Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13781
DOI URL: http://dx.doi.org/10.21474/IJAR01/13781

RESEARCH ARTICLE

GENETIC RESISTANCE TO VITAMIN K ANTAGONISTS: NO DELAY IN INTRODUCING DIRECT ORAL ANTICOAGULANTS! A CASE REPORT

Benyamna I.[1], Bouzid F.[2], El Mousadik A.[2] and Alif N.[2]

1. Ph D at Faculty of Sciences, Ibn Zohr University, Agadir, Morocco.
2. Laboratory of Biotchnologies and Valorisation of Natural Resources (LBVRN), Ibn Zohr University, Agadir, Morocco.

Manuscript Info

Manuscript History
Received: 25 September 2021
Final Accepted: 27 October 2021
Published: November 2021

Key words:-
Vitamin K Antagonists, Resistance, Direct Oral Anticoagulants, VKORC1

Abstract

Because of their cost and the large amount of experience, vitamin k antagonists are widely prescribed in the world for the prevention and treatment of thrombosis. However, cases of resistance to VKA exist, although they are difficult to authenticate. Direct oral anticoagulants DOA represent a good alternative. We report a case of true hemodynamic and genetic resistance to VKA in which rivaroxaban was the solution.

Introduction:-

Case description

A 53 year old black woman was referred to our structure after a stay in intensive care because of an acute respiratory distress syndrome attributed to a distal bi-lateral pulmonary embolism occurring during an unexplained sural venous thrombosis of the right lower limb. As a history, she has type 2 diabetes that has been poorly controlled for 10 years on NPH insulin, and severe hypertension with very labile numbers on bitherapy for 5 years.

She was non-smoker and was in good health before the hospitalization, had never had a miscarriage, she had 5 pregnancies, 5 parities and 5 alive children. She had no family history of cancer or sudden death. She reported a short duration of oral contraception with estroprogens. At her admission, she was still dyspneic class III NYHA. She weighed 85 kg for a height of 174cm. She had an arterial pressure of 180/120 under Irbesartan 300mg per day and 40mg of furosemide per day with a heart rate of 100 beats/minute. EKG showed sinus rhythm with left ventricular hypertrophy (figure2), however echocardiogram was normal. The chest X-ray showed cardiac enlargement with bilateral pleurisy (figure 1). The control thoracic angioscan and the venous echodoppler of the lower limbs proved to be normal. Abdominal pelvic CT scan was normal. Blood cell count showed anemia at 8, 6 g/dl, creatinin rate was normal with positive proteinuria. Liver test was normal while the lipid test showed total cholesterol at 2 mmol/l and triglycerides at 2.5 mmol/l. The inflammation parameters were a bit increased. We had to keep the patient on low molecular weight heparin since she showed a resistance to vitamin K antagonists, in fact she constantly had an INR of 1 on both 24mg of acenocoumarol and 120mg of fluindione. ANA and APL antibodies weren't detectable. After a 45-day period of hospitalization, the evolution was favourable; blood pressure was controlled with less lability under quadritherapy associating amlodipine 10 mg, irbesartan 300, indapamide 1.5mg and nitrates. It should be noted that dyspnea worsened when the beta-blockers were introduced and the decision was taken to stop them. For diabetes, we had to introduce rapid-acting insulin and metformin to achieve a satisfactory glycemic cycle. At the time for discharge, the problem that arose was the choice of anticoagulant treatment, as the patient refused to remain

Corresponding Author:- Benyamna Ilham
Address:- Faculty of Sciences, Biology Department, Ibn Zohr University, Agadir, Morocco.

on injections of low molecular weight heparins. Thus so we started her on rivaroxaban 20mg per day after a loading dose. The patient remained stable for 2 months of follow-up, but for economic reasons she stopped treatment. She then presented 1 week after a basilar vein thrmbosis of the upper right limb, and 10 days later a distal deep vein thrombosis of the lower left limb. We then rehospitalised her, we took this opportunity to carry out a coagulation check-up before putting her back on LMWH. Vitamin k-dependent clotting factors were normal while vitamin k1 was excessive. We then undertook a genetic study, the patient was found to carry the single nucleotide polymorphism 5417G/T which is relevant to warfarin resistance.

Discussion:-

Vitamin K antagonists (VKA) have been prescribed for a long time for the prevention and treatment of thrombosis. However, they have the disadvantage of inducing a very variable response, both within and between individuals. Some patients may even develop a resistance to treatment. So it is impossible to define a precise dose for a person for whom this treatment is indicated (3).

In 1958, the first cases of resistance to VKA-type rodenticides (coumafen) appeared in Scotland, with even a local spread of the phenomenon between 1960 and 1971. Resistance to VKA has only been confirmed in a limited number of rodent species (12).

