EFFECTS OF REPEATED APPLICATION OF ISOFLURANE AND DESFLURANE ON ELECTROCARDIOGRAM, ANAESTHESIA INDUCTION, AND RECOVERY CHARACTERISTICS IN RATS

ATAKAN ÖZTÜRK, AND MUHAMMED ENES ALTUĞ

Konya Big City Municipality, Dog Care House, 42020 Konya, Turkey
1Department of Surgery, Faculty of Veterinary Medicine, Mustafa Kemal University, 31040, Hatay, Turkey
ealtug@mku.edu.tr

Received for publication March, 06, 2007

Abstract

Thirty male Wistar albino rats were equally divided into two groups. All the animals were sedated with 5 mg kg⁻¹ of xylazine hydrochloride, and then 2.5% isoflurane or 8% desflurane with 100% oxygen by mask induction were given and anaesthesia maintenance was continued for 60 min with 5.7% desflurane or 1.4% isoflurane. Anaesthesia applications were repeated on the 1st, 3rd, and 7th d in both groups. Heart and respiratory rates, rectal temperature, and electrocardiogram recordings were monitored periodically at the control time and at the 15th, 30th, and 60th min during anaesthesia. Anaesthesia induction and recovery times were also controlled. Compared to the 1st d, the repeated administration of desflurane and isoflurane caused no statistically significant change in QT and QTc intervals. The P wave duration (ms) decreased on the 7th d in both groups (P<0.05), and the R wave amplitude (mV) significantly decreased on the 3rd d in the desflurane group (P<0.05). Although significant differences in the QRS interval (ms) (P<0.001) and R wave amplitude (mV) on the 1st d (P<0.05) were found, their values changed within normal reference ranges and did not lead to left ventricular enlargement. However, anaesthesia induction (P<0.05) and recovery times (P<0.01-0.001) in the desflurane group were performed faster than the isoflurane group. We concluded that a repeated application of desflurane and isoflurane caused no significant QT and QTc prolongation and myocardial repolarisation abnormalities, whereas they decreased anaesthesia induction and recovery times.

Key words: rat, desflurane, isoflurane, electrocardiogram, anaesthesia.

Anaesthetics increase the sympathetic nervous system’s activity, which can lead to tachycardia, hypertension, and ischaemic electrocardiogram (ECG) changes. Therefore, it is importance to understand the effect of anaesthetics and analgesics on cardiorespiratory control and the mechanism and action of these agents. Desflurane is a new inhalation anaesthetic with rapid induction and fast recovery due to its low blood/gas solubility ratio (29). Its lower solubility provides faster control of the haemodynamic response to surgical stimulation than that with isoflurane (5). It is minimally metabolised and cardiovascular variables are stable. It can however, depress myocardial contractility (14).

As desflurane and isoflurane are commonly used to maintain anaesthesia, their repeated administrations may be cause of some disadvantage in animal and humans (20). It has been also reported that inhalational anaesthetics lead to cumulative effect in the liver and kidneys after a subsequent application (19). In addition, it is well known that the subsequent applications of thiopental unnecessarily prolong the recovery period (24). Moreover, volatile anaesthetics may prolong the QT and QTc intervals and may result in grave cardiac arrhythmias. In early studies, it was proved that both sevoflurane and isoflurane prolonged the QT and QTc intervals of the ECG during inhalational induction of anaesthesia (31). The QT interval is the time interval from the beginning of the QRS complex to the return of the T wave to the baseline of the ECG. The QT interval represents the ventricular activating time. Decision factors including heart rate (HR), corrected QT (QTc), interval prolongation (QTc<440 ms), are clinically important for the choice of the inhalational anaesthetic agent to be used. Although several studies have evaluated the cardiopulmonary effects of desflurane and isoflurane (6, 7), those evaluating the electrocardiographic effects of these agents under conditions of repeated applications have not been reported. Therefore, the aim of the study was to compare the effects of repeated application of desflurane and isoflurane on ECG, anaesthesia induction, and recovery characteristics.
Material and Methods

