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Spectroscopic Investigation of Amiodarone Effect on the Rabbits' lacrimal Gland

Sahar A. Morsy[1] , Ahlam M. Ibrahim[1] , Eman M. Aly[2] , Sherif S. Mahmoud[2] , Gehan M. Kamal[1] .

[1] Physics Department, Faculty of Science, Al-Azhar University, Cairo, Egypt

[2] Biophysics and Laser Science Unit, Research Institute of Ophthalmology, Giza, Egypt

DRUG amiodarone (AMIO) is vital for the anti-arrhythmic patient, but it has numerous adverse effects. The lacrimal gland is accessory apparatus essential for tear production, which is critical for visual functions, so this study aims to investigate the effect of AMIO on it. Three groups' rabbits from both sexes (2-2.5 kg), each group containing five rabbits, were used in this study. The experiment was carried out in the following manner: one of these groups functioned as a control and got an intraperitoneal injection of normal saline. The second group received an intraperitoneal injection of AMIO (80 mg/kg BW) once daily for two weeks. The third group received a daily dosage of AMIO (160 mg/kg BW) intraperitoneally for two weeks. The obtained FTIR spectra revealed that the molecular structure of the lacrimal gland is sensitive to AMIO treatment. The AMIO treatment caused considerable changes in the frequencies and bandwidths of the NH-OH region's functional groups. The stretched CH region, used as an indicator of lipid status, also changed significantly, particularly at the higher AMIO dosage (160 mg/kg). Significant alterations in α-helix and β-turn contents were observed in the amide I of the AMIO higher dosage treated group. In conclusion, the short-term administration period of AMIO is associated with conformational and structural changes in the lacrimal gland's molecular structure, especially lipids and proteins structure.

Keywords: Lacrimal gland, Amiodarone, FTIR, Anti-arrhythmic drug, Rabbits.

Introduction

Amiodarone (AMIO) is an iodinated benzofuran derivative that uses as an anti-arrhythmic drug by blocking ion channels -potassium, sodium, and calcium channels- in myocardial cells that cause reduction of excitability and prolongation of repolarization. It was discovered in Europe in 1961 to manage ventricular fibrillation, but the US Food and Drug Administration did not approve it until 1985 [1].

AMIO has a three-day to three-week beginning of action and has a very long half-life, causing it to accumulate in numerous tissues [2]. As the drug's usage has increased, a variety of toxicities have been induced, such as liver [3], thyroid [4], genital [5], pulmonary [6], renal [7], and ocular side effects. The first report of visual side effects was in 1978 by Bockhardt, who studied the impact of AMIO on retinal pigment epithelium; after that, keratopathy and optic neuropathy were reported [8, 9].

Most studies on the side effects of AMIO on the eye have focused on the optic nerve, retina, and cornea but not on the lacrimal glands [10]. Because of the importance of the lacrimal gland in the production of tears which in turn affects the cornea and visual function, and because the molecular structure investigations of the lacrimal gland cells due to AMIO administration have been limited, our study was carried out to investigate the molecular structure and conformational changes of lacrimal gland cells due to short term administration of AMIO.

Materials and Methods

Chemicals

Cordarone®, a 200 mg tablet containing AMIO hydrochloride, was obtained from Global Napi Pharmaceuticals Company. All remaining compounds utilized in this investigation were bought from Sigma Aldrich (St. Louis, MO, USA).

Correspondsing author:saharattia.519@azhar.edu.eg
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Methodology

Three groups of healthy New Zealand white rabbits from both sexes (2-2.5 kg), since each group contains ten rabbits (20 eyes), were obtained from the animal house facility at the Research Institute Ophthalmology, Giza, Egypt. The use of animals in this work was following the ARVO Declaration for the Use of Animals in Ophthalmic and Vision Research, and the Research Institute also approved it of Ophthalmology Ethical Committee.

Rabbits were kept separately in stainless cages under suitable environmental conditions (good ventilation, adequate standard diet, temperature: 25 ± 2 °C, and 12 hours light/dark cycle). The ree search methodology was as follows: one of these groups functioned as the control, which received an intraperitoneal injection of saline (2 ml/rabbit). The second group was intraperitoneally injected for two weeks with a daily dosage of AMIO (80 mg/kg body weight (BW)) (2 ml/rabbit) [10], while the third group was treated intraperitoneally with 160 mg/kg BW AMIO daily for two weeks [11]. Rabbits were decapitated at the end of the administration period, and their lacrimal glands were removed. Each lacrimal gland sample was preserved at -20 °C in a sterile dark glass vial flushed with dry nitrogen gas.

