Cyclophosphamide-induced early cardiotoxicity: Comparison of ECG changes and disorders in adult and senile rats

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ABSTRACT
Cyclophosphamide (CP) is a valuable chemotherapeutic agent used in the treatment of many neoplastic tumours. Cardiotoxicity is a major dose-limiting factor in intensive CP therapy. The current study was designed to compare the early toxic effects of administration of a single dose (300 mg/kg body wt) of CP on the electrical activity of the cardiac muscles (ECG parameters and abnormalities) of adult and senile rats. The results show that the heart rate started to fall significantly, as early as 30 min following CP injection in the adult and senile rats. The PR interval prolonged significantly after 120 min in adult rats, and after 60 and 120 min in senile groups. The QT interval and T-wave amplitude increased significantly only after 120 min in both treated groups. The values obtained from the senile animals were much higher and significantly different compared to the adult rats. On the other hand, the R-wave amplitude decreased significantly after 120 min in both adult and old animals. Some ECG disorders were recorded in both adult and senile rats 120 and 150 min after cyclophosphamide injection. These abnormalities include: AV nodal rhythm, bradycardia with junctional escape, first and second degree heart block. These results present evidence of early serious pathophysiological alterations of the normal electrical activity of the heart following a single injection of a high dose of CP, and the myocardial damage seemed to be worst in the senile animals. We conclude that cardiotoxicity induced by CP administration involves several direct and indirect mechanisms.

KEYWORDS: Cyclophosphamide, ECG, abnormalities, adult, senile

INTRODUCTION
Cyclophosphamide (CP) is a valuable chemotherapeutic agent used in the treatment of many neoplastic tumours, and in addition it has been used for immunosuppression prior

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It is inactive until metabolised in the liver by the P-450 mixed function oxidases to 4-hydroxycyclophosphamide, which forms aldophosphamide reversibly. This later compound is conveyed to other tissues, where it is converted to phosphoramide mustard, the actual cytotoxic molecule, and acrolein (Rang & Dale 1991). CP metabolism is responsible for its immunosuppression effect (Moore 1991). The use of cyclophosphamide is accompanied by a number of side effects such as nausea, vomiting, alopecia, leukopenia and cardiac necrosis (Fisher et al. 1993).

Risk factors for developing CP-induced myocardial injury have been reported to include: (1) CP dose > 1.55 g/m^2/day (Goldberg et al. 1986); (2) administration of doses over 6 hours instead of 30-60 min (Kushner & Cheung 1991); (3) enhanced CP activation of alkylating metabolites (Ayash et al. 1992); and (4) low cardiac glutathione levels (Friedman et al. 1990; Dorr & Lagel 1994). Evidence on CP-induced cardiotoxicity have also been obtained from animal studies (Storb et al. 1970; O’Connell and Berenbaum 1974; Stokes et al. 1981; Dorr & Lagel 1994; Kemi et al. 1996). Cardiac haemorrhages and necrosis were found in rhesus monkeys after administration of doses of 240 mg/kg (Storb et al. 1970). Electrocardiographic changes and early myocarditis have been described in dogs that died 4-6 hr after administration of 500 mg/kg CP (O’Connell & Berenbaum 1974). Kumar et al. (1992) reported that intraperitoneal injection of 180 mg/kg of CP in Swiss albino rats induced multiple interstitial myocardial haemorrhage, multifocal myofibre necrosis, inflammatory reaction, vascular changes, pericarditis and vasculitis, mainly in the heart ventricles. Moreover, early myocardial lesions were observed 4 hr after injection of 160 mg/kg CP into rats (Kemi et al. 1996). These authors mentioned that the lesions were scattered all over the ventricular walls including the left, right and septal walls, and the papillary muscles of the heart, with formation of contractile bands and fragmentation of the cardiac muscle fibres.

Two different types of acute cardiac effects from high dose of CP are described: a myocarditis that can be asymptomatic, and congestive heart failure, which may be fatal (Appelbaum et al. 1976; Mills & Roberts 1979). Recently, some case reports documented that CP in transplant regimes causes serious cardiac damage, often leading to immediate death. The reported incidence of fatal cardiomyopathy varies between 2 and 9.5% depending on different regimes and patient population (Bearman et al. 1990; Dow et al. 1993; Lee et al. 1996). In addition, a significant proportion of transplant patients was shown to have reduced cardiac function, accompanied by decrease in summated QRS voltage and changes of echocardiographic indices in the absence of overt clinical symptoms or signs (Kupari et al. 1990).

