Long Term Oral Anticoagulant Therapy With Warfarin: Experience With Local Patient Population in Kuwait

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Abstract Warfarin (Coumadin) continues to remain the mainstay of oral anticoagulant therapy (OACT) for thromboprophylaxis for both venous thromboembolic disease (VTD) and cardiac indications. However it needs careful monitoring because of its narrow window of target activity level, interaction with numerous medications and food items, caution for use in patients with co-morbidities like hepatic and renal impairment and bleeding lesions and the risk of major hemorrhage. A large part of its success and safety requires the patients own understanding and participation in its control. In a retrospective study on 153 patients on long term OACT with warfarin, we have analyzed the influence of various personal characteristics of the local patient population like age, gender, nationality, education and financial status, family size, family style, manner of drug administration and number of other medications prescribed for co-morbidities. Ability to achieve consistently efficacious target level of anti coagulant activity is adversely affected by older age, female gender, lower education status, larger family size, joint family setting, dependence on domestic servants to administer warfarin and larger number of other medications taken for co-morbidities. Thirty-seven patients were identified from

such vulnerable personal characteristics and assigned to a separate anticoagulant therapy control clinic with specific arrangements for stricter control. This group of patients was studied prospectively for 18 months. Significant improvement was apparent on comparison of their performance before and after assignment to the separate clinic.

Keywords Oral anticoagulant therapy · Warfarin · Coumadin · Thrombo-prophylaxis

Introduction

Oral anticoagulant therapy (OACT) with warfarin has been the mainstay of thrombo-prophylaxis all over the world. However it is fraught with several inherent problems [1, 2]. These include a wide variation in dose requirement, delayed onset of anticoagulant effect, prolonged continuation after cessation of therapy, need for bridging with heparin, serious interaction with a wide range of medications and food items, risk of major hemorrhage related to overdosing, drug interaction and unpredictable control in presence of co-morbidities such as hepatic and renal impairment. Therefore, OACT with warfarin requires tight monitoring. The laboratory test that is universally employed for its monitoring, that is Prothrombin Time (PT) is also affected by several external factors that include sampling errors, variation in reagent quality and test performance [3, 4]. Jointly, all these problems call for extraordinary care and caution, especially when prescribed for long term use. A large part of its success and safety is dependant upon the patient's own understanding and careful participation in its control.

We present here our experience in long-term use of warfarin in 153 subjects of local patient population in

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Kuwait. The population here is widely and in certain respects uniquely different from other countries in terms of literacy, education, socioeconomic status, family size, family style, dietary habits and health care consciousness. We have analyzed the influence of these factors (henceforth called “Personal characteristics”) on the efficacy and failure of long term OACT with warfarin. We have tested the inferences drawn in a prospective study on 37 specially selected patients.

Patients and Methods

The study is based on a retrospective analysis of 153 patients who have been on long term warfarin therapy for chronic atrial fibrillation ($n = 41$), dilated cardiomyopathy ($n = 26$), ischemic heart disease with mural thrombus ($n = 16$), cardiac valve prosthesis ($n = 22$), unprovoked proximal (including recurrent) deep vein thrombosis (DVT), pulmonary embolism (PE) and thrombosis at unusual sites ($n = 17$), DVT/PE with heritable thrombophilia and family history of thrombosis ($n = 8$), malignancy ($n = 8$) and bed ridden state ($n = 7$). The patients were taken randomly irrespective of the age, gender, nationality, religion, co-morbidity or indication for OACT, except that the patient should have been taking warfarin therapy for more than 2 years and was not grossly non-compliant.

For analysis of the data the participant authors were divided into three groups.

- One group analyzed the technical data to determine the consistency of target INR, occurrence of major hemorrhage related to warfarin therapy and recurrence of thrombo-embolic disease (TED).
- The second group analyzed the data about the patient's personal characteristics—that is: Age, gender and nationality, educational status, financial status, family size, family style, manner of taking medication and use of other medications for co-morbidity.
- The third group, who was kept unaware of the findings of the other two groups, was assigned the task of correlation and computation of the findings of the other two groups for meaningful inferences in respect of (a) the overall rate of success or failure of OACT. (b) Identification of the patients' personal characteristics that adversely affected the efficacy of OACT. (c) The lessons that are obtainable from this retrospective study.

