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A Case Series on Bleeding Complications Secondary to Clopidogrel and Acenocoumarol: Clinical Patterns and Management Outcomes

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ABSTRACT

Drug-induced coagulopathy refers to life-threatening adverse effects associated with anticoagulant and antiplatelet drugs. This article describes a case series of clinical patterns and management outcomes of bleeding complications secondary to clopidogrel and acenocoumarol. In case of the first and second case reports, patients who were receiving aspirin and clopidogrel revealed spontaneous bleeding from the mucous membranes in the gastrointestinal tract. Their predisposition to hemorrhagic phenomena may be attributed to their advanced age, diabetes, ischemic heart disease and possible interactions between medications. Therefore, standard doses of clopidogrel and aspirin might induce hemorrhage in at-risk groups of patients. Supportive therapy was sufficient for stabilizing patients' conditions. The third, fourth and fifth case reports demonstrate the consequences of acenocoumarol overdose. Acenocoumarol is a vitamin K antagonist that interferes with the production of clotting factors II, VII, IX and X. As shown, there was a considerable increase in PT and INR (up to 8.6). The extent of bleeding symptoms, including hematemesis and melena with severe anemia, was directly proportional to the magnitude of INR. Treatment included the introduction of vitamin K and fresh frozen plasma, which contributed to normalizing blood coagulation. This review highlights that insufficient monitoring of INR is one of the key factors contributing to the development of drug-induced bleeding events. The current case reports reveal that older people, those with polypharmacy and patients with underlying cardiovascular pathologies are at increased risk of experiencing side effects related to anticoagulation therapy. As evidenced by the clinical cases, INR is reduced by vitamin K and FFP. Thus, this case series contributes to the discussion of the topic, adding specific data. In summary, this case series confirms the available information concerning the role of antiplatelet and anticoagulant drugs in drug-induced coagulopathy. The comparison with the results of a pharmacovigilance study strengthens the understanding that careful monitoring, individualized dose adjustment and proactive intervention are crucial for preventing this condition.

Introduction

Antiplatelet Therapy

Antiplatelets are used all over the world to prevent cardiovascular disease both on a primary and secondary basis and their long-term use aims at reducing mortality rates [1]. Clopidogrel is a newer antiplatelet drug that belongs to the thienopyridine family and its molecular structure bears significant similarity to that of ticlopidine [2]. Clopidogrel is prescribed to lower atherosclerotic events in ACS (Acute Coronary Syndrome), stroke and peripheral arterial disease patients. Moreover, this antiplatelet agent can be taken by patients who experience resistance to aspirin therapy [3]. The starting dose of clopidogrel includes 300 mg of loading and 75 mg of maintenance daily dosage [4].

Gastrointestinal bleeding, liver injury, neutropenia and thrombotic microangiopathy are some of the adverse drug reactions with clopidogrel. Severe fatigue syndrome, hypoglycemia/insulin autoimmune syndrome, small bowel ulcers and bleeding, Rowell's syndrome, lupus erythematosus variant and inflammatory arthritis are some of the rare adverse reactions with clopidogrel [5].

Anticoagulants

Anticoagulant medications are used for treating and preventing recurrent thromboembolic disorders. Oral anticoagulants based on vitamin K antagonists have been popular globally. Acenocoumarol belongs to a unique family of coumarins derivatives. It acts as a powerful anticoagulant drug to prevent the development of blood clots. It inhibits vitamin K reductase to block the process of carboxylation of vitamin K-dependent factors of blood coagulation II, VII, IX and X. The disruption of the blood coagulation cascade makes it

necessary to monitor the hematocrit, hemoglobin levels, international normalized ratio (INR) and liver function tests. Adults without abnormalities in thromboplastin time are treated using acenocoumarol daily with a dosage of 4 mg [6,7].

Coagulopathy

Coagulopathies are diseases that are associated with a decreased capability to stop hemorrhage, thus causing bleeding and a tendency toward thrombus formation. Coagulopathies may have various origins, which include such events as serious trauma, sepsis, malignancy, particularly of hematologic organs, as well as complications in pregnancy period. Moreover, there are many drug-induced coagulopathies.

Coagulopathy is a significant problem that is responsible for morbidity and even mortality all over the world. About 26-45% of apparently healthy individuals, report frequent nose bleeding and bleeding gums. Prothrombin time (PT) with international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen and thrombin time (TT) are among the most common analyses performed in a coagulation lab and such tests are referred to as routine or screening coagulation studies [8-10].

This article describes a case series of clinical patterns and management outcomes of bleeding complications secondary to clopidogrel and acenocoumarol observed at Vijayanagara Institute of Medical Sciences, Ballari, Karnataka.

CASE REPORT - 1

A 65-year-old male presented with complaint of epistaxis and gum bleeding. The total volume of blood loss estimated was around 100 mL. History of chronic pulmonary tuberculosis on ATT for a month, ischemic heart disease (coronary angiography performed two months prior undergoing dual antiplatelet treatment with aspirin and ticagrelor) and type 2 diabetes mellitus (treated with insulin for ten years) was present. Family history was observed to be insignificant.

On clinical examination, the patient was conscious and oriented, blood pressure was 110/60 mmHg, pulse rate was 110 beats per minute, oxygen saturation of 95% on room air was observed. Random blood glucose of 170 mg/dL was detected. Systemic examination did not reveal anything pathologic apart from normal findings (S1 and S2 auscultated) from cardiovascular system, bilateral lung fields had normal air entry and soft non-tender abdomen.

Normal level of hemoglobin and leukocyte count with good renal functions were revealed by laboratory investigations. Hyperglycemia (random blood sugar 316 mg/dL) with poor glycemic control, which was confirmed by significantly high level of HbA1c (10.9%) was detected. Elevated level of C-reactive protein indicated the mild inflammation process ongoing. The main laboratory abnormality is represented by the disturbances in coagulation factors: markedly increased prothrombin time (PT 85.7 seconds), activated partial thromboplastin time (APTT 60.8 seconds) and INR (8.8).

Laboratory Investigations

Parameters	Result	Reference range
Haemoglobin	13.1	13-18gm%
WBC	4620	4000-11000cells/cumm
RBS	316	70-140mg/dl
Blood urea	21	15-45mg/dl
Serum creatinine	1.0	0.7-1.4mg/dl
Sodium	145	135-145mEq/L
Potassium	4.1	3.48-5 mEq/L
ESR	10	0-20mm/hr
CRP	7.0	0-6mg/L
APTT	60.8	30-40 seconds
PT	85.7	11-18 seconds
INR	8.8	0.8-1.1
HbA1C	10.9	<6

From the clinical point of view, gum bleeding is explained by severe disturbances in coagulation factors. As far as possible causes, the usage of dual antiplatelet treatment increases the risk of bleeding since it affects platelets' aggregating properties. Anti-tubercular therapy, especially with rifampicin, has the property to increase the activity of enzymes in the liver, which can lead to changes in the work of the coagulation pathway.

Even though the use of antiplatelet agents does not influence INR directly, their concomitant use can cause more negative consequences when there is hepatic dysfunction or some disturbances in vitamin K synthesis. Significantly high INR is the evidence that there might be vitamin K insufficiency, interaction of medications, or a disturbance in the mechanism of coagulation factors' synthesis.

Treatment

S.No	Name of the Medications	Dose	Route	Frequency
1.	INJ.TRANEXAMIC ACID	1gm in 100ml NS	IV	BD FOR 2 DAYS
2.	INJ.PANTOPRAZOL	40mg	IV	OD FOR 2 DAYS
3.	SYP.SUCRAFIL	10ml	PO	TID FOR 2 DAYS
4.	INJ.INSULIN	10-0-8	S/C	FOR 2 DAYS
5.	TAB.ATORVASTATIN	40mg	PO	OD FOR 2 DAYS
6.	TAB.ATT	4-0-0	PO	OD FOR 2 DAYS
7.	TAB.PYRIDOXINE	40mg	PO	OD FOR 2 DAYS
8.	TAB.TICAGRELOR	90mg	PO	OD FOR 2 DAYS
9.	TAB.ASPIRIN	75mg	PO	OD FOR 2 DAYS
10.	INJ.CEFOPERAZONE	1.5gm	PO	BD FOR 1 DAY

Management included hemodynamic stabilization and treatment of bleeding. Tranexamic acid for the promotion of haemostasis was used intravenously. In order to protect from the gastrointestinal tract bleeding because of the usage of antiplatelet agents, gastro-protection (pantoprazole, sucralfate) was done. Glycemic control was managed by insulin therapy in the case of marked elevation of random glucose and HbA1c. ATT and pyridoxine were continued as well as aspirin and ticagrelor (taking into account coronary intervention). Statins and insulin therapy were used together. To prevent infections, cefoperazone was administrated inpatient.