Although detection of cardiovascular toxicity requires a complete physical and clinical examination in both experimental animal and humans, and the ECG is generally applicable indicator of cardiac function, very few detailed reports have been published on the ECG changes induced by CP treatment (Sculier et al. 1985; Shachor et al. 1985). In addition, age-related susceptibility to the severity of the ECG changes as a result of using CP in humans or experimental animals has not been reported before. The current study was designed to compare the early toxic effects of CP on the electrical activity of the cardiac muscles of adult and senile rats.
MATERIALS AND METHODS

Animals
In this experiment, two groups of 10 male adult (7-10 months old) and 10 male senile (20-24 months old) Wistar rats were used. All rats were maintained in controlled animal house (2 animals/cage) at 18-22 °C and relative humidity of 55 ± 5%. They were fed on standard rat chow and had free access to food and water. Each group was divided into two subgroups of 5 animals each. The animals of the first subgroups (adult and senile) were each given a single intraperitoneal dose of CP (300 mg/kg body wt) dissolved in saline. This dose was reported to induced cardiotoxic effects, and elevated some serum enzyme levels that are associated with certain types of heart damage (Friedman et al. 1990). Adult and senile rats of the second subgroup were considered as control animals and were injected intra-peritoneally with an equivalent amount of the vehicle (saline). All procedures were in strict accordance with guidelines for the care and use of laboratory animals.

ECG recording
All animal were intraperitoneally anaesthetised with 1.25 g/kg of urethane (Sigma, St. Louis, MO, USA) before making insertion of the ECG electrodes. ECG recordings were according to the method described by Buschmann et al. (1980) using bipolar electrodes (Lead II). Electrodes were connected to the combined coupler FC117 (Life Science Product, Bioscience, UK) and the ECG was recorded on two-channel Oscillograph (MD2, Bioscience, UK). Animals were kept in a thermoregulated cage (30 °C ± 2) during the recording time to control their body temperature. After the subcutaneous insertion of the electrodes, animals were left for about 30 40 min until stabilisation of the normal respiration and ECG patterns prior to the intraperitoneal injection of CP. Monitoring and recording of ECG waves were continued for 3 hr following CP treatment. The paper speed was 50 mm/sec and the wave voltage was calibrated after the stabilisation period. Heart rate (HR) and different ECG parameters (PR and QT intervals; R- and T-wave amplitudes) were measured and calculated from the calibrated recording chart paper. ECG disorders were detected, analysed and classified according to the type of the abnormality.

The heart rate was calculated by measuring the R-R distance (Budden et al. 1980) and by using the equation: HR (beat/min) = paper speed (50mm) x 1 min (60sec) / distance between 2 consecutive R waves in mm.

The P-R interval was measured from the beginning of the P-wave to the onset of the QRS complex, while the Q-T interval was measured from the start of the Q-wave to the highest point of the T-wave. Heering (1970) defined the termination of the T-waves as the point at which it becomes horizontal or where the next P-wave begins.

The amplitude of both R- and T-waves were measured from the isoelectric line up to the highest point of the waves in mV. The point at which the P-wave terminates and the QRS complex begins was considered the point of the isoelectric line (Beinfield & Lehr 1968).

Statistical analysis
Data are presented as means ± standard error of five animals per treatment group. Comparison between the means of the control and treated subgroups were made using Student's t-test for independent samples, while two-way ANOVA was performed for
the comparison between the means of the data of the adult and senile rats. In all cases, a probability level of p<0.05 was considered to indicate a significant difference.

RESULTS

ECG Parameters
Animals of both control subgroups (adult and senile) showed no significant changes in the ECG parameters as a result of administration of either the anaesthetic agent and the vehicle.

Table 1 shows that the HR started to fall significantly as early as 30 min following CP injection in the adult and senile rats. The maximum decrease in the HR values was 26% in adult animals after one hour, while it was 39% in senile group after two hours. The slowing of the HR in the aged rats as a result of CP treatment seems to be time-related.

The effect of cyclophosphamide on the PR interval, which represents the conduction time of the impulse through the atrioventricular node, is shown in Table 2. In the adult group there was a slight non-significant increase after 60 min followed by a significant elongation (6.6%) after 120 min. On the other hand, the change in the PR interval was more prominent in the senile animals since it was significantly increased by 26% and 37% compared to the control group after 60 and 120 min respectively.