Criteria

The various criteria that have been adopted for different aspects of the present study are shown below:

Criteria for Assessment of Consistency in Achieving the Target INR

The INR values of the same patient recorded at the time of the patient's structured follow-up visits for monitoring were grouped into segments of four consecutive readings that were.

The efficacy was graded as Grade I (excellent), Grade II (intermediate) and Grade III (poor) on the basis of the following parameters.

Grade I (excellent): if

- No INR reading in the same segment differed from each other by more than ± 0.5
- No more than one INR reading in any segment was outside the target range by ± 0.8
- The mean INR value of one segment did not differ from the other by 0.5

Grade II (Intermediate): if

- No more than 20 % of the INR readings in the same segment differed from each other by ± 0.8
- No more than 20 % of the INR readings in the same segment were outside the target INR by ± 0.8
- The mean INR value of one segment did not differ from the other by ± 0.8

Grade III (poor): if

- More than 20 % of the INR readings in the same segment differed from each other by ± 0.8
- More than 20 % of the INR readings were outside the target range by ± 0.8
- The mean INR values of different segments varied from each other by more than 1.0.
- More than one of the INR values in any segment jumped to more than 5.0 or if the patient had more than one episode of major bleeding.

Note

A patient was considered as non-compliant and was excluded from the study, if he or she had:

- Missed more than one appointment in more than one segment in a period of 6 months.
- Missed more than two appointments in more than two segments in a period one year.
- Missed four or more appointments in a period of two years.

Criteria for Major Hemorrhage [5, 6]

- Unexplained blood loss accounting for drop in hematocrit (Hct) by ≥ 10 %.
- Unexplained hemorrhage requiring blood transfusion with more than two units of blood or unexplained hemorrhage requiring hospitalization.

3. Unexplained gross gastro-intestinal bleeding even if the drop in Hct was $<10\%$.
4. Unexplained intracranial, intra-abdominal or intra-articular hemorrhage.
5. Unexplained fatal hemorrhage.

Criteria for Classification of Patients' "personal Characteristics"

Educational status:

Each subject was assigned to one of the following groups:

- Ea* No formal education or vocational training
- Eb₁* School education up to 8th standard
- Eb₂* School education up to 12th standard
- Ec* College/University/Board Education leading to award of academic or vocational bachelor degree
- Ed* Professional/technical or post graduate academic education with award of the relevant degree

Criteria for Financial Status

Each subject was assigned to one of the following groups:

- Fa* Unemployed with no consistent income, dependant on state subsidy/dole, charity or family income
- Fb* Unskilled or semi skilled worker with income <100 Kuwaiti Dinars (KD) i.e. \$ 330 per month
- Fc* Skilled worker with regular family earning of 101–500 KD (\$ 330–1500) per month
- Fd* Skilled worker with regular family income of 501–1000 KD or more (\$ 1500–3300) per month

Results

The results of this retrospective study on long term thrombo-prophylaxis with OACT with warfarin are presented in two respects:

1. Overall efficacy of OACT
2. Impact of the various "personal characteristics" of our local patient population on efficacy of OACT

The assessment of efficacy of OACT is determined on the upside by the proportion of patients who achieved grade I consistency of INR and on the down side by the proportion of patients who achieved grade III consistency of INR. The extent of the occurrence of major hemorrhage was also taken as an indicator of down side efficacy.

The proportion of patients who showed recurrence of thrombotic episodes (TE) while on OACT should also be taken as an indicator of downside efficacy in relation to

the patient's personal characteristics. But it would be difficult to exclude the influence of disease specific factors such as antiphospholipid syndrome, heritable thrombophilia, co-morbidity with malignancy or autoimmune disease as a contributory factor for recurrence. We have, therefore, excluded this aspect of our observations to reflect on the efficacy of OACT in the particular context of the objective of the present study. However, it is worthy of note that only 11 out of 153 of our patients showed recurrence of TE. Among them two patients had heritable thrombophilia, two suffered from antiphospholipid syndrome, two had carcinoma, one had Paroxysmal Nocturnal Haemoglobinuria (PNH) and one had Bachel's disease while no particular reason could be assigned to the remaining three patients.

