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Leflunomide or Teriflunomide
falsely decreased ionised calcium

Quick Read

Leflunomide and its active metabolite teriflunomide interfere with the laboratory tests used to determine ionised calcium levels producing falsely decreased results. When in doubt the total serum calcium concentration should be determined as adjusted for total albumin.

Leflunomide is indicated for the treatment of adult patients with active psoriatic arthritis or with active rheumatoid arthritis as a disease-modifying anti-rheumatic drug (DMARD). In vivo it is rapidly and almost completely metabolized into A77 1726 or teriflunomide, the active metabolite which is presumed to be responsible for the drug's therapeutic effect. Teriflunomide selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which is necessary for de novo synthesis of pyrimidine in cell multiplication processes. Medicinal products containing teriflunomide are indicated for the treatment of adult patients with relapsing-remitting multiple sclerosis (MS). The exact mechanism of teriflunomide's therapeutic effect in MS is not totally known but is presumably mediated by a decrease in the number of lymphocytes.

Within the scope of its routine pharmacovigilance activities Finland detected a safety signal (potential problem) based on a report of a serious case of a patient on leflunomide who had to receive multiple calcium infusions. The cause underlying the patient's hypocalcaemia remained unknown until it was found that the low calcium levels were due to laboratory test interference.

Another 21 cases with leflunomide and 11 cases with teriflunomide of decreased calcium levels were meanwhile identified. With the exception of six literature cases reported by Verhoeven *et al.*,[1] none reported lab test interference, though it is possible that it did occur in some.

Verhoeven *et al.* observed this event in six patients who had received a renal transplant and who had been treated off label for Polyomavirus-associated nephropathy (PVAN), a serious complication of kidney transplantation.[1] The precise mechanism of interference of leflunomide or teriflunomide is not clear but is probably related to the absence of a protective cellophane membrane on the blood gas analyser (*Rapidlab-1265*), which facilitates direct contact between teriflunomide and the selective calcium ion electrode.

Hubeek *et al.* have also described in the literature the occurrence of falsely decreased ionised calcium levels in patients on teriflunomide[2]; the mechanism here probably being dependent on the type of blood gas analyser as well.

Verhoeven *et al.* argue that serum albumin levels should be determined to adjust for calcium concentration in patients treated with leflunomide, in order to prevent errors in calcium homeostasis interpretation and hence to prevent any unnecessary treatments.

Taking into account the data available on the European database EudraVigilance and in the literature, the Pharmacovigilance Risk Assessment Committee (PRAC) at EMA (European Medicines Agency) has recommended an update in the Summary of the Product's Characteristics (SmPC) and Patient Information Leaflet (PIL) of the medicines containing teriflunomide or leflunomide:[3]

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Summary of the Product's Characteristics (SmPC)

4.4 - Special warning and precautions for use

Interference with determination of ionised calcium levels

The measurement of ionised calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionised calcium analyser used (e.g. blood gas analyser). Therefore, the plausibility of observed decreased ionised calcium levels needs to be questioned in patients under treatment with leflunomide or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.

Elsa de Fátima Costa

References

[1] *Verhoeven Y et al. Falsely decreased ionized calcium levels in kidney transplant recipients with polyomavirus-associated nephropathy treated with leflunomide. Transpl Int. 2015 Jul;28(7):874-5.*

[2] *Hubeek I et al. Falsely decreased ionized calcium results due to analytical interference by teriflunomide, the active metabolite of leflunomide (Arava®). Clin Chem Lab Med. 2012 Feb 10;50(4):755-6.*

[3] *PRAC recomendations on safety signals – Adopted at the 3-6 April 2017 PRAC meeting: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500226577.pdf*

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Medicinal product (DCI)	Click on the links (in Portuguese)
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Educational Materials published in the Infomed product information webpage

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Compiled by Rita Dias

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA, the European Medicines Agency, is undertaking a survey to better understand levels of knowledge on adverse drug reaction (ADR) reporting processes and how those reactions actually are reported by patients/consumers and by healthcare professionals.

The results will be analysed by EMA and an aggregate report will be delivered to the European Commission (DG SANTE) and later disseminated to the public in general.

The survey is available in Portuguese. It contains 10 questions and should take 5 to 10 minutes of your time. From the Boletim's experience it may be filled out in as little as 3 to 4 minutes.

Take part now by clicking here.

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics