Oral anticoagulation therapy using acenocoumarol during the month of ramadan: a comparative study between fasting and non-fasting patients

L'anticoagulation orale par Acenocoumarol durant le mois de Ramadan : étude comparative entre les jeûneurs et les non-jeûneurs

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RÉSUMÉ

Introduction : Les impacts du jeûne du Ramadan sur l'anticoagulation par les antivitamines K ont été étudiés sur des nombres limités de patients avec des résultats controversés. L'objectif de cette étude a été de comparer les fluctuations de l'anticoagulation au long cours par l'Acenocoumarol entre les patients jeûneurs et non jeûneurs du Ramadan mais aussi d'identifier les facteurs associés à de telles fluctuations.

Méthodes : Il s'agissait d'une étude comparative qui a été menée entre mai et août 2018. L'étude a comporté trois périodes : Pré-Ramadan (Pré-R), Ramadan (R) et post-Ramadan (Post-R). Les critères d'inclusion ont été les suivants : patients ambulatoires âgés de plus de 18 ans, un «international normalized ratio» (INR) à la cible aux trois mois Pré-R et l'absence de contre-indications médicales au jeûne (pour le groupe des jeûneurs). Le suivi de l'anticoagulation a été assuré par cinq dosages successifs de l'INR : INR0 (14 jours pré-R), INR1 (entre le 1er et le 14ème jours du R), INR2 (entre le 15ème et 28ème jours du R), INR3 (28 jours après INR2) et INR4 (28 jours après INR3). L'équilibre INR a été évalué par les quatre pourcentages de temps dans l'intervalle thérapeutique (TIT) : TIT0 (entre INR0 et INR1), TIT1 (entre INR1 et INR2), TIT2 (entre INR2 et INR3) et TIT3 (entre INR3 et INR4). L'hypothèse nulle a été la survenue d'une instabilité de l'anticoagulation (jugée sur les valeurs du TIT) chez les jeûneurs comparativement aux non-jeûneurs.

Résultats : Cent vingt-deux patients (84 jeûneurs) âgés de 60 ± 19 ans ont été inclus. Chez les jeûneurs, les moyennes des différences des INR1, 2, 3 et 4 par rapport à l'INR0 n'ont pas été statistiquement significatives, respectivement de +0,46, +0,34, +0,28, +0,30. Chez les jeûneurs, parmi les trois TIT, seul le TIT2 a significativement diminué par rapport au TIT0 (respectivement 50,3 ± 37,4 contre 63,6 ± 39,3%, p=0,004). Les valeurs des TIT1 à 3 ont été similaires entre les deux groupes de jeûneurs et non jeûneurs.

Conclusion : Les modifications de l'équilibre de l'anticoagulation, jugées par les TIT, ont été similaires entre les patients jeûneurs et non jeûneurs recevant l'Acenocoumarol.

Mots-clés
Religion, Alimentation, Coagulation, Sang, Médicaments, AVK

SUMMARY

Background and objectives: The effect of Ramadan fasting on anticoagulation by vitamin K antagonists has been previously investigated in small scale studies with controversial results. From this perspective, this study aimed to compare the fluctuations of anticoagulation in fasting and non-fasting patients taking Acenocoumarol and to identify the factors associated with such fluctuations.

Methods: The study, conducted between May and August 2018, was a comparative one. Three study periods were defined: before Ramadan (BR), Ramadan and after Ramadan (AR). Enrolment involved ambulatory patients aged over eighteen, without medical contraindications to fasting (for the fasting group) and whom international normalized ratio (INR) was within the therapeutic target range during the last three months BR. Anticoagulation monitoring consisted in five consecutive INR assays; INR0 (during the 14 days BR), INR1 (between the 1st and the 14th day of Ramadan), INR2 (between the 15th and the 28th day of Ramadan), INR3 (28 days after INR2) and INR4 (28 days after INR3). INR stability was assessed by calculating four percentages of time in therapeutic range (TTR); TTR0 (between INR0 and INR1), TTR1 (between INR0 and INR2), TTR2 (between INR2 and INR3) and TTR3 (between INR3 and INR4). The null hypothesis was the occurrence of an anticoagulation imbalance (evaluated by TTR) in fasting patients in comparison with non-fasting ones.