Experimental and anaesthesia procedures. Thirty healthy male Wistar albino rats, weighing 250 ± 20 g, divided equally into two groups were used. The animals were housed in quiet rooms and were given *ad libitum* feed and water in cages. Experimental procedures were approved by the Health Scientific Institute, Mustafa Kemal University. All the animals were sedated with 5 mg kg⁻¹ of xylazine hydrochloride (Rompun®, Bayer, Turkey). Five and ten minutes after the sedation, 2.5% isoflurane (Aerrane®, Baxter, Germany) or 8% desflurane (Suprane®, Baxter, Germany) anaesthesia with a 100% oxygen by mask induction were given to the animals. Anaesthesia maintenance was continued for 60 min with 1 MAC (5.7%) desflurane or 1 MAC (1.4%) isoflurane. Anaesthesia applications were repeated on days 1 (T1), 3 (T3) and 7 (T7) in both groups. Mask induction and anaesthesia maintenance were followed in the two groups with an anaesthetic machine (AMS 200, AMS International, Inc. USA) and vaporisers (desflurane – Tec. 6 Plus Vaporizer from Datex-Ohmeda, USA; isoflurane – Blease, Datum Vaporizer, England).

Cardiopulmonary responses and ECG. Heart rate (HR), respiration rate (RR), rectal temperature (RT), and electrocardiograms (ECGs) of all animals were monitored periodically at 15, 30, and 60 min during anaesthesia. These measurements were repeated on days T1, T3, and T7 in both groups and averaged for each day. Control recordings (T0) were obtained before anaesthesia induction. All ECG recordings were monitored at the right lateral position. Hair was clipped from the areas of electrode attachment and the skin was covered with gel and then crocodile electrodes were situated almost above knee joint in the hind legs and elbow joint in the front legs. ECGs were recorded with I, II, III, aVR, aVL and AVF derivations. Measurements of the amplitude (mV) of R waves, and the durations (ms) of P and T waves, PR, QT, QTc, and QRS intervals were performed in lead II. The mean electrical axes were also measured in lead I and III. The ECG device (ECG- 6851K Nihon Kohden Corporation, Japan) was used with the writing speed adjusted to 50 mm/s and 1 mV=10 mm. The QT interval was measured from the onset of the QRS to the point at which the T wave rejoined the baseline. The QT intervals were corrected for HR (QTc) using Bazett’s formula QTc= QT/ √ RR interval (s). In the Bazett’s formula, the corresponding RR interval at each lead was used for calculating QTc. HR was determined in R-R intervals. RT was kept at 36±0.5 °C using heating-pad. Rats breathed spontaneously throughout the study and the RR was measured by counting chest movements, and the RT was recorded using a digital thermometer.

Anaesthesia induction and recovery. The inhalant agent induction times were calculated from the start of the mask’s induction to the first inactivity time-point. Recovery responses were also evaluated using stand-up moments.

Statistical analyses. The data is reported as means ± standard error. Statistical analyses were accomplished with the use of SPSS computer programmes (version 13.0). The data in each group were analysed using repeated measures ANOVA with regard to the time effect. If statistically significant effects were found, the Tukey’s test was used for post hoc comparisons. Anaesthetics were compared at each time point using a one-way ANOVA. Differences were considered significant when *P*<0.05.

Results

There were no significant ventricular dysrhythmias observed during the study and no animal was excluded from the study. The HR was significantly decreased by desflurane and isoflurane compared with the baseline values (T0) (*P*<0.001, Table 1). A decrease in the HR was more pronounced in the isoflurane group than in the desflurane group. The differences in HR between groups were found statistically significant at the T3 time-point (*P*<0.05, Table 1). There was no significant difference in the mean RR between groups during the repeated anaesthesia periods (*P*>0.05, Table 1).

