Drug interactions with levothyroxine therapy: tablets versus oral liquid formulations

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Background

Several medications may interact with levothyroxine (LT4) and impair its intestinal absorption. A new oral liquid formulation of LT4 showed promising results in overcoming LT4 malabsorption due to interacting medications. Namely, previous studies reported a significant reduction of thyroid-stimulating hormone (TSH) measurements in patients who switched from tablets to oral liquid LT4 formulations. As well, variability of TSH circulating levels was remarkably less pronounced with LT4 liquid formulation, resulting in significant clinical benefits especially for elderly patients. Nevertheless, these studies were limited to local and/or special populations and/or their findings stem from explorative statistical analyses which only partly considered the role of confounding. We therefore aim to analyse the Italian general practice patients exposed to oral liquid vs. tablets LT4 from 2012–2015, in terms of variation of TSH levels, and prescribed daily dosages (PDDs) of LT4 before and during potential drug–drug interactions (DDI).

Methods

We adopted the Italian general practice Health Search Database (HSD). The study population included individuals aged 18 years and older with at least one LT4 prescription from 2012 to 2015 (entry date), and at least one year of clinical history recorded in HSD. The incident prescription of interacting medications (e.g., proton pump inhibitors, calcium carbonate, phenytoin) was the study index date. A pre-post analysis was carried out using a self-controlled study design. To test the association between the increase of TSH, LT4 PDDs, and use of liquid or tablets formulations, we estimated a multivariable generalized linear latent models for data pairs. By doing so, we were able to assess the variations of TSH and PDDs values in the period preceding or coexistent the exposure to potential DDIs.

Results

Overall, 3673 users of LT4 formed the study cohort (84.1% women, mean age: 56.1, SD: 16.54). Of patient, 3643 and 54 were exposed to tablets or liquid formulations, while 66 switched in between on the index date. The most used interacting medications mainly encompassed proton pump inhibitors (n=3233 (88%)), and calcium/iron carbonates (n=558 (15.2%)). TSH variability on the entry date was greater in users of liquid LT4 than those prescribed with tablets (interquartile difference: 3.8 vs. 3.0). The incidence rate ratio (IRR) comparing users of liquid vs. tablets formulations in terms of TSH values before and during the period of exposure to potential DDI, showed no significant difference. Instead, the PDDs of oral liquid LT4 decreased before the potential DDI (IRR=0.83; 95% CI: 0.76-0.90) as well as during the exposure period compared with those prescribed with tablets formulation (IRR=0.84; 95% CI: 0.77-0.92).

Conclusions

The co-prescription of LT4 and potentially interacting drugs results in an increased use of

LT4 tablets, which likely explains the absence of association with TSH increase. Of note, the fact that we observed higher variability of TSH with liquid than tablets formulations may suggest that more complex and/or severe patients were likely channelled towards liquid LT4. Nevertheless, the use of oral liquid LT4 was associated with a significant reduction of PDDs. Clinicians should carefully consider these findings to tailor patients therapy whenever co-prescription of LT4 and potentially interacting drugs is needed.

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