Results: One hundred and twenty-two patients (84 fasting patients), aged 60 ± 19 years, were included. In fasting patients, the average differences of INR1, 2, 3 and 4 compared with INR0 were statistically non-significant and accounted for +0.46, +0.34, +0.28 and +0.30 respectively. Among the three TTRs, only TTR2 significantly decreased in comparison with TTR0 in fasting group (50.3 ± 37.4 vs. 63.6 ± 39.3%, p=0.004). TTR1, 2 and 3 were comparable between fasting and non-fasting patients.

Conclusions: The fluctuations of anticoagulation balance, assessed by TTR, were comparable between fasting and non-fasting patients taking Acenocoumarol.

Key-words
Religion, Diet, Coagulation, Blood, Medications, VKA

INTRODUCTION

To date, Acenocoumarol, a vitamin K antagonist (VKA), is the most widely used oral anticoagulation therapy for thromboembolic diseases in Tunisia. Acenocoumarol is a drug with a narrow therapeutic range on which several medications (1), dietary (2) and individual factors (3) may interfere. Every year, Tunisians, predominantly Muslims, practice fasting from sunrise to sunset during the month of Ramadan. During Ramadan, relevant dietary modifications are noticeable including not only the types and the amount of food but also the mealtimes (4-7). The effects of Ramadan fasting on anticoagulation by vitamin K antagonists remain controversial (8-12). Unlike diabetes mellitus (13), there is no consensus on the anticoagulation therapy using VKA during the month of Ramadan. With the purpose to improve the management of patients taking long-term Acenocoumarol, the present study aimed to investigate the fluctuations of anticoagulant activity in fasting and non-fasting patients under Acenocoumarol and to identify the factors associated with such fluctuations. The null hypothesis was the occurrence of an anticoagulation imbalance in fasting patients in comparison with non-fasting ones.

METHODS

Study Design:

The Study was a prospective, observational single centre study (Department of cardiological investigations and resuscitation - La Rabta University Hospital - Tunis) and was conducted between May and August 2018. Ramadan began on the sixteenth of May twenty eighteen and ended on the fourteenth of June twenty eighteen. Ethical approval for this study was granted by the ethics committee of La Rabta University Hospital of Tunis. All patients gave oral informed consent to the protocol.

Study population:

The enrolment involved patients over the age of eighteen, taking Acenocoumarol for anticoagulation and followed up on an ambulatory basis in the department of cardiological investigations and resuscitation of La Rabta University Hospital. All enrolled patients had prior international normalized ratio (INR) within the therapeutic target range during the last three months before Ramadan (BR) and had not any medical contraindication to fasting.

Initiation of Acenocoumarol therapy for less than three months, absence of INR supervision within the last three months BR, overt clinical signs of acute heart failure or decompensation and fasting against medical advice were non-inclusion criteria. Moreover, non-consenting patients and patients who did not wish to be regularly followed up in the outpatient consultation for their INR monitoring during the study period were not enrolled.

Exclusion Criterion was the absence of INR monitoring in due course (cf. data collection).

Two study groups were established; the fasting group (FG) and the non-fasting group (NFG). Follow-up lasted three months. The sample size analysis was performed using the GPower software (14). By referring to the percentage of patients with on target anticoagulation status, the software established that 143 patients must be included in the survey in order to demonstrate an average difference between fasting and non-fasting patients with minimal power (0.8) and a risk of error of 5%. The null hypothesis was the occurrence of an anticoagulation imbalance in fasting patients in comparison with non-fasting ones.

Study Protocol:

Three study periods were defined: BR, Ramadan (R) and after Ramadan (AR) **(**figure 1).

Data collection:

The evaluation of adherence to Acenocoumarol therapy was performed at inclusion, by Morisky's medication adherence scale (15) **(**Boxe 1**)**. Bleeding risk was evaluated by the Outpatient Bleeding Risk Index (16,17) (Boxe 2). Thromboembolic risk was evaluated by the CHA_2DS_2-VASc score in case of non-valvular atrial fibrillation (18) (Boxe 3).

Demographic, educational, social and professional data as well as risk scores were collected from patients during outpatient consultations by the same investigator. Medical data were collected in the same time from the patient's medical records.

Routine blood assays included aspartate aminotransferase (IU/l), total cholesterolemia (g/l), and serum creatinine (mg/l) with calculation of creatinine clearance (ml/min) determined by Crockroft and Gault's formula (19). Chronic kidney disease was diagnosed when creatinine clearance was inferior to 60ml/min (20).

Anticoagulation monitoring consisted in five consecutive INR assays (INR0, INR1, INR2, INR3 and INR4) detailed in figure 1.

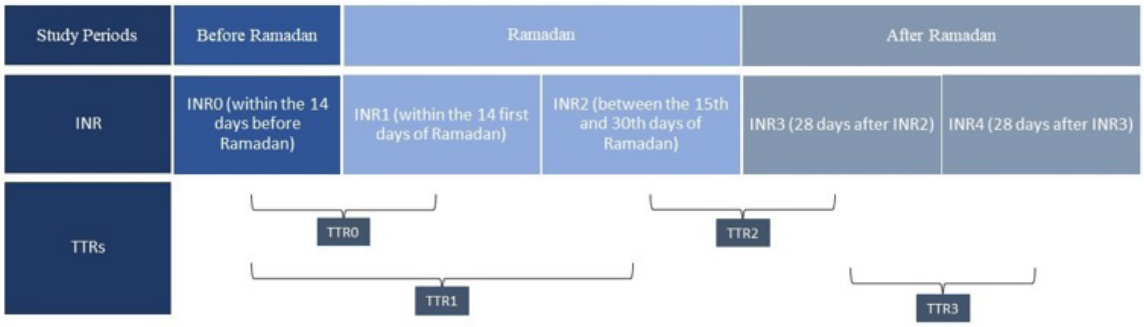

Figure 1. The study protocol
INR: International nationalized ratio; TTRs: Times in therapeutic range

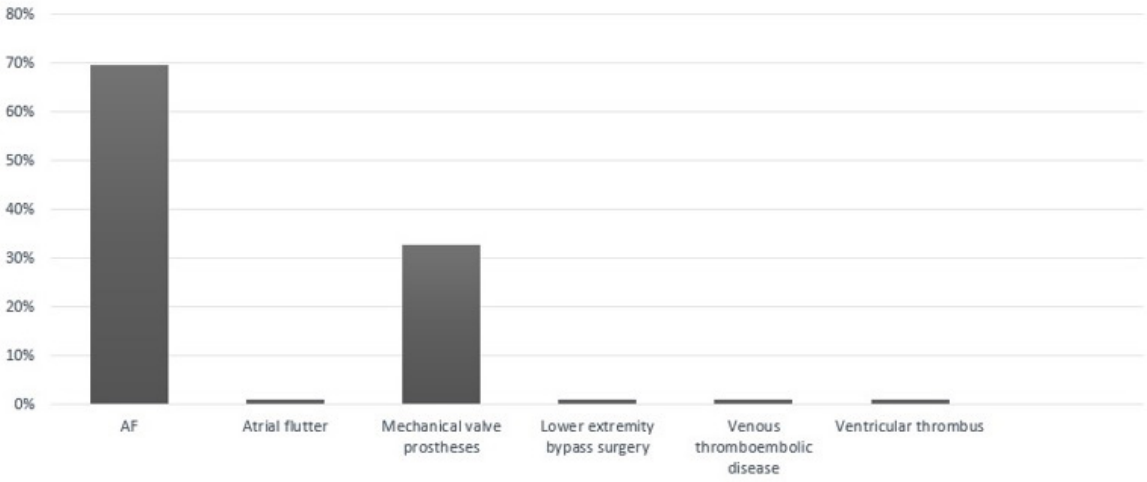

Figure 2. Indications of the anticoagulation therapy
AF: Atrial fibrillation

INR was determined by measuring the prothrombin time using STA-R automate (DiagnosticaStago, Asnier, France). INR targets were established according to the European guidelines (21-24). INR balance was assessed by the percentage of time in therapeutic range (TTR) (25). TTR target threshold lower than 65% indicated imbalance in anticoagulation level (25). TTR was calculated using the linear interpolation of Rosendaal et al. (26) for each stage of the survey; TTR0 (between INR0 and INR1), TTR1 (between INR0 and INR2), TTR2 (between INR2 and INR3) and TTR3 (between INR3 and INR4) (figure 1). While INR > 4.5 was set to define overdosage of vitamin K antagonists, INR < 1.7 defined underdosing (27).

Bleeding definitions were established according to the Bleeding Academic Research Consortium (28). Bleeding type 1 is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. Bleeding type 3c indicate intracranial haemorrhage, intraocular bleed compromising vision or subcategories confirmed by autopsy or imaging or lumbar puncture (28).

