
Multimed 2024; 24:e2941

Original Article

Factors associated with treatment adherence in patients with oral anticoagulation

Factors associated with adherence to therapy in patients taking oral anticoagulants

Factors associated with the treatment of patients with oral anticoagulation

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SUMMARY

Introduction:Treatment with anticoagulants has proven effective in preventing cardioembolic complications; however,Adherence probably has the greatest impact on the quality of anticoagulation.



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Aim:To determine the factors that influence adherence to anticoagulant treatment and the stability of the international standardization ratio (INR).

Methods: An analytical, observational and prospective study was carried out that corresponds to a pharmacoepidemiological study of drug use (Therapeutic Schedule), in patients diagnosed with coagulation disorders, in the health area of the Manzanillo municipality, between September 1, 2018 to December 1, 2020. The research data were obtained from an interview and their medical history. The Xi-square test (X²), Student's t, ANOVA and Kruskal Wallis were used, with a p value = 0.05 during statistical processing.

Results:A low level of pharmacotherapy adherence was observed in the study population. Sociodemographic variables related to therapeutic adherence were sex, education, and occupation. There is a relationship between economic resources, patient knowledge of their disease, adherence to non-pharmacological treatment, and adherence to pharmacological treatment and adherence. Adverse reactions and medication availability were the treatment-dependent factors related to adherence. Physician guidance to the patient, patient follow-up, and the physician-patient relationship were the physician-dependent factors.

Conclusions:The five dimensions of therapeutic adherence proposed by the WHO (socioeconomic, patient-related, disease-related, treatment-related, and health system-related factors) were associated with treatment adherence and stability of the international standardization index.

Keywords:Oral anticoagulants/therapy; Associated factors; Treatment compliance and adherence.

ABSTRACT

Introduction:Anticoagulant therapy has demonstrated efficacy in preventing cardioembolic complications. However, adherence is probably the most important determinant of the quality of anticoagulation.



Objective: The aim of this research was to determine the factors that influence adherence to anticoagulation therapy and the stability of the international normalized ratio (INR). **Methods:** Between September 1, 2018 and December 1, 2020 was conducted an analytical, observational and prospective study, corresponding to a pharmacoepidemiological study of drug utilization (Therapeutic Scheme). The object of this study were patients with a diagnosis of coagulation disorders, in the health area of the municipality of Manzanillo. The research data were obtained through an interview and their clinical history. The Chi-squared test (χ^2), Student's t-test, ANOVA and Kruskal Wallis were used, with a value of $p = 0.05$ in statistical processing.

Results: As a result, a low level of pharmacotherapeutic adherence was observed in the studied population. The sociodemographic variables associated with adherence were sex, education and occupation. There was an association between economic resources, patients' knowledge of their disease, compliance with nonpharmacological treatment, and compliance with pharmacological treatment and adherence. Also, adverse drug reactions and drug availability were the treatment-related factors associated with adherence. And, physician orientation to the patient, patient follow-up, and physician-patient relationship were the physician-dependent factors.

Conclusions: To sum up, the five dimensions of adherence proposed by WHO (socioeconomic, patient-related, disease-related, treatment-related and health system-related factors) were associated with adherence and stability of the international standardization index.

Keywords: Oral anticoagulants/therapy; Associated factors; Compliance and adherence.

SUMMARY

Introduction: Anticoagulant therapy has been shown to be effective in preventing cardioembolic complications.



Aim:The objective of this investigation was to determine the factors that influence the adequacy of anticoagulant therapy and the stability of the international normalized ratio (INR).

Methods:An analytical, observational and prospective study, corresponding to a pharmacoepidemiological study of drug use (Therapeutic Scheme) was carried out between September 1, 2018 and December 1, 2020. The object of this study is for patients diagnosed with coagulation disorders, in the health area of the municipality of Manzanillo. The research data are obtained through an interview and your clinical history. The Xi-square test (X²), Student's t test, ANOVA and Kruskal Wallis were used, with a p value = 0.05 without statistical processing.

Results:As a result, a low level of adherence to pharmacotherapy was observed in the studied population. The sociodemographic variables associated with sex, education and occupation are also variable. Observe the association between financial resources, knowledge of patient care, non-pharmacological treatment and appropriate pharmacological treatment. Also, adverse reactions to medications and availability of medications are factors related to the treatment associated with the disease. The doctor-patient orientation, or the accompaniment of the patient, is the doctor-patient relationship for the factors dependent on the doctor.