Cyclophosphamide-induced changes in the QT interval are shown in Table 3. In the ECG, QT interval means the time between the onset of ventricular excitation to the end of ventricular repolarization. The present data show that the only significant effect, an increase in QT interval, was recorded two hours post-treatment in the adult group, while in the aged animals the significant elevations were observed after 60 and 120 min following CP administration. The values obtained from the senile animals (28.6%) were much higher and significantly different compared to the adult rats (7.3%).

Table 4 shows that CP administration produced mild depressor effects on the cardiac muscles. The depolarization of the ventricular muscles expressed by the amplitude of the R-wave in the ECG traces declined significantly from 0.41 and 0.42 mV to 0.37 mV after 120 min in both adult and senile rats respectively.

The amplitude of the T-wave (ventricular repolarization, table 5) showed a gradual increase in both treated groups and the only significant change was observed at the end of the time course (120 min). The elevation of the T-wave was significantly higher in the senile rats (40%) compared to the adult animals (13.6%).

| Table 1: Effect of cyclophosphamide* on the heart rate (beat/min) of rats |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Time (min)** | **Control** | **Treated** | **%*** | **Control** | **Treated** | **%*** |
| **00*** | 375 ± 14 | 379 ± 24 | + 1.1 | 328 ± 25 | 335 ± 18 | + 2.1 |
| 30    | 377 ± 18 | 333 ± 28 | - 11.7 | 335 ± 22 | 276 ± 26 | - 17.6 |
| 60    | 370 ± 16 | 273 ± 14 | - 26.0 | 332 ± 18 | 215 ± 18 | - 35.2 |
| 120   | 376 ± 13 | 291 ± 17 | - 22.6 | 320 ± 21 | 195 ± 14 | - 39.1 |
### Table 2: Effect of cyclophosphamide* on the P-R interval (msec) of rats

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Adult</th>
<th>Senile</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
<td>%*</td>
<td>Control</td>
<td>Treated</td>
</tr>
<tr>
<td>00*</td>
<td>62 ± 0.5*</td>
<td>61 ± 0.6</td>
<td>- 1.6</td>
<td>62 ± 0.8</td>
<td>60 ± 0.7</td>
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<tr>
<td>30</td>
<td>60 ± 0.6</td>
<td>60 ± 0.5</td>
<td>0.0</td>
<td>60 ± 0.7</td>
<td>63 ± 0.5</td>
</tr>
<tr>
<td>60</td>
<td>61 ± 0.6</td>
<td>63 ± 0.5</td>
<td>+ 3.3</td>
<td>62 ± 0.6</td>
<td>78 ± 0.6b</td>
</tr>
<tr>
<td>120</td>
<td>61 ± 0.5</td>
<td>65 ± 0.5b</td>
<td>+ 6.6</td>
<td>59 ± 0.5</td>
<td>81 ± 0.6b</td>
</tr>
</tbody>
</table>

### Table 3: Effect of cyclophosphamide* on the Q-T interval (msec) of rats

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Adult</th>
<th>Senile</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
<td>%*</td>
<td>Control</td>
<td>Treated</td>
</tr>
<tr>
<td>00*</td>
<td>40 ± 0.6*</td>
<td>41 ± 0.4</td>
<td>+ 2.5</td>
<td>42 ± 0.3</td>
<td>40 ± 0.6</td>
</tr>
<tr>
<td>30</td>
<td>41 ± 0.5</td>
<td>41 ± 0.6</td>
<td>0.0</td>
<td>40 ± 0.6</td>
<td>42 ± 0.5</td>
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<tr>
<td>60</td>
<td>40 ± 0.5</td>
<td>41 ± 0.6</td>
<td>+ 2.5</td>
<td>39 ± 0.6</td>
<td>42 ± 0.5b</td>
</tr>
<tr>
<td>120</td>
<td>41 ± 0.6</td>
<td>44 ± 0.5b</td>
<td>+ 7.3</td>
<td>42 ± 0.6</td>
<td>54 ± 0.3b</td>
</tr>
</tbody>
</table>