This case demonstrates an example of a high-risk situation associated with severe disturbances in the coagulation mechanism manifested with mucosal bleeding in a patient with several disorders and polypharmacy.

CASE REPORT - 2

A 77-year-old female was admitted with complaints of bleeding from the mouth not stopping despite external pressure. The patient had a history of mitral valve prolapse associated with severe mitral regurgitation and was on antiplatelet treatment comprising of aspirin 75 mg OD + clopidogrel 75 mg OD. No significant family history was present. She was conscious and oriented. On examination, her blood pressure was 110/70 mm Hg, pulse 83/min and saturation 97% on room air. Systemic examination revealed vesicular breathing sounds, normal heart sounds and soft non-tender abdomen.

Her laboratory investigations revealed hemoglobin levels of 10.2 g/dL, which suggested mild anemia most likely secondary to continuous blood loss. Her total white blood cells count was normal. However, her serum creatinine levels were elevated (1.8 mg/dL), suggestive of a certain degree of renal dysfunction. Her inflammatory marker test results were normal, with only the presence of slightly elevated C-reactive protein level of 8.9 mg/L. Most importantly, her coagulation function test revealed severely deranged results with highly elevated APTT (71.8 seconds), PT (67.7 seconds) and INR (7.8).

Laboratory Investigations

Parameters	Result	Reference range
Haemoglobin	10.2	13-18gm%
WBC	8948	4000-11000cells/cumm
Serum creatinine	1.8	0.7-1.4mg/dl
Sodium	138	135-145mEq/L
Potassium	3.9	3.48-5 mEq/L
ESR	14	0-20mm/hr
CRP	8.9	0-6mg/L
APTT	71.8	30-40 seconds
PT	67.7	11-18 seconds
INR	7.8	0.8-1.1

Based on the findings, this clinical scenario most probably suggests the occurrence of acute hemorrhage due to coagulation disorders. Even though the patient is on platelet inhibitors (aspirin & clopidogrel), they do not interfere with her coagulation factors as indicated by PT/INR values. However, INR is very high, implying a probable additional factor leading to a coagulation disorder like vitamin K deficiency, liver dysfunction, drug effect or rarely, unknown anticoagulant use. Since there is renal impairment, it will make the effect of the drugs worse. An increase in CRP levels suggests a mild inflammation, which might contribute to the bleeding.

The patient received tranexamic acid infusion for hemorrhage control along with intravenous vitamin K. Additionally, pantoprazole was prescribed for gastric protection, while ondansetron for symptoms of nausea. Empirical antibiotics like amoxicillin-clavulanate were used. In conclusion, the patient needs close monitoring of her coagulation factors, hemoglobin and renal functions. It might be

appropriate to stop or reassess her antiplatelet therapy since the risk of bleeding is very high.

Treatment

S.No	Name of the Medications	Dose	Route	Frequency
1.	INJ.TRANEXAMIC ACID	500mg	IV	BD FOR 2 DAYS
2.	INJ.PANTOPRAZOL	40mg	IV	OD FOR 2 DAYS
3.	INJ.VITAMIN K	1Omg	IV	OD FOR 2 DAYS
4.	INJ.ONDANSETRON	4mg	IV	BD FOR 2 DAYS
5.	INJ.AMOXICLAV	1.2gm	IV	BD FOR 2 DAYS

CASE REPORT - 3

A 55-year-old man was presented with the symptom of oral bleeding from the previous night amounting to 50 mL, associated with pain in the right flank. His medical history revealed a diagnosis of HIV, which was being managed with antiretroviral therapy for 8 years. He suffered from Rheumatic Heart Disease. Anticoagulation was being done for him using Acenocoumarol (3 mg). Moreover, the patient had an episode of Deep Vein Thrombosis. Family history was unremarkable.

The patient appeared to be conscious and oriented. His vitals remained stable (BP:110/70 mmHg, PR:102 beats/minute, O2 Saturation: 96%). The systemic examination revealed normal vesicular breath sounds and heart sounds (S1, S2) and a soft, non-tender abdomen. In spite of clinically stable findings, investigations revealed severely deranged coagulation. On Day 1, his coagulation tests came out to be very abnormal (prothrombin time: 85.9 seconds, activated partial thromboplastin time (APTT): 60.6 seconds and international normalized ratio (INR): 8.6). By Day 3, there was a remarkable improvement (prothrombin time: 18.8 seconds, APTT: 43.8 seconds and INR: 1.76).

