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Hemorrhagic Stroke and Spontaneous Hemoperitoneum In Patients on Vitamin K Antagonists: Case Reports and Review

Maghrabi O*, A Taqui, O Lmejjati, A Zerhouni, A Mounir, R Cherkab C Kettani

Intensive Care Department P17 at Ibn RochdUniversity hospital Casablanca.

***Corresponding author:** Maghrabi O, Intensive Care Department P17 at Ibn Rochd University hospital Casablanca. Email: maghrabi.othman@gmail.com

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Abstract

Introduction: *Vitamin K antagonists (VKAs) are widely used therapeutics and have been the go-to means of anticoagulation therapy for over 50 years.Acenocoumarol remains the most prescribed VKA in Morocco (Warfarin worldwide). VKAs usage is limited by their numerous drug-food and drug- drug interactions and their especially narrow therapeutic window. Nevertheless, they still benefit from a wide range of indications including supraventricular arrhythmias and treatment and/or prevention of deep vein thrombosis. VKAs overdose is a fairly rare event that could be responsible for potentially fatal hemorrhages.*

Cases: *We report the cases of a 28 years old female and a 58 years old male. The first patient had a history of valvular replacement due to acute rheumatic fever at the age of 8 on 2mg of Acenocoumarol daily. The second patient had a history of mitral valve stenosis on 4mg of Acenocoumarol daily. Both patients had no recent control INRs. The first patient had a notion of increase in dosage up to 6mg 2 days prior to her admission. The female patient was admitted to the ER with an altered mental status following an episode of severe headaches and loss of consciousness. The second patient presented with severe abdominal pain and rapid onset pallor and fatigue. No physical trauma was reported in both cases. On admission, the 28 years old patient was comatose and showed signs of hemodynamic distress. The 58 years old patient showed signs of shock. Physical examination found a mydriasis of the right eye and diffuse coarse crackles in both lungs in the first case and abdominal tenderness and dullness in percussion over the flanks in the second case. The initial treatment included rapid sequence intubation and large bore venous access to start isotonic serum perfusion. Laboratory findings contained INRs of 9.6 and 10, hemoglobin levels of 10.2 g/dL and 9.2 g/dL and a prothrombin time of 68.3 seconds (15% prothrombin time ratio) and prothrombin time of 82 seconds respectively. CT scans were performed and showed a cerebellar hemorrhage in the former and a high abundance hemoperitoneum in the latter. Both patients received vitamin K, prothrombin complex concentrate (4F-PCC) and packed red blood cells. They both had unfavorable outcomes and passed away shortly after admission.*

Discussion: Bleedings in patients on anticoagulants are frequent and potentially fatal situations. For that, the treatment options should obey a unified and universal approach. Care for VKA overdose must include, in all cases, interruption of VKAs, followed by a fast administration of vitamin K and prothrombin complex concentrate (4F-PCC). Vitamin K and 4F-PCC work in harmony as antagonists of VKAs. Acenocoumarol has a short half-life of 10 to 24 hours. 4F-PCC (the half-life of FII is 60–72 h, the half-life of other factors is 6–24 h. FVII has the shortest half- life of approximately 6 h) and Vitamin K (half-life of 24.7 hours) adjudication allows the restoration of Vitamin K dependent coagulation factors until VKAs are eliminated.

Our case reports are particularly interesting due to the spontaneity of the hemorrhages and the rarity and fatality of such clinical presentations.

Introduction

Vitamin K antagonists (VKAs) are widely used therapeutics and have been the go-to means of anticoagulationtherapy for over 50 years.

Though Warfarin is the most frequently prescribed VKA worldwide, Acenocoumarol remains the most prescribed VKA in Morocco.

VKAs usage is limited by their numerous drug-food and drug-drug interactions and their especially narrow therapeutic window. Nevertheless, they still benefit from a wide range of indications including supraventricular arrhythmias and treatment and/or prevention of deep vein thrombosis, especially in the context of valvular replacement. VKA overdose is a fairly rare event that could be responsible for potentially fatal hemorrhages.

