MEDICINE UPDATE

Passi HealthCom

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Issue 12

Clinical impact of EGb 761® on the pharmacology of rivaroxaban in healthy individuals

Prologue

The primary pharmacological benefits of EGb 761®, a dry extract of *Ginkgo biloba* leaves, are improved mitochondrial function, neurogenesis and synaptogenesis stimulation, and improvement of microcirculation. It also protects against peroxidation of brain lipids and mitochondrial DNA. Several neurotransmitter pathways important in cognitive function are impacted by EGb 761®. Various pharmaceutical medications including the active ingredient EGb 761® are widely used to treat dementia and cognitive impairment. General herbal formulations made from *Ginkgo biloba* leaves are thought to interact, namely through cytochrome P-450 (CYP-450) enzymes and transporters (e.g., P-glycoprotein, P-gp). In the scientific literature, case studies on bleeding events connected to *Ginkgo biloba* preparations are often considered as indicators for pharmacodynamic interactions with antiplatelet medications (e.g., by inhibiting platelet-activating factor) or anticoagulants.

Rivaroxaban inhibits clot-bound Factor Xa as well as Factor Xa in the prothrombinase complex. It is licenced for the treatment and

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prevention of a number of thromboembolic diseases, including pulmonary embolism, stroke, and venous thromboembolism. Rivaroxaban is administered orally, and gets absorbed quickly. The amount of rivaroxaban that is excreted as an unmodified drug in the urine is around 36%. In light of this, a single-center trial was conducted to determine the efficacy and tolerability of rivaroxaban concurrently with single or multiple doses of EGb 761® in healthy individuals.

Aim

To assess the pharmacodynamics (PD), pharmacokinetics (PK), safety, and tolerability of rivaroxaban administered concomitantly with single and multiple doses of EGb 761®.

EGb 761® IS WIDELY USED TO TREAT DEMENTIA AND COGNITIVE IMPAIRMENT

KEY PHARMACOLOGICAL BENEFITS OF EGb 761® INCLUDE IMPROVED MITOCHONDRIAL FUNCTION, NEUROGENESIS AND SYNAPTOGENESIS STIMULATION, AND, IMPROVEMENT OF MICROCIRCULATION

Methodology

- This was a single-center, open-label, single-arm trial done with a total of 42 healthy individuals with a mean body mass index of 25.0 ± 2.6 kg/m^2, age of 46.7 ± 14.4 years, and body weight of 77.9 ± 13.1 kg
- Patients were treated on the basis of two treatment periods in this trial:
  - » Period 1: Subjects received a single dosage of 20 mg of rivaroxaban on Day 1