Laboratory Investigations

Parameters	Result(day-1)	Result(day-3)	Reference range
APTT	60.6	43.8	30-40 seconds
PT	85.9	18.8	11-18 seconds
INR	8.6	1.76	0.8-1.1

Clinically, the cause of the bleed is attributed to excessive anticoagulation because of Acenocoumarol, which is a vitamin K antagonist. INR 8.6 indicates very high chances of spontaneous bleeding. The cause of coagulopathy was probably multifactorial, including inappropriate anticoagulant dosage, drug interactions between Acenocoumarol and antiretroviral drugs, changes in the metabolism of vitamin K, etc. The presence of right flank pain could point towards internal bleeding like retroperitoneal hemorrhage. However, physical examination did not reveal any signs.

Treatment was mainly aimed at reversal of anticoagulation and stabilization of the patient. Administration of IV Vitamin K helped reverse the effect of acenocoumarol and facilitated the formation of clotting factors. Transfusion of Fresh Frozen Plasma was carried out to make up for the lack of clotting factors, thereby rapidly lowering INR. Pantoprazole IV was administered for gastrointestinal protection. The patient was also treated with Ceftriaxone and Metronidazole empirically. He showed considerable improvement in both laboratory and clinical findings after therapy.

Treatment

S.no	Name of the Medications	Dose	Route	Frequency
1.	INJ.VITAMIN K	10mg	IV	OD FOR 2 DAYS
2.	INJ.PANTOPRAZOLE	40mg	IV	OD FOR 2 DAYS
3.	INJ.ONDANSETRON	4mg	IV	BD FOR 2 DAYS
4.	INJ.CEFTRIAXONE	1gm	IV	BD FOR 1 DAY
5.	INJ.METRONIDAZOLE	100ml	IV	TID FOR DAY
6.	INJ.FFP	6 PINT	PO	STAT

This is one of the classical cases of anticoagulant-related coagulopathy with mucosal bleeding. INR monitoring was highly imperative in a person who was on acenocoumarol, especially an HIV patient in whom drug interactions are frequent. Immediate action in terms of administration of vitamin K and plasma products must be taken to avoid complications arising from massive hemorrhage.

CASE REPORT - 4

A 67 years old female patient, presented with a chief complaint of hematemesis for three days, occurring once a day with blood output between 20 - 50 ml and exertional dyspnea with the same duration. Patient is known to suffer from rheumatic heart disease with severe mitral regurgitation and previous mitral valve replacement. On maintenance therapy with oral anticoagulant-acenocoumarol. No significant history noted regarding her family.

On examination, patient was found to be awake, conscious, coherent and oriented. Her vital signs were as follows: Blood Pressure was 110/70 mmHg, Pulse rate was 80 bpm and her Oxygen saturation was 98%. On systemic examination, there was noted right sided crepitations on breathing, while her cardiac examination was remarkable for S1 and S2 sounds being within the normal range. On abdominal examination, abdomen was soft and non-tender to palpation.

Laboratory investigations revealed that there was anemia, as seen in hemoglobin of 9.8 g/dL, along with a low RBC count of 3.76 million/ µL, along with a low PCV 30.5%. On red cell indices, there was evidence of low MCH, but highly raised RDW, signifying the presence of anisocytosis. Coagulation studies revealed prothrombin time of 21.5 seconds and INR of 3.8 seconds, suggestive of supratherapeutic anticoagulation with her medication, while APTT is normal. All these point towards high probability that the bleed is secondary to the patient being anticoagulated.

Laboratory Investigations

Parameters	Result	Reference range
Haemoglobin	9.8	13-18gm%
WBC	5740	4000-11000cells/cumm
RBC count	3.76	4.5-5.5million/cumm
PCV	30.5	35-45%
MCH	25.5	27-34pg
RDW-CV	33.6	11.5-14.5%
PDW-CV	36	10-18%
APTT	35.6	30-40 seconds
PT	21.5	11-18 seconds
INR	3.8	0.8-1.1

Clinically, the case is indicative of Upper GIT bleeding, due to acenocoumarol causing coagulopathy. The significantly elevated INR would cause spontaneous bleeding, especially in the elderly population. In addition to the anemia, which is secondary to acute blood loss due to hematemesis, breathlessness and right-sided crepitations may indicate pulmonary congestion, possibly secondary to her underlying cardiac condition, but cannot be ruled out as being a sign of lower respiratory tract infection.

Patient was managed through a multidisciplinary approach. First, reversal of anticoagulation with intravenous vitamin K and fresh frozen plasma (FFP) was done to correct the coagulopathy rapidly and INR levels. To help stop the bleeding, tranexamic acid was administered to inhibit the fibrinolysis process, which helps in promoting hemostasis. Pantoprazole was administered intravenously to inhibit her stomach acid formation, to maintain an optimal environment in her upper GIT. To avoid further vomiting, leading to more blood loss, she was treated with ondansetron. Due to the possibility of having a lower respiratory tract infection, she was given empirical treatment of amoxicillin-clavulanate. Finally, for her breathlessness, furosemide was administered.

Treatment

S.no	Name of the Medications	Dose	Route	Frequency
1.	INJ.TRANEXAMIC ACID	500mg	IV	BD FOR 2 DAYS
2.	INJ.PANTOPRAZOL	40mg	IV	OD FOR 2 DAYS
3.	INJ.VITAMIN-K	10mg	IV	BD FOR 2 DAYS
4.	INJ.AMOXICLAV	1.2gm	IV	BD FOR 2 DAYS
5.	INJ.ONDANSETRON	4mg	IV	BD FOR 2 DAYS
6.	INJ.FUROSEMIDE	20mg	IV	BD FOR 2 DAYS
7.	4PINT FFP		IV	OD STAT

Management includes continuous monitoring of her vitals, hemoglobin and INR to guide any further management of anticoagulation therapy. Further evaluation and modification of her anticoagulation regime are crucial, in order to balance the risk of thromboembolism, considering the prosthetic valve, against further bleeds.

CASE REPORT - 5

A 74 years old male was admitted with complaints of black tarry stools (Melena) for two days with giddiness and blurred vision. Melena strongly suggests an upper gastrointestinal (GI) bleed, while giddiness and blurring of vision are secondary to severe anemia. Other known medical problems include hypertensive disease managed with Metoprolol, Type II diabetes mellitus, dilated cardiomyopathy and atrial fibrillation for which anticoagulation with acenocoumarol is required. No family history was reported.

Examination showed patient being drowsy with GCS of E2V5M6 indicating mild alteration in consciousness probably secondary to severe anemia. Blood pressure was 130/80 mmHg, pulse rate was 64 beats per minute (bpm) and oxygen saturation was

97% on room air. Systemic examination reveals that the heart sound was S1 and S2 (+), both sides were clear bilaterally and no acute abdomen with a soft non-tender abdomen.

Investigations revealed profound anemia with hemoglobin level of 4.2 gm/dl, low red blood cells count, low packed cell volume indicative of blood loss anemia. Elevated red cell distribution width (RDW) suggests anisocytosis indicative of mixed or evolving anemia. Low total protein, low albumin and low globulin indicate poor nutrition or chronic disease. Vitamin B12 is also decreased in the body, contributing to anemia. Coagulation profile showed prothrombin time (PT), activated partial thromboplastin time (APTT) being significantly prolonged with international normalized ratio (INR) of 2.9 indicative of anticoagulant effect by acenocoumarol causing significant derangement of coagulation factors.

Laboratory Investigations

Parameters	Result	Reference range
Haemoglobin	4.2	13-18gm%
WBC	8210	4000-11000cells/cumm
RBC	2.26	5.5-6.5 million/cumm
PCV	21.2	45-55%
RDW-CV	18.3	11.5-14.5%
Total protein	4.4	6-8.3g/dl
Albumin	2.9	3.2-5.4g/dl
Globulin	1.5	2.5-3g/dl
Vitamin B12	135.5	211-911 Pg/ml
APTT	56	30-40 seconds
PT	22.5	11-18 seconds
INR	2.9	0.8-1.1

From the above discussion, this case is suggestive of an acute upper GI bleed in an elderly patient with multiple comorbid conditions, especially Atrial fibrillation leading to anticoagulation and thus more prone to bleeding. Profound anemia accounts for giddiness. Absence of abdominal tenderness makes perforation unlikely and vitals being stable implies a compensated condition despite severe anemia.

For the above patient, the management involved correcting the coagulopathy, stabilizing the patient and treating the cause. Intravenous vitamin K was administered to reverse the effects of anticoagulant and correct coagulation profiles. Proton pump inhibitors such as pantoprazole were administered to lower gastric acid secretion and achieve hemostasis in a suspected case of upper GI bleeding. Administration of iron sucrose was done for iron deficiency. However, correction of severe anemia requires blood transfusion, which is clearly required for this patient in view of severely low hemoglobin concentration. Antibiotics like piperacillin/tazobactam and ceftriaxone were administered, possibly as prophylaxis for infection. Diuretic such as furosemide was administered with precautions in view of cardiomyopathy to avoid fluid overload.