Case reports

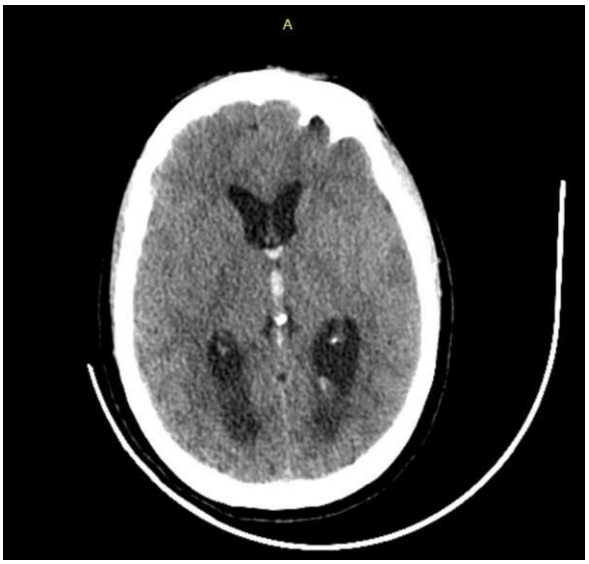
Case #1:

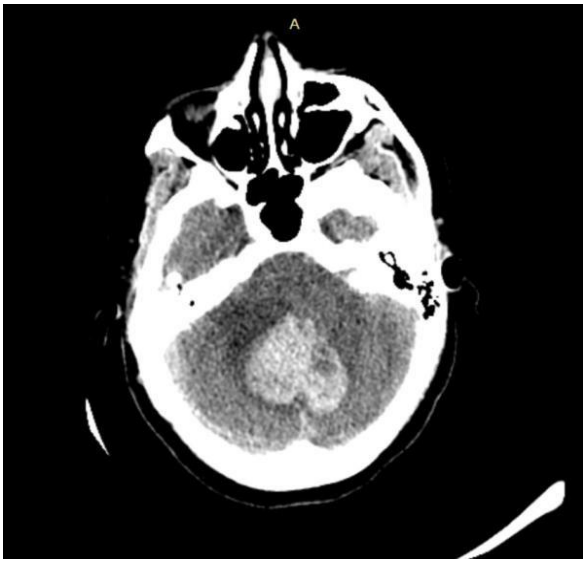
A 28 year old female was admitted to the hospital with an altered mental status following an episode of severe headaches and loss of consciousness. Surgical history included a mitral valve replacement at theage of 8 due to acute rheumatic fever, treated by 2 mg of Acenocoumarol daily. Anamnestic findings revealed a recent (about 2 days before admission) increase in dosage up to 6 mg of Acenocoumarol. Nophysical trauma was reported in the past months before the symptoms (including brain surgery).

On admission, the patient was comatose (GCS 7/15), bradycardic (62 beats per minute), had a widened pulse pressure (11/5). Respiration rate was correct though irregular (17 cycles per minute), pulse oximetry showed an SpO2 of 88%. A temperature of 36.8°. Physical examination found mydriasis of theright eye and diffuse coarse crackles in both lungs.

Laboratory values showed a hemoglobin level of 10.2 g/dL, a prothrombin time of 68.3 seconds (15% prothrombin time ratio) and an INR level of 9.6 which would most likely indicate a vitamin K antagonistoverdose.

The brain CT scan confirmed the presence of a cerebellar hemorrhagic stroke inducing a triventricularhydrocephalus and what appeared to be the beginning of a downward cerebellar (tonsillar) herniation.The CT scan of the abdomen and pelvis showed no visceral hemorrhage nor deep muscular hematoma.