Sample preparation and FTIR technique

The lacrimal gland samples were separately freeze-dried to eliminate water before blended with potassium bromide (KBr) (at a 5 mg lacrimal gland ratio: 95 mg KBr) to create a transparent KBr pellet for use in the FTIR spectrometer. Measurements were taken using an infrared spectrophotometer model Nicolet-iS5 (Thermo Fisher Scientific Inc, USA) with an effective resolution of 2 cm^{-1}. Typically, each sample has one hundred interferograms. Savitsky–Golay was used to correct the baseline and smooth the spectra to eliminate noise. Using the OriginPro 2016 [64-bit] (Origin Lab Corporation, Northampton, MA 01060, USA) software program for other analysis for obtained data.

Statistical analysis

Results were expressed as the mean ± standard deviation (SD). A commercially accessible software program (SPSS-11 for Windows, SPSS Inc., Chicago, IL, USA) was used to compare groups, with the significance level set at $p < 0.05$.

Results

The FTIR spectra of control and treated lacrimal glands are shown in figure 1, which covers the range from 4000 to 900 cm^{-1}. From this figure, it was noticed that the administration of the AMIO decreased the absorption intensity compared to the control in a direct manner with the applied doses. Because of the complexity of these spectra, the three regions of the spectrum were studied as follows: 4000-3000 cm^{-1} (NH-OH region), 3050-2800 cm^{-1} (C-H stretching region), and 1800-900 cm^{-1} (fingerprint region). The band extended from 1700 to 1600 cm^{-1} (Amide I region) was studied.

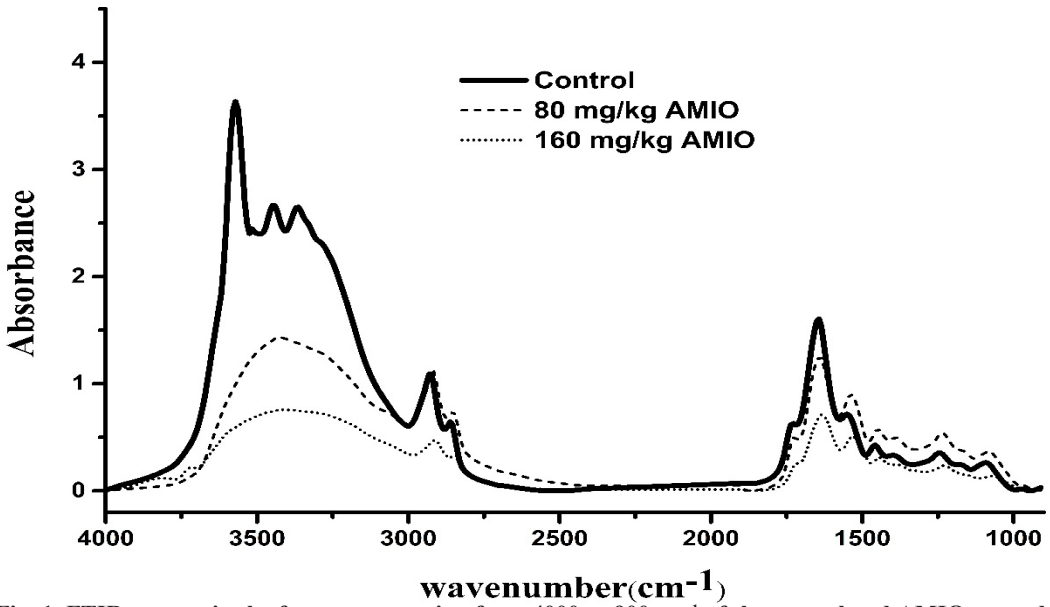

Fig. 1. FTIR spectra in the frequency ranging from 4000 to 900 cm^{-1} of the control and AMIO treated lacrimal glands.