Conclusões:In conclusion, the five dimensions of the assessment proposed by the WHO (socioeconomic factors, related to the patient, related to the teaching, related to the treatment and related to the health system) are associated with the achievement and stability of the international normalization index.

Keywords:Oral/therapeutic anticoagulants; Associated factors; Admission and compliance.

Received: 5/09/2023



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Approved: 01/19/2024

Introduction

Anticoagulant treatment has proven effective in preventing cardioembolic complications. (1) Vitamin K antagonists such as warfarin have been the only treatment for many years, and the standardization of the International Normalized Ratio (INR) has allowed for widespread monitoring of these drugs, decentralization, and extension of control to other areas such as primary care. (2)

However, despite the greater ease of monitoring anticoagulated patients, the enormous individual variability inherent to these drugs and their influence by external factors such as diet, weight changes and concomitant diseases or treatments, makes it difficult to maintain treatment within the narrow therapeutic range required (INR between 2 and 3). (1)

Adherence probably has the greatest impact on the quality of anticoagulation. Therefore, factors that can influence treatment adherence can also determine variations in anticoagulation levels, although results may vary depending on the characteristics of the study populations. (3,4)

Some studies reflect this. An association has been shown between better control of oral anticoagulant therapy and residence in a rural setting and patient social support; no relationship has been found with comorbidity or educational level. (5) In another study, (6) stability is related to the latter factors.

The complexity of managing oral anticoagulant treatment, the high number of comprehensive actions that must be carried out to keep the patient within the therapeutic range for as long as possible, along with motivation to adhere to the treatment, highlights the need to establish monitoring systems in which the health professionals in charge of the patient's care actively participate. (1,7)



The best intervention to improve adherence is one that considers prevention and early detection. From the moment an oral anticoagulant is prescribed, the risk of patient noncompliance must be taken into account. However, physicians often do not directly inquire about adherence and underestimate it. Most patients who discontinue medication do not inform their physicians. (8,9)

In Cuba, and especially in the province of Granma, more research of this type is needed, as limited results have been obtained to date. This would provide solid information that would allow for developing strategies to improve the quality of therapeutic arsenal. All these factors provided more than enough justification for conducting this study and, as a result, identifying the factors that influence adherence to oral anticoagulant (OAC) therapy and the stability of the international standardized ratio (INR).

Methods

An analytical, observational, and prospective study was conducted, corresponding to a pharmacoepidemiological study of drug use (Therapeutic Regimen), in patients diagnosed with coagulation disorders, in the health area of the Manzanillo municipality, from September 1, 2018 to December 1, 2020.

To calculate the sample size, the sample size model for comparing survival curves was used and the procedure was as follows: it is known from clinical practice that the adherence rates to anticoagulant treatment are 40% (group 1) adherent and 60% (group 2) in non-adherent patients, so the following parameters were set: a confidence level of 95%, an error $\alpha=0.05$, a power of 80% and a ratio between samples (group 2/group 1) of 1.3 and it was expected to lose 0.1% of patients during follow-up, resulting in a sample size of 325 patients, being calculated using the statistical package EPIDAT version 3.

Patients of both sexes, 18 years of age or older, chronically anticoagulated for any clinical indication, and taking 2 mg warfarin were included. They expressed their willingness to



participate in the study and completed the informed consent form. Patients with cognitive impairment or neurological sequelae that could interfere with the completion of the instrument were excluded.

The dependent variable was treatment adherence, defined as compliance (taking medication according to the prescribed dosage schedule) and persistence (taking medication for the prescribed period of time), i.e., the degree to which the patient's behavior coincides with all the recommendations made by the physician, both pharmacological and non-pharmacological measures. (8,12)

It was operationalized as adherence if the patient answers "always" in sections a, b, c, d of question 16 (compliance with non-pharmacological measures is measured) and correctly completes the Morisky test. Green, and non-adherence, when it did not meet these requirements. This variable is classified as a nominal dichotomous qualitative variable.