Statistical analysis:

Data were analyzed using SPSS (version 22.0). Comparison of quantitative variables (INR) was performed using the non-parametric Wilcoxon test. Comparison of qualitative variables between groups was performed using the Fisher test. Comparison of two means in independent series was performed using the non-parametric Mann and Whitney test (intergroup analysis). Comparison of several means (>2) in matched series was performed using the non-parametric test of Friedman (intra-group

Boxe 1. Factor Loadings of the 8-Item Medication Adherence Scale (15)

1. Do you sometimes forget to take your pills?	No=1
2. Sometimes, patients don't take their medications for reasons other than forgetfulness. Over the past 2 weeks, were there any days when you did not take your medicine?	No=1
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?	No=1
4. When you travel or leave home, do you sometimes forget to bring along your medications?	No=1
5. Did you take your medicine yesterday?	Yes=1
6.When you feel like your health status is improving, do you sometimes stop taking your medicine?	No=1
7. Do you ever feel hassled about sticking to your treatment plan?	No=1
8. How often do you have difficulty remembering to take all your medication?	Never/rarely=1 From time to time=0.75 Sometimes=0.5 Regularly=0.25 Always=0
Low adherence: score <6 Medium adherence: score 6-7 High adherence: score ≥8	

Boxe 2. The Outpatient Bleeding Risk Index (16)

Risk factors	Points
Age ≥ 65 years	1
History of stroke	1
History of gastrointestinal bleeding	1
Recent myocardial infarction, haematocrit < 30%, serum creatinine > 1.5mg/dl or diabetes mellitus	1
Score	**Estimated 12 months risk of major bleeding**
0: Low risk patient	3%
1-2: Intermediate risk patient	12%
3-4: High risk patient	48%

Boxe 3. The CHA_2DS_2-VASc score (18)

Risk Factors	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Age 65-74	1
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Sex Female	1

TIA: Transient ischemic attack

analysis). The analysis of variance was made to assess the difference in TTR between periods. Comparison of INR dispersion between the two groups was performed by confronting the areas under the curve of INR for each stage of the survey. Moreover, univariate and multivariate analysis using a logistic regression model were performed in order to identify predictive factors of TTR<65%. Variables with p<0.20 in univariate analysis as well as those known in literature as predictive of the anticoagulation level, were introduced in the model. The validity conditions of logistic regression were met so that for each explicative variable introduced in the model, at least five events were found. Furthermore, the suitability of each model was confirmed using the Hosmer-Lemeshow non-significant test (29). The most sparing model was set out as the final model. Adjusted and non-adjusted odds ratio (OR) with a confidence interval (CI) of 95% were calculated for each variable of the final model. A p value <0.05 was considered statistically significant for every test.

RESULTS

General characteristics of the study population

One hundred and twenty-nine patients were enrolled. Seven patients were excluded (four patients were lost to follow up and three patients withdrew from the study). Among the study population (122 patients), 84 patients (68.9%) were fasting and 38 (31.1%) were not. Mean age was 60 ± 19 years with extremes ranging from 25 to 88 years. Women represented more than half the study population (51.2%). Forty-eight percent of patients were hypertensive and 22% were diabetics. Eighty seven percent of patients had received therapeutic education for VKA management. Fifty-one percent of patients had history of bleeding and 7.4% of patients had already experienced thromboembolic complications. The FG was found to have more female patients (48.8 vs. 28.9%, p=0.05) and a lower CHA_2DS_2-VASc score in case of non-valvular atrial fibrillation. All other characteristics were comparable between the two groups (table I).

Anticoagulation modalities and indications for treatment

The indications for Acenocoumarol are illustrated in figure 2. Main indications for Acenocoumarol were atrial fibrillation reported in 69.7% of patients (71.4 vs. 65.8%, in the FG and the NFG, respectively, p=0.53) and mechanical heart valve prostheses noted in 32.8% of patients (31% vs. 36.8%, in the FG and the NFG, respectively, p=0.34). The average dose of Acenocoumarol was 2.7 ± 1.2 mg/day and treatment was given once daily in 95.1% of patients. Treatment adherence was considered high in 81.1% of patients.

Level and fluctuations of anticoagulation

Comparison between FG and NFG

The evolution of both INR and TTR in fasting and non-fasting groups is described in table II. No significant difference in TTRs was found. Therefore, the primary endpoint was not achieved. INR4 was higher in fasting patients (p=0.04). No significant differences were noticed regarding the other INRs.

