Levothyrox formula change: "bioequivalent" doesn't mean "switchable"

CATHERINE HILL, MARTIN SCHLUMBERGER
INSTITUT GUSTAVE ROUSSY, VILLEJUIF, FRANCE

The French medicines agency asked Merck to improve the stability of its levothyroxine formulation (Levothyrox®). The pharmaceutical company complied by introducing a new formulation to the market in the spring of 2017. At this time, Levothyrox® was the only brand of levothyroxine as a solid formulation on the French market. It was prescribed for approximately 3 million patients. Numerous unwanted side-effects of the new formulation were notified shortly after its introduction. The French authorities and the drug company downplayed the expressed concerns, which they attributed to a miscommunication with the patients. In 2019, a publication[1] suggested that the statistical analysis of the bioequivalence (BE) study comparing the two formulations of Levothyrox®, as conducted by Merck,[2] did not suffice to ensure the switchability of the old formulation (OF) with the new formulation (NF); the latter intended to replace the former. For transparency reasons, the raw (individual subject) data from this BE trial were released online by the French Authorities.[3,4] This allowed us to deploy this complicated problem as a tutorial presentation.[5]

Merck had studied the BE of its two formulations of levothyroxine by giving them, successively and in a random order, to 204 healthy volunteers. Nineteen blood samples per subject were taken: three before drug administration (30 minutes, 15 minutes and immediately before) and 16 commencing 30 minutes after drug administration and final samples taken 72 hours later (t72). For each subject and each formulation, the three plasma thyroxine concentrations obtained before Levothyrox® administration were averaged to indicate the basal endogenous concentration of levothyroxine.

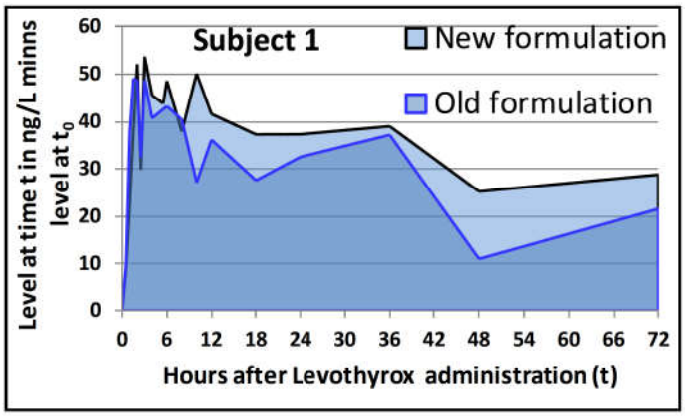


Figure 1: Thyroxine concentration (ng/mL) at time t minus basal concentration for the first subject.

This baseline levothyroxine concentration was subtracted from measured concentrations following administration of the two Levothyrox® formulations. This difference indicated the net contribution of the drug (in OF and NF) to plasma levothyroxine concentrations. **Figure 1** illustrates the plasma thyroxine concentration at the 16 sampling times for the first subject, after subtraction of basal concentrations, as recommended by the European (EU) Authorities. From these derived data, one can compute, for each formulation and each subject, the Area Under the Curve (AUC) of thyroxine concentrations. This area directly measures the relative bioavailability of levothyroxine for each formulation.

Analysis of the average bioavailability, as conducted by Merck, is neither conclusive nor sufficient

Merck submitted to the French agency an analysis, comparing the average levothyroxine bioavailability of the NF, for the 204 subjects, to the average bioavailability of the OF in the same 204 subjects. They concluded that the two formulations were, in average, bioequivalent. This data analysis did not take into account the fact that an irreversible replacement of the OF by the NF was going to be imposed on almost three million French patients. Merck simply followed the European guideline on BE. However, they ignored the key consideration that this guideline is not intended to demonstrate, for individual subjects, switchability between two formulations, but only the prescribability of a new product (formulation). Prescribability refers to the choice between two possible marketed products: typically between a new generic and the pioneer product when initiating a treatment in a naïve patient. Switchability differs fundamentally: for this French situation, it refers to the irreversible substitution in a patient who is already being treated and well controlled with the OF by the NF. The EU guideline does not address formulation switchability to support a substitution – simply because substitution policy is a national issue, not one regulated by the EU. A more appropriate trial would have involved comparing the individual subject AUC for the NF and OF. To conclude an individual BE of the two formulations (as opposed to the average BE) the differences between the two formulations must be close to zero for each subject. **Figure 1** shows the time course of levothyroxine concentration with each formulation for the first subject in the study, as a specimen example.

