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CASE REPORT

Sustained safe and effective anticoagulation using Edoxaban via percutaneous endoscopic gastrostomy

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Abstract

Extensive data support the safety of direct oral anticoagulants compared with vitamin K antagonists in patients with non-valvular atrial fibrillation, leading to a significantly increase in the use of these compounds in clinical practice. However, there is no compelling evidence supporting the use of direct oral anticoagulant in individuals who are intubated or have a percutaneous endoscopic gastrostomy (PEG): patients with several co-morbidities are underrepresented in clinical trials, so the best long-term strategy for anticoagulation is difficult to ascertain. The aim of the present report was to evaluate the safety and efficacy of edoxaban administered via PEG in a patient with heart failure and a history of atrial fibrillation affected by amyotrophic lateral sclerosis (ALS). A 71-year-old man with atrial fibrillation, advanced ALS, type II diabetes mellitus, and hypertension presented to the emergency department with dyspnoea and tachycardia. Because vitamin K antagonist and rivaroxaban 15 mg were dropped because of difficult international normalized ratio control (time in therapeutic range $<$30%) and severe haematuria, respectively, edoxaban 30 mg (crushed pill) daily was administered based on the patient's weight of 58 kg. Mean edoxaban plasma concentration–time profiles were measured, as anti-Xa activity, 2 h before and at 2, 6, and 22 h after drug administration and then compared with the pharmacokinetic profile of edoxaban 30 mg in healthy subjects. An additional testing of steady-state peak plasma concentration of edoxaban after 10 days and a 30 day follow-up were evaluated. The values of the pharmacokinetic parameters, analysed with a non-compartmental analysis by PKSolver module, showed that C_{max} and $AUC_{0\rightarrow t}$ were only slightly higher than those observed in healthy subjects, while the half-life and observed clearance were significantly longer and lower, respectively, than in normal subjects. Steady-state peak plasma concentration of edoxaban was very similar to the levels reported in healthy subjects, and neither relevant bleeding nor thromboembolic event was reported at a 30 day follow-up. These results support safe and effective anticoagulation with edoxaban 30 mg but suggest caution with the use of full dose of edoxaban (60 mg daily) in this kind of patients. We report, for the first time, a safe and effective anticoagulation based on the administration of edoxaban 30 mg daily through PEG in a patient with advanced ALS, acute respiratory, and heart failure, presenting with Takotsubo syndrome and atrial fibrillation.

Keywords Takotsubo syndrome; Edoxaban; Amyotrophic lateral sclerosis; Atrial fibrillation; Percutaneous endoscopic gastrostomy

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Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease, characterized by both upper and lower motor neuron dysfunction.[1] Most patients die of respiratory complications 3–5 years after its onset. Patients treated with invasive ventilation through tracheostomy show an average further survival of 2 years.[1,2] Difficult swallowing is another frequent complication often requiring percutaneous endoscopic gastrostomy (PEG) in order to provide proper nutritional support and minimize the risk of aspiration pneumonia. Although autonomic dysfunction is not considered a main feature of the disease, sudden hypertensive or hypotensive crises, followed by circulatory collapse, have been described, especially in the advanced stages of ALS.[1,3] Recent publications have reported that heart diseases, including atrial fibrillation and heart failure, are common in ALS patients and are independently associated with reduced survival.[4,5]

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, represents an acute heart failure syndrome characterized by ST-segment elevation and reversible left ventricular regional wall motion abnormalities (typically involving the apex).[6,7] The precise pathogenesis of TTS remains unknown; a neurogenic origin with excessive catecholamine production causing microvascular spasm and direct cardiotoxicity may be involved.[6] Several recent publications suggest that TTS, presenting with acute exacerbation of dyspnoea and chest discomfort, is relatively common in ALS patients, particularly in the advanced stages of ALS.[8,9]

Additionally, atrial fibrillation (AF) is a common complication of both TTS and ALS,[5,7] and the use of anticoagulation in such fragile patients may be particularly challenging.