As independent variables, the factors that influence adherence to medications related to sociodemographic characteristics (age, sex, residence, education and occupation), the patient (economic resources, knowledge of the patient's disease, compliance with non-pharmacological treatment, and compliance with pharmacological treatment), the treatment (complexity of treatment, adverse reactions, availability of medications and cost of medications) and the physician (physician's guidance to the patient, patient follow-up and physician-patient relationship) were operationalized.

The research data were obtained from a primary data collection form, which was completed through a medical interview with each individual patient who participated in the study.

The degree of control of oral anticoagulation was taken into account, the time in therapeutic range (4) and the three ranges of values for the INR:

- ✓ Therapeutic range: INR 2.0 to 3.0.
- ✓ Subanticoagulated: INR less than 2.0.
- ✓ Overanticoagulated: INR greater than 3.0.

Statistical analysis was carried out using the Statistical Package for Social Sciences version 22 software package with frequencies and percentages for the variables of sex, marital status, diagnosis, origin, risk of adherence; mean, standard deviation and percentiles for age, treatment duration and treatment adherence; in addition, Pearson's test was performed to determine the association between the risk of adherence and related factors; Student's t test was used to compare adherence according to the sex and origin of the research subjects; ANOVA and Kruskal Wallis tests were used to compare adherence according to the length of treatment and academic level, respectively. Significance was considered at $p < 0.05$.

This research took into account the ethical criteria on Biomedical Research in human beings.

Results

Table 1 shows that of the 325 patients included in the study during the study period, therapeutic adherence was present in 57 of them, representing 17.54%; and adherence was not present in 268 patients, representing 82.46% of the total.

The mean age was 76.12 years ($SD=9.498$; range: 50-90). The largest number of individuals on OCPs were between 60 and 79 years of age (65.85%); of these, 43 were adherent. Statistical analysis showed no relationship between age and treatment adherence ($p=0.221$). 53.54% of the patients included were male; however, the largest number of patients enrolled were female, with statistically significant differences when applying the Chi-square test ($p=0.000$).

No significant association was found between treatment adherence and geographic area of origin ($p=0.1623$); treatment complexity (0.0664); and medication cost ($p=0.9682$).



However, an association was found between adherence and educational level ($p=0.0000$); occupation ($p=0.0000$), and financial resources ($p=0.0275$).

Regarding knowledge of their disease, the intermediate level predominated in 187 individuals, representing 57.54% of the total. Lack of adherence was more common, accounting for 46.46% of the total; an association between the two variables was observed ($p=0.0000$). Similar results were obtained regarding adherence to non-pharmacological treatment.

In 195 patients, 60% of the sample underwent pharmacological treatment incorrectly, and non-adherence was also prevalent. The main difficulties with adherence were caused by forgetfulness and errors in scheduling. There was also a statistically significant influence between this variable and treatment adherence, as determined by the chi-square test ($p=0.0000$).

Table 1. Factors patient dependent and treatment adherence.

Variables	Adherence to treatment				Total		X2	p
	Affiliated		Not attached					
	No	%	No	%	No	%		
	57	17.54	268	82.46	325	100.00		
Economic resources								
High	23	7.08	121	37.23	144	44.31	7.19	0.0275
Intermediate	31	9.54	103	31.69	134	41.23		
Low	3	0.92	44	13.54	47	14.46		
Knowledge that the patient has about his or her illness.								
High	21	6.46	38	11.69	59	18.15	30.48	0.0000
Intermediate	36	11.08	151	46.46	187	57.54		
Low	0	0.00	79	24.31	79	24.31		
Compliance with non-pharmacological treatment								
Appropriate	57	17.54	81	24.92	138	42.46	90.83	0.0000

Inappropriate	0	0.00	187	57.54	187	57.54		
Compliance with drug treatment								
Appropriate	57	17.54	73	22.46	130	40.00	100.65	0.0000
Inappropriate	0	0.00	195	60.00	195	60.00		

Regarding treatment-dependent factors: 65.85% of patients reported it as not complex, in whom lack of adherence was significant (52.31%); 186 did not experience adverse reactions (57.23%); drug availability was predominant in 147 patients (45.23%), where lack of adherence was significant in 98 of those belonging to this group (30.15% of the total); as a result of the application of the Chi-square test, the statistically significant influence between these variables and lack of adherence was confirmed ($p = 0.0000$). (Table 2).