NHOH region

The stretching NH-OH region of control and all treated animals covering the range 4000-3000 cm^{-1} are shown in figure 2. After normalization of the existing data, the deconvolution of the spectra revealed that the contour of the control group could be resolved into nine structural components. These components were centered at 3619,1± 1±3506 ,6±3571 cm^{-1} and assigned as stretching O-H ($_{str}$O-H), 34465± cm^{-1} that assigned as asymmetric O-H (O-H_{asym}), 33712± cm^{-1} assigned as asymmetric N-H (N-H_{asym}). Two components centered at 32962±3249 ,7± cm^{-1} and assigned as symmetric O-H (O-H_{sym}), 31745± cm^{-1} assigned as symmetric N-H (N-H_{sym}), and finally 30912± cm^{-1} which assigned as C-H ring (C-H_{ring}). According to Dovbeshko et al. [12], these assignments were performed and listed in table (1). As illustrated in figure 2: the contour of the group treated with the lower dose of AMIO (80 mg/kg) was resolved to six components with a new component of $_{str}$O-H that was detected at a higher frequency, and the other component showed a significant reduction in band position and increase in bandwidth compared to control. The band position of O-H_{sym} shifted to a higher frequency with an increase in its bandwidth. N-H_{asym} vibrational band disappeared either at the administration of the lower or higher dose of AMIO. On the other hand, O-H_{sym} was restricted to only one component, increasing its bandwidth of both AMIO treated groups. The last observation in this group was the significant increase of N-H_{sym} bandwidth and a decrease of both band position and bandwidth of the C-H_{ring} vibrational band.

The group's contour treated with a higher dose of AMIO (160 mg/kg) was resolved to seven components with a new one related to $_{str}$O-H detected at a higher frequency. On the other hand, the other vibrational bands showed the same changes in the previous AMIO treated group.

CH region

Figure (3) shows the CH stretching region that extends from 3050 to 2800 cm^{-1}. As illustrated in this figure, the contour of the control group was resolved into five components. These components centered at 30201±2858 ,2±2892 ,1±2923 ,3±2954 ,1± cm^{-1} and was assigned as Olefinic=CH, asymmetric CH_3 ($_{asym}CH_3$) asymmetric CH_2 ($_{asym}CH_2$), and symmetric CH_2 ($_{sym}CH_2$), respectively. This assignment was performed according to Severcan et al. [13]. Table (2) illustrates the changes in these five components in the AMIO treated groups compared to control. Due to the administration of 80 mg/kg AMIO, there were no changes either in the band positions or bandwidth of the CH stretching bands except for the bandwidth of Olefinic=CH, which showed a significant increase compared to control. On the contrary, the AMIO higher dose (160 mg/kg) increased bandwidth of Olefinic=CH, $_{asym}CH_2$, beside $_{asym}CH_3$ frequency. In addition to a significant decrease in the band position of Olefinic=CH and bandwidth of $_{asym}CH_3$.

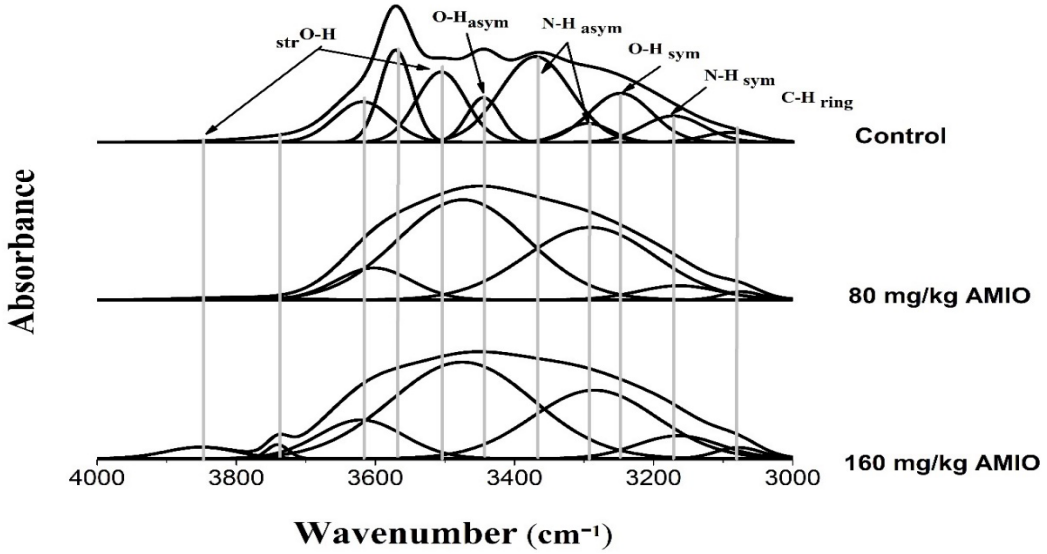

Fig.2. FTIR spectra in the frequency ranging from 4000 to 3000 cm^{-1} that relates to the NH-OH region of the normal lacrimal glands and AMIO treated groups.