Overall Efficacy

- a. The overall performance in achieving consistency of INR by all the 153 subjects taken together shows that 69.4 % subjects achieved grade I (excellent consistency) while 16.3 % subjects achieved grade III (poor) consistency.
- b. Occurrence of major hemorrhage was observed in 16 of 153 (10.4 %) patients. Nine out of 16 patients reported with more than two episodes of major hemorrhage, three patients showed two episodes while the remaining four patients had one episode. Fortunately, there was no case of fatal haemorrhage accountable to OACT.

Impact of "Personal Characteristics"

The results presented below are customized to depict the influence of various 'personal characteristics' of the patients taking long term OACT, on the efficacy of the treatment outcome.

Age, Gender and Nationality (Fig. 1)

Excellent consistency of target INR (80–83 % in grade I with 6 % in grade III) was achieved by patients below the age of 40 years. The performance was poor (33–66 % in grade I and 18–33 % in grade III), $p < 0.01$ in the higher age group (41–80 years). In general male patients performed better (81 % in grade I with 7 % in grade III) than the female patients (50 % in grade I with 31 % in grade III), $p < 0.01$. In terms of nationality, expatriates showed greater consistency (80 % in grade I with 10 % in grade III) than the Kuwaiti patients (51 % in grade I with 26 % in grade III), $p < 0.01$. The incidence of major hemorrhage (40 %) was also higher in older patients (61–80 years) than

Fig. 1 Showing the relationship of the consistency of achieving target INR with age, gender and nationality

Fig. 2 Showing the relationship between the consistency of achieving target INR and the educational status

in the younger population (3 % in patients of <40 years of age), $p < 0.001$. It was also higher in female patients (19 %) than the male patients (4 %), $p < 0.01$ and in Kuwaiti patients (19 %) than in expatriates (5 %), $p < 0.01$.

Educational Status (Figs. 2, 3)

A larger proportion of male patients with higher educational status (Ed and Ec) showed excellent consistency of achieving target INR (84–89 % in grade I with 5–5.5 % in grade III). The number of female patients in this educational group is too small for valid inference on the influence of gender difference. Among the patients with lower educational level (Ea, Eb₁ and Eb₂), except for the male patients with relatively better education (Eb₂), performance was comparatively less efficient (50–60 % in grade I with 10–15 % in grade III) $p < 0.01$. Among these groups of patients (Ea, Eb₁, Eb₂) the incidence of major hemorrhage (5–20 %) was more as compared with patients (5 %) in the higher education group (Ec & Ed). Also, the episodes of major hemorrhage were observed more commonly in female patients (20 %) as compared with male patients (5–6 %), $p < 0.01$. In terms of nationality, there was no significant difference between Kuwaiti and non-Kuwaiti

patients ($p < 0.1$) across the various segments of educational status.

Financial Status (Fig. 4)

There is no significant difference in the degree of consistency in achieving target INR among the patients over different financial strata.

Family Style (Fig. 5)

Three manners of family units are encountered among the participant subjects:

- Joint family—to three generations living together ($n = 54$)
- Satellite units—Constituted by husband, wife and children as single unit ($n = 31$)
- Singleton—Living alone ($n = 68$)

The efficacy of achieving target INR was observed to be excellent among patients who were living alone (93 % in grade I and 3 % grade III). It was worst among patients living in joint families (44 % in grade I and 26 % in grade III), $p < 0.001$. Performance of patients living in satellite units was intermediate (61 % in grade I and 26 % in grade

Fig. 3 Showing the impact of nationality on the relationship between consistencies of achieving target INR along various segments of the educational status

Fig. 4 Showing the relationship between the consistency of achieving target INR and the financial status

III). The incidence of major hemorrhage was also high (20 %) among the patients living in joint families.