Intragroup fluctuations of anticoagulation

In comparison with INR0, the average differences of INR, regarding fasting patients, were +0.46, +0.34, +0.28 and +0.30 for INR1, INR2, INR3 and INR4 respectively (p=0.17). The average TTR was 57.2 ± 25.9%. Within this group, a significant decrease of TTR2 was noticed in comparison with TTR0 (63.6 ± 39.3 vs. 50.3 ± 37.4%, p=0.004).

Within the NFG, the average TTR was 51.5 ± 22.1% without any significant difference between the different TTRs (p=0.43).

Complications

Twelve bleeding complications were reported (9.5 vs. 10.5% in the FG and the NFG, respectively, p=0.51). Bleeding type 3c (intracranial hemorrhage) occurred within the FG in two patients with intermediate risk of bleeding (Outpatient Bleeding Risk Index of 1 and 2) and high adherence to Acenocoumarol (Morisky's medication adherence score of 8). The two patients did not take concomitant antiplatelet therapy and had target INR of 2.5 and 4.0 with Acenocoumarol administration for 4 and 7 years. Intracranial bleeding occurred in the second half of Ramadan and within the month following Ramadan respectively. In addition to intracranial hemorrhage, ten bleedings type 1 were observed.

Predictive factors of anticoagulation imbalance

Predictive factors of TTR < 65% in univariate and multivariate analysis are summarized in table III. Fasting was not significantly associated with anticoagulation

Table 1 : General characteristics of the study population

	Total N=122	Fasting patients N=84	Non-fasting patients N=38	p
Age (years)	60 ±19	60.5 ±12	59±13	0.60
Males (%)	48.8	51.2	71.1	**0.05**
Educational level (%)				
Primary school level	34.4	40.5	21.1	0.07
Secondary stage level	21.3	16.7	31.6	
University level	5.70	7.15	2.6	
Residence in Tunis (%)	75.4	76.2	82.3	0.50
Arterial hypertension (%)	48.7	41.7	52.6	0.33
Diabetes mellitus (%)	22.1	20.2	26.3	0.48
Myocardial infarction (%)	6.6	6	7.7	0.70
Chronic kidney disease (%)	3.3	2.6	3.3	1.00
History of bleeding under VKA (%)	51.6	52.4	50.0	0.85
History of thromboembolic complications (%)	7.4	6	10.5	0.46
Daily Acenocoumarol dosing* (mg/day)	2.71±1.23	2.70±1.15	2.73±1.41	0.91
Patients taking single dose (%)	95.1	95	94.7	1.00
Alternation in daily medication (%)	50.8	51.2	50	1.00
Duration of anticoagulation therapy* (years)	7.81±9.32	8.11±9.49	7.13±9.04	0.59
VKA therapeutic education (%)	87.7	89.3	84.2	0.55
CHA2DS2Vasc Score* (number)	1.85±1.09	1.65±1.08	2.30±0.96	**0.02**
Morisky's medication adherence scale (%):				
Low adherence	14.8	13.1	81.6	0.25
Medium adherence	4.1	6	10.5	
High adherence	81.1	81	7.9	
Associated treatments (%):				
Acetyl salicylate	6.6	6	7.9	0.77
Non-steroidal anti-inflammatory drugs	0	0	0	
Outpatient Bleeding Risk Index (%):				
Low risk	33.7	38.1	23.7	0.25
Intermediate risk	62.3	58.3	71.1	
High risk	4	3.6	5.1	
Bleeding complications (%) :	9.8	9.5	10.5	0.51
Type 1	8.2	7.1	10.5	
Type 3c	1.6	2.4	0	
Serum creatinine * (mg/l)	8.52±2.49	8.48±2.56	8.60±2.36	0.81
Total cholesterolemia* (g/l)	1.70±0.82	1.73±0.76	1.78±0.97	0.74
Aspartate aminotransferase* (IU/l)	20.6±7.41	21.4±7.69	19.0±6.54	0.09

Values are expressed in number (percentage) or in * means (standard deviation). VKA: Vitamin K antagonists

imbalance. In multivariate analysis, atrial fibrillation was the only protective factor independently associated with TTR ≥ 65% (OR=0.35 [0.13-0.91], p=0.03).