### Table 4: Effect of cyclophosphamide* on the R-wave amplitude (mV) of rats

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Adult</th>
<th>Senile</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
<td>%*</td>
<td>Control</td>
<td>Treated</td>
</tr>
<tr>
<td>00*</td>
<td>0.41 ± 0.01*</td>
<td>0.42 ± 0.01</td>
<td>+ 2.4</td>
<td>0.42 ± 0.03</td>
<td>0.40 ± 0.02</td>
</tr>
<tr>
<td>30</td>
<td>0.42 ± 0.01</td>
<td>0.40 ± 0.01</td>
<td>- 4.8</td>
<td>0.43 ± 0.01</td>
<td>0.41 ± 0.01</td>
</tr>
<tr>
<td>60</td>
<td>0.40 ± 0.01</td>
<td>0.38 ± 0.02</td>
<td>- 5.0</td>
<td>0.41 ± 0.01</td>
<td>0.38 ± 0.01</td>
</tr>
<tr>
<td>120</td>
<td>0.41 ± 0.02</td>
<td>0.37 ± 0.01b</td>
<td>- 9.8</td>
<td>0.42 ± 0.02</td>
<td>0.37 ± 0.02b</td>
</tr>
</tbody>
</table>
Table 5: Effect of cyclophosphamide* on the T-wave amplitude (mV) of rats

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Adult</th>
<th></th>
<th></th>
<th>Senile</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
<td>%*</td>
<td>Control</td>
<td>Treated</td>
<td>%</td>
</tr>
<tr>
<td>00*</td>
<td>0.21 ± 0.04*</td>
<td>0.22 ± 0.03</td>
<td>+4.8</td>
<td>0.20 ± 0.02</td>
<td>0.21 ± 0.02</td>
<td>+5.0</td>
</tr>
<tr>
<td>30</td>
<td>0.21 ± 0.01</td>
<td>0.22 ± 0.01</td>
<td>+4.8</td>
<td>0.20 ± 0.01</td>
<td>0.20 ± 0.02</td>
<td>0.0</td>
</tr>
<tr>
<td>60</td>
<td>0.23 ± 0.01</td>
<td>0.24 ± 0.02</td>
<td>+4.3</td>
<td>0.21 ± 0.02</td>
<td>0.23 ± 0.02</td>
<td>+9.5</td>
</tr>
<tr>
<td>120</td>
<td>0.22 ± 0.04</td>
<td>0.25 ± 0.02,*</td>
<td>+13.6</td>
<td>0.20 ± 0.01</td>
<td>0.28 ± 0.01,*</td>
<td>+40.0*</td>
</tr>
</tbody>
</table>

* Cyclophosphamide was injected intraperitoneally in a single dose (300mg/kg body wt).
*: Represents time after injection of the drug.
*: % Change between treated animals and their respective controls.
*: Values present are in mean ± S.E.M., n = 5/group.
*: Significantly different from control, student’s t-test, P<0.05.
*: Significantly different compared to treated adult, 2-way ANOVA, P<0.05.

ECG abnormalities

Some ECG disorders were recorded in both adult and senile rats after 120 and 150 min from administration of a single dose (300 mg/kg body wt) of cyclophosphamide (Table 6 and Plate 1). The first case was an ectopic beat (AV nodal rhythm) observed in two animals in each treated group. In this case the AV node become the pacemaker of the heart instead of the sinoatrial node, and the rhythm is represented by the inverted P-wave in the ECG chart (Plate 1A). This kind of abnormal cardiac rhythm is also known as supraventricular rhythm, in which the depolarization wave spreads to the ventricles in the normal way via the His bundle and its branches, and therefore the QRS complex is normal.

The second ECG disorder was bradycardia with junctional escape recorded in one animal and two animals of CP treated adult and senile rats respectively after 150 min post-treatment. ECG charts (Plate 1C) shows that the negative chronotropic response (bradycardia) was characterized by normal wave sequences, but the heart rate was slower than the control records. In the junctional escape rhythm, the region around the AV node takes over where there is no P-waves (Plate 1C) which either means that there is no atrial contraction or P-wave lost in QRS complex.

Heart block implies that there is some defect in the conduction of the impulse from the atria to the ventricles. In this investigation CP induced first and second degree heart block in three senile animals after 120 and two animals after 150 min (Plate 1B&D). Only one rat in the adult group suffered from first degree block after 150 min post-treatment. When each wave of depolarization that originates in the SA node is conducted to the ventricles, but there is some delay along the conduction pathway characterized by the prolongation of the PR interval, this is known as first degree heart block. A development of second degree heart block (2:1 type) was noted following the first degree block in the aged rats. In this case there are two P-waves per QRS complex, one of which show itself as a distortion of a T-wave, while a relatively long and constant PR interval appeared in the conducted beats.
It is very important to mention that none of the control animals suffered from the above mentioned ECG abnormalities during the recording time course.

