to investigate whether hypertonic saline or sodium bicarbonate administration prevented the development of cardiotoxicity in rats that received toxic doses of amitriptyline.

Method: Thirty-six Sprague Dawley rats were used in the study. The animals were divided into six groups. Group 1 received toxic doses of i.p. amitriptyline. Groups 2 and 3 received toxic doses of i.p. amitriptyline, plus i.v. sodium bicarbonate and i.v. hypertonic saline, respectively. Group 4 received only i.v. sodium bicarbonate, group 5 received only i.v. hypertonic saline, and group 6 was the control. Electrocardiography was recorded in all rats for a maximum of 60 minutes. Blood samples were obtained to measure the serum levels of sodium and ionised calcium.

Results: The survival time was shorter in group 1. In this group, the animals’ heart rates also decreased over time, and their QRS and QTc intervals were significantly prolonged. Groups 2 and 3 showed less severe changes in their ECGs and the rats survived for a longer period. The effects of sodium bicarbonate or hypertonic saline treatments on reducing the development of cardiotoxicity were similar. The serum sodium levels decreased in all the amitriptyline-applied groups. Reduction of serum sodium level was most pronounced in group 1.

Conclusion: Empirical treatment with sodium bicarbonate or hypertonic saline can reduce the development of cardiotoxicity during amitriptyline intoxication. As hypertonic saline has no adverse effects on drug elimination, it should be considered as an alternative to sodium bicarbonate therapy.

Keywords: amitriptyline, poisoning, cardiotoxicity, sodium bicarbonate, hypertonic saline

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Tricyclic antidepressant (TCA) drugs are commonly used to treat many neuropsychiatric diseases.1 Amitriptyline is the most commonly prescribed antidepressant, and it is a frequent cause of toxicity in drug overdoses. TCA overdose primarily affects the neurological, cardiovascular and respiratory systems.1,2 Blockage of the rapid sodium channels is responsible for drug-induced cardiotoxicity, which clinically manifests as PR, QT and QRS prolongation, ventricular or supraventricular arrhythmias, hypotension and heart failure.1,3 Sodium bicarbonate (NaHCO₃) administration is the most widely accepted treatment to reduce amitriptyline-induced cardiotoxicity.2,4 However, at an alkaline pH, the volume distribution of amitriptyline expands, and the elimination time is longer. Therefore, NaHCO₃ treatment is suggested only in the presence of cardiac findings.4 Hypertonic saline (HS) administration has been shown to be useful, particularly when cardiotoxicity is accompanied by hypotension.5,6

There is always a need for a medication to prevent cardiotoxicity that will save patients’ lives, especially when toxic
The QRS duration was measured from the beginning of the Q wave to the end of the S wave. The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as the return to the TP isoelectric line. The QT interval was defined as the average of the QT intervals of three consecutive beats in each of the ECG leads. The QT intervals were also corrected for heart rate using Bazett’s formula. The QTc is equal to the QT interval in seconds divided by the square root of the preceding R–R interval in seconds. A decrease in the heart rate below 100 beats/minutes or the presence of asystole during recording was accepted as the exodus.

To measure serum levels of sodium and ionised calcium, blood samples were obtained from the carotid arteries of the living rats 60 minutes after the administration of amitriptyline or other treatments, but immediately from the rats that had died.

**Statistical analysis**

Statistical analyses were performed with IBM SPSS 21.0 (Chicago, IL, USA). The Kolmogorov–Smirnov test was used to evaluate the distribution of variables in relation to normal. Descriptive statistics were presented as the mean ± standard deviation. Statistical comparisons between all groups were performed with one-way ANOVA with a Tukey post-hoc test. Correlations between the quantitative data were analysed by the Pearson correlation test. The level of statistical significance was set at \( p < 0.05 \).

**Results**

The characteristics of the rats in all groups were similar. In group 1, all the rats died in the first 25 minutes. Therefore, the statistical analyses with group 1 included data for only the first 25 minutes. The other inter-group statistical analyses included data obtained over 60 minutes.

The initial heart rate was similar among the groups. The heart rates of the rats in groups 1, 2 and 3 decreased in direct proportion to time, with the decrease more marked in group 1. The heart rates of the rats in groups 4, 5 and 6 did not show significant change over time.

Hypertonic saline or NaHCO₃ administration, along with amitriptyline, ameliorated the reduction in the heart rates. There was no significant difference in the heart rates between the HS and NaHCO₃ groups. Table 2 shows a comparison of the heart rates changes with time according to group.
rates of the rats in each group in each time period. The changes in the heart rates in the amitriptyline-treated groups (groups 1, 2 and 3) and the control group are shown in Fig. 1.