TABLE 1. NH-OHt region (4000-3000 cm^{-1}) of lacrimal glands tissue for control and AMIO treated groups.

	$_{str}$O–H					O-H$_{asym}$	N-H$_{asym}$	O-H$_{sym}$		N-H$_{sym}$	C-H$_{ring}$
Control			3619±1 95±4	3571±6 54±5	3506±1 82±5	3446±5 56±4	3371±2 119±3	3296±7 78±2	3249±2 105±4	3174±5 103±3	3091±2 92±5
80 mg/kg AMIO	3800±1 171±3		3602±2† 126±5†			3474±1† 218±5†		3290±5 218±4†		3163±6 138±5†	3073±2† 65±2†
160 mg/kg AMIO	3851±3 118±2	3740±2 36±2	3620±2 143±5†			3475±2† 240±4†		3285±5 210±6†		3164±6 140±4†	3078±2† 76±3†

The first line in each cell indicates the vibrational frequency(cm^{-1}), the second line reflects the bandwidth. †Statistically significant.

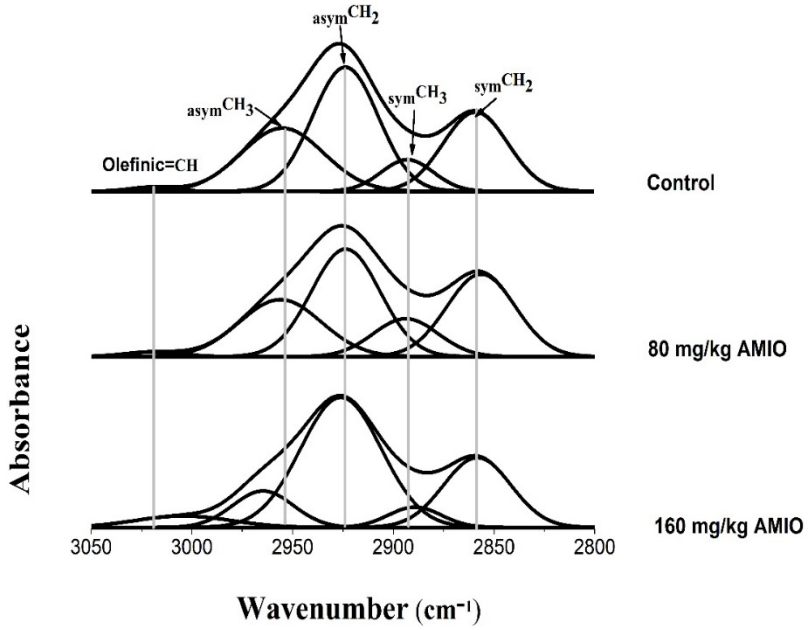

Fig.3. FTIR spectra in the frequency ranging from 3050 to 2800 cm^{-1} related to the CH stretched region of the control and AMIO treated lacrimal glands.

TABLE 2. CH region (3050-2800 cm^{-1}) of lacrimal glands tissue for control and all AMIO treated groups.

	Olefinic=CH	$_{asym}$CH$_3$	$_{asym}$CH$_2$	$_{sym}$CH$_3$	$_{sym}$CH$_2$
Control	3020±2 25±1	2954±3 48±2	2923±1 38±3	2892±2 30±3	2858±1 37±2
80 mg/kg AMIO	3019±2 34±1†	2956±2 47±1	2923±1 40±2	2893±1 37±4	2856±3 40±2
160 mg/kg AMIO	3004±1† 56±3†	2964±1† 35±2†	2926±2 47±2†	2889±2 35±3	2858±1 39±2

The first line in each cell indicates the vibrational frequency(cm^{-1}), the second line reflects the bandwidth. †Statistically