Table 2 : Comparison of mean INR and TTR between fasting and non-fasting patients

INR and TTR	Fasting patients N=84	Non-fasting patients N=38	p
INR0	2.70 ± 0.51	2.65 ± 0.51	0.62
INR1	3.16 ± 1.33	2.99 ± 1.34	0.55
INR2	3.04 ± 1.23	3.05 ± 1.29	0.95
INR3	2.98 ± 1.13	2.81 ± 0.92	0.50
INR4	3.00 ± 1.11	2.56 ± 0.89	0.04
TTR0	63.6 ± 39.3	61.2 ± 40.4	0.69
TTR1	62.6 ± 39.3	51.5 ± 38.3	0.16
TTR2	50.3 ± 37.4	48.4 ± 36.9	0.75
TTR3	54.2 ± 40.7	49.3 ± 36.2	0.67

INR and TTR are expressed in means (standard deviation). INR: International normalized ratio; TTR: Time in therapeutic range

DISCUSSION

In this study, no significant increase of INR during Ramadan was noted. Only the INR during the month of Shawal was significantly higher in fasting patients. The lowest TTR was noted during the period from the second half of Ramadan to Shawal in which two patients presented bleeding type 3c. With regard to TTRs, no significant difference was found between fasting and non-fasting patients; therefore, the null hypothesis was not confirmed.

The present study was amongst the few studies with a comparative evaluation of anticoagulation between fasting and non-fasting patients. Provided that only patients with balanced INR BR were included, the specific effect of fasting could be evaluated.

Historically, the first animal studies, conducted in rats during the seventies, had concluded that fasting enhanced the anticoagulant response to Warfarin, potentially explained by an interference of endogenous free fatty acids with binding of Warfarin to plasma proteins (30,31). Lai et al. (8) have demonstrated a significant increase of INR (+0.23, p=0.006) during Ramadan in 32 fasting and stable warfarinised patients. Time above range significantly increased from 10.8% BR to 29.8% during Ramadan (p=0.02). In accordance with the present study results, TTR declined from 80.9% BR to 65.5% during Ramadan which was statistically non significant (p=0.45). However, unlike the present study findings, an overcorrection of those fluctuations occurred AR with a time below range increasing from 0.57% during Ramadan to 15.4% AR (p=0.006) and there was no significant difference between TTRs during R and AR. Paradoxically, Awiwi et al. (9), while monitoring weekly INR in 18 patients taking Warfarin

Table 3 : Factors associated with TTR imbalance

Independent Variables	Univariate analysis			Multivariate analysis		
	Non-adjusted OR	$CI_{95\%}$	P	Adjusted OR	$CI_{95\%}$	p
Fasting	0.54	[0.25-1.18]	0.12	0.58	[0.25-1.34]	0.21
Age	0.99	[0.96-1.02]	0.59	0.94	[0.94-1.01]	0.14
Female	1.37	[0.66-2.83]	0.39	1.5	[0.67-3.34]	0.32
Atrial fibrillation	0.39	[0.17-0.86]	0.02	0.35	[0.13-0.91]	0.03
Morisky's score	1.3	[0.52-3.24]	0.57	0.95	[0.36-2.51]	0.92
History of bleeding	0.16	[0.03-0.78]	0.02	0.25	[0.05-1.26]	0.09

CI: Confidence interval; OR: Odds ratio; TTR: Time in therapeutic range

for prosthetic heart valve BR, during R and AR, have noticed a significantly better quality of anticoagulation during Ramadan. Eighty two percent of INR values obtained during Ramadan were within the therapeutic range versus 70% and 75.5% BR and AR, respectively ($p<0.001$). The lowest ratio of therapeutic anticoagulation was noticed in the 1st week AR (60.0%). The highest ratios of therapeutic anticoagulation were recorded in the last two weeks of Ramadan (88.89 and 87.5%). Such results have to be viewed critically as long as inclusion involved patients with significantly larger ratio of infra-therapeutic INR BR ($p<0.05$). It should be noted that those studies have been conducted in patients taking Warfarin which is, like Acenocoumarol, found almost exclusively protein-bound in the plasma but with longer half-life (32,33).

The effect of Ramadan fasting in patients taking Acenocoumarol have been previously investigated by two Tunisian studies (10,11). Both have reported a significant increase of INR during Ramadan. According to Addad et al. (10), INR increased during the first two weeks of Ramadan for the majority of patients with a mean variation of +46.5% ($p<0.0001$). Furthermore, a significant increase in INR was also noticed during the last two weeks of Ramadan. About half (44.8%) of the patients developed VKA overdose (INR>4.5) and 7.4% of patients experienced bleeding complications.