Table 6: ECG abnormalities recorded as a result of cyclophosphamide* injection into adult and senile rats

<table>
<thead>
<tr>
<th>ECG Abnormalities</th>
<th>Treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>- Ectopic beats (AV nodal rhythm)</td>
<td>0/5</td>
</tr>
<tr>
<td>- Bradycardia with junctional escape</td>
<td>0/5</td>
</tr>
<tr>
<td>- First degree heart block</td>
<td>0/5</td>
</tr>
<tr>
<td>- Second degree heart block</td>
<td>0/5</td>
</tr>
</tbody>
</table>

* Cyclophosphamide was injected intraperitoneally in a single dose (300mg/kg body wt).

\[ a \]: Number of rats with disorders post-treatment per total number of treated animals.

Plate (I): ECG abnormalities recorded after single intraperitoneal administration of cyclophosphamide (300 mg/kg body wt) into rats: (A) Ectopic beat (AV-nodal rhythm), (B) 1\textsuperscript{st} degree heart block, (C) Bradycardia with junctional escape, and (D) 2\textsuperscript{nd} degree heart block.
DISCUSSION

The dose-limiting toxicity of cyclophosphamide, a bifunctional alkylating agent commonly used in the treatment of human neoplasia, is haemorrhagic myopericarditis (Gottdiener et al. 1981). Although modest doses of CP are commonly used without adverse cardiac effect, cardiotoxicity has recently been recognized with the high doses of CP used in therapy in preparation for bone marrow transplantation (Hanaki et al. 1990; Dow et al. 1993).

Dorr & Lagel (1994) reported that cardiotoxicity following high doses of CP is a major risk in patients undergoing autologous or allogeneic bone-marrow transplantation, and the clinical risk factors are not well delineated. In 1985, Sculier et al. mentioned that cardiac toxicity with CP was reported at doses varying from 60 mg/kg to 240 mg/kg. It started after a few days and was associated with ECG perturbations, pericardial effusions, congestive heart failure and diffuse myocardial necrosis concomitant with marked increase of serum cardiac isoenzymes, which mimicked acute myocardial infarction (Dow et al. 1993). Kumar et al.(1992) reported that cardiotoxicity is a major dose-limiting factor in intensive CP therapy.

Disturbances of cardiac rhythm have been recognised for many years. Under normal circumstances contractions of the atria and the ventricles occur sequentially. The sequence is controlled by the specialised conducting tissue of the heart, which transmits the electrical impulses initiating the heart beat from the sinus node to the rest of the heart. Although ECG changes following administration of some cytotoxic agents are a well documented phenomenon, we have found very few reports describing such changes and the concomitant arrhythmia or conduction disturbances related to CP treatment. In this study, the heart rate was decreased significantly in both adult and senile rats during the first 2 hours after CP injection. The negative chronotropic effect was clearer in the senile animals and seemed to be time-related. A few asymptomatic episodes of bradycardia (Sculier et al. 1985) occurred in patient (59 years old) after three days from receiving CP (200 mg/kg) in combination with etoposide (1.5 g/m²). Another patient (58 years old) showed runs of premature ventricular beats followed by bradycardia a long time after receiving a dose of about 300-400 mg of CP (Shachor et al. 1985). The same author assumed that this effect which was accompanied with vomiting was due to increased vagal tonus induced by CP. Our results show that bradycardia develops very early, within 2 hours, regardless the age of the treated animals, but that the aged group (senile) was much more affected. This could be related to the release of significant amounts of acetylcholine in the heart. Hanaki et al. (1990) reported that administration of CP significantly increased the acetylcholine content in the heart, which is closely associated with cardiac damage and arrhythmias. Lethal myocarditis is a well documented complication of high-dose (>150 mg/kg ) CP therapy, with an estimated incidence of 7-25% in adults and 5% in children (Dow et al. 1993). Our explanation of this early depressant effect is based on the relation between the myocardial contractility, represented by the amplitude of the R-wave in the ECG, and the heart rate, as well as the histopathological findings reported by many investigators (Kumar et al. 1992; Dow et al. 1993; Kemi et al. 1996). It is well established that changes in the cardiac rate and rhythm affect myocardial contractility and vice versa (Ganong 1997). The significant negative inotropic effect observed in this experiment in both treated groups might be related to the early recorded significant decrease in the heart rate. Moreover, Kemi et al. (1996) reported that there are severe myocardial lesions appearing 4 hours after
administration of CP (160 mg/kg), with the formation of contraction bands in some affected cells. Based on the distribution, they mentioned that these myocardial lesions might have been related to restricted hypoxia or ischaemia to very small heart regions due to the microvascular circulation. This might be another important coupling factor in CP inducing potent early histopathological changes, which of course would alter the normal electrical activity of the myocytes. Pihkala et al. (1994) reported that the worst myocardial damage was recorded in some paediatric patients who received high doses of CP as a pre-bone-marrow transplantation therapy. They had persistent decrease in the QRS amplitude, and the treatment was associated with decreased myocardial contractility.

The observed elongation of the PR interval in this investigation produces a delay of the impulse conduction through the AV node, which could be associated with the negative chronotropic effect recorded during the time course. The increased PR interval values were more potent in the senile animals, that would correlate well with the recorded incidences of first- and second-degree heart block in this group. It is very important to mention that first-degree heart block is an advanced case of bradycardia, and in the same manner second-degree heart block is always preceded by first-degree heart block. Heger et al. (1994) reported that causes of first- and second-degree heart block include parasympathetic tone, toxic drugs which prolong AV conduction and conduction system deformation. We suggest that these conduction problems and the recorded AV blocks are probably due to the direct histopathological effects of CP on the myocytes (Kumar et al. 1992; Dow et al. 1993; Kemi et al. 1996) and hereby the conductive system. The recent findings of Sulkowska et al. (1998) might give further support of the involvement of CP in inducing tissue and cell injury directly and indirectly through activation of inflammatory cells. They reported that pulmonary injury induced by CP is very potent and significant, and is associated with the production of reactive oxygen species concomitant with an increase in the lipid peroxidation products in lung tissue homogenates. Generation of reactive oxygen species and lipid peroxide formation in lung microsomes are thought to be a mediator of lung damage (Patel 1990). It has also been demonstrated that CP can enhance pulmonary toxic reactions through effects on immunocompetent cells, specifically T lymphocytes (Cooper et al. 1986). All these mechanisms explaining the serious damage induced by CP to the respiratory system’s main organ, the lungs, might lead to the proposed ischaemia and hypoxia to most of the body organs especially the heart. In the same respect, it was documented that CP-injured heart mitochondria and indices of mitochondrial respiratory function were significantly decreased by administration of CP (Hanaki et al. 1990; Al-Nasser 1998). They claimed that CP causes cardiac dysfunction through an impairment of mitochondrial metabolism. These hypotheses may support our observations because an agent altering normal oxygen supply to the myocytes and affecting the energy consuming process presumably could produce cell injury and inhibitory mechanisms concomitant with a delay in the impulse conduction through the AV bundle.

The effect of CP administration on the QT interval and T-wave amplitude have not been reported before. The results of this study indicated that their values were increased significantly in both treated groups after two hours from CP injection. It is well established that these two ECG parameters are mostly affected by the electrolyte abnormalities (Smith & Kampin 1984). The delay in the duration of the ventricular action potential, indicated by the elongation of the QT interval, are related to a low plasma calcium levels (Hampton 1992). On the other hand, a high serum potassium
levels causes tall and peaked T-waves (Hampton 1992; Ganong 1997) which indicates an increase in the ventricular depolarisation period. Gottdiener et al. (1981) mentioned that electrical and functional cardiac alterations seen with CP treatment can result from an inability to regulate cellular ion concentrations. Levine et al. (1993) observed that cardiac cells exposed to the activated CP derivative had a significantly increased content of sodium and calcium concomitant with a decreased potassium content. These findings give more evidence about the cellular mechanisms of the cardiotoxicity induced by CP through disturbances of the myocytes' ion homeostasis, which is essential to normal heart cell function.