Fingerprint Region

The analysis of the fingerprint region that extends from 1800 to 900 cm^{-1} is shown in Fig. 4. This region result from the absorption of functional groups relates to lacrimal gland proteins and lipids constituents. Up on deconvolution, the contour of the control group resolved into ten components. These components were centered at 17331± cm^{-1} was $_{Ester}C=O$, 16463± cm^{-1} Amide I, 15453± cm^{-1} assigned as Amide II ($N=H_{bend}$) while the band located at 1456,4±1393 ,2± 3±1093 ,2±1172 ,5±1243 ,6±1325, and 9633± cm^{-1} were set as $_{bend}CH_2$, $_{str}COO^-_{sym,}$ $_{def}CH_3$, $_{str}PO_2^-{}_{asym}$, $_{str}COOC_{asym,}$ $_{str}PO_2^-{}_{sym,}$ and COC respectively. These assignments were carried out following that previously mentioned by Gamal et al. [14]. Table (3) summarized the band position changes and bandwidth of AMIO treated groups compared to control. From this table, it was noticed that the band position of the $_{Ester}C=O$ was shifted to a higher frequency accompanied by a significant decrease in the bandwidth in AMIO treated groups while only the bandwidth of amide I showed a significant increase compared to control. Only the administration of the higher dose of AMIO caused an increase in the bandwidth of Amide II ($N=H_{bend}$) and $_{str}COO^-_{sym}$ while the bandwidth of $_{bend}CH_2$ displayed a significant decrease. The bandwidth of the $_{def}CH_3$ showed a significant increase in both AMIO treated groups while this band's band position shifted to lower wavenumber due to administration of higher dose only. The bandwidths of $_{str}PO_2^-{}_{asym}$ and $_{str}PO_2^-{}_{sym}$ were decreased and increased -respectively- due to the administration of the two doses of AMIO. Finally, the treatment with 160 mg/kg AMIO caused a reduction in the bandwidth of the COC vibrational band.