Table 2. Treatment-dependent factors and treatment adherence.

Variables	Adherence to treatment				Total		X2	p
	Affiliated		Not attached					
	No	%	No	%	No	%		
	57	17.54	268	82.46	325	100.00		
Complexity of treatment								
Complex	13	4.00	98	30.15	111	34.15	3,369	0.0664
Not complex	44	13.54	170	52.31	214	65.85		
Adverse reactions								
Occasional	3	0.92	54	16.62	57	17.54	26,254	0.0000
Rare	4	1.23	78	24.00	82	25.23		
Not experienced	50	15.38	136	41.85	186	57.23		
Availability of medicines								
Available	49	15.08	98	30.15	147	45.23	47,948	0.0000
Relatively available	8	2.46	99	30.46	107	32.92		
Not available	0	0.00	71	21.85	71	21.85		
Cost of medications.								

High	1	0.31	2	0.62	3	0.92	0.002	0.9682
Not elevated	56	17.23	266	81.85	322	99.08		

When investigating the medical recommendations proposed to patients, 199 who received them relatively predominated (61.23%), likewise, there were more who did not adhere in this condition, which symbolized 59.38% of the total ($p = 0.0000$). In 168 patients (51.69%) medical follow-up was inadequate, this being the most significant data ($p = 0.0000$); of these, 165 did not adhere, representing 50.77%. However, a predominance of patients who reported having a good relationship with their doctor was observed (75.08%), and lack of adherence prevailed in them, representing 57.85% of the sample. (Table 3).

Table 3 Physician-dependent factors and treatment adherence.

Variables	Adherence to treatment				Total		X2	p
	Affiliated		Not attached					
	No 57	% 17.54	No 268	% 82.46	No 325	% 100.00		
Physician's guidance to the patient								
Oriented	51	15.69	75	23.08	126	38.77	72,294	0.0000
Relatively oriented	6	1.85	193	59.38	199	61.23		
Patient follow-up								
Appropriate	54	16.62	103	31.69	157	48.31	57,437	0.0000
Inappropriate	3	0.92	165	50.77	168	51.69		
Doctor-patient relationship								
Good	56	17.23	188	57.85	244	75.08	19,832	0.0000
Regular	1	0.31	73	22.46	74	22.77		
Bad	0	0.00	7	2.15	7	2.15		

It was found that the majority of INR determinations were within the optimal range (191 patients), of which 134 patients, representing 41.23%, were non-adherent, confirming the influence of the degree of oral anticoagulation control on adherence (Table 4).

Table 4 Degree of control of oral anticoagulation, time in therapeutic range and adherence to treatment.

Oral anticoagulation control	Adherence to treatment				Total	
	Affiliated		Not attached			
	No	%	No	%	No	%
Subanticoagulated	0	0.00	71	21.85	71	21.85
Therapeutic range	57	17.54	134	41.23	191	58.77
Overanticoagulated	0	0.00	63	19.38	63	19.38

p=0.0000

Discussion

The results of the present study show a low adherence consistent with 42.1% reported by Rodriguez Rocha, (2) 39% reported by Gumbinger et al, (10) a little lower than the data published by Emren et al, in a multicenter cross-sectional observational study in Turkey (51%), (11) and that published by Salmasi et al in the most recent published meta-analysis (30%). (12) These differences could be a result of the different methods used to evaluate adherence.

However, they differ from that found by Álvarez et al, cited by Rodríguez Rocha, (2) where 90% of patients presented a good level of adherence; the factors that intervened in favor are those related to the system and the health team; the dimension linked to socioeconomic factors negatively influenced adherence to treatment.

In relation to age, the results are similar to those reported by Emren et al. (11) and differ from those reported by Rodríguez Rocha (2) where, when analyzing its relationship with therapeutic adherence, it was found to be moderate-high in the three age groups included. Salmasi et al. (12) in their meta-analysis conclude that the results are contradictory (some studies reported low adherence, others high adherence, and in others it had no impact on adherence).



Regarding sex, the study by Oliveira et al (13) showed that, although they did not use the same treatment, adherence is significantly higher in women than in men. However, an article was reviewed that contradicts this information, and mentions that adequate compliance predominated in men with 83.3%, in addition to greater errors of omission in women. (14)

In the present study, a predominance of patients living in urban areas was found with better therapeutic adherence, although the results were not statistically significant. Unlike this study, Rodriguez (2) found that patients living in rural areas have better therapeutic adherence, consistent with that reported by Salmasi et al. (12).