The baseline QRS durations were similar among groups. The changes in the QRS durations in the groups that did not receive amitriptyline (groups 4, 5 and 6) were non-significant, whereas the amitriptyline-administered groups (groups 1, 2 and 3) showed a statistically significant increase in the QRS duration. This increase was more marked in group 1. The increase in QRS duration was limited in the groups that received amitriptyline with HS or NaHCO3 (groups 2 and 3). There was no statistically significant difference between these groups in terms of increase in the duration of the QRS. A comparison of the QRS duration of the amitriptyline-treated groups and the control group is shown in Fig. 2.

The baseline QTc durations were similar among the groups. There was no significant change in the QTc durations in the groups that did not receive amitriptyline (groups 4, 5 and 6). The QTc duration increased in the amitriptyline-treated groups (groups 1, 2 and 3), but the increase was more marked in group 1. The increase in the QTc duration was reduced in the groups administered HS or NaHCO3, with amitriptyline. There was no statistically significant difference between the two groups (groups 2 and 3) in terms of QTc prolongation. A comparison of the QTc duration of the groups in each time period is shown in Table 4, and a comparison of the change in duration of the QTc in the amitriptyline-treated groups and the control group is shown in Fig. 3.

Serum samples for sodium and ionised calcium analyses were taken from the surviving rats at the 60th minute and from the non-survivors immediately after death. In the groups that received amitriptyline (groups 1, 2 and 3), the serum sodium levels had decreased. This decline was most evident in group 1, which did not receive any sodium-containing treatment. Hyponatraemia was more pronounced in group 2 than group 3. No subject developed hypernatraemia.

The serum ionised calcium levels were higher in the groups that received amitriptyline and highest in the amitriptyline-only group (group 1). The distribution of the serum levels of ionised calcium and sodium in the groups is shown in Table 5. The serum sodium levels showed a strong positive correlation with heart rates, a strong negative correlation with QRS duration, and a

\[ r = 0.782 \]

\[ p = 0.032 \]

\[ 0.000 \]

\[ 0.000 \]

\[ 0.001 \]

1 The increase in the QTc duration was reduced in the groups administered HS or NaHCO3, with amitriptyline. There was no statistically significant difference between the two groups (groups 2 and 3) in terms of QTc prolongation. A comparison of the QTc duration of the groups in each time period is shown in Table 4, and a comparison of the change in duration of the QTc in the amitriptyline-treated groups and the control group is shown in Fig. 3.

Table 3. QRS changes with time according to group

| Group | Start  | 5th minute | 10th minute | 15th minute | 20th minute | 25th minute |
|-------|--------|------------|-------------|-------------|-------------|-------------|
| 1     | 0.210 ± 0.001* | 0.0303 ± 0.0015* | 0.042 ± 0.014*** | 0.057 ± 0.014*** | 0.061 ± 0.130*** | 0.072 ± 0.022*** |
| 2     | 0.208 ± 0.001* | 0.022 ± 0.010* | 0.027 ± 0.006* | 0.030 ± 0.006* | 0.032 ± 0.006** | 0.032 ± 0.006** |
| 3     | 0.208 ± 0.003* | 0.022 ± 0.002* | 0.034 ± 0.008** | 0.038 ± 0.008** | 0.037 ± 0.008** | 0.038 ± 0.009** |
| 4     | 0.198 ± 0.001* | 0.019 ± 0.001* | 0.020 ± 0.001* | 0.020 ± 0.001* | 0.019 ± 0.001* | 0.020 ± 0.001* |
| 5     | 0.202 ± 0.001* | 0.020 ± 0.001* | 0.020 ± 0.002* | 0.020 ± 0.002* | 0.021 ± 0.002* | 0.020 ± 0.001* |
| 6     | 0.195 ± 0.003* | 0.018 ± 0.002* | 0.019 ± 0.001* | 0.019 ± 0.002* | 0.019 ± 0.000* | 0.019 ± 0.000* |
| Mean  | 0.204 ± 0.002 | 0.022 ± 0.007 | 0.027 ± 0.010 | 0.030 ± 0.015 | 0.031 ± 0.016 | 0.031 ± 0.018 |

*p-value

\[ p = 0.782 \]

\[ p = 0.032 \]

\[ 0.000 \]

\[ 0.000 \]

\[ 0.001 \]

The group with no difference from the others, *p < 0.05 (compared with groups 1 and 2, compared with groups 1 and 3, compared with groups 1 and 4, compared with groups 1 and 5, compared with groups 1 and 6, compared with groups 2 and 3, compared with groups 2 and 4, compared with groups 2 and 5, compared with groups 2 and 6, compared with groups 3 and 4, compared with groups 3 and 5, compared with groups 3 and 6).
It causes toxicity by blocking the voltage-gated sodium channels, which facilitate the fast flow of sodium into the cells. Anticholinergic and α-adrenergic blockage also contribute to this. Blockage of cardiac sodium and potassium channels may result in cardiac conduction delay, dysrhythmia and hypotension due to myocardial depression. This process may appear on the ECG as prolonged PR, QRS and QT times, sinus tachycardia, and supraventricular and ventricular arrhythmias. The most important cause of death is persistent hypotension resulting from myocardial depression due to arrhythmias.