Number of Family Members (Fig. 6)

There is distinct inverse relationship between consistency of achieving target INR and the number of family members living together in the patient's family. The patients whose family is constituted by less than four members achieved much higher consistency (85 % in grade I and 3 % in grade III) than the patients whose family members numbered more than 10 (8 % in grade I and 63 % in grade III), $p < 0.001$. The incidence of major hemorrhage was also distinctly higher in the latter group (29 %) than in the former group (3 %) $p < 0.001$.

Number of Other Medications Prescribed for Co-morbidity (Fig. 7)

Inverse correlation is observed between the consistency of achieving target INR and the number of other medications

prescribed by physician colleagues for co-morbidity. Patients taking less than 2 medications in addition to warfarin showed the highest consistency (80 % in grade I and 7 % in grade III). Patients taking more than eight additional medications showed the poorest performance (27 % in grade I and 27 % in grade III) $p < 0.001$. Performance of patients taking 5–8 additional medicines was of middle order (44 % in grade I and 34 % in grade III). Occurrence of major hemorrhage was also high among patients taking more than five other medications (27 % among patients taking 5–8 other medicines and 31 % among patients taking more than eight medicines).

Manner of Drug Administration (Fig. 8)

Among the expatriate patients, the consistency of achieving target INR among those who self-administered Warfarin was higher (91 % in grade I and 3 % in grade III) than among the Kuwaiti patients with similar practice of drug administration (65 % in grade I and 18 % in grade III) $p < 0.01$.

Fig. 5 Showing the relationship between the consistency of achieving target INR and the family style

Fig. 6 Showing the relationship between the consistency of achieving target INR and the number of family members

Fig. 7 Showing the relationship between the consistency of achieving target INR and the number of family members

The number of non-Kuwaiti patients who were dependent on either a domestic helper or a family member for administering warfarin to them is too small to draw any valid inference. Among the Kuwaiti patients, a large

proportion of them depended routinely on the domestic servant for this purpose. Only 5 out of 29 such patients (17 %) achieved grade I consistency of target INR and as many as 14 out of 29 (48 %) achieved grade III consistency. Moreover, the episodes of major hemorrhage occurred with alarmingly high frequency, being observed in 9 out of 29 (31 %) among this group of patients.

Discussion

The present study was performed primarily to understand the influence of personal characteristics of our local patient population on the efficacy and safety of long term thromboprophylaxis with oral anticoagulant therapy with warfarin. The local population of this region has certain peculiarities that are uncommon in other parts of the world. In the context of the present study it is important to know these peculiarities in order to understand their real impact.

1. The resident population in Kuwait is markedly heterogeneous [7]. The Kuwaiti citizens constitute 34.7 % residents. While the remaining population is comprised of expatriates who come here on job permits from more than 50 nationalities, amongst which Indians, Egyptians, Philipinos Bangladeshis, Srilankans, Pakistanis, Iranians, Syrians, Jordanians, Indonesians and Africans dominate. Lately, Europeans, Americans and nationals of Far-East countries like Singapore and China have also contributed to the extent of 2–3 % of population.
2. Kuwaiti nationals are profusely affluent financially and are universally state-supported. They are provided with cradle-to-grave social security at all levels. Since the affluence is largely doled by the state, they tend to be less cautious, even negligent, towards their responsibilities including personal health care needs.
3. The expatriate populations, who have come here primarily for employment for economic reasons, are of younger age group (20–50 years). Majority are males. They remain financially tight and are heavily accountable for job/work responsibilities. Thus, they tend to be more cautious and consistently serious about work culture, family responsibilities and health-care.
4. Majority of the Kuwaiti female population, especially of the older age group is either uneducated or meagerly educated. Though, of late, the school education in Kuwait is free and compulsory, yet the drop out rate is enormous. As a result, even majority of the younger population remains poorly educated.
5. The average number of children in Kuwaiti satellite families (mean = 5, range = 3–9) is significantly higher than in expatriate families (mean = 2). The

Fig. 8 Showing the relationship between the consistency of achieving target PT-INR and the manner of taking medication

numbers in joint families is even larger (mean = 7, range = 4–15). The expatriates do not have joint families in Kuwait.