A strong involvement of genetic factors in this resistance was suspected very early on by Martin et al in 1979; further work followed and allowed the precise location of the gene responsible for the resistance in brown rats (12).

In humans, the term VKA resistance covers several entities; a distinction is made between biological resistance, which may be primary or secondary and clinical resistance (1).

● Biological resistance is defined as a difficulty in achieving hypocoagulability at doses higher than the dose usually used to achieve therapeutic equilibrium.

Primary, or genetic, resistance shows ineffectiveness with an INR close to 1, despite an adapted dosage after at least ten days of treatment.

Secondary, or acquired, resistance shows ineffectiveness after correct equilibrium for a certain period of time.

● Clinical resistance consists in a recurrence of thrombosis despite an apparent biological efficacy assessed on the INR. Before mentioning VKA failure or undertaking a cancer search, the reality of hypocoagulability must be assessed.

When faced with biological resistance, the classic causes of resistance should first be investigated (figure 2) (insufficient serum VKA concentration, poor compliance, poor drug absorption, drug interaction, excess vitamin K intake, or laboratory error). Only then can genetic resistance be considered.

In most cases, the problem is a matter for patient education, where complete information is paramount. It is important not to speak prematurely of "resistance", especially after a single examination or too early in relation to a change in dose.

When all the classic causes of resistance are ruled out, genetic resistance can be envisaged. The genes involved in VKA resistance are summarized in table 3.

Since 2005, several studies have been conducted to investigate the effect of Vkorc1 polymorphisms on the required dose of warfarin and other coumarins. A few rare mutations are associated with warfarin resistance (4; 11; 12). The most common mutations lead to insensitivity to treatment due to altered VKORC1 expression. At least 28 human mutations have been identified to date in the Vkorc1 gene (ref). The G5417T and p.Asp36Tyr mutations are associated with high doses of warfarin. Generally, mutations in the Vkorc1 gene can lead to two types of genotypes: -the first for which homozygous false-sense mutations in Vkorc1 lead to a deficiency of Vitamin K-dependent coagulation factors and cause a hemorrhagic syndrome. Rost et al then described in 2004 the VKCFD2 phenotype (p.Arg98Trp), it is a very rare mutation, and only 4 families have been listed in the literature.

- The second for which the heterozygous false-sense mutations in Vkorc1 lead to hereditary coumafen resistance in humans and rodents (12).
In patients with true resistance to VKA, with an indication for anticoagulation, DOAs represent an ideal alternative with a lower risk of major bleeding events (5; 6; 8).

There is no study comparing the different DOAs in this indication (VKA resistance), but the results and patients follow-up were satisfactory with rivaroxaban, apixaban, edoxaban and dabigatran (5; 6; 7; 8; 10).

In our patient's case, VKA resistance was of genetic origin .The single polymorphism 5417G/T disrupts vitamin K metabolism and consequently the synthesis and activation of vitK-dependent factors and this probably explains the high levels of vitamin K1 and certain dependent factors. She remained stable on rivaroxaban, without any thrombotic or hemorrhagic event, but we recorded a thrombotic event after one week of stopping the treatment, which underlines the need for long-term therapy in these cases.

The measurement of the blood concentration of VKA facilitates the etiological orientation of the resistance to treatment (9; 13). Unfortunately, we were not able to do this either while the patient was taking acenocoumarol or when we switched to fluindione. We propose how to manage VKA resistance in figure 4.

Figures and tables:
Table 1:- laboratory characteristics of the reported case.

Biologic parameter	Value in our case		Normal laboratory value
	AD	D	
HbA1C (%)	10	8,4	
Glycemia (G/l)	1,98	1,58	
Hemoglobin (g/dl)	8,6	10,2	
Platlets(x10 3/mm 3)	410	355	
WBC (/mm3)	8100	6250	
RBC(x10 6/mm3)	4	4,7	
TSH US (IU/l)	0,98		0,27-4,2
Microalb (mg/24h)	163		<14
ANA (IU/ml)		0,2	<1
Anticardiolipin (IU/ml)		0,01	<0,1
CRP (mg/l)	40		
K1 vitamin (ng/ml)	3392		150-900
Protein S (%)	126		60-130
Protein C (%)	127		80-130
II factor (%)	107		70-150
V factor (%)	127		62-150
VII factor(%)	209		67-143
IX factor(%)	186		55-160
X factor(%)	155		70-150

(AD: admission; D: discharge; Microalb: microalbuminuria; ANA: antinuclear antibodies; CRP: C reactive protein)

Table 2:- Main causes of resistance to vitamin k antagonists (1; 9).