Several hypotheses had been advanced to explain the variations of the anticoagulation level during R and AR. A correlation between blood lipid parameters and prothrombin time during R and AR have been reported (34), although such biochemical and haematological modifications were equivocal in literature and might depend on eating patterns and the patient's background (34-39). The interaction of fatty acids with the binding site I on human serum albumin diminishing the binding capacity of Warfarin to human serum albumin (40), hypoalbuminemia (41), a decreased fibrinogen and factor VII (34), a decreased dietary intake of K vitamin, dehydration, stress (42) were all factors contributing to anticoagulation fluctuations. In that respect, some of these factors are the consequence of the specific effect of fasting on metabolism, while others are bound to modifications in dietary habits and in circadian rhythm during Ramadan. In the present study, an assumption was made that non-fasting patients would experience modifications in diet and day/night cycle (based on common practices), although not affected by fasting itself. A comparative study between 106 fasting and 143 non-fasting patients taking Warfarin had been conducted by Saour et al. (12). Target INR was achieved in more than 90% of visits. After five years of follow up, no significant difference between the two groups were reported regarding thromboembolic events and bleeding complications.

Study limitations

The number of included patients, not allowing enough statistical power, might explain our negative results. Unlike TTR, the times above and below range were not studied. Furthermore, diet, a crucial factor of INR variations, was not studied.

CONCLUSIONS

Previous studies had reported variable fluctuations of anticoagulation during and beyond Ramadan. With regard to variations of VKA activity, the present study did not demonstrate any significant difference between fasting and non-fasting patients undermining the specific effect of fasting. Still, close monitoring of anticoagulation is advised during Ramadan as well as two months later. Further studies are needed in order to yield better information on suspected pathophysiological hypotheses and to better define the clinical and biological monitoring of patients under VKA.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Freedman MD, Olatidoye AG. Clinically significant drug interactions with the oral anticoagulants. Drug Saf. 1994;10(5):381-94.
2. Sottilotta G, Romeo E, Consonni D, Siboni S, Latella C, Oriana V, et al. Dietary interactions and INR variability: retrospective evaluation of patients couples on oral anticoagulant therapy. Minerva Med. 2011;102(4):271-5.
3. Jimenez-Varo E, Canadas-Garre M, Henriques CI, Pinheiro AM, Gutierrez-Pimentel MJ, Calleja-Hernandez MA. Pharmacogenetics role in the safety of acenocoumarol therapy. Thromb Haemost. 2014;112(3):522-36.
4. Lamine F, Bouguerra R, Jabrane J, Marrakchi Z, Ben MR, Ben CS, et al. Food intake and high density lipoprotein cholesterol levels changes during Ramadan fasting in healthy young subjects. Tunis. Med. 2006;84:647–50.