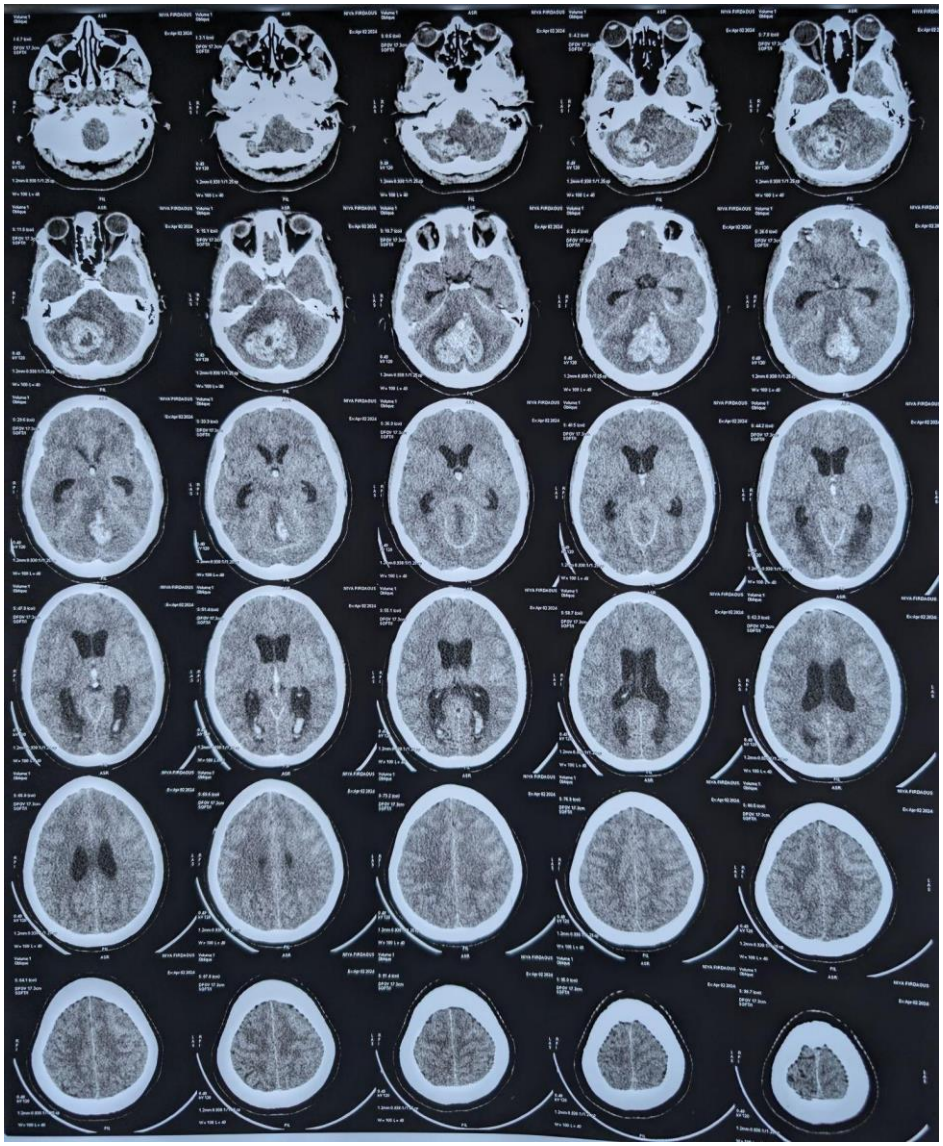




Therapeutic care was based on interruption of VKA treatment, orotracheal intubation, tranexamic acid (TXA), fibrinogen, packed red blood cells, vitamin K and prothrombin complex concentrate (4F-PCC). In addition, blood pressure control included norepinephrine and intracranial pressure control included steroids.

Emergency surgery was considered to be more harmful than beneficial due to the patient's clottingproblems induced by the VKA overdose.

The patient had an unfavorable outcome and passed away shortly after admission due to uncontrolled and active bleeding leading to brain stem compression.