Descriptive statistics and statistical analysis of the variables studied concerning ECG findings are shown in the Table 1. Compared to T0, P wave duration (ms) and R amplitude value (mV) on the T7 d, T wave duration and QTc intervals (ms) on the T1, T3, and T7 d in the desflurane group, and also R amplitude value (mV), T wave duration, and QTc intervals (ms) on the T1, T3, and T7 d in the isoflurane group significantly decreased (Table 1). Contrary to these results, the QRS intervals (ms) were markedly increased in both groups compared to T0. When comparing the T1 means to that of the following days, the P wave duration (ms) was significantly decreased at T7 d in the desflurane and isoflurane groups (*P*<0.05 and *P*<0.01, respectively, Table 1). The differences of P wave duration (ms) between groups were found statistically significant at T3 d (*P*<0.05; Table 1). The differences of the QRS interval (ms) between groups were also found statistically significant at T1 d (*P*<0.001; Table 1). Compared to T1 d, R amplitude value (mV) significantly decreased at T3 d in the desflurane group (*P*<0.05; Table 1). The differences of R amplitude value (mV) between groups were found statistically significant at T1 d (*P*<0.05; Table 1). However, this value did not exceed the normal limit in any cases and did not lead to left ventricular enlargement. On the other hand, no significant difference was encountered in the T wave duration and QT and QTc intervals (ms) during the study between groups (*P*>0.05, Table 1). Moreover, the QTc values were lower than 440 ms in both groups at T1, T3, and T7 d after 1 MAC of steady end-tidal anaesthetic concentrations (Table 1).

A satisfactory quality of the induction of the anaesthesia was achieved without excitation. The quality of recovery was smooth and uneventful in all cases. The
repeated desflurane and isoflurane anaesthesia applications caused decreases in the anaesthesia induction and recovery times. In addition, in the desflurane group, anaesthesia induction and recovery times were performed faster than in the isoflurane group. Desflurane caused irritation of the airways at minimal levels during the anaesthesia induction. The anaesthesia induction times were found statistically significantly different at T1 d between groups (P<0.05; Fig. 1). Compared to T1 d, the decreases of recovery times in the isoflurane group were found statistically significant at T3 d (P<0.05; Fig. 2). The differences of recovery times were found significant at T1, T3, and T7 time-points between groups (P<0.01; Fig. 2). Post-induction apnoea and vomiting were not registered in any animal throughout the procedures.

![Anaesthesia induction](image1)

**Fig. 1.** The differences of anaesthesia induction in the isoflurane and desflurane anaesthesia groups on the days 1, 3, and 7. Data indicate mean ± SE. T1 - 1st d, T3 - 3rd d, T7 - 7th d. There were no significant differences within the groups at each time point compared with T1 values. § P<0.05 between groups at T1.

![Stand up times](image2)

**Fig. 2.** The differences of recovery times in the isoflurane and desflurane anaesthesia groups on the days 1, 3, and 7. Data indicate mean ± SE. T1 - 1st d, T3 - 3rd d, T7 - 7th d. † P<0.05 within the groups at each time point compared to T1 values. # P<0.01 between groups at T3. ‡ P<0.001 between groups at T1 and T7.
Table 1
The effects of repeated application of desflurane and isoflurane on ECG and cardiopulmonary system

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T3</th>
<th>T7</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (ms)</td>
<td>Isoflurane</td>
<td>24.1±1.0</td>
<td>26.0±1.0</td>
<td>25.0±0.8 $^+$</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>23.5±0.9</td>
<td>23.4±1.2</td>
<td>22.4±0.8</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>Isoflurane</td>
<td>42.4±1.75</td>
<td>46.4±1.1</td>
<td>46.6±1.6</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>41.6±1.52</td>
<td>43.6±1.4</td>
<td>43.5±1.5</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>Isoflurane</td>
<td>28.0±3.40</td>
<td>37.9±0.8 $^+$</td>
<td>40.8±1.4</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>28.8±3.58</td>
<td>42.1±0.5</td>
<td>42.4±1.5</td>
</tr>
<tr>
<td>R (ms)</td>
<td>Isoflurane</td>
<td>0.596±0.026</td>
<td>0.379±0.025 $^+$</td>
<td>0.417±0.035 *</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>0.629±0.025</td>
<td>0.518±0.041</td>
<td>0.382±0.028 $^+$, †</td>
</tr>
<tr>
<td>T (ms)</td>
<td>Isoflurane</td>
<td>34.6±2.66</td>
<td>24.9±2.4*</td>
<td>19.4±1.1 **</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>34.0±2.80</td>
<td>22.3±1.1 **</td>
<td>22.6±1.8 *</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>Isoflurane</td>
<td>69.2±0.95</td>
<td>65.3±2.5</td>
<td>61.4±2.3</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>69.0±1.28</td>
<td>62.1±1.6</td>
<td>61.3±2.2</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>Isoflurane</td>
<td>190.2±2.09</td>
<td>127±4.7 **</td>
<td>119±4.9 ***</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>184.7±3.38</td>
<td>121±3.4 **</td>
<td>121±3.9 **</td>
</tr>
<tr>
<td>Electrical axis</td>
<td>Isoflurane</td>
<td>57.53±4.40</td>
<td>71.71±11.06</td>
<td>58.82±9.77</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>56.25±4.41</td>
<td>67.26±6.58</td>
<td>70.12±8.38</td>
</tr>
<tr>
<td>Heart rate (beats.min$^{-1}$)</td>
<td>Isoflurane</td>
<td>458.2±10.82</td>
<td>237.7±6.0 ***</td>
<td>233.2±6.0 §, ***</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>441.3±11.61</td>
<td>236.7±5.41 ***</td>
<td>247.2±4.45 ***</td>
</tr>
<tr>
<td>Respiratory rate (min)</td>
<td>Isoflurane</td>
<td>14.93±0.74</td>
<td>11.87±0.55</td>
<td>10.97±0.61 *</td>
</tr>
<tr>
<td></td>
<td>Desflurane</td>
<td>14.80±0.59</td>
<td>11.84±0.75</td>
<td>12.33±0.78</td>
</tr>
</tbody>
</table>

Data indicate mean ± SE. T0 - Control, T1 - 1st d, T3 - 3rd d, T7 - 7th d.
Changes within the groups at each time point compared to T0 values: * P < 0.05; ** P < 0.01; *** P < 0.001.
Changes within the groups at each time point compared to T1 values: † P < 0.05; ‡ P < 0.01.
$ P < 0.05$ compared to desflurane, $^+$ P < 0.001 compared to desflurane.

Discussion

Mask induction of anaesthesia with volatile agents is frequently used in the experimental and clinical operations (18). Desflurane has a pungent odour and irritates airways with the effect of sympathetic stimulation (8). Therefore, it is noted that when its concentration exceeds 1 MAC, and desflurane is unsuitable for the use for inhalation in humans (2, 31). Yıldırım et al. (31) have reported that these adverse effects may be avoided using premedication before desflurane anaesthesia. In our study, all the animals received similarly xylazine hydrochloride before anaesthesia and inhalation inductions were performed without problem, except for slight airway irritation in the desflurane group.

Regarding the other inhaled agents, both isoflurane and desflurane cause dose-dependent respiratory depression and decreases RR (7, 26). In our study, the mean RR in the two groups significantly decreased when compared to the T0 values (Table 1). However, repeated administration of desflurane and isoflurane had not any important effect on the RR in both groups. Although desflurane causes minimal airway irritation during induction, it has many desirable qualities for the maintenance of anaesthesia. It is minimally metabolised and cardiovascular variables are stable (14). Desflurane provides a rapid anaesthesia induction and fast recovery due to its low blood/gas solubility ratio (0.42) (15, 29). In this study, when compared with isoflurane, desflurane revealed a more rapid anaesthesia induction (Fig. 1) and recovery (Fig. 2). These results are consistent with findings of Martin et al. (15). In addition, we found that the repeated desflurane and isoflurane administrations decreased significantly anaesthesia induction and recovery times.

The cardiovascular effects of desflurane and isoflurane have been reported to be similar (7, 30). However, desflurane consistently causes increases in HR more than isoflurane and other volatile anaesthetics (8, 22). In the current study, compared to daily averages, the decreases in HR in the isoflurane group at the T3 (P < 0.05) and T7 time point were found lower than those in the desflurane group. These results may be explained...
when desflurane increases more rapidly the sympathetic activity than isoflurane.

The normal ECG of a rat resembles the essential details similar to that of man. However, certain important differences need to be pointed out. Although the deflections of the P, Q, R, S, and T wave are well observed, the record characteristically displays the absence of the ST segment and small QT interval. T wave is not seen as completely differentiated from the QRS complex (1, 3, 10, 23). In this study, we confirmed the absence of the ST segment and small QT interval.