5. Haouari-Oukerro F, Ben-Attia M, Kaabachi N, Haouari M. Ramadan fasting influences on food intake consumption, sleep schedule, body weight and some plasma parameters in healthy fasting volunteers. Afr. J. Biotechnol. 2013;12:3327–32.
6. Lamri-Senhadji MY, El Kebir B, Belleville J, Bouchenak M. Assessment of dietary consumption and time-course of changes in serum lipids and lipoproteins before, during and after Ramadan in young Algerian adults. Singap. Med. J. 2009;50:288–94.
7. Shadman Z, Poorsoltan N, Akhoundan M, Larijani B, Soleymanzadeh M, Akhgar Zhand C. Ramadan major dietary patterns. Iran Red Crescent Med J. 2014;16(9):e16801
8. Lai YF, Cheen MH, Ng HJ. The effects of fasting in Muslim patients taking warfarin: reply. J Thromb Haemost. 2014;12(5):808-9.
9. Awiwi MO, Yagli ZA, Elbir F, Aglar AA, Guler E, Vural U. The effects of Ramadan fasting on patients with prosthetic heart valve taking warfarin for anticoagulation. J Saudi Heart Assoc. 2017;29(1):1-6.
10. Addad F, Amami M, Ibn Elhadj Z, Chakroun T, Marrakchi S, Kachboura S. Does Ramadan fasting affect the intensity of acenocoumarol-induced anticoagulant effect? Br J Haematol. 2014;166(5):792-4.
11. Mzoughi K, Zairi I, Fennira S, Kamoun S, Jnifene Z, Ben Moussa F, et al. Effect of Ramadan fasting on acenocoumarol-induced antocoagulant effect. Ann Biol Clin. 2017;75(5):513-8.
12. Saour NJ, Siek JO, Khan M, Mammo L. Does Ramadan fasting complicate anticoagulation therapy. Ann Saudi Med. 1989;9:538–40.
13. Ibrahim M, Abu Al Magd M, Annabi FA, Assaad-Khalil S, Ba-Essa EM, Fahdil I, et al. Recommendations for management of diabetes during Ramadan: update 2015. BMJ Open Diabetes Res Care. 2015;3(1):e000108
14. Erdfelder E, Faul F, Buchner A. GPOWER: A general power analysis program. Behav Res Methods Instrum Comput. 1996 ;28(1) : 1–11
15. Morisky DE AA, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens. 2008;10(5):348-54.
16. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105(2):91-9.
17. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med. 1989;87(2):144-52.
18. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976. 16(1):31-41.
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013; 3: 1–150
21. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18(11):1609-78.
22. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
23. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(45):3145-6.
24. Konstantinides S, Torbicki A. Management of venous thrombo-embolism: an update. Eur Heart J. 2014;35(41):2855-63.
25. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118(20):2029-37.
26. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69(3):236-9.
27. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160s-98s.
28. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.
29. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. Stat Med. 1997;16(9):965-80.
30. Laliberte R, Chakrabarti S, Brodeur J. The influence of fasting on the disposition of warfarin in rats. J Pharmacol Exp Ther. 1977;200(1):44-51.
31. Laliberte R, Chakrabarti S, Brodeur J. The influence of fasting and stress on the response of rats to warfarin. J Pharmacol Exp Ther. 1976;196(1):194-203.
32. Kelly JG, O'Malley K. Clinical pharmacokinetics of oral anticoagulants. Clin Pharmacokinet. 1979;4(1):1-15.
33. Dieterle W, Faigle JW, Montigel C, Sulc M, Theobald W. Biotransformation and pharmacokinetics of acenocoumarol (Sintrom) in man. Eur J Clin Pharmacol. 1977;11(5):367-75.
34. Arraf-Zadegan N, Atashi M, Naderi GA, Baghai AM, Asgary S, Fatehifar MR, et al. The effect of fasting in Ramadan on the values and interrelations between biochemical, coagulation and

hematological factors. Ann Saudi Med. 2000;20(5-6):377-81.
35. Shehab A, Abdulle A, El Issa A, Al Suwaidi J, Nagelkerke N. Favorable changes in lipid profile: the effects of fasting after Ramadan. PloS one. 2012;7(10):e47615.
36. Temizhan A, Tandogan I, Donderici O, Demirbas B. The effects of Ramadan fasting on blood lipid levels. Am J Med. 2000;109(4):341-2.
37. Unalacak M, Kara IH, Baltaci D, Erdem O, Bucaktepe PG. Effects of Ramadan fasting on biochemical and hematological parameters and cytokines in healthy and obese individuals. Metab Syndr Relat Disord. 2011;9(2):157-61.
38. Nachvak SM, Pasdar Y, Pirsaheb S, Darbandi M, Niazi P, Mostafai R, et al. Effects of Ramadan on food intake, glucose homeostasis, lipid profiles and body composition composition. Eur J Clin Nutr. 2019;73(4):594-600.
39. Khan NB, Khan MH, Shaikh MZ, Khanani MR. Effects of Ramadan fasting on glucose levels and serum lipid profile among type 2 diabetic patients. Saudi Med J. 2010;31(11):1269-70.
40. Zaton AM, Ferrer JM, Ruiz de Gordoa JC, Marquinez MA. Binding of coumarins to site I of human serum albumin. Effect of the fatty acids. Chem Biol Interact. 1995;97(2):169-74.
41. Kawai M, Harada M, Motoike Y, Koshikawa M, Ichikawa T, Watanabe E, et al. Impact of serum albumin levels on supratherapeutic PT-INR control and bleeding risk in atrial fibrillation patients on warfarin: A prospective cohort study. Int J Cardiol Heart Vasc. 2019;22:111-6.
42. Hawk TL, Havrda DE. Effect of stress on international normalized ratio during warfarin therapy. Ann Pharmacother. 2002;36(4):617-20.