Original article

ORal anticoagulants In fraGile patients with percutAneous endoscopic gastrostoMy and atrIal fibrillation: the (ORIGAMI) study

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Aims **The ORal anticoagulants In fraGile patients with percutAneous endoscopic gastrostoMy and atrIal fibrillation (ORIGAMI) study investigates the safety and efficacy of Edoxaban administered via PEG in patients with atrial fibrillation and a clinical indication for a long-term anticoagulation.**

Design **In this prospective, single-centre observational study, 12 PEG-treated patients with indication to anticoagulation will receive edoxaban via PEG and will be followed up to 6 months. Plasma antifactor Xa activity and edoxaban concentrations will be assessed. Thromboembolic (ischaemic stroke, systemic embolism, venous thromboembolism) and bleeding events (Bleeding Academic Research Consortium and Thrombolysis in Myocardial Infarction) will be recorded at 1 and 6 months.**

Preliminary results **A retrospective analysis of five atrial fibrillation cases undergoing PEG implantation at our Institution who received edoxaban via PEG showed plasma anti-FXa levels at a steady state of 146 ± 15 ng/ml, without major adverse event at a mean follow-up of 6 months.**

Conclusion **ORIGAMI prospectively investigates PEG-administration of edoxaban in PEG-treated patients requiring long-term anticoagulation. Our preliminary retrospective data support this route of DOAC administration.**

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Keywords: atrial fibrillation, direct oral anticoagulant, edoxaban, percutaneous endoscopic gastrostomy

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ORIGAMI rationale

Direct oral anticoagulants (DOACs) have a more predictable anticoagulant effect and a remarkably more favourable efficacy/safety ratio compared with vitamin K antagonists (VKAs) and thus are recommended over VKAs whenever possible to prevent stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation.[1] DOACs use, however, may require a multidisciplinary approach and careful balancing of individual risks and benefits when prescribed to fragile and comorbid patients in complex clinical settings. A relatively common issue in a fragile and complex clinical scenario is the need for drug administration through enteral feeding devices placed in patients who are unable to maintain adequate oral intake.

Of note, DOACs' bioavailability may be widely affected by different drug formulations or administration routes. Comparable bioavailability was observed in healthy adults for oral apixaban solution, tablet, nasogastric tube (NGT) administration of solution flushed with 5% dextrose in water (D5W) and infant formula, and NGT administration of crushed tablet suspension. Exposure was less when oral solution was administered via NGT with nutritional supplement, supporting alternative methods of administering apixaban that may be useful in certain clinical situations.[2] In healthy adults, crushed rivaroxaban 20 mg tablet was stable and displayed similar relative bioavailability compared to a whole tablet via oral administration when administered orally or via NGT.[3] Among Japanese stroke patients receiving rivaroxaban, significantly lower rivaroxaban concentrations were observed in those taking crushed rivaroxaban tablets compared with those receiving the whole tablets at the equivalent dose.[4] Following ingestion of rivaroxaban, the

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mean plasma concentration for the 20 mg dose of rivaroxaban in the atrial fibrillation population at 3 h is reported to be 246 ng/ml (5th–95th percentile: 172–361). The concentrations achieved by these patients are significantly lower than expected. Thus, two patients were shifted to apixaban and one to warfarin. Consequently, the authors have claimed that if rivaroxaban is administered via a gastric tube, it would be prudent to measure plasma concentrations to ensure that adequate exposure is achieved.[5] Dabigatran cannot be administered via gastric tubes due to the significantly increased bioavailability of dabigatran if it is administered without the capsule shell.[6]

Edoxaban has also shown similar exposure to that seen in healthy subjects receiving a single 60 mg dose, when crushed, mixed with water and administered via a nasogastric tube.[7]

Norton *et al.*[8] have shown that patients fed by NGT were at a greater risk of pulmonary aspiration, although there were no cases of inadvertent removal of a gastrostomy tube. Even if some phenomena such as the reduction in serum albumin concentration may represent a distinct effect, the changes in the various parameters suggest an overall impairment of nutritional state in the NGT group compared with the gastrostomy group.[8]

Percutaneous endoscopic gastrostomy (PEG) introduced in the 1980 s is a valid option, especially for long-term feeding. In the USA, PEG placements rose 14-fold from 15 000 in 1989 to 216 000 in 2000.[9] The most common indication is dysphagia secondary to neurological disorders (stroke, dementia, Parkinson's disease, amyotrophic lateral sclerosis or trauma), followed by stenosing oncological diseases involving the upper digestive tract.[10] Main advantages include correction of food deficits, recovery of body weight and improved quality of life.