Generally, the data obtained from this experimental study indicate that aged animals (senile) are more affected and more susceptible to the early cardiotoxic effects associated with serious changes in the electrical activity of the cardiac muscles induced by high doses of CP. Ageing is the progressive accumulation of changes with time associated with the increasing susceptibility to carcinogens, drugs and diseases (Stohe et al. 1984; Molina & Garcia 1997). We suggest that there are two main factors related to the increased susceptibility of old animals to the early cardiotoxicity of CP, which are: (1) ageing is associated with an increase in myocardial susceptibility to ischaemia and a decrease in post-ischaemic recovery of function (Boucher et al. 1998); and (2) ageing produces an elevation in lipid peroxidation processes and an increased formation of oxygen radicals concomitant with an impaired glutathione "GSH" redox cycle (Teramoto et al. 1995; Rodrigues Martinez et al. 1998). It is well documented now that cellular mechanisms of cardiotoxicity are mediated by an increase in free oxygen and GSH was shown to protect cardiac myocytes against CP-induced damage (Levine et al. 1993; Lee et al. 1996). Furthermore, it was reported that high doses of CP deplete cardiac cell and hepatic GSH levels as early as 1-4 hours post-treatment in both animals and patients (Dorr & Lagel 1994; Sulkowska et al. 1998). The conclusion gained from this study and other related investigations are presented in Plate 2.

In conclusion, we have presented evidence of early serious pathophysiological alterations of the normal electrical activity of the heart following single administration of high dose of CP, and the myocardial damage seemed to be worst in the senile animals. Further studies concerning this subject are needed before any firm conclusion can be made whether early ECG monitoring in such cases should be mandatory rather than optional, especially in aged persons.
Plate (2): Simplified scheme showing the different possible mechanisms that might be involved in the pathogenesis of the heart following injection of high dose of cyclophosphamide.

REFERENCES


Abdel-Nabi & Omran: Cyclophosphamide-induced early ECG changes


الملخص العربي

السيكلوفوسفاميد يحدث تسبيب مبكر للقلب: مقارنة التغييرات والذذوذ في رسم القلب الكهري للفئران البالغة والمُسنَّة

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يعتبر عقار السيكلوفوسفاميد علاجًا كيميائيًا فعال يتم استخدامه في علاج حالات كثيرة من الأورام السرطانية. وقد صممت هذه الدراسة لإجراء مقارنة للتأثيرات السامة الميكروية التي تم يمكن أن تنتج عند استخدام هذا العقار في جرعة واحدة عالية (300 مجم/كمجم) على معدل ضربات القلب والنشاط الكهري الطبيعي لعضلات القلب وذلك في الفئران البالغة (P-R & Q-T intervals / R & T-wave amplitudes) والفئران المسنة. أوضحت النتائج أن معدل ضربات القلب قد تناقص تناقصًا ملحوظًا بعد 30 دقيقة من الحقن في كل من المجموعتين وفي المقابل فقد حدثت زيادة ملحوظة في الفئران P-R interval بعد 120 دقيقة في الفئران البالغة وبعد 60 و120 دقيقة في الفئران المسنة. كما سُجلت هذه الزيادة أيضاً في قيم T-wave amplitude وQ-T interval بعد 120 دقيقة فقط من المعالجة بالعقار في جميع الفئران المحفوظة مع ملاحظة أن تلك القيم كانت دائمًا أعلى وذات دلالة إحصائية معنوية في الفئران المسنة مقارنة بالفئران البالغة. وبالنسبة لقيم R-wave amplitude فقد نقصت نسبة معنويًا بعد 120 دقيقة في الحيوانات المحفوظة بالسيكلوفوسفاميد. وقد سجلت الدراسة أيضاً بعض حالات الذذوذ في رسم القلب الكهري للكملا المجموعتين من الفئران (البالغة والمسنَّة) وذلك بعد حوالي 120 و150 دقيقة من الحقن بالعقار. وجدير بالذكر أن هذه الحالات التي لوحظت كانت عبارة عن عدم اتساق أو تغيير في التوصيل الطبيعي لعضلات القلب وتشمل على نشوب بؤرات جديدة للرتم القلبي ودرجات مختلفة من السدة القلبية.
أيضا أعطت نتائج هذا البحث بعض الدلائل على حدوث تغييرات فسيولوجية مرضية مبكرة وشديدة للنشاط الكهربائي لعضلة القلب كنتيجة لحقن مادة السيكلوفوساميد بجرعة واحدة عالية ومن الواضح أن التأثير أكبر وأعمق على الحيوانات المسننة مقارنة بالحيوانات البالغة.