Case report

A 71-year-old man with advanced ALS, type II diabetes mellitus, and hypertension presented to the emergency department with dyspnoea and tachycardia. The family reported a history of paroxysmal atrial fibrillation treated with subcutaneous low molecular weight heparin (4000 IU twice daily). Vitamin K antagonist and rivaroxaban 15 mg had been tried and then suspended because of difficult international normalized ratio control (time in therapeutic range <30%) and severe haematuria, respectively. The patient was bedridden and had a PEG—placed 2 years before—and a permanent urinary catheter. On admission, blood pressure was 80/60 mmHg, heart rate was 118 b.p.m., oxygen saturation was 84%, and body temperature was 38.1 °C. Blood tests showed 19.95 × 10^9/L white blood cells, C-reactive protein 249.9 mg/dL, and creatinine 0.28 mg/dL. The calculated estimated glomerular filtration rate was 138 mL/min/1.73 m^2. On admission, high-sensitivity troponin I levels were 2.874 ng/mL (normal range <0.040 ng/mL). Chest X-rays documented bilateral interstitial pulmonary oedema and pleural effusion. Antibiotic therapy with levofloxacin and piperacillin–tazobactam was empirically started. However, the 12-lead electrocardiogram showed anterior ST-segment elevation with diffuse repolarization abnormalities (*Figure 1*), and ultra-sensitive serum troponin I concentrations were elevated (peak 3.589 ng/mL). Urgent coronary angiography revealed no significant epicardial coronary artery obstructions, while ventricular angiography showed apical ballooning typical of TTS (*Figure 2*). Because of respiratory failure and severe hypotension, the patient was treated in the coronary care unit with inotropes and orotracheal intubation. Echocardiography showed a left ventricular ejection fraction of 30%, with

Figure 1 A 12-lead electrocardiogram showing sinus tachycardia with anterior ST-segment elevation and diffuse repolarization abnormalities.

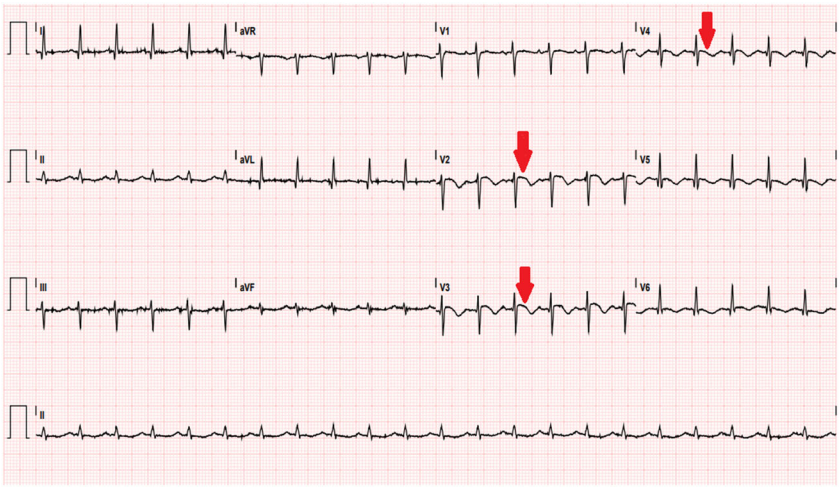

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Figure 2 Ventricular angiography showing apical ballooning.

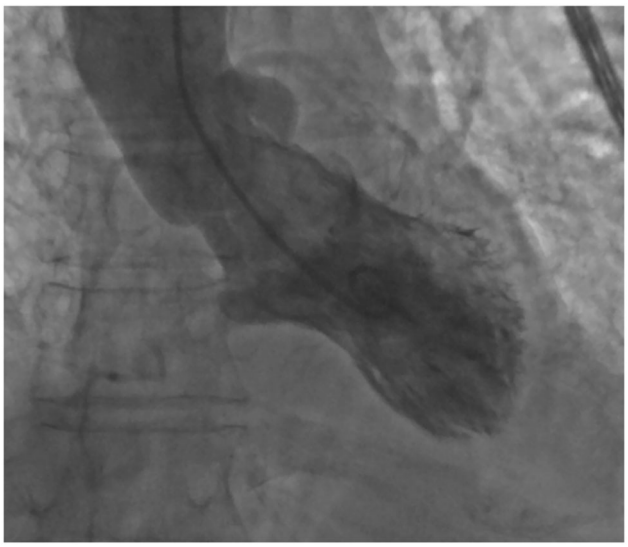
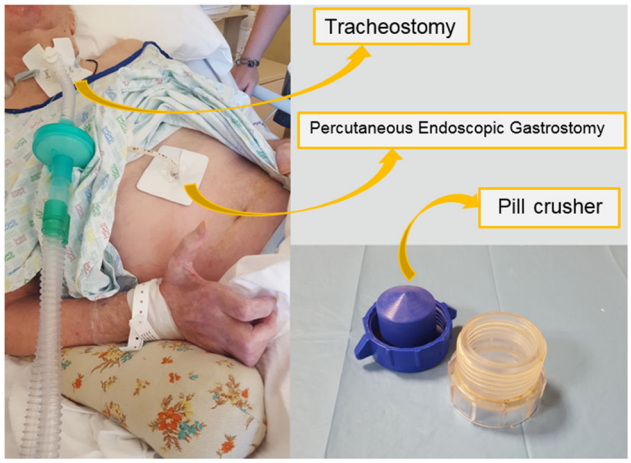


Figure 3 The patient underwent tracheostomy and had a permanent urinary catheter and percutaneous endoscopic gastrostomy (PEG). Edoxaban 30 mg daily (crushed with a dedicated tool) was administered with 10 mL of saline solution through the PEG.



akinesia of the mid and apical segments. The patient required prolonged respiratory support (5 days) followed by tracheostomy. AF at high ventricular rate occurred after coronary angiography. A rate control strategy was initiated along with low molecular weight heparin 4000 IU twice daily (CHA_2DS_2-VASc score: 4). Nevertheless, a long-term oral anticoagulation strategy was needed in order to avoid chronic subcutaneous administration of heparin by the caregivers. Edoxaban 30 mg (crushed pill) daily was administered based on the patient's weight of 58 kg.

Mean edoxaban plasma concentration–time profiles were measured as anti-Xa activity using the STA®-Liquid Anti-Xa assays and STA®-Edoxaban Calibrator (0–500 ng/mL) on a STA Compact Max® instrument (all from Diagnostica Stago, Asnières-sur-Seine, France). Edoxaban concentration was measured 2 h before and 2, 6, and 22 h after drug administration and compared with the pharmacokinetic profile of edoxaban 30 mg in healthy subjects (*Figure 3*).[10] An additional blood sample 2 h after edoxaban administration was performed 10 days later to assess the steady-state peak plasma concentration of edoxaban. In our patient, edoxaban peak plasma concentrations, both after the first administration and at steady state, were similar to the values reported for healthy subjects treated with edoxaban 30 mg (*Figure 3*).[10–14] However, the values of the pharmacokinetic parameters, analysed with a non-compartmental analysis by PKSolver module of the Excel software, showed that C_{max} and $AUC_{0\rightarrow t}$ were only slightly higher than those observed in healthy subjects,[15] while the half-life and observed clearance were significantly longer and lower, respectively, than in normal subjects[15] (*Table 1*). These results suggest great caution with the use of full dose of edoxaban (60 mg daily) in this kind of patients, as supra-normal edoxaban concentrations might occur even in the presence of apparently normal kidney and liver function.

After 7 days, echocardiography showed improved ejection fraction (45%). At the 30 day follow-up, only minimal and self-limiting haematuria (Bleeding Academic Research Consortium Type 1) was reported related to replacement of the urinary catheter, not requiring drug suspension; no thromboembolic event occurred.