A significant proportion of individuals with PEG have an indication to long-term anticoagulation, mainly atrial fibrillation. Although VKAs need regular monitoring and frequent dose adjustments, given multiple interactions with food, drugs and genetic background, DOACs do not require routine monitoring and their clinical benefit in patients with nonvalvular atrial fibrillation is well established.[1,11–14]

Inhibition of Factor Xa (FXa) is considered crucial for anticoagulation, as both the intrinsic and extrinsic pathways converge on FXa. Direct FXa inhibitors block free and bound FXa, the latter forming the prothrombinase complex that generates thrombin; indirect FXa inhibitors, such as low molecular weight heparin, inhibit only free FXa.[12,15] Among the DOACs, edoxaban is a direct, reversible, rapid FXa inhibitor with linear and predictable pharmacokinetics and an oral bioavailability of 62%. Maximum concentrations are reached within 1–2 h of intake, with 50% excreted by the kidneys. A pharmacodynamic in-vitro study showed direct dose-dependent direct inhibition of FXa activity.[15]

In a randomized, phase II trial versus warfarin involving 1146 atrial fibrillation patients, edoxaban (60 or 30 mg) was safer when given in a single daily dose than split into twice-daily dosing.[16] The phase III ENGAGE AF-TIMI 48 phase III trial demonstrated similar efficacy and superior safety of edoxaban 60 mg once daily (reduced to 30 mg in selected patients) compared with warfarin in atrial fibrillation patients.[17,18] A phase III study involving 8292 patients with acute venous thromboembolism also showed that once-daily edoxaban 60 mg (reduced to 30 mg in selected patients) was as effective as warfarin in preventing recurrent symptomatic venous thromboembolism, with significantly lower rates of bleeding.[17] Edoxaban, therefore, in single daily dosing, has demonstrated comparable efficacy to warfarin in atrial fibrillation and acute venous thromboembolism, with superior safety.[17,18] Moreover, it has been positively tested in oncological patients for the prevention of recurrent venous thromboembolism.[19]

Although the latest EHRA/ESC practical guide on non-VKA oral anticoagulants states that the administration in crushed form (e.g. via nasogastric tube) does not alter DOAC bioavailability,[1] systematic evidence supporting the use of DOACs via PEG is currently lacking.

Therefore, there is an unmet need to provide prospective evidence supporting the feasibility and anti-FXa effect of DOACs in patients with PEG.

Preliminary cases

According to guidelines, for nonvalvular atrial fibrillation and DVT/pulmonary embolism prevention and treatment, the recommended Edoxaban dose is 30 mg once daily in patients with one or more of the following clinical factors: moderate or severe renal impairment [creatinine clearance (CrCl) 15–50 ml/min]; concomitant use of the following P-glycoprotein inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole; and low body weight of 60 kg or less (https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf).[1]

Our group was the first to describe sustained anticoagulation through PEG-administration of edoxaban 30 mg daily (crushed and diluted in 10 ml of physiological saline solution) in a patient with advanced amyotrophic lateral sclerosis, tracheostomy, atrial fibrillation and recent acute heart failure.[20] Considering the clinical indication for PEG and for long-term anticoagulation, despite lack of definitive evidence supporting this route of administration, after multidisciplinary discussion, it was decided to maintain DOAC therapy via PEG, assessing the anticoagulant effect of edoxaban via anti-Xa activity measurements.[21]

Table 1 Clinical characteristics of preliminary cases

	Age (years)	Sex (Male)	Hyper-tension	Diabe-tes	Smoke	Dyslipi-daemia	CHADS-VASc	HAS-BLED	EF	CAD	Cystatin C clearance	ASA	P2Y 12	BBlockers	Acei/ ARB	Diuretic	Statin	Stroke history	Prior bleeding	Post bleeding	Dose (mg)	PEG indication
Patient 1	72	Y	Y	Y	N	N	4	1	35	N	64	N	N	Y	N	N	N	N	N	N	30	Dysphagia in ALS
Patient 2	72	Y	Y	Y	N	Y	4	3	72	Y	26	Y	Y	Y	N	Y	Y	N	N	N	30	Dysphagia in ALS
Patient 3	77	Y	N	N	N	N	2	1	61	N	46	N	N	N	N	N	N	N	N	N	30	Dysphagia in ALS
Patient 4	67	N	N	Y	N	N	4	2	63	N	17	N	N	Y	N	Y	N	N	N	N	30	Dysphagia in ALS
Patient 5	84	Y	Y	N	N	Y	5	2	61	Y	24	N	N	Y	N	Y	Y	N	N	N	30	Dysphagia in ALS
	74.4	80%	60%	60%	0%	40%	3.8	1.8	58.4	40	35.4	20%	20%	80%	0%	60%	40%	0%	0%	0%		

Acei/ARB, ACE inhibitors or angiotensin receptor blockers; ALS, amyotrophic lateral sclerosis; ASA, aspirin; BBlockers, beta blockers; CAD, coronary artery disease; EF, ejection fraction; N, no; P2Y12, P2Y12 platelet inhibitors; Y, yes.

