

Interaction study between antiplatelet agents, anticoagulants, thyroid replacement therapy and a bioavailable formulation of curcumin (Meriva®)

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Abstract. – **OBJECTIVE:** The objective of this clinical study is to evaluate possible interactions between antiplatelet agents, anticoagulants, thyroid hormone replacement therapy and a formulation of curcumin (Meriva®) that resulted effective for the complementary treatment of osteoarthritis.

PATIENTS AND METHODS: Interaction between antiplatelet agents and Meriva® was evaluated by measuring anti-platelet activity with the *in-vivo* bleeding-time (BT) in patients assuming acetylsalicylic acid or ticlopidine or clopidogrel from at least 2 years. The BT was evaluated before and after 10 days of supplementation with Meriva®.

The interaction between anticoagulants and Meriva® was evaluated in patients using warfarin or dabigatran for previous venous thrombosis. The INR level was evaluated before and after 10 days of supplementation with the curcumin formulation. Thyroid function tests in hypothyroid patients using LT4 replacement therapy (Eutirox®) were evaluated before and after 15 days of supplementation with Meriva®. Similarly, levels of glycemia and glycated hemoglobin were evaluated in diabetic patients in treatment with metformin, before and after 10 days of supplementation with the studied product.

RESULTS: After 10 days of supplementation with Meriva® the average BT value was not significantly different for patients assuming acetylsalicylic acid, ticlopidine or clopidogrel at standard dosages. Similarly, after 10 days of Meriva® treatment, the INR level in the two groups of patients assuming warfarin or dabigatran was not statistically different from that observed at baseline. In the analyzed patients assuming LT4 or metformin, no interactions between the therapy and Meriva® were observed.

CONCLUSIONS: Results from this non-interaction clinical study suggest that Meriva® does not interfere with the antiplatelet activity of the most common antiplatelet agents nor alters the INR values in stable patients assuming warfarin or dabigatran. Similarly, dosages of LT4 or metformin do not need to be adjusted in case of complementary treatment with Meriva®.

Key Words

Non-interaction study, Meriva®, Antiplatelet agents, Anticoagulants, Thyroid hormone replacement therapy, Curcumin, Osteoarthritis, Supplementation.

Introduction

Better medical care and improved living conditions have increased both health and life expectancy to over 80 years in developed countries^{1,2}. However, age is the main risk factor for major debilitating and life-threatening conditions, such as cardiovascular diseases and metabolic disorders, all of which are, therefore, increasing in prevalence^{3,4}. Anticoagulant and antiplatelet agents are frequently used for prevention and treatment of a wide range of cardiovascular and cerebrovascular diseases^{5,6}. Factors affecting the pharmacokinetics of anticoagulants and antiplatelet agents are important because deviations from their therapeutic window can result in bleedings due to over-anticoagulation or thrombosis because of under-anticoagulation⁷. In addition to interactions with drugs and over-the-counter medications, interactions with foods and herbs may affect the risk/benefit ratio of these agents, particularly of vitamin K antagonists (VKAs)⁸.

Hypothyroidism is one of the most common endocrine disorders affecting especially women and the elderly⁹. The prevalence of hypothyroidism in the developed countries is about 4-5%^{10,11}, whilst the prevalence of subclinical hypothyroidism - a condition characterized by high thyroid TSH and normal free T4 (fT4) levels - approaches 20% in women who are older than 60 years⁹. Interaction between levothyroxine (LT4) replacement therapy and complementary medicines may hinder the achievement of normal serum TSH, prevention of any symptoms of hypothyroidism, and patient well-being and satisfaction that are the main goals of thyroid hormone replacement therapy¹². Herbal remedies are increasingly used in Western countries. However, their interaction with synthetic drugs must be correctly assessed. In this clinical study, possible interactions between antiplatelet agents, anticoagulants, thyroid hormone replacement therapy, metformin and a proprietary highly bioavailable formulation of curcumin (Meriva®), were evaluated. Meriva® is a curcumin-phospholipid lecithin formulation that resulted to be highly absorbed and clinically effective in the complementary management and treatment of osteoarthritis¹³⁻¹⁵, in addition to several other conditions. Furthermore, in a "real-life scenario" study, the 4-months administration of the association of Meriva® and glucosamine resulted in a faster onset of action and improved outcomes than the administration of an association of chondroitin sulphate and glucosamine in patients with osteoarthritis¹⁶.

Patients and Methods

Patients

In this pilot non-interaction study, we evaluated the effect of Meriva® – used as an anti-inflammatory agent for the management of osteoarthritis with moderate symptoms – in different groups of patients assuming concomitantly antiplatelet agents, anticoagulants, thyroid hormone replacement therapy or metformin. Exclusion criteria included assumption of additional medical treatments.