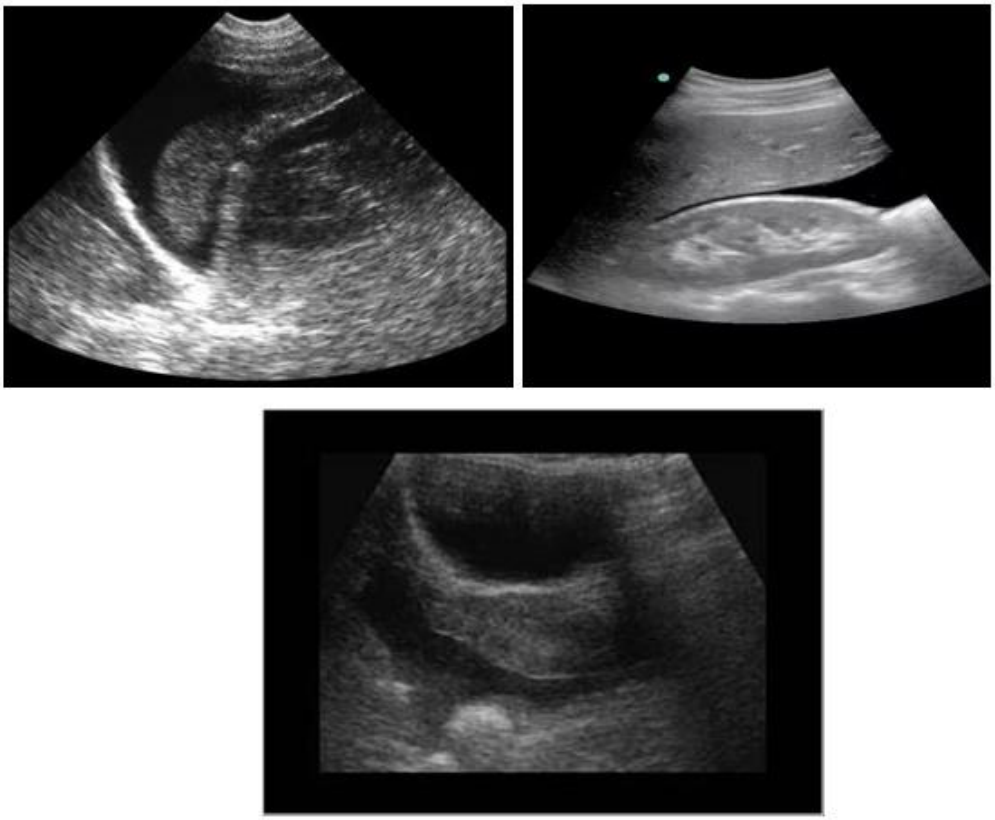
Case #2:

A 58 years old patient was admitted to our institution with severe abdominal pain associated with recent and rapid onset pallor and fatigue. The patient had a medical history of severe mitral stenosis treated by 4 mg daily Acenocoumarol. No recent INR was found in his medical file. No historyof recent physical trauma was reported (including abdominal surgery)

On admission, the patient was confused (GCS 10/15), heart rate was normal: 84 beats per minute, was inshock (8/6), extremities were clammy and cold, polypneic at 23 cycles per minute, pulse oximetry showed an SpO2 of 95%. A central temperature of 35.8°. Physical examination found diffuse abdominaldistension and tenderness with dullness on percussion of both flanks.

Laboratory values showed a hemoglobin level of 9.2 g/dL, a prothrombin time of 82 seconds and anINR level of 10 which would most likely indicate a vitamin K antagonist overdose.

A beside abdominal ultrasound was performed and showcased the presence of blood in the hepatorenal (Morrison's pouch) and splenorenal (Koller's space) spaces, as well as the Douglas pouch.



Therapeutic care was based on isotonic serum perfusion, packed red blood cells and platelet concentrates, fibrinogen, calcium, tranexamic acid (TXA), norepinephrine and eventually, sedation and intubation. VKA overdose management relied on vitamin K and prothrombin complex concentrate (4F-PCC).

The patient had an unfavorable outcome and passed away shortly after admission due to refractoryshock.

Discussion

Hemorrhagic complications in patients on VKAs are amongst the most frequent iatrogenic events. They account for 7.5 to 16.5% of all hemorrhagic events, 1 to 3% of them being major, and only 0.25 to 0.65%being fatal.

Hemorrhagic strokes in patients on VKAs are extremely rare. 6 cases have been reported in the series ofSerghini et al [1], 3 cases in the series of Dia et al [2], 2 cases in that of Zemouri et al [3], 1 case in the series of Ben Mbarka et al [4] while no case was reported in the series of Shibane et al [5].

Hemoperitoneum, on the other hand, are relatively frequent. In fact, gastrointestinal bleeding and hemoperitoneum were the most frequent manifestations of bleeding in VKA overdosage. 13 (44%) cases were reported in the series of Serghini et al, 10 (30%) cases were reported in the series of Shibaneet al. and only 4 cases were reported in the series of Zemouri et al. No cases of hemoperitoneum were reported in the series of Dia et al. (cases of melena only) nor in that of Ben Mbarka et al.