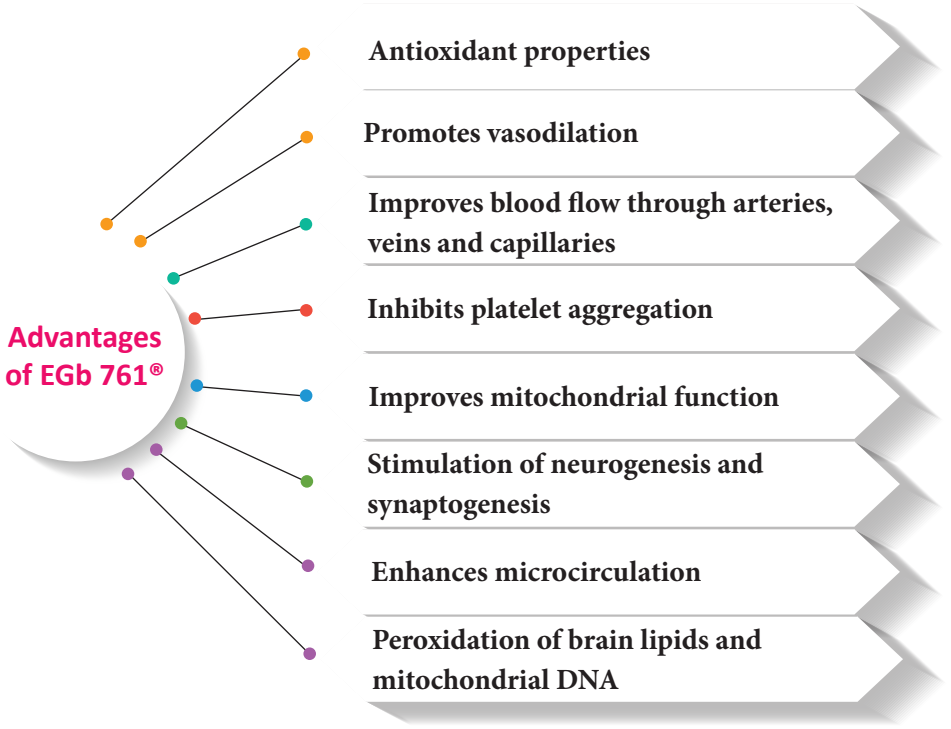

Table 1: Comparing the geometric mean ratio of the pharmacokinetics and pharmacodynamics parameters following a single (Day 8) or recurrent administration of 240 mg EGb 761® (Day 15) to the administration of rivaroxaban alone (Day 1)		
	Ratio Day 8/Day 1 (%)	**Ratio Day 15/Day 1 (%)**
Pharmacokinetics parameters of rivaroxaban		
C_{max}	97.97 (91.78–104.58)	96.78 (90.67–103.31)
$AUC_{0-\infty}$	98.55 (94.43–102.84)	97.82 (93.73–102.08)
Pharmacodynamics parameters of rivaroxaban		
E_{max}	98.19 (92.00–104.80)	99.78 (93.43–106.55)
$AUEC_{0-48}$	99.46 (93.63–105.66)	99.12 (93.25–105.35)
Abbreviations: C_{max}; maximum concentration, E_{max}; maximum effect, $AUC_{0-\infty}$; area under the concentration-time curve, $AUEC_{0-48}$; area under the effect curve.		

EGb 761® DOES NOT INTERACT WITH THE PHARMACOKINETICS AND PHARMACODYNAMICS OF RIVAROXABAN

  - » Period 2: 240 mg EGb 761® was taken once daily for 8 days (Day 8 to Day 15) and rivaroxaban was given on Day 8 and Day 15.
- On Day 1, Day 8, and Day 15, plasma concentrations of rivaroxaban and anti-Factor Xa (anti-FXa) activity were measured up to 48 hours after each rivaroxaban administration.

Results

- In comparison to rivaroxaban administered alone, geometric mean ratios (90% confidence intervals) for rivaroxaban administered concurrently with a single or multiple doses of EGb 761® were 97.97 and 96.78 for maximum concentration (C_{max}), 98.55 and 97.82 for area under the concentration-time curve ($AUC_{0-\infty}$) of rivaroxaban in plasma (primary endpoints), 98.19 and 99.78 for maximum effect (E_{max}), 99.46 and 99.12 for area under the effect curve ($AUEC_{0-48}$) (Table 1)
- No clinically significant abnormalities or hemorrhage-related adverse events were found in hematology or coagulation parameters
- The PK profiles of rivaroxaban were quite similar, whether given alone (Day 1), after EGb 761® in a single dosage (Day 8), or after EGb 761® in multiple doses (Day 15)
- There were no discernible differences in C_{max} and $AUC_{0-\infty}$ of rivaroxaban in plasma on Day 1, Day 8, or Day 15 (Table 1)
- There were no changes in any significant laboratory parameters, such as erythrocyte count, hemoglobin, hematocrit, platelet count, urine hemoglobin, or urine erythrocytes, after the treatment of rivaroxaban combined with EGb 761®
- No bleeding events or adverse events related to hemorrhages were observed.

Conclusion

- EGb 761® could be beneficial in not increasing the risk of bleeding events associated with concomitant intake of antiplatelet or anticoagulant drugs
- EGb 761® does not interact with the pharmacokinetics and pharmacodynamics of rivaroxaban
- The dosage is well-tolerated, efficient, and has no detrimental effects on the plasma concentrations of rivaroxaban and anti-Factor Xa activity in healthy people.