The majority of patients who take toxic doses of amitriptyline enter a coma, but a minority develop life-threatening complications. Others often recover with supportive care, without subsequent problems. Despite defined scoring systems such as the Antidepressant Overdose Risk Assessment (ADORA), it is often difficult to distinguish these two groups of patients. In addition, the correlation between serum drug levels and clinical outcome is weak, and routine drug level analyses are not recommended.

Various methods have been used to treat patients with severe cardiotoxicity due to amitriptyline overdose. These include serum alkalinisation with hypertonic NaHCO₃ or hypertonic saline, inotropic agents, magnesium sulphate, anti-arrhythmic drugs, glucagon, haemoperfusion, or lipid emulsion. Although many studies have compared these treatment methods, no treatment has been shown to prevent or reduce the toxicity in patients who may potentially develop severe toxicity.

### Table 4. QTc changes with time according to group

| Group | Start | 5th minute | 10th minute | 15th minute | 20th minute | 25th minute |
|-------|-------|------------|-------------|-------------|-------------|-------------|
| 1     | 0.119 ± 0.005* | 0.115 ± 0.007* | 0.154 ± 0.019** | 0.187 ± 0.025** | 0.255 ± 0.11** | 0.277 ± 0.084** |
| 2     | 0.118 ± 0.005* | 0.115 ± 0.009* | 0.119 ± 0.004** | 0.124 ± 0.021** | 0.124 ± 0.021** | 0.129 ± 0.020** |
| 3     | 0.119 ± 0.006* | 0.124 ± 0.009* | 0.143 ± 0.016** | 0.150 ± 0.018** | 0.146 ± 0.021** | 0.149 ± 0.021** |
| 4     | 0.121 ± 0.006* | 0.123 ± 0.007* | 0.123 ± 0.007** | 0.127 ± 0.007** | 0.124 ± 0.005** | 0.123 ± 0.008** |
| 5     | 0.120 ± 0.002* | 0.119 ± 0.005* | 0.119 ± 0.004** | 0.123 ± 0.005** | 0.119 ± 0.004* | 0.122 ± 0.005** |
| 6     | 0.117 ± 0.006* | 0.111 ± 0.009* | 0.113 ± 0.007** | 0.117 ± 0.007** | 0.118 ± 0.003** | 0.119 ± 0.008** |
| Mean  | 0.119 ± 0.006* | 0.118 ± 0.009* | 0.128 ± 0.180 | 0.138 ± 0.03 | 0.148 ± 0.065 | 0.146 ± 0.057 |

*p-value 0.654 0.055 0.000 0.000 0.000

*The group with no difference from the others, p < 0.05 (compared with groups 1 and 2, ccompared with groups 1 and 3, dcompared with groups 1 and 4, ecompared with groups 1 and 5, fcompared with groups 1 and 6, gcompared with groups 2 and 3, hcompared with groups 2 and 4, icompared with groups 2 and 5, jcompared with groups 2 and 6, kcompared with groups 3 and 4, lcompared with groups 3 and 5, and mcompared with groups 3 and 6).

### Table 5. Distribution of serum levels of ionised calcium and sodium according to group

| Group | Sodium | Calcium |
|-------|--------|--------|
| 1     | 111.2 ± 4.3* | 4.14 ± 0.4* |
| 2     | 121.2 ± 6.2* | 4.19 ± 0.4* |
| 3     | 133.4 ± 10.9* | 4.15 ± 1.0* |
| 4     | 143.5 ± 3.4* | 2.85 ± 0.6* |
| 5     | 145.7 ± 4.7* | 2.52 ± 0.7* |
| 6     | 147.8 ± 4.6* | 1.83 ± 0.7* |
| Mean  | 133.8 ± 14.9 | 3.28 ± 1.1 |

*p-value 0.000

*No statically significant differences among groups 1, 2 and 3.

*No statically significant differences among groups 4, 5 and 6.

### Table 6. Correlation between heart rate, QRS and QTc intervals and serum sodium and calcium levels

| Levels | Rate | QRS duration | QTc duration |
|--------|------|--------------|--------------|
| Sodium | p    | 0.000        | 0.000        | 0.000        |
| r      | 0.794** | -0.776**     | -0.612**     |
| Calcium| p    | 0.000        | 0.002        | 0.016        |
| r      | -0.0620* | 0.500**     | 0.399*       |

*Correlation significant at the 0.05 level.

**Correlation significant at the 0.01 level.
Conclusion

Amitriptyline poisoning is a common occurrence. Although the majority of cases improve with supportive therapy, cardiac complications may be life threatening in some cases. Although prospective, controlled human studies are needed, the results of this preliminary study suggest that amitriptyline poisoning leads to hyponatraemia, and early HS or NaHCO₃ treatment may reduce the development of cardiac toxicity. As HS treatment does not affect serum levels of ionised calcium and potassium or change the drug elimination time, it may be preferred to NaHCO₃, therapy.

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