6. In most of the Kuwaiti families, the day-to-day household chores and care of the children ends up with domestic servants, who come from poor countries and are largely uneducated or meagerly educated. Their number varies from two in financially moderate families to five or more in more affluent families. Hardly any expatriate family engages domestic help. Therefore, in many Kuwaiti families, the patient is dependent on the domestic servant for administration of medications.

In the present study, attempt has been made to understand the impact of these personal settings of our patient population on the efficacy and safety of OACT with warfarin. We are not aware of any other study in which such or other personal characteristics of local patient population have been analyzed in relation to OACT in their region, though some general comments do exist in some publications [8–10]. Therefore, it is not possible to compare our results with others.

In the following discussion, we try to explain the background of our observations and to attempt to identify such personal characteristics that are found to adversely influence the efficacy of OACT. This has largely helped us to frame better practices for more efficacious and safer OACT for our patient population.

Female patients of older age group (60–80 years) showed less efficacious achievement of target INR and also showed higher frequency of major hemorrhages while taking warfarin on long term basis. Also, the performance of Kuwaiti female patients was distinctly worse. Similarly, the Kuwaiti patients with lower educational status did not perform well. Incidentally, this group includes a large number of women of older age.

Both these factors that are low educational status and old age seem to be jointly related to the poor performance. A minimum reasonable level of education is imperative to

understand the importance of continuous OACT for long term thromboprophylaxis, the need for structured monitoring in order to keep safe and effective level of anticoagulant effect, the adverse effects of drug and food interaction and the need to understand the correct combination of warfarin tablets (of 1, 2 & 5 mg) for the prescribed dose that may also need to be altered from time to time. Not only that the older women among our patient population are meagerly educated, but also, like the rural women folk of yester years, find it inherently difficult to comprehend such information.

The patients who live singly (mostly expatriates) and those who live in satellite units performed significantly better than those living in joint families. The efficacy of OACT is inversely proportional to the number of family members living together, being more efficacious when the patient belonged to the family of less than four members and worst when family members numbered more than 10, particularly in the joint family setting. It is not difficult to understand that, the larger the number of family members living together, the smaller is the private space available for personal life. The personal time, attention and resource gets proportionately divided and is likely to tell upon the mental space for personal health care needs. Care to take medications regularly and timely and the caution for drug and food interaction becomes a natural casualty and these are crucial for efficacy and safety of warfarin therapy. The senior older women suffer most, as in this part of the world; they are traditionally responsible for the overall household management. And in a large family it takes priority over the personal needs, including health care.

Inverse correlation was observed between the number of other medications that were prescribed to the patient for comorbidities and the efficacy of OACT. Patients taking less than two other medications performed much better than those taking more than five. Performance by the patients who were prescribed more than eight other medications was the poorest. Not only that warfarin is notorious for

Table 1 Showing the difference of achieving efficacy of target INR by the selected group of vulnerable patients before and after assignment to special clinic

Age (years)	Number (<i>n</i> =)	Before (%)		After (%)		<i>p</i> value
		Grade I	Grade III	Grade I	Grade III	
<i>a- Relationship with age</i>						
41–60	24	57	17	83	11	<0.01
61–80	11	58	28	71	15	<0.01
>80	2	30	30	71	14	<0.01
<i>b- Relationship with sex</i>						
Male	8	73	7	80	4	<0.1
Female	29	43	23	68	11	<0.01
<i>c- Relationship with educational status</i>						
Ea	17	53	10	71	8	<0.01
Eb1	13	46	11	77	5	<0.01
Eb2	7	47	9	68	4	<0.01
<i>d- Relationship with family style</i>						
Singleton	3	–	–	–	–	–
Satellite unit	14	57	11	87	4	<0.01
Joint family	20	43	23	63	11	<0.01
<i>e- Relationship with number of family members</i>						
<4	5	83	3	87	3	<0.01
4–9	20	59	15	78	7	<0.01
9–10	12	8	57	38	21	<0.01
<i>f- Relationship with number of other medications prescribed for co-morbidities</i>						
<2	–	–	–	–	–	–
3–4	9	83	5	89	3	<0.01
5–8	22	39	27	74	11	<0.01
>8	6	29	25	73	9	<0.01

serious drug interaction with several medications, but also shows cumulative effect. It is understandable that the larger the number of medications a patient is required to take in addition to warfarin, the greater are the chances of unexpected drug interaction and the risk of mistaken dosing.