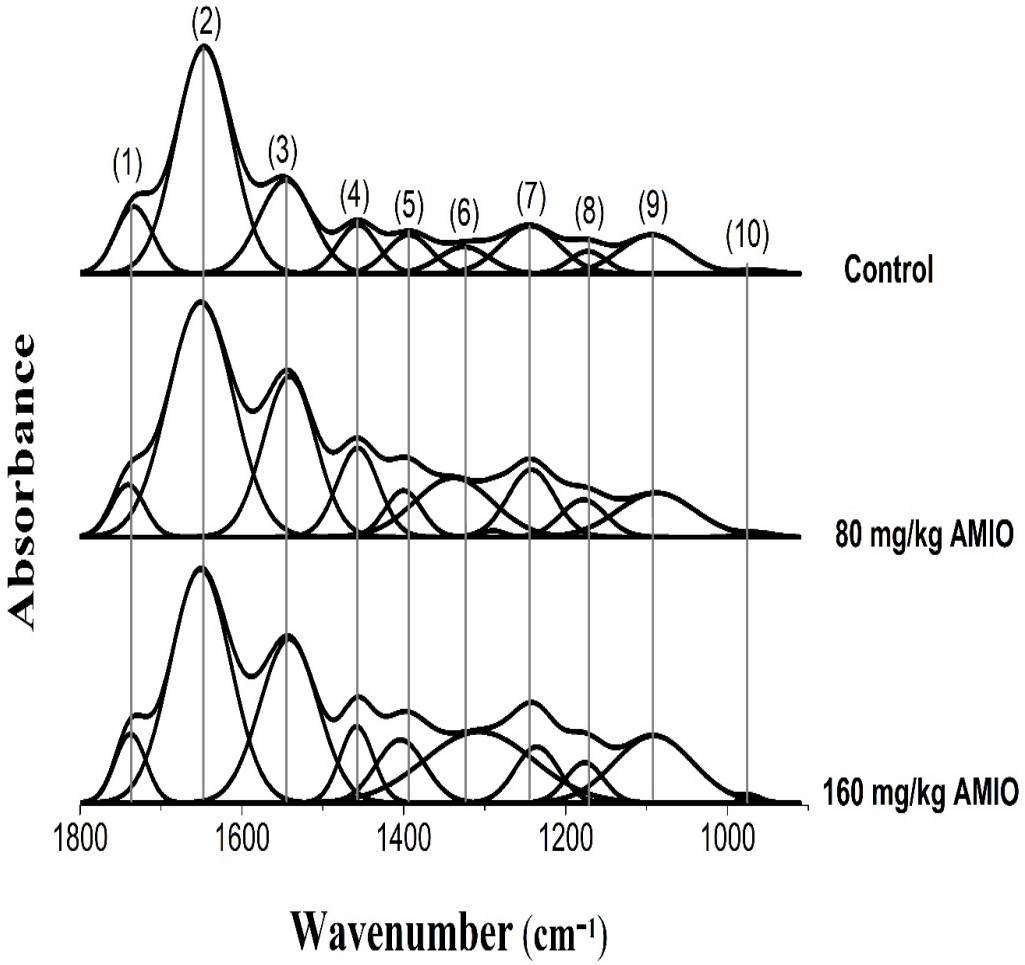

Fig.4. FTIR spectra in the frequency ranging from 1800 to 900 cm^{-1} that relates to the fingerprint region of the control and AMIO treated lacrimal glands. (1) $_{Ester}C=O$, (2) amide I, (3) amide II ($N=H_{bend}$), (4) $CH_{2\ bend}$, (5) $_{str}COO^-_{sym}$, (6) $_{def}CH_3$, (7) $_{str}PO_{2\ asym,}$ (8) $_{str}COOC_{asym}$, (9) $_{str}PO_2^-{}_{sym}$ and (10) COC.

TABLE 3. Fingerprint region (1800-900 cm $^{-1}$) of lacrimal glands tissue for control and all AMIO treated groups.

	Control	80 mg/kg AMIO	160 mg/kg AMIO
$_{Ester}C=O$	1733±1	1740±2†	1737±1†
	53±1	48±1†	45±2†
Amide I	1646±3	1650±3	1651±3
	81±1	94±2†	89±1†
Amide II	1545±3	1540±2	1541±2
($N=H_{bend}$)	77±1	76±2	84±1†
$_{bend}CH_2$	1456±2	1456±3	1458±2
	57±3	60±3	48±2†
$_{str}COO^-_{sym}$	1393±4	1399±2	1404±1†
	61±3	55±3	71±2†
$CH_{3\ def}$	1325±6	1336±5	1307±3†
	72±3	112±4†	158±5†
$_{str}PO_2^-_{asym}$	1243±5	1241±3	1235±4
	84±2	68±2†	63±1†
$_{str}COOC_{asym}$	1172±2	1177±3	1176±3
	54±4	61±4	54±4
$_{str}PO_2^-_{sym}$	1093±3	1087±3	1091±1
	93±3	112±4†	113±3†
COC	963±3	959±2	969±4
	49±3	46±4	27±3†

The first line in each cell indicates the vibrational frequency(cm^{-1}), the second line reflects the bandwidth. †Statistically significant.

Amide I

the protein secondary structure conformation, the deconvolution was performed to this band covering the range 1705-1595 cm^{-1} (this band associated with the stretching vibration of C=O of protein amide I). The curve enhancement procedure revealed that the contour of the control group could be resolved into five components which centered at 16891±1673 ,2± cm^{-1} which assigned as β-turn; 16473± cm^{-1} assigned as α-helix and 16232±1612 ,3± cm^{-1} and assigned as β-sheet. Assignments were carried out following Mahmoud et al. [15]. The changes in the percentage of the three types of secondary structural protein constituents in AMIO treated groups compared to control were registered in the table (4) and illustrated in histogram figure (6). As displayed in this figure, the administration of 160 mg/kg AMIO caused a significant increase in the percentage of β-turn while the percentage of α-helix was decreased.

TABLE 4. The percentage of protein secondary structure components of the lacrimal glands treated with AMIO compared to control.

	β-turn	α-helix	β-sheet
Control	16.5±2.3	68.3±3	15.2±2
80 mg/kg AMIO	19.2±3.7	64±2	16.8±1.8
160 mg/kg AMIO	22.4±1.6†	58.9±0.8†	18.7±2.7

†*Statistically significant.*

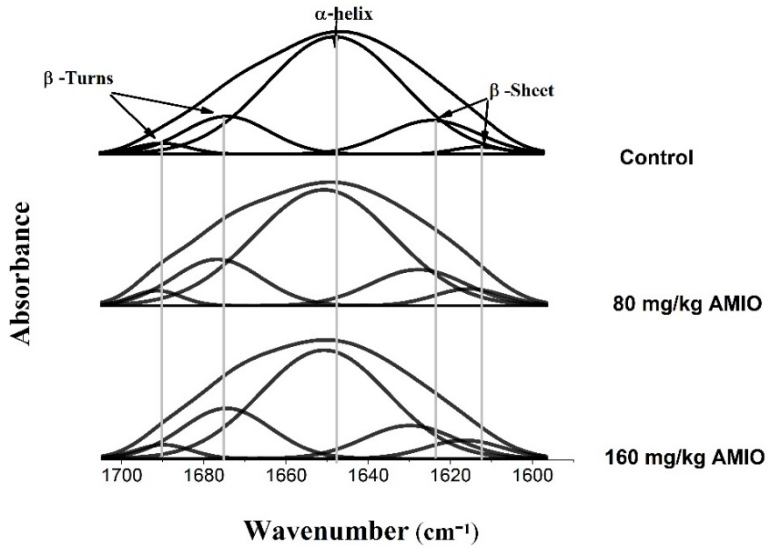

Fig.5. FTIR spectra in the frequency ranging from 1705 to 1595 cm^{-1} related to the Amide I region of the control and AMIO treated lacrimal gland.

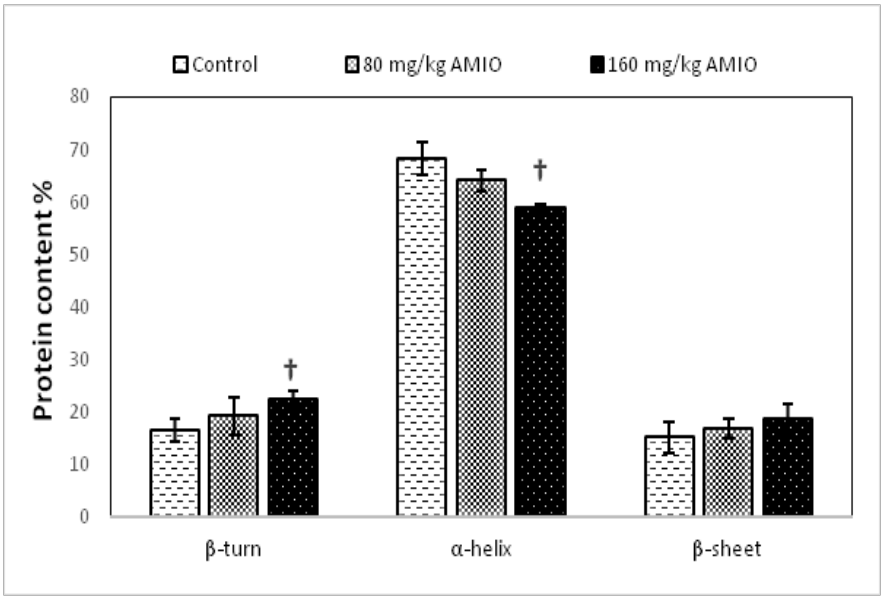

Fig.6. Percentage of lacrimal glands protein secondary structure components of control and AMIO treated groups, †Statistically significant.

Discussion

Since the lacrimal gland is vital for visual functions and there are many studies on AMIO showing that this drug causes numerous adverse effects [16-18], this study aims to investigate the effect of AMIO on this accessory apparatus.

The absorption of infrared light by vibrational transitions in the covalent bonds of the examined material is the basis for FTIR spectroscopic analysis. So that, this examination provides extensive information regarding the chemical structure and conformation of the object under consideration [19]. Numerous studies have demonstrated the effectiveness of this method in diagnosing illnesses such as diabetes, cancer, and Alzheimer's disease [20-22].

In our study, FTIR spectroscopy revealed that AMIO administration induced various molecular structural alterations in the lacrimal glands, as evidenced by changes in the absorption frequencies and bandwidth of functional groups of analyzed samples. The changes that occurred in the frequencies and bandwidths of NH-OH vibrational bands due to AMIO indicate the formation/destruction of the hydrogen bonds since these bands are found in membrane constituents as the lipid, protein, and genetic material [23, 24]. The changes displayed in the $N\text{-}H_{asym}$ and $N\text{-}H_{sym}$ related to the molecular alteration in lacrimal gland proteins [14]. The CH stretched region, mainly used for characterizing the tissue's lipid structure, displayed sensitivity to the AMIO treatment spatially at a higher dose of AMIO (160 mg/kg). The expansion of the ${}_{asym}CH_2$ bandwidth implies a rise in the degree of acyl-chain disorder and an increase in membrane fluidity in the lacrimal gland. The changes in the Olefinic C=H correspond to changes in the unsaturated hydrocarbon chains [20].

