CORRELATION BETWEEN DIZZINESS AND LEVOTHYROXINE INEFFICACY: NEW INSIGHTS FROM THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) DATABASE

Vera Battini[1], Faizan Mazhar[1], Giulia Mosini[1], Andrea Vicenzi[2], Emilio Clementi[3], Sonia Radice[1], Carla Carnovale[1]

[1]Unit of Clinical Pharmacology Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università di Milan, Milan - Italy, [2]Emergency Department University Hospital "Luigi Sacco", University of Milan ASST Fatebenefratelli-Sacco, Milan - Italy, [3]Unit of Clinical Pharmacology Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università di Milan, Scientific Institute, IRCCS E. Medea, Bosisio Parini LC, Milan - Italy

Introduction: Long-standing decompensated hypothyroidism or suboptimal treatment of hypothyroidism may lead to myxedema coma, a rare life-threatening clinical condition associated with a high mortality rate. Hypothyroid symptoms increase with the severity of the hypothyroidism except in the older patients, who often present with minimal or atypical symptoms. Moreover, signs and symptoms of hypothyroidism are easily mistaken for other common disorders in old age and the diagnosis of myxedema coma is often delayed. Previous evidence showed that "dizziness" is the patient's primary reason for Emergency Department (ED) visit leading to a diagnosis of myxedema coma. Treatment guidelines recommend Thyroid-Stimulating Hormone (TSH) and Free Thyroxine (FT4) concentrations should be monitored 4–6weeks after therapy initiation, dose changes, or any other events that may be expected to alter thyroid functioning or therapy efficacy. Moreover, according to Italian Society of Endocrinology and the Italian Thyroid Association a significant proportion of hypothyroid patients are not at target or show fluctuation over time in their TSH values. However. a specific suggestion for TSH levels monitoring in case of dizziness, vertigo, fatigue is not reported.

Material and methods: Here, we present our experience with four hypothyroid patients [mean age (S.D) = 56± 6.73] visited to the ED at our centre with a chief complaint of dizziness and fatigue. All patients' medical history was unremarkable except hypothyroidism. All patient had been receiving stable doses of levothyroxine for the management of hypothyroidism. Three out of 4patients were diagnosed with "labyrinthitis" while in one patient betahistine was subsequently initiated. None of the patients referred to endocrinology for the assessment of TSH and FT4concentrations. With the aim to assess this issue further, we conducted a case/non-case analysis of US Food and Drug Administration Adverse Event Reporting System (FAERS) database. We retrieved data without any time restriction till 12th April 2019, concerning reports of dizziness, vertigo and fatigue associated with levothyroxine and levothyroxine sodium. In order to reduce risk of bias, we excluded all reports with any other suspect drug.

Results: 29,836cases of suspected AE related to levothyroxine were reported. After excluding all cases with any other suspect or concomitant drug, 23,310 were retained for the analysis. Reporting odds ratio (ROR) with 95% confidence interval (CI) for the pertinent adverse events were as follows: dizziness [n = 1855; ROR: 2.40 (95% CI 2.29-2.51)]; vertigo [n = 1952; ROR: 21.15(20.18-22.17)]; and fatigue [n = 6148; ROR: 6.84(6.65-7.03)]. Drilling down into further detail of the 23,310 cases, preferred term (PT) "increase of TSH" was reported in 2,144cases along with pertinent symptoms of hypothyroidism interest [dizziness (n= 289), vertigo (n=333) and fatigue (n=969)]. Of note, co-PT 'drug inefficacy' was recorded only in 18cases, suggesting a reporter suspected suboptimal treatment.

Discussion and conclusion: FAERS analysis suggests that physicians tend to report manifestation of hypothyroidism as an ADR cause by levothyroxine. According to our experience, hypothyroidism patients visiting ED with the sign and symptoms evident for the suboptimal levothyroxine treatment were more likely to be mistaken for a new medication condition, and consequently a new medication is prescribed. Currently available information needs to be expanded with more clinical and pharmacological data, especially in view of the large use of levothyroxine. Valuable information might be provided by monitoring TSH levels and physicians should take into account these symptoms, although rare, in order to adjust dosage in patient referring dizziness, vertigo or fatigue.