Interaction between antiplatelet agents and Meriva® was evaluated by measuring anti-platelet activity with the *in-vivo* bleeding time (BT - 17) in patients assuming acetylsalicylic acid (Cardioaspirin®) or ticlopidine (Ticlid®) or clopidogrel (Plavix®) from at least 2 years. The BT was eval-

uated before and after 10 days of supplementation with Meriva® (2 tablets/day, corresponding to 1 g/day).

Interaction between anticoagulants and Meriva® was evaluated in patients using warfarin (Coumadin®) or dabigatran (Pradaxa®) for previous venous thrombosis at doses adequate to keep an International Normalized Ratio (INR) level of about 3. The INR level was evaluated before and after 10 days of supplementation with the preparation of curcumin (1 g/day Meriva® corresponding to 200 mg curcumin/day in two separate administrations).

Thyroid function tests in hypothyroid patients using LT4 replacement therapy (Eutirox®, 100 mg/day) were evaluated before and after 15 days of supplementation with Meriva® (1 g/day), in order to assess possible interactions between the thyroid replacement therapy and the studied preparation of curcumin.

Lastly, levels of glycemia (fasting blood sugar test) and glycated hemoglobin in diabetic male patients using metformin (500 mg twice daily for at least 1 year before the study) were evaluated before and after 10 days of supplementation with Meriva® (1 g/day).

Ethical Committee approval was granted as an observational study (registry) by the Research Ethics Committee of the IAPSS (International Agency For Pharma Standard Supplements) (PSS-17/212 7G).

In-vivo Blood Test

The BT is defined as the time taken for spontaneous bleeding to stop after an incision is made into the skin, generally onto the anterior surface of forearm. For this study, the BT test was performed with 2 small horizontal skin cuts (3 mm); excess blood was removed using a filter paper and the time was recorded until bleeding stop¹⁷. Environmental factors such as room temperature control (22°C) was considered in order to favour BT reliability^{18,19}. Normal BTs are usually between 2 and 10 min. In patients with severe platelet defects BT can be longer than 30 min.

Statistical Analysis

Descriptive statistics were used to analyze patients' demographic characteristics and baseline measurements. The Mann-Whitney U-test was used to compare BT before and after the supplementation period with Meriva®. All statistical analyses were performed with SPSS for Windows version 22 (Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA), and the significance level was set at 0.05.

Table I. Comparison of mean blood times (BTs) before and after the 10 days of supplementation with Meriva[®], by type of antiplatelet agent.

Antiplatelet agent	Patients	Blood time Minutes; SD	Range
Cardioaspirin [®]	18	5.54; 1.11	4.1-7.1
Cardioaspirin [®] +Meriva [®]		5.51; 1.21 ns	4-6.9
Ticlid [®]	16	5.22; 1.21	4.1-6.8
Ticlid [®] +Meriva [®]		5.23; 1.2 ns	4.11-6.9
Plavix [®]	10	5.28; 1.1	4.1-6.8
Plavix [®] +Meriva [®]		5.29; 1.12 ns	4.2-6.9

SD: standard deviation; ns: not statistically significant - Mann-Whitney U-test.

Results

Interaction between Antiplatelet Agents and Meriva[®]

Enrolled patients assumed standard antiplatelet treatments from at least 2 years with standard dosage in line with the British National Formulary (BNF). Studied patients had a mean age of 55.3 years (SD 2.5), whilst Body Mass Index was >22 and <26. As indicated in Table I, patients who assumed acetyl-salicylic acid (100 mg/day) were 18, patients that assumed ticlopidine (250 mg/day) were 16, whilst patients assuming clopidogrel (75 mg/day) were 10. Before supplementation, BTs were on average within normal values for all the three groups of patients. After 10 days of supplementation with Meriva[®] the average BT value was not significantly different for patients assuming acetylsalicylic acid (Table I). Comparable results were obtained with the groups of patients assuming ticlopidine or clopidogrel at standard dosages (Table I).

Interaction between anticoagulants and Meriva[®]

As indicated in Table II, patients that assumed warfarin were 14, of these 7 were females. On the other hand, patients assuming dabigatran were 16

(8 females). Before the 10 days of complementary treatment with Meriva[®] their INR was on average close to 3; after 10 days of Meriva[®] treatment, the INR level in the two groups of patients was not statistically different from that observed at baseline.