A series by Crétel et al. [6] reports the cases of 63 patients and 79 episodes of hemoperitoneum in patientson VKAs due to the rupture of ovarian cysts.

Table 1: Intracranial hemorrhage in patients on VKAs

Author	Reference	Year	VKA	Cases of sympto matic bleeding	Cases described of stroke	Neurologic recovery
Serghini et al.	1	2011	Acenocoumarol	30	6	Died
Dia et al.	2	2016	Acenocoumarol	17	3	Died
Zemouri et al.	3	2021	Fluindione	23	2	Died
Ben Mbarka et al.	4	2018	Acenocoumarol	14	1	Died
Shibane et al.	5	2020	Acenocoumarol	33	0	-

Table 2: Hemoperitoneum in patients on VKAs.

Author	Reference	Year	VKA	Cases of symptomatic bleeding	Cases described of hemoperitoneum	Neurologic recovery
Crétel etal.	6	2000		79	79	2 deceased
Serghini etal.	1	2011	Acenocoumarol	30	13	5 deceased
Dia et al.	2	2016	Acenocoumarol	17	0	-
Zemouri etal.	3	2021	Fluindione	23	4	Good
Ben Mbarka etal.	4	2018	Acenocoumarol	14	0	-
Shibane etal.	5	2020	Acenocoumarol	33	10	1 deceased

Except for the series of Shibane et al. the sex ratio was in favor of women with a mean ratio of 1.4 in favor of men. The mean age of the patients in all studies was above 50, with a combined ratio of 61.9. The youngest documented case being 20 years old [4] [5] and the eldest being 85 years old [2].

The most common indication was atrial fibrillation (= supraventricular arrhythmias). Other indications included mechanical valves (60% in the series of Shiban et al. [5]) and deep veinthrombosis.

The common risk factors found in all series and in our case are insufficient knowledge about treatment, bad compliance and insufficient biological monitoring. Advanced age is recognized as the main factor in many of the studied references in our case report. Furthermore, all studies found a direct connection between VKA hemorrhagic events and the absence of a recent INR control. The age of VKA therapy is considered an important risk factor by all studies, with a proportional relation between VKA therapy duration and the risk of major bleeding. Adversely, in theseries of Dia et al. [2] 34% of the patients had no risk factors.

In the series of Crétel et al. major risk factors included pregnancy, combined estrogen-progesterone, and progesterone only intake, ovarian dystrophies (8-10%) and ovarianstimulation.

The uage of the Beyth & Landefeld index [1] and HAS BLED score (when ≥ 3) [4] has shown to be useful in predicting the risk of bleeding. In our case, the HAS-BLED score was 1 due to the presence ofa notion of labile INR (and lack of usual INR check).
No study mentioned the Kuijer score to predict hemorrhagic risks in patients on VKAs. Table 3. HAS BLED score and bleeds per 100 patients.

HAS-BLED criteria	Score
Hypertension	1
Altered renal/ liver function (1 each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly	1
Drugs or Alcohol (1 each)	1 or 2

Total score	Bleeds per 100 patients
0	1.13
1	1.02
2	1.88
3	3.74
4	8.7
5	12.5

Table 4: Beyth and Lendefeld score vs Kuijer score.

Criteria (Beyth et Landefeld et al.)	Points	Criteria (Kuijer et al.)	Points
Age	1	Age	1.6
History of stroke	1	Female	1.3
GI bleed	1	Malignancy	2.2
One or more of - MI			
- Haematocrit - Creatinine - Diabetes	1		
Low risk	0	0	
Medium risk	1-2	1-3	
High risk	3-4	>3	

In all studies, VKA overdose patients had comorbidities, with the most frequent being heart failure and hypertension (mean ratios of 34.75% and 32% respectively) , other comorbidities included type 2 diabetes, tobacco and/or alcohol consumption, cardiac surgery, renal failure (mean ratio of 14.2%) and ahistory of stroke. Other than an ancient history of cardiac surgery, our patient had no risk factors of bleeding.