Other cardiac medicines such as metoprolol, amiodarone and digitalis were prescribed for controlling Atrial fibrillation and underlying heart disease. Careful monitoring of vitals, hemoglobin and coagulation parameters are important.

Treatment

S.no	Name of the Medications	Dose	Route	Frequency
1.	INJ.VITAMIN K	10mg	IV	OD FOR 5 DAYS
2.	INJ.FUROSEMIDE	40mg	IV	BD FOR 5 DAYS
3.	INJ.PIPZO	4.5gm	IV	TID FOR 3 DAYS
4.	INJ.CEFTRIAXONE	1gm	IV	BD FOR 5 DAYS
5.	INJ.IRON SUCROSE	2amp in 100ml NS	IV	OD FOR 2 DAYS
6.	TAB.ATORVASTATIN	40mg	PO	OD FOR 5 DAYS
7.	TAB.METAPROLOL	25mg	PO	OD FOR 5 DAYS
8.	TAB.AMIODARONE	200mg	PO	OD FOR 5 DAYS
9.	TAB.DIGOXIN	0.25mg	PO	BD FOR 5 DAYS
10.	INJ.PANTOPRAZOLE	40mg	PO	OD FOR 5 DAY

This case represents an acute upper GI bleed complicated by severe anemia and coagulopathy due to anticoagulants in an elderly patient with underlying cardiovascular diseases.

Discussion

Drug-induced coagulopathy refers to life-threatening adverse effects associated with anticoagulant and antiplatelet drugs. These drugs are widely used in the prevention of thrombotic events due to cerebrovascular and cardiovascular diseases. However, the beneficial effects of antiplatelet agents are associated with the high risk of bleeding, especially among elderly patients with multiple morbidities. Antiplatelet drugs act by inhibiting ADP receptors of platelets to block their aggregation. Though they do not change PT or INR, antiplatelets impair primary hemostasis. In case of the case reports 1 and 2 of

patients who were receiving aspirin and clopidogrel revealed spontaneous bleeding from the mucous membranes in the gastrointestinal tract. Their predisposition to hemorrhagic phenomena may be attributed to their advanced age, diabetes, ischemic heart disease and possible interactions between medications. Therefore, standard doses of clopidogrel and aspirin might induce hemorrhage in at-risk groups of patients. Supportive therapy was sufficient for stabilizing patients' conditions. The case reports 3, 4 and 5 demonstrate the consequences of acenocoumarol overdose. Acenocoumarol is a vitamin K antagonist that interferes with the production of clotting factors II, VII, IX and X. As shown, there was a considerable increase in PT and INR (up to 8.6). The extent of bleeding symptoms, including hematemesis and melena with severe anemia, was directly proportional to the magnitude of INR. Treatment included the introduction of vitamin K and fresh frozen plasma, which contributed to normalizing blood coagulation.

This review highlights that insufficient monitoring of INR is one of the key factors contributing to the development of drug-induced bleeding events. The current case reports reveal that older people, those with polypharmacy and patients with underlying cardiovascular pathologies are at increased risk of experiencing side effects related to anticoagulation therapy. It is vital to conduct regular laboratory tests to adjust the dose of drugs to avoid adverse consequences. Moreover, patients should be educated about the signs of bleeding.

It is important to compare this paper with a recent pharmacovigilance study by Lu Y et al., which was published in Frontiers in Pharmacology (2024) in which similar observations were noted. This work examined adverse events associated with anticoagulants and antiplatelet agents. Based on the analysis of data obtained from the FDA Adverse Event Reporting System database, the authors concluded that age and concomitant medications play critical roles in the occurrence of drug-induced coagulopathy [8]. These findings are similar to the results of this case series, where elderly patients taking acenocoumarol experienced a marked increase in INR and acute bleeding episodes. Although the cited work provides general evidence based on statistics from pharmacovigilance, the present case series allows for analyzing bleeding manifestations and their treatment. As evidenced by the clinical cases, INR is reduced by vitamin K and FFP. Thus, this case series contributes to the discussion of the topic, adding specific data.

Conclusion

In summary, this case series confirms the available information concerning the role of antiplatelet and anticoagulant drugs in drug-induced coagulopathy. The comparison with the results of a pharmacovigilance study strengthens the understanding that careful monitoring, individualized dose adjustment and proactive intervention are crucial for preventing this condition.

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