Conduction disturbances also should be considered, when there is a prolongation of the QRS complex (9). It is known that the R wave of the QRS complex exceeds 0.9 mV in lead II in left ventricular enlargement (28). Although we also observed significant difference in the QRS complex durations (ms) and the R wave amplitudes (mV) between groups (P<0.001, Table 1), these changes remained in the normal ranges. Moreover, the R wave amplitude (mV) levels did not exceed the limit (0.9 mV), which was reported above in any cases. The T wave represents the recovery period or repolarisation of the ventricles. The reversal of T wave polarity on serial ECCIs is most often abnormal and it may indicate myocardial hypoxia (28). Our obtained T wave results did not exhibit any abnormality. The P wave represents atrial depolarisation. In the atrial enlargement, the duration of the P wave is greater than 40 ms in leads II (11). Conversely, we observed that both inhalant agents decreased the P wave duration (ms) (Table 1).

It has been reported that inhalation anaesthetics have the antiarrhythmic and arrhythmogenic effects in both humans and animals (16). Atrioventricular conduction disorders prolong the PR and QT intervals in ECG (4). The prolongation of the QT interval has a clinical importance in the inhalation anaesthesia and a long QT syndrome is characterised by the prolongation of a ventricular repolarisation time (3, 10, 31). Although several anaesthetic agents cause a prolongation of the QT interval along with the risk of dysrhythmia, they may show an antidyssrhythmic effect. In the previous studies, it was proved that isoflurane and desflurane prolonged the QT interval in ECGs during the inhalation anaesthesia induction (4). We determined that both volatile agents had a similar effect concerning the QT interval, also no significant difference was found between these anaesthetics (Table 1). Yıldırım et al. (31) reported that desflurane, sevoflurane, and isoflurane did not lead to statistically significant differences in the QT interval. Our obtained QT results are consistent with the findings of Yıldırım et al. (31).

It has been known that the prolongation of the QTc interval is observed within the first minute of desflurane anaesthesia (21, 31). Schouten et al. (25) stated that the long QTc interval (QTc>440 ms) led to ventricular fibrillation threshold and ventricular dysrythymia with regard to the imbalance of the cardiac autonomic nerve system. Güler et al. (13) found that isoflurane increased the QTc interval; halothane shortened it, and it did not change with sevoflurane. Thomson et al. (27) compared the use of isoflurane and desflurane in the patient subjected to coronary artery surgery and they did not encounter in ECG any pronounced difference indicated myocardial ischaemia. Fukuda et al. (12) reported that sevoflurane and isoflurane decreased the dysrhythmias occurring after bupivacaine application in rats. Michaloudis et al. (17) reported that 2.5% end-tidal isoflurane concentrations in humans prolonged significantly the QTc interval. Yıldırım et al. (31) reported that desflurane, isoflurane, and sevoflurane prolonged significantly the QTc interval, but there were no significant differences between these agents. They advised carefully the use of these agents in the patients with dysrhythmia. In contrast to previous human reports (17, 31), in this study it was encountered firstly with significant decreases in the QTc levels at T1, T3, and T7 time points compared with control (T0) values (Table 1). Considering Bazett’s formula (QTc= QT/√RR interval (s)), it was produced by an increase in HR and a decline in the RR intervals connected with rising stress during the control (no anaesthesia) rat ECG recordings. However, these decreases were not observed during the repeated anaesthesia applications compared with T1 values (Table 1). Therefore, we interpreted the QTc results in rats concerning the T3 and T7 values compared with T1 values. In the light of this assessment, we found that the effects of desflurane and isoflurane on the QTc interval were similar, and no significant difference was found between groups and within groups in the repeated applications compared with T1 d (Table 1).

In conclusion, we determined that repeated desflurane and isoflurane applications did not prolong QT and QTc intervals and did not cause myocardial repolarisation abnormalities in rats. Therefore, both agents revealed almost similar cardiovascular effects. On the other hand, the repeated desflurane and isoflurane applications decreased anaesthesia induction and recovery times, but desflurane caused faster anaesthesia induction and recovery than isoflurane.

References