Pharmacokinetic
Decreased absorption (cholestyramine, colestipol)
Enhanced elimination (e.g by enzyme inducers)
Decreased compliance (apparent resistance)
Pharmacodynamic
Excess vitamin K intake (health-foods, dietary supplements, enteral feeds)
Hyperlipidaemia
Certain drugs (e.g. oestrogens, griseofulvin, 6-mercaptopurine)
Hereditary resistance (extremely rare)
Acquired resistance (very rare)
Unknown

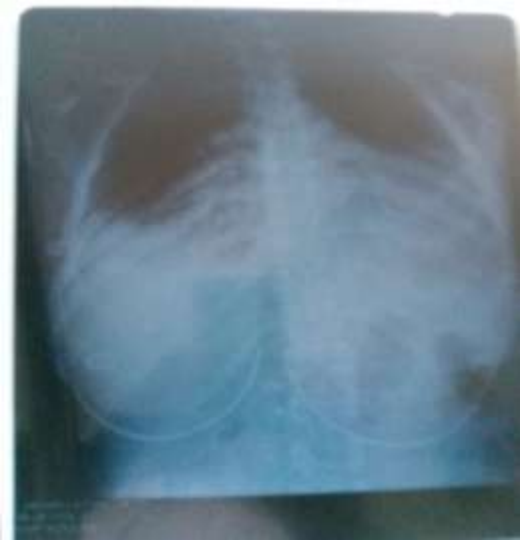

Figure 1:- chest X-ray on admission of our patient.

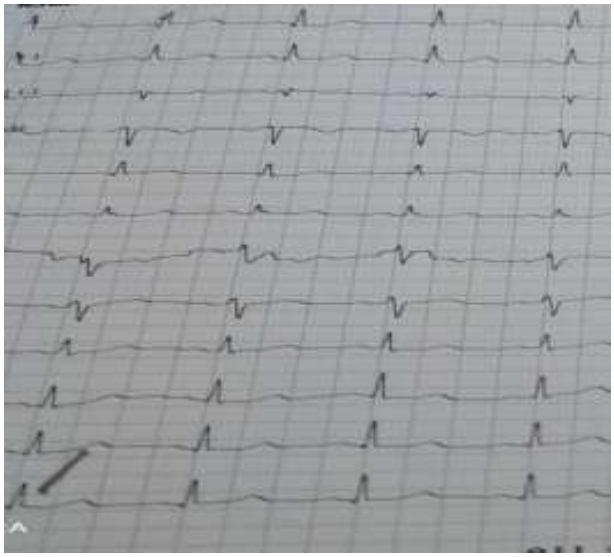

Figure 2:- EKG of our case to the ICU showing bilateral pleural effusion.

Figure 3:- Some thoracic CT angiography sections showing the embolism of the distal pulmonary arteries in our case.

