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CASE REPORT

Major bleeding of the upper aerodigestive tract due to oral anticoagulant/antibiotic interactions

L. Nisa[a,*], **K. Nicoucar**[a], **R. Giger**[b]

[a] *Service d'ORL et de chirurgie cervicofaciale, hôpitaux universitaires de Genève, rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland*
[b] *Universitätsklinik für Hals-Nasen-Ohrenkrankheiten - Kopf- und Halschirurgie, Inselspital, Bern, Switzerland*

KEYWORDS
Hemorrhage;
Acenocoumarol;
Antibiotics;
Drug interactions

Summary
Introduction: Although a well-known complication in certain medical specialties, major bleeding due to the interaction between oral anticoagulants and antibiotics has been rarely reported concerning the upper aerodigestive tract. We report three cases of life-threatening bleeding of the upper aerodigestive tract in a context of antibiotic therapy in patients treated with oral anticoagulants.
Case series: Three male patients under coumadin anticoagulation therapy presented major bleeding in three different contexts (epistaxis, peritonsillar abscess and postoperative course after total laryngectomy). Surgical intervention for hemostasis was required in all cases, with coagulation correction in two. Complications were severe anemia (2/3) and chronic heart failure (1/3).
Discussion/conclusions: Interactions between two drugs commonly used in otolaryngology can result in major bleeding. The goal of this article is to raise practitioners' awareness of a potentially fatal, although rare, complication. We also review the main preventive strategies.

Introduction

Oral anticoagulants are widely used in the management or prevention of thromboembolic disease. Vitamin K antagonists (coumadins) are the main group of oral anticoagulants used in clinical practice in most European countries. Their most frequent severe complication is major bleeding [1].

Increased risk of major bleeding induced by drug interaction is well established for anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet drugs and antibiotics [1].

Antibiotic-anticoagulant interaction resulting in increased bleeding risk has been clearly proven only for quinolones and cotrimoxazole, but similar interactions have also been suggested for several other antibiotic agents, especially amoxicillin (with or without clavulanate), cephalosporins and doxycycline [2]. The underlying mechanisms of such interaction are poorly understood and experimental studies in humans are sparse and based on small series of patients [3]. A particularly relevant observation is reduced hepatic concentration of vitamin K resulting in modified intestinal flora during antibiotherapy [4]. It should also be borne in mind that the main pharmacokinetic feature of oral anticoagulants is the

* Corresponding author. Tel.: +41 79 5533922; fax: +41 27 6034449.
E-mail address: llnisa@yahoo.ca (L. Nisa).

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inter-individual variability of response, mainly induced by genetic polymorphisms involving two major enzymes of the acenocoumarol metabolic pathway: cytochrome P4502C9 (CYP2C9) and vitamin K epoxide reductase [5].

Cases

It must be stressed that the patients reported below:

- showed international normalized ratio (INR) values prior to antibiotherapy between two and three on repeated measurement;
- were not administered any drugs interacting with acenocoumarol;
- were not prescribed any change in diet (Table 1).

Case 1

A 67-year-old man was treated for Calcinosis, Raynaud's syndrome, Esophageal motility disorder, Scleroderma and Telangectasia (CREST) syndrome, with acenocoumarol for two episodes of pulmonary embolism and extensive thrombosis of the lower limbs. He had previously suffered occasional nose-bleeds.

He was managed by amoxicillin-clavulanate for an episode of upper respiratory tract infection, diagnosed (without further details) by his general practitioner. Three days later he presented to the emergency department with severe epistaxis.

Rhinoscopy found diffuse bleeding in the posterior right nasal cavity. Nasal packing was ineffective, and surgery was performed for sphenopalatine artery ligature and hemostasis of other vessels. INR was 7.2. Postoperative course involved severe anemia (hemoglobin: 50 g/L; normal range 120—160) and myocardial infarction. Bleeding recurred on postoperative day 2 and nasal packing was required for 5 days. After consultation with a cardiologist, anticoagulant therapy was maintained: acenocoumarol was reintroduced before discharge at day 21.

During follow-up, the patient showed moderate chronic heart failure.

Case 2

A 78-year-old man was under treatment with acenocoumarol and digoxin for atrial fibrillation. He presented in a community clinic with a left peritonsillar abscess, for which he was prescribed amoxicillin-clavulanate. Despite two negative needle-aspirations, the peritonsillar abscess recurred, causing severe odynodysphagia and respiratory discomfort. An incision was performed under local anesthesia at day 2 of antibiotic treatment, to drain the abscess; the patient was then switched to intravenous amoxicillin-clavulanate for 2 days and discharged with 5 days' antibiotics. Two days after discharge, he consulted again due to sudden-onset odynophagia and left oropharyngeal hematoma in regard of the incised abscess sac (Fig. 1). INR was 9.7, and the patient was administered 20 mg phytomenadione (synthetic vitamin K1). Over the next 6 hours the hematoma increased, provoking respiratory obstruction and prompting urgent intubation for 7 days in the intensive care unit. Acenocoumarol was replaced by standard heparin, until endoscopically-controlled extubation. There were no complications, and acenocoumarol reintroduced before discharge.