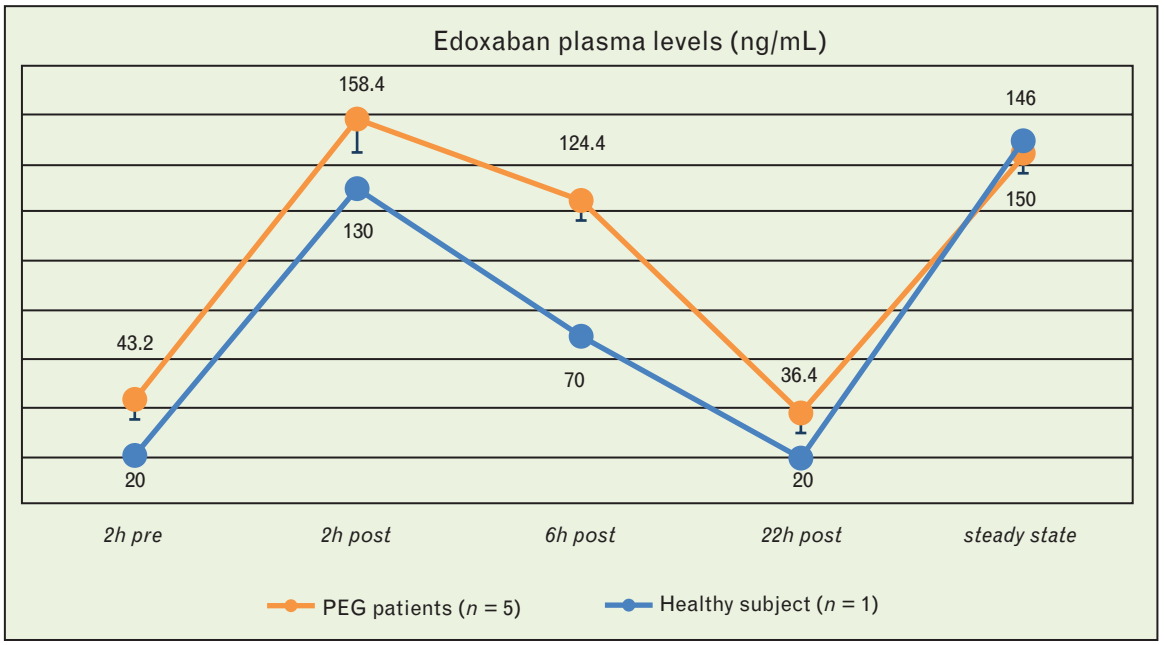
We subsequently screened all patients admitted to our Institution with an indication for PEG implantation from November 2018 to December 2019. Among these ($n = 95$), five in-hospital patients with atrial fibrillation, already on chronic DOAC treatment with edoxaban, underwent PEG implantation. In all five cases (Table 1), the DOAC was suspended 24 h before the procedure and restarted 48 h after PEG placement, according to our current institutional perioperative procedure. Clinical data are shown in Table 1.

Mean plasma edoxaban concentration–time profiles, 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), 2 h before and 2, 6, 22 h after drug administration and at the steady state, were compared with the pharmacokinetic profile of oral edoxaban 30 mg in a healthy individual (Fig. 1).

Edoxaban concentrations, at steady state, were similar in patients who received crushed edoxaban pills via PEG compared with a healthy individual (146 ± 15 vs. 150 ng/ml), supporting the anticoagulant effectiveness of this route of administration.