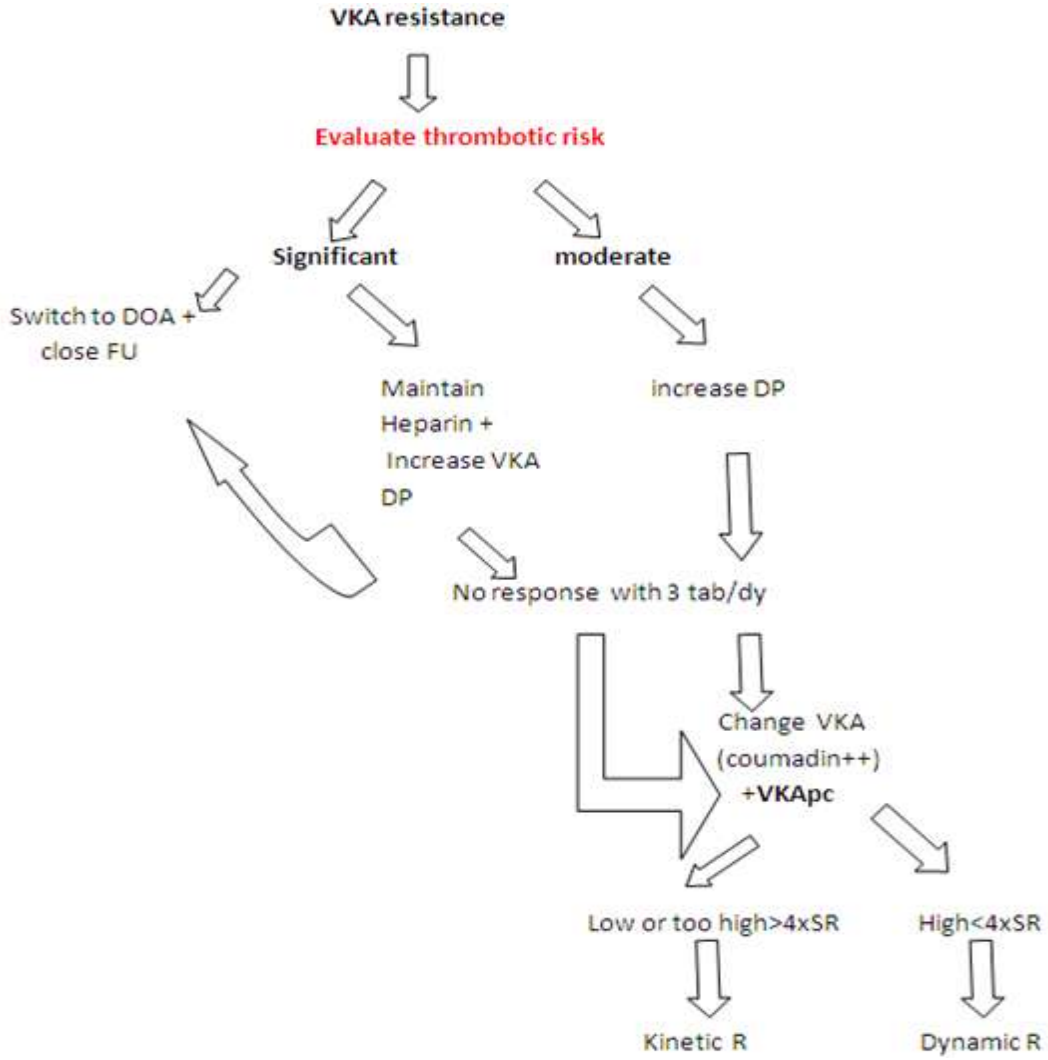

Figure 4:- Proposed course of action in the event of VKA resistance (1 ,9).

R : resistance ; DP : daily posology ; tab : tablets ; dy : day ; VKApc : VKA plasmatic concentration ; SR : superior range ; FU :follow up ; VKA : vitamin K antagonists ; DOA : direct oral anticoagulants.

Conclusion:-

Resistance to VKAs exists although rare and is often genetic. We should not hesitate to replace a VKA by a DOA to avoid aggravation or recurrence of thrombosis. Also the cost of DOAs should become more accessible to ensure better compliance. Moreover, close monitoring of this type of patient is necessary since resistance has also been described with the DOA (14).

References:-

1-Batisse, G. Helft. Résistance aux anticoagulants oraux. La Lettre du Cardiologue - n° 365 - mai 2003: 50-52.
2-Kereveur A et al. Vitamin K metabolism in a patient resistant to vitamin K antagonists. Hemostasis 1997; 27: 168-73.
3-Samama MM, Acar J. Traitements antithrombotiques. Masson 1998. Blood 2000; 96: 5.
4-Diale F et al. Hereditary warfarine resistance. South Med J 1994; 87 (3): 407-9.
5- okusai-VTE Investigators, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369:1406–15.
6- Yamada N, Hirayama A, Maeda H, Sakagami S, Shikata H, Prins MH, Lensing AW, Kato M, Onuma J, Miyamoto Y, Iekushi K, Kajikawa M. Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism – the J-EINSTEIN DVT and PE program. Thromb J 2015; 13:2.
7- EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363:2499–510.
8- Tadasuke Chitose (MD, PhD), Takuro Yamashita (MD), Mitsutoshi Miura (MD), Koshi Matsuyama (MD). Complete response to rivaroxaban in a case of invaginated thrombus thought to have extended through a patent foramen ovale with an accompanying pulmonary embolism. Journal of Cardiology Cases 14 (2016) 65–68.
9- Routledge P. A, Shetty H. G. M, White J. P and Collins P. Case studies in therapeutics: warfarin resistance and inefficacy in a man with recurrent thromboembolism, and anticoagulant-associated priapism. Br J Clin Pharmacol 1998; 46: 343–346.
10- Hiroaki K, Yusuke K, Seiya I, Akira T, Satoki F, Masayoshi T, Yuji K and Koji M. Rivaroxaban Therapy Resulting in the Resolution of Right Atrial Thrombosis Resistant to Ordinary Control with Warfarin in a Patient with Atrial Fibrillation. Intern Med 54: 601-604, 2015.
11- Nolan Ch. VKORC1 et résistance aux antivitamines K: étude par modélisation moléculaire. Biologie moléculaire. Université Paris Saclay (COmUE), 2017. Français. NNT : 2017SACLN008.
12- Hodroge A. Les mutations spontanées du gène Vkorc1 chez l'homme et le rat : réalité de la résistance. Sciences agricoles. Université Claude Bernard - Lyon I, 2011. Français. <NNT: 2011LYO10281>.
13- Bentley DP, Backhouse G, Hutchings A, Haddon RL, Spragg BP, Routledge PA. Investigation of patients with abnormal
response to warfarin. Br J Clin Pharmacol 1986; 22:37–41.
14- Laurence Pellegrina, Pharmacogénétique et variabilité de réponse aux antivitamines-K (AVK). Biomnis Focus 2014, 49.