The literature describes educational level as an important factor in treatment adherence. It is stated that people with a low educational level have difficulty communicating and are at greater risk of abandoning treatment. (1,2,5,7)

When examining the relationship between occupation and adherence, workers emerged as the most irresponsible. This is likely due to the concerns that accompany employees, which lead them to neglect their illness treatment.

Patient knowledge and beliefs about their illness, motivation to treat it, confidence in their ability to engage in therapeutic behaviors, and expectations regarding treatment outcome interact in ways that are not yet fully understood to influence adherence behavior. (1,2,5,7)

The patient's knowledge about his or her disease was associated with adherence to treatment with oral contraceptives, similar to that reported by Perreault et al. (1) as well as that reported by Hwang et al. (3)

Medical practice requires the professional to foster a warm relationship with the patient. This facilitates the very development of the consultation, which implicitly involves exploring the individual's intimate aspects, overcoming barriers, in order to establish an adequate level of communication regarding understanding of the patient's illness, the needs, and the goals of treatment.^(2,7,8)



Thus, the patient's perception of potentially subjective aspects during the consultation generates a tendency to neglect treatment. (2,10,11)

Regarding the influence of patient knowledge of the disease and treatment on therapeutic adherence, studies are fairly unanimous: a lack of understanding of the disease and/or its treatment, a misunderstanding of the prescription and treatment instructions, ignorance of the possible consequences of non-adherence, or misconceptions about medication have been described as barriers to correct therapeutic adherence. (15,16)

Emphasis is also placed on the ability to follow instructions related to medications, diets, exercise, and general healthy habits. (15,16) Relevant and effective medication that generates perceived improvement by the patient is the factor that most contributes to adherence. (2)

Lack of adherence was also noted in the present study, as a high number of patients did not comply with non-pharmacological treatment.

Several studies have concluded that the lack of adherence to treatment with anticoagulants, (2,5,9) and especially with warfarin is high. (17)

In relation to warfarin, an article was found that talks about the adherence that people have to this anticoagulant medication and it was found that 35.1% of patients have a poor treatment, 58.9% a moderate treatment and only 6% of patients a good adherence to warfarin therapy. It was concluded from this study that people who had low adherence to treatment were at greater risk of suffering numerous complications that can affect the overall treatment plan and therapeutic goals. (14) Similar to what was found in the present study.

Many treatment-related factors influence adherence. The most notable are those related to the complexity of the medical regimen, treatment duration, previous treatment failures, frequent treatment changes, side effects, and the availability of medical support to manage them. (2,10,11) These results are consistent with the present study.



Finally, various factors have been shown to interfere with the control of anticoagulation levels and the stability of the INR. Socioeconomic, physiological, psychological and emotional factors, as well as adherence to treatment, age, concomitant use of other drugs, comorbidities, genetic polymorphisms and vitamin K intake, have been associated with instability in the levels of hypocoagulability required from a therapeutic point of view. (16)

In a study conducted by Remigio, (18) knowledge of pharmacological treatment was related to adherence to oral anticoagulant treatment where it was determined that 60.8% of the sample was non-adherent, and that 63.1% had inadequate knowledge in relation to oral anticoagulant. As a result of this, the study concluded that non-adherence was related to a longer treatment time and with patients with INR values outside the therapeutic range.

Among the study's limitations is the subjectivity inherent in the questionnaires, which implies a potential bias in data collection as it depends on the veracity of the information provided by patients. However, one advantage of the study is the inclusion of the INR level.

Conclusions

A low level of pharmacotherapeutic adherence was observed in the study population, with gender, education, and occupation being the sociodemographic variables related to therapeutic adherence. There is also a relationship between economic resources, patient knowledge of their disease, compliance with non-pharmacological and pharmacological treatment, and medication adherence and stability of the condition. international standardization index, which was also influenced by adverse reactions and drug availability as treatment-dependent factors, as well as the physician's guidance to the patient, as a result of the relationship between the two and the follow-up.



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Conflict of interest:

The authors declare no conflicts of interest.

Authorship contribution

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