Moreover, the fingerprint region confirmed the above finding by shifting the EsterC=O (phospholipids head group) to a higher frequency than the control, indicating that the band at weakly hydrogen-bonded and the decrease in its bandwidth refers to an increase in freedom around this bond [25]. Another vibrational band related to the scissoring motion of lipid hydrocarbon chains (${}_{bend}CH_2$) displayed narrowing in the bandwidth due to administration of 160 mg/kg AMIO, which indicates a change in the acyl chain packing of hydrocarbon chains moreover an increase in the degree of disorder inside these hydrocarbon chains [15]. The remaining vibrational bands of this region (${}_{asym}PO_2$, ${}_{str}COO^-{}_{sym}$, and ${}_{sym}PO_2$) also supported the above finding.

Because of its high sensitivity to tiny changes in molecular geometry and peptide hydrogen bonding, the amide I band, primarily caused by the C=O stretching motions of the peptide backbone, has been used for protein structural and conformational investigations. Amide I region displayed sensitivity to administering the higher dose of AMIO (160 mg/kg). An increase in the β-turn and a reduction in the α-helix implies that the AMIO's higher dose (160 mg/kg) caused an increase in the folding of lacrimal gland protein. β-turn is a minor type of protein secondary structure, joining other secondary structure elements such as α-helix and β-sheets and enabling the protein to adopt globular structures, serving as a nucleation site for folding/refolding of proteins [14].

Conclusion

The short administration period of AMIO with lower (80 mg/kg) or higher dose (160 mg/kg) had noticeable side effects on the lacrimal gland (conformational changes in the lacrimal gland's molecular structure, especially lipids and protein structure mainly due to AMIO's higher dose).

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التحقيق الطيفي لتأثير الأميوداورون على الغدة الدمعية في الأرانب

سحر عطية مرسى[١] ، أحلام محمد إبراهيم[١] ، إيمان محمد علي[٢] ، شريف صديق محمود[٢] ، جيهان محمد كمال[١]

[١] قسم الفيزياء - كلية العلوم(بنات) - جامعة الازهر - مدينة نصر – مصر.

[٢] وحدة علوم الفيزياء الحيوية والليزر - معهد بحوث امراض العيون – الجيزة – مصر.

يعتبر عقار الأميوداورون دوائًا حيويًا لمرضى عدم انتظام ضربات القلب، ولكن له العديد من الآثار الجانبية. تعد الغدة الدمعية جهازًا ضروريًا لإنتاج الدموع، والذي بدورها أمر بالغ الأهمية للوظائف البصرية، لذلك تهدف هذه الدراسة إلى التحقق من تأثير الاميوداورون على هذا الجهاز. استخدمت في هذه الدراسة ثلاث مجموعات من الأرانب من كلا الجنسين (٢-٢,٥ كجم) تحتوي كل مجموعة على خمسة أرانب. أجريت التجربة بالطريقة التالية: عملت إحدى هذه المجموعات كعنصر تحكم وحقنت داخل الغشاء البريتوني بمحلول ملحي عادي. حقنت المجموعة الثانية داخل الغشاء البريتوني بالاميوداورون (٨٠ ملجم / كجم من وزن الجسم) مرة واحدة يوميًا لمدة أسبوعين. تلقت المجموعة الثالثة جرعة يومية من AMIO (١٦٠ مجم / كجم من وزن الجسم) داخل الغشاء البريتوني لمدة أسبوعين. كشفت أطياف FTIR التي تم الحصول عليها أن التركيب الجزيئي للغدة الدمعية حساس لعلاج بالاميوداورون. تسبب علاج الاميوداورون في تغييرات كبيرة في الترددات وعرض النطاق الترددي للمجموعات الوظيفية لمنطقة NH-OH. منطقة CH الممتدة، المستخدمة كمؤشر لحالة الدهون، تغيرت أيضًا بشكل كبير، خاصة عند جرعة الاميوداورون الأعلى (١٦٠ مجم / كجم). لوحظت تغييرات كبيرة في محتويات α-helix وβ-turn في الأميد الأول من المجموعة المعالجة بجرعات أعلى من الاميوداورون. في الختام، ترتبط فترة الإدارة قصيرة المدى للاميوداورون بالتغيرات التوافقية والهيكلية في التركيب الجزيئي للغدة الدمعية، وخاصة بنية الدهون والبروتينات.