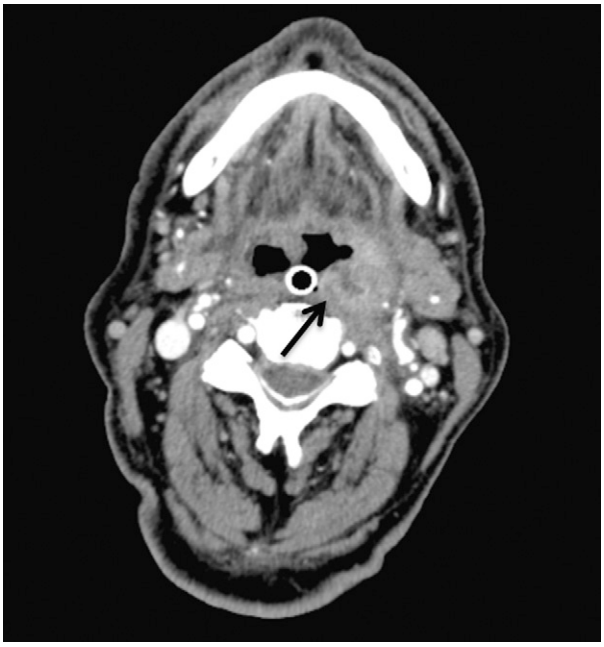

Figure 1 Computed tomography scan showing the left oropharyngeal hematoma underlying upper airway obstruction in patient 2 (black arrow).

Case 3

A 62-year-old man had been re-admitted after salvage laryngectomy, presenting with a left pharyngocutaneous fistula. He was treated with acenocoumarol for atrial fibrillation and an episode of pulmonary embolism, and by angiotensin-converting enzyme inhibitor for hypertension.

Antibiotic treatment with amoxicillin-clavulanate was started for perifistular dermo-hypodermitis. Onset of severe bleeding through the fistula on the fourth day of treatment was immediately identified, requiring intubation and transfer to surgery. The left common carotid artery was identified as the source of bleeding, and was ligatured after multiple repair attempts failed. INR was 12.3 at the time of bleeding, compared to 2.1 the day before initiation of antibiotic treatment. He developed anemia (57 g/L; normal range, 120—160), and transitory sensory-motor syndrome of the right hemi-body, which recovered completely.

The patient survived without neurologic sequelae and was discharged 3 months later. Six months after discharge, however, he presented with esophageal varice rupture, which was endoscopically cauterized (the patient was not taking antibiotics at that time).

Discussion

The essential goal of these reports is to highlight the importance of pharmacological interaction between two drugs frequently used in routine otorhinolaryngological practice.

Table 1 Clinical and laboratory features of patients treated with oral anticoagulants and antibiotics.

Patients	Clinical features		INR value		Management		Follow-up		
	Context of bleeding	Daily dose of aceno-coumarol (mg)	Prior to antibi-otic therapy	At time of bleeding	Invasive procedures	Medical intervention	Early complications	Late complications	Time of follow-up
Case 1	Epistaxis	3	1.9	7.2	Sphenopalatine artery ligature Antero-posterior nasal packing	Vitamin K transfusion	Severe anemia Myocardial infarction	Chronic heart failure	8 months
Case 2	Peritonsillar abscess (quinsy)	2	2.5	9.7	Orotracheal intubation	Coagulation factors II, VII, IX, X, proteins S and C	Upper airway obstruction	Full recovery	4 months
Case 3	Carotid artery rupture	2	2.1	12.3	Carotid artery ligature	Coagulation factors II, VII, IX, X, proteins S and C Transfusion frozen plasma	Severe anemia	Transitory sensory-motor syndrome of the right hemi-body	2 years

INR: international normalized ratio.

Antibiotic prescription is common in tonsillar and peritonsillar infection, which are the two most frequent diagnoses in otorhinolaryngology [6].

Epistaxis is the most frequent complication associated with anticoagulants, and spontaneous hematoma is also frequently reported [7]. Specifically concerning the upper aerodigestive tract, we were able to identify only one case report of pharyngolaryngeal hematoma in an anticoagulated patient treated with clindamycin [8].

A large-scale cohort study indicated that life-threatening bleeding of the upper aerodigestive tract due to antibiotic-anticoagulant interaction is indeed a rare occurrence [2]. It is therefore difficult to formulate evidence-based recommendations for prevention strategies and identification of patients at risk [1].

In order to avoid severe bleeding as a result of oral anticoagulant/antibiotic interaction, previously proposed approaches included:

- preventive reduction of anticoagulant dose, with consequently increased risk of thrombosis;
- INR-guided dose reduction [9].

These considerations and exhaustive assessment of indications for antibiotherapy seem to be especially important in patients under anticoagulants with a history of recurrent epistaxis, stomatorragia, hemoptysis, hematemesis, or recent surgery of the head and neck region.

Severe bleeding can be life-threatening in any context, but in the upper aerodigestive tract there is a supplementary risk of respiratory obstruction which must be kept in mind. Early intervention in such cases is mandatory.

Conclusion

Despite the lack of strongly evidence-based guidelines or the supposed rarity of the interaction reported here, awareness on the part of otorhinolaryngologists is important.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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