On admission, heparin intake and infection was found in over ¾ of the patients in the series of Zemmouri et al[3].

Concerning concomitant treatment, the series of Serghini et al. reports a percentage of 76.6% polymedicatedpatients (at least 3 medications) vs only 10% on VKA alone. In almost all studies [2] [3] [4], there was at least one concomitant treatment reported, with the most frequent beingFurosemid (56% [1]) [2] followed by Aspirin (mean ratio of 22%) [1] [2] [4]. Other commonly prescribed medications included amiodarone, paracetamol, antibiotics, nitrated, statins and beta- blockers.

Concomitant treatments' involvement further confirms the importance of drug to drug interactionsrelated to VKAs.

On admission, patients presented mostly with hemodynamic instability followed by neurological symptoms and rarely respiratory distress.

The average PT ratio was 22.4 % with the lowest PT ratio being 12% [5] and the highest PT ratiobeing 32.85% [1]. INR findings were 6.52 on average with a low of 4.5 [4] and a high of 11.4 [5].

In the series of Crétel et al. 50% of the patients had a PT ratio ≤ 20% Theaverage hemoglobin level was 7.8 g/dL [1] [5] [6].

Management included VKA stoppage in all studies. All patients benefited from VKA treatment interruption [1] [2] [4] [5] except for the series of Zemmouri et al. [3]where only 78% patients were subject to VKA withdrawal. Vitamin K administration was present in all the above mentioned series (93% in the series of Shibane et al [5]). Packed red blood cells were necessary in over 90% of the cases inthe series of Shibane et al. [5], while only needed in less than 11.7% of the patients in the Dia et al. [2] series. Other means of treatment included fresh frozen plasma (63% in the series of Shibane et al [5] vs 40% in the series of Serghini et al. [1]). The series ofCrétel et al. [6] points to the importance of 4F-CCP usage and the importance of surgery, be it conservative or invasive.

The series of Zemmouri et al. [3] points out interesting factors in the management of VKA overdose. 22% of patients were subject to false interruption of VKA treatment. The supplementation of vitamin K,in terms of dosage, was wrong in 100% of cases. The management didn't follow the national recommendations in over 43% of the cases and 44% of the patients suffered from a delay in care.

The series of Dia et al [2] recommends the usage of 24-48h control INR.

Conclusion

In summary, hemorrhagic complications in patients on VKA therapies remain infrequent events, with strokes being extremely rare. It is clear that the origin stems from insufficient knowledge about treatment,bad compliance and insufficient biological monitoring. All of these factors could be linked to a poor doctor-patient relationship. Therapeutic management must include VKA interruption, vitamin K administration and 4F-CCP. Mortality could be linked to delayed INR results and poor following of national recommendations.

Despite all this, VKAs remain a pillar of anticoagulant therapy, mostly in cases of auricular fibrillation and mechanical valves.

Future investigations are needed to prevent and treat hemorrhagic strokes and hemoperitoneum in patients on VKAs. It seems to be necessary to also produce and frequently update national recommendations in the treatment of VKA overdose.

References

1. Serghini I, Aissaoui Y, Quamouss Y, Sedikki R, Taj N, Salim Alaoui J, Zoubir M,Boughanem M. Les accidents aux AVK: étude rétrospective à propos de 30 cas [Accidents to AVK: a retrospective study of 30 cases]. Pan Afr Med J. 2012; 11:24.French. Epub 2012 Feb 15. PMID: 22514758; PMCID: PMC3325062
2. Dia K, Sarr SA, Mboup MC, Ba DM, Fall PD. Les surdosages en antivitamines K à Dakar: aspects épidémiologiques, cliniques et évolutifs [Overdose in Vitamin K antagonists administration in Dakar: epidemiological, clinical and evolutionary aspects]. Pan Afr Med J. 2016 Jul 1; 24:186. French. doi: 10.11604/pamj.2016.24.186.8256. PMID: 27795783; PMCID: PMC5072863.
3. A. Zemouri, F. Lin, O. Billuart, E. Sacco, J. Emmerich, P. Priollet, A. Yannoutsos.Prevalence and management of antivitamin K overdose in a hospital setting.