Interaction between thyroid hormone replacement therapy and Meriva[®]

As indicated in Table III, in the 15 patients assuming LT4 replacement therapy for hypothyroidism no interaction between the thyroid hormone replacement therapy and Meriva[®] was observed, following the 15 days of complementary administration of the studied formulation (1 g Meriva[®], i.e. 200 mg highly bioavailable curcumin/day in two separate administrations). Specifically, mean Free Thyroxine index (FT4I) was 5.30 at baseline and 5.32 following the 15 days of complementary administration.

In the 15 diabetic patients no interaction between metformin and Meriva[®] was observed, Specifically, no statistically significant difference in mean levels of glycemia (mmol/L) and glycated hemoglobin (%) were observed before and after 10 days of complementary administration of the studied formulation (Table IV).

Table II. Comparison of mean INR levels before and after the 10 days of supplementation with Meriva[®], by type of anticoagulant.

Anticoagulant	Patients	INR level; SD	Platelet
Coumadin [®]	14	2.91; 0.22	NV
Coumadin [®] +Meriva [®]		2.9; 0.19 ns	NV
Praxada [®]	16	2.88; 0.16	NV
Praxada [®] +Meriva [®]		2.87; 0.1 ns	NV

SD: standard deviation; NV: Normal value; ns= not statistically significant.

Table III. Comparison of mean values of different thyroid function tests at baseline (T0) and after the 15 days (T15d) of supplementation with Meriva®, by function test.

Test	Abbreviation	Normal Ranges	T0	T15d	p-value
Serum thyroxine	T4	4.6-12 µg/dL	5.40	5.38	ns
Free thyroxine fraction	FT4F	0.03-0.005%	0.32	0.33	ns
Free thyroxine	FT4	0.7-1.9 ng/dL	1.22	1.24	ns
Free thyroxine index	FT4I	4-11	5.30	5.32	ns
Serum triiodothyronine	T3	80-180 ng/dL	166	168	ns

ns: not statistically significant.

Discussion

Interactions between herbal medicines and synthetic drugs exist and can have serious clinical consequences²⁰. In particular, medications with anticoagulant or antiplatelet activity are most likely to have interactions with herbal medicines²¹. Specifically, compared with other cardiovascular drugs, patients given anticoagulant agents are at a higher risk of suffering from potentially harmful drug interactions when co-administered with herbal drugs²². Similarly, there are foods, herbs and other substances such as calcium and iron supplements, proton pump inhibitors, aluminum, NSAIDs, etc., that can interfere with absorption of LT4²³, leading to severe adverse effects.

In this pilot registry study, Meriva® showed no pharmacological interactions with antiplatelet agents, anticoagulants and thyroid replacement therapy, at least at the dosages routinely used as complementary support in different conditions. These results provide some guidance to health care professionals on the complementary treatment with Meriva® in patients with osteoarthritis assuming antiplatelet agents, anticoagulants or LT4 replacement therapy. This is of particular relevance when considering the widespread use of these drugs for the

prevention of very common cardiovascular and metabolic diseases such as thrombotic events or hypothyroidism.

Of note, besides traditional anticoagulants that include VKAs (warfarin or coumadin) and heparins, since the 2000s a number of new agents have been introduced - collectively referred to as the novel oral anticoagulants (NOACs) - that directly inhibit factor Xa (e.g., rivaroxaban or apixaban) or factor IIa (e.g., dabigatran)⁶. Therefore, further interaction studies should be also looking at possible interactions between food, botanical extracts and these new agents as already done with Meriva®. Similar to the core study, in an extension study, interaction between metformin and the preparation of curcumin was evaluated in 15 male patients with diabetes. No significant variations were observed in the levels of glycemia (fasting blood sugar test) and glycated hemoglobin in the enrolled patients that were in stable metabolic control after 10 days of treatment with Meriva®. These findings lend support to the use of Meriva® in different clinical or sub-clinical conditions.^{24,25}

Conclusions

We suggest that Meriva® does not interfere with the antiplatelet activity of the most common antiplatelet agents nor alters the INR values in stable patients assuming warfarin or dabigatran. Similarly, due to lack of interactions, dosages of LT4 and metformin do not need to be adjusted in case of complementary treatment with Meriva®.

Table IV. Comparison of mean levels of glycemia (fasting blood sugar test) and glycated hemoglobin at baseline (T0) and after the 10 days (T10d) of supplementation with Meriva®.

Test	T0	T10d	p-value
Glycemia (fasting blood sugar test)	5.40	5.38	ns
Glycated hemoglobin	0.32	0.33	ns

ns: not statistically significant.

Conflict of Interests

AR and ST are employees of Indena SpA. LG is a consultant of Indena SpA, Milan, Italy

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