The patients who were self-dependant for drug administration performed significantly better than those who depended upon others. Also, patients who depended upon domestic helpers achieved lesser efficacy than those who depended upon family members. Most domestic helpers who come from poor countries are either uneducated or meagerly educated and are under constant physical and emotional strain. Their care in regularity and accuracy in administering medicines to others does not find place of priority. Quite expectedly, therefore, errors of omission and commission would not be uncommon.

Each of the above factors individually influenced the efficacy of long term OACT. Co-existence of these factors in the same individual leads to worse scenario. For example, the female patients of older age group (60–80 and above) showed poor efficacy of achieving the target INR and higher

frequency of major hemorrhages than the patients of younger age. This could be attributed to multifactorial reasons. This category of patients (i) is largely uneducated or meagerly educated (ii) has usually to look after a large number of family members, often in joint family settings (iii) may requires to take several other medications for co-morbidities and (iv) is often dependent on domestic helpers or other family members to administer medicine to them.

Based on the above observations on the influence of “personal” characteristics, the most vulnerable individual appeared to be an old aged uneducated or meagerly educated Kuwaiti female living in a large sized or a joint family, taking several other medications for co-morbidities and dependent on others (a domestic helper or a family member) for administration of warfarin.

We have performed another prospective study for 18 months on patients who were considered vulnerable on the basis of the findings of our retrospective study. Thirty-seven such patients were identified. They were assigned to a specific group and advised to attend a separate anticoagulant therapy control clinic on a specially assigned day.

They were individually explained and emphasized about (i) the purpose of anticoagulant therapy in respect of their specific needs (ii) importance of the need of regular periodic monitoring with the laboratory test (iii) the narrow window of target INR (iv) the risks of over dosing and under dosing (v) the risks of interaction with other medications and food items for which they were provided with an updated list, with the instructions to show this to the other doctors whom they may consult for co-morbidities. As far as possible, the dose of warfarin for these patients was selected in such a way that the combination of tablet (1, 2 and 5 mg) for the prescribed dose was easy and there was minimum day to day variation in dosing. On each follow up day, these patients were advised to return to the clinic after obtaining all the medicines from the pharmacy and were made to identify the tablets for the exact dose of warfarin to be taken. At the same time it provided an opportunity for a recheck on the possibility of interaction with other drugs prescribed by other colleagues for co-morbidities.

They were initially subjected to more frequent monitoring with 3–7 days intervals followed by frequency of 2–4 weeks, depending upon improvement in consistency of achieving the target INR. The recall interval for monitoring was not allowed to exceed 4 weeks whereas they had been monitored at intervals of 4–12 weeks during the period of the retrospective study. For monitoring, the arrangements were made to check their INR on-the spot while waiting in the clinic so that any sampling error or discrepancy could be verified and corrected immediately.

They were all provided with a pill-box with separate slots for each day of the week so as to keep each day's doses of all medications in separately marked slots.

They were given a purse-friendly booklet in local language that contained information about the reasons for their taking warfarin, the dose of warfarin prescribed and the target INR so that relevant and ready information would be available to the treating doctors at all times.

These specially selected 37 patients were followed up for 18 months, after which the INR values of these patients were analyzed and compared with their own INR values that were obtained in the previously conducted retrospective study, taking them as their own control subjects. The results are presented in Table 1.

Comparison of the efficacy of achieving target INR by this group of 37 patients before and after they were assigned to the specific clinic shows distinctly significant improvement over all the parameters of personal characteristics that were meant to be studied. It, therefore, appears convincing that the risk factors that were identified amongst the personal characteristics of our local population in the retrospective study are truly important and need to be given special consideration for greater efficacy and safety of long term OACT.

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