(continued on page 20)

Levothyrox® formula change... *(continued from page 19)*

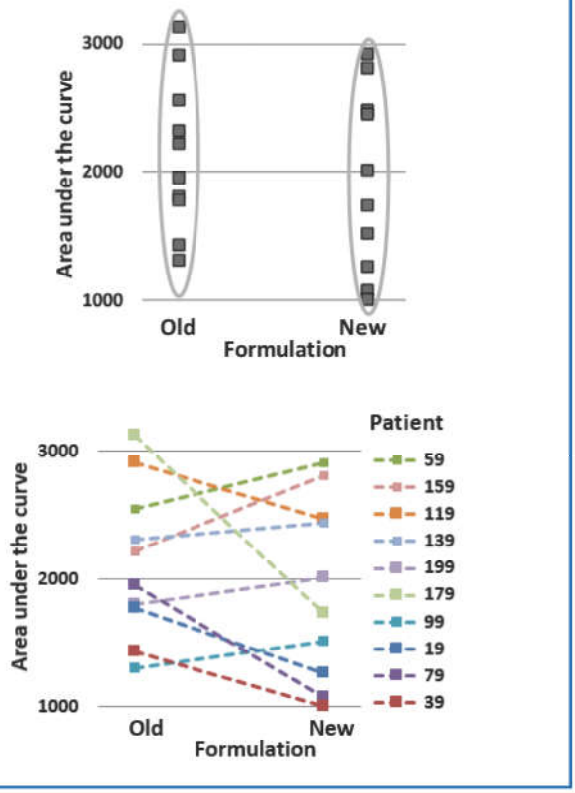
Patient's number	Old formulation a	New formulation b	Difference (b- a)/a
19	1772	1265	-29%
39	1429	1003	-30%
59	2556	2914	+14%
79	1952	1073	-45%
99	1306	1515	+16%
119	2913	2472	-15%
139	2316	2446	+6%
159	2218	2807	+27%
179	3122	1729	-45%
199	1800	2008	+12%

Table: Values of area under the curve from the basal value, for 10 subjects selected every 20 subjects starting from a number taken at random between 1 and 20.

The **Table** and **Figure 2** present the AUC data for 10 patients. **Figure 2A** shows the data as analysed by the drug company, i.e. comparing the two averages. **Figure 2B** shows the same data, taking the subjects into consideration.

Considering the 204 subjects, the individual differences between the two formulations for the AUC ranged from -89 % to +100 % (plus one extreme value of 369 %), demonstrating an important level of individual variability for the relative bioavailability of the two formulations from one subject to another. **Figure 3** shows that, with the new formulation, 26 % of the subjects were underdosed by at least 15%, and 27 % were overdosed by at least 15%; 2.9 % of subjects were underdosed by at least 45% and 11% were overdosed by at least 45%. This analysis demonstrates the importance of within-subject variability in considering the relative bioavailability of the two formulations. The daily dose of levothyroxine, generally between 50 and 150 ug, is usually adjusted by steps of 25 or even 12.5 ug/d; in this respect, a sudden overdose of 45% is indeed considerable.

Figure 2: Bioavailability of levothyroxine in old and new formulations, as measured by the area under the curve, for subject 19 selected at random between 1 and 20, and 1 in every 20 subjects afterwards. To the left, data as analysed by Merck, to the right taking the subjects into account.



In their second article,[6] Concordet et al explained that by planning an average BE trial with more than 200 subjects, Merck admitted knowing, à priori, that there was a large intra-individual variability for its formulations. Indeed, most BE trials are conducted with a number of subjects ranging between 24 and 36, this number being generally sufficient to demonstrate an average BE. On the other hand, when the intra-subject variability is large, a greater number of subjects is needed to successfully demonstrate an average BE. This is because it is the confidence interval of the difference (or of the AUC ratio) of the two formulations which must meet the regulatory requirements – and the confidence interval, all other things being equal, becomes smaller as the number of subjects used in the trial increases. The EU regulatory authorities set the limits, within which the calculated confidence intervals must be enclosed. For a drug with a narrow therapeutic margin, like Levothyrox®, the limits are set at -10% /+ 11%. This a priori interval is narrower than that used for most drugs, for which they are set at -20 /+ 25%. This narrowing of the limits is said by the EU Authorities to be a precautionary measure for drugs with narrow therapeutic margins. In fact, it is not. By simply increasing the number of subjects, it is always possible to encompass between these limits, when the difference between the means of the formulations does not exceed 10%. From a patient perspective, this is unacceptable. As Figure 3 illustrates, for many patients the difference can reach 45% even when the means are practically equal. It is specifically to avoid this situation that the FDA now requires – in its guideline on levothyroxine[7] – that, in comparing the bioavailability of two formulations of levothyroxine, not only the means of the two formulations, but also their intra-individual variances must be compared. This requires the adoption of a more complicated experimental design, involving repeating twice the administration of each formulation. It is then possible to evaluate the intra-individual variance for each formulation. It is our firm opinion that such a protocol must now be implemented as an essential requirement at European level. We acknowledge that this BE study in healthy volunteers does not itself provide evidence that the symptoms experienced

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Levothyrox® formula change... *(continued from page 20)*

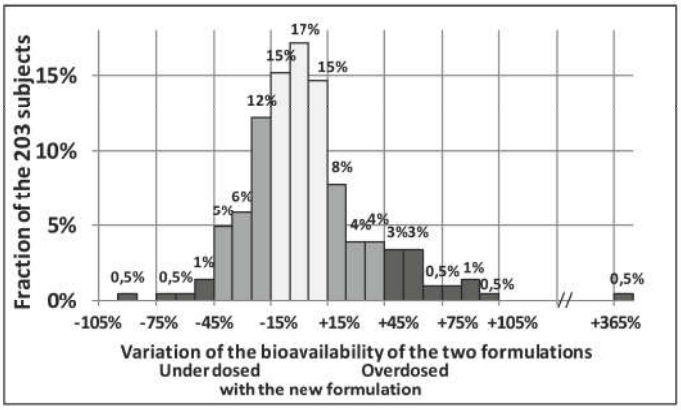

Figure 3: Distribution of differences in bioavailability between the two formulations of Levothyrox for the 204 subjects. For 17 % of the subjects, the two bioavailabilities differed by less than 5 %.

by many patients, after introduction of the new formulation, were related to an over- or an under-dosing of the drug. However, the comparison of the bioavailabilities of the two formulations within each subject reveals that some individuals may be facing a large change in drug exposure with the new formulation. The data therefore support the hypothesis of a causal relationship between the adverse effects and the formulation switch from the OF to the NF, in at least some patients.

Instead of being warned of the possible difference in the bioavailability of the two formulations and advised to consult their doctor in case of any concerns, patients who complained of adverse effects were told that the problem was "only a communication problem" – or even a "nocebo effect".

Final comment on our request for information from Merck

We wrote to the first author of the Merck' paper describing the analysis conducted by the company,[2] querying that analysis. The reply was that the analysis had been conducted "as required by the Authorities", and this is confirmed by Concordet et al.[1] It therefore seems that the Authorities encouraged Merck to correctly answer an irrelevant question – the relevant questions being: "is it acceptable to switch 3 million stable / euthyroid patients from the old to the new formulation and what test should be done to support this switch?"

There have been other occasions when a drug company has placed responsibility on the requirements of the regulatory authorities: for instance, Sanofi explained its lack of information on the teratogenicity of sodium valproate – despite numerous signals demonstrating an 11% risk of malformation and a 30% to 40% risk of neurodevelopmental problems - by stating that it followed the recommendations from the regulatory agency.[8]

And Merck persists, even now, in this strategy by stating that "the equivalence of the two formulations has been studied according to the approach required by the European authorities"– but omitting to acknowledge that a guideline is not set in tablets of stone. It is a non-binding document, which aims at facilitating European harmonization in BE studies. Any company can perfectly well adopt an alternative protocol, provided it is scientifically justified and when, manifestly, it is in the best interests of future patients.

Conclusion

We conclude that Merck has not demonstrated that the substitution of its OF by its NF, in a monopoly situation, has been done with adequate safety conditions for a majority of patients in mind. We propose that the European Authorities now seriously consider the American guideline for adoption in the EU. Had it been implemented in this case, it would very probably have confirmed that the two formulations were bioequivalent "on average", but would also have demonstrated that they were not "switchable".

References:

1 Concordet D, Gandia P, Montastruc JL, et al. *Levothyrox new and old formulations: are they switchable for millions of patients?* Clin Pharmacokinet. 2019 Apr 4. doi: 10.1007/s40262-019- 00747-3.

2 Gottwald-Hostalek U, Uhl W, Wolna P, Kahaly GJ. *New levothyroxine formulation meeting 95-105% specification over the whole shelf-life: results from two pharmacokinetic trials.* Curr Med Res Opin. 2017;33:169-74.

3 Agence nationale du médicament et des produits de santé. *Levothyrox.* http://bit.ly/2WpwycZ

4 Agence nationale du médicament et des produits de santé. *Levothyrox. Bioequivalence trial of new Levothyrox formulation versus old formulation.* http://bit.ly/2IkcM8R (page 442)

5 Hill C, Schlumberger M. *Les deux formules du Levothyrox sont-elles bioéquivalentes ?* La Revue du Practicien, oct. 2019, 2°10 ;69(8) ;831-37

6 Concordet D, Gandia P, Montastruc JL, et al. *Why Were More Than 200 Subjects Required to Demonstrate the Bioequivalence of a New Formulation of Levothyroxine with an Old One?* doi: 10.1007/s40262-019-00812-x

7 Food and Drug Administration. *Draft Guidance on Levothyroxine Sodium.* November 2018. https://bit.ly/3lAkyxU

8 Agence nationale du médicament et des produits de santé. *Valproate et dérivés : contre-indication pendant la grossesse (sauf situations exceptionnelles) et programme de prévention des grossesses.* Lettre aux professionnels de santé, ANSM 2018. http://bit.ly/2EPGNw3