Discussion

The use of direct oral anticoagulants has not been described in patients with PEG, and the pharmacokinetics of these agents in such patients is unknown. Our report is the first to describe the successful administration of edoxaban 30 mg daily (crushed and diluted in 10 mL of saline solution) through a PEG in a patient with advanced ALS, tracheostomy, atrial fibrillation, and acute heart failure (*Figure 4*). Edoxaban was ultimately chosen, given its good safety profile and its balanced renal and biliary clearance (respectively 50 and 50%).[10,12,13] This precaution was considered necessary because the Cockcroft–Gault estimate of renal function (based on serum creatinine, sex, body weight, and age) might have been distorted by the extremely low muscle mass of this totally bedridden patient with advanced ALS.[14]

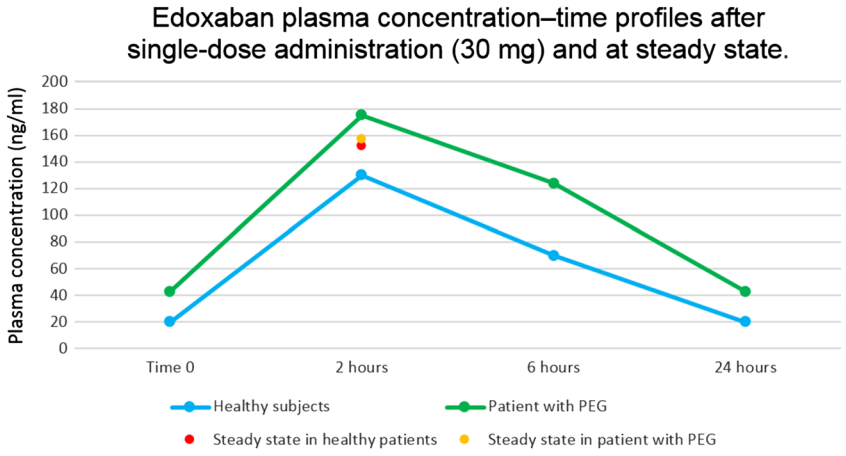
We support the evaluation of the effect on anticoagulation by using a calibrated quantitative anti-factor Xa assay,

Table 1 Pharmacokinetic parameters of the patient analysed with a non-compartmental analysis by PKSolver module of the Excel software

Parameter	Unit	Value
λ_z	1/h	0.062954806
$t_{1/2}$	h	11.01023459
t_{max}	h	2
C_{max}	ng/mL	178
t_{lag}	h	0
$C_{last\ obs}/C_{max}$		0.241573034
$AUC_{0\rightarrow t}$	ng/mL·h	2338
$AUC_{0\rightarrow\infty obs}$	ng/mL·h	3021.029666
$AUC_{0\rightarrow t/0\rightarrow\infty obs}$		0.773908322
$AUMC_{0\rightarrow\infty obs}$	ng/mL·h^2	45 848.23581
$MRT_{0\rightarrow\infty obs}$	h	15.17636067
V_z/F_{obs}	(mg)/(ng/mL)	0.15773838
$Clearance_{obs}$	(mg)/(ng/mL)/h	0.009930389

C_{max} and $AUC_{0\rightarrow t}$ were only slightly higher than those observed in healthy subjects,[15] while the half-life and observed clearance were considerably longer and lower, respectively, than in normal subjects.

Figure 4 The edoxaban plasma concentration after a single dose of edoxaban 30 mg in a patient with percutaneous endoscopic gastrostomy was compared with that reported by Parasrampuria and Truitt[10] in healthy subjects. Steady-state concentration after 10 days in the patient with percutaneous endoscopic gastrostomy was also assessed and compared with that reported by Chung *et al.*[11] in healthy subjects after 28 days (steady state is reached on average after 4 days[10]).



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which may help to inform clinical decisions in particular situations.

Although further data are needed to confirm that edoxaban administration via PEG is safe and effective, this case supports its feasibility and potential favourable profile to treat fragile, complex, co-morbid patients with AF, acute heart failure, advanced ALS, and PEG.

Conflict of interest

F.A. is a consultant or speaker for Actelion, Amgen, Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. The other authors do not have any conflicts of interest to declare.

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