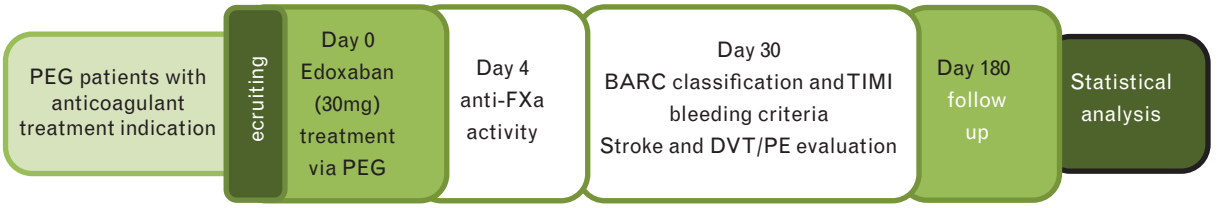
On the basis of these premises, the The ORal anticoagulants In fraGile patients with percutAneous endoscopic gastrostoMy and atrIal fibrillation (ORIGAMI) pilot study was designed.

Fig. 1



Edoxaban plasma concentrations after PEG administration of a single dose of Edoxaban 30 mg in five patients (orange line) and after oral administration in a healthy individual (blue line), expressed as mean ± standard deviation.

Fig. 2



ORIGAMI study design. BARC, Bleeding Academic Research Consortium; F, factor; PEG; percutaneous endoscopic gastrostomy; TIMI, Thrombolysis in Myocardial Infarction.

ORIGAMI design

Brief description

ORIGAMI is a prospective, single-centre, single-arm, observational study (ClinicalTrials.gov Identifier: NCT04271293) investigating the feasibility and anti-FXa effect of edoxaban PEG-administration in 12 PEG-treated patients with indication to anticoagulation (Fig. 2).

Patients, treatment and follow-up

Inclusion and exclusion criteria are listed in Table 2. Enrolled PEG-treated patients receive single daily doses of edoxaban, according to current guidelines, crushed and diluted in 10 ml of saline, administered via gastrostomy. Patients are followed for up to 6 months.

Pharmacokinetics/dynamics

Peripheral blood plasma anti-FXa activity and edoxaban concentrations are measured on day 4, using the STA-Liquid Anti-Xa assay and STA-Edoxaban Calibrator (0–500 ng/ml) on a STA Compact Max instrument (Diagnostica Stago, Asnières-sur-Seine, France). Values are compared with internal and established literature values.

Study endpoints

Although not powered for clinical outcomes, the primary endpoint of this pilot study is to describe the number of cardioembolic events consisting of stroke, systemic embolism or symptomatic relapse of deep vein thrombosis/pulmonary embolism in patients treated with Edoxaban via PEG at 1 month. The secondary endpoints include the description of bleeding events, according to the Bleeding Academic Research Consortium (BARC) scale and Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria, and the assessment of drug efficacy by measuring the antifactor Xa activity at 1 month. Primary and secondary endpoints will be re-evaluated at 6 months as well.

Table 2 Inclusion and exclusion criteria of the ORIGAMI study

Inclusion criteria	Exclusion criteria
Patients with PEG and clinical indication to long-term oral anticoagulant therapy	× Age < 18 years
Signed and dated informed consent	× Any clinical contraindication to Edoxaban
Atrial fibrillation	× Life expectancy < 30 days

Statistical analysis

The sample will be described in its clinical and demographic characteristics through descriptive statistics methods. In particular, the quantitative variables will be represented by minimum, maximum, range, average and standard deviation. The qualitative variables will be illustrated in tables of absolute frequencies and percentages. Kolmogorov–Smirnov test will be performed to verify the equality of continuous variables. The primary endpoint will be achieved by calculating the frequency (absolute and relative) of stroke events, systemic embolism and symptomatic recurrence of DVT/pulmonary embolism. The evaluation of adverse events will be assessed by calculating the incidence of bleeding described as the BARC scale and TIMI bleeding criteria. Pharmacokinetic parameters will be described with a noncompartmental analysis by means of the PKSolver module of the Excel software. SPSS and Graphpad 8.0 software will be used for statistical data analysis.

Conclusion

PEG-administration of DOACs in PEG-treated patients with an indication to anticoagulation has not been described previously. Our preliminary retrospective data support its feasibility and effectiveness. ORIGAMI is a single-arm, single-centre study designed to prospectively assess the feasibility and anti-FXa effect of edoxaban via PEG in patients requiring long-term anticoagulation. The results may reinforce the appropriateness of this route of DOAC administration to treat fragile, complex, comorbid patients.

Conflicts of interest

FA reports speaker/consultant fees from Amgen, Bayer, B-I, BMS/Pfizer and Daiichi-Sankyo, outside the present

work. AML received speaking honoraria from St. Jude Medical/Abbott and Bracco Imaging, outside the present work. FC reports receiving personal fees from Biotronic, Amgen, Astra Zeneca, Servier, Menarini, BMS, outside the present work. The other authors have nothing to declare.

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