Press release – 20th August 2020

Two rare mutations responsible for the toxicity of treatment for scabies

Ivermectin is a drug that is widely used to treat parasitic diseases. Initially developed during the 1980s for veterinary use, it was then adapted to deal with human parasites in tropical countries. Considered to be safe in humans, it is now used to treat scabies and head lice. INRAE scientists working with clinicians and biologists at Toulouse and Montpellier University Hospitals have reported on a boy treated with ivermectin to prevent scabies who was found to present with rare mutations associated with its acute toxicity. Their findings were published on 20th August 2020 in the *New England Journal of Medicine*.

Ivermectin is currently one of the most widely prescribed antiparasitic drugs. Developed initially to treat animals in the 1980s, it is now used in millions of people against tropical parasitic diseases such as onchocerciasis[1] and lymphatic filariasis[2]. Ivermectin is also recommended for the treatment of scabies and head lice resistant to standard therapies, and is considered to be extremely well tolerated in humans. In recognition of all its benefits, its discoverers, W. Campbell and S. Omura, were awarded the Nobel Prize in Physiology or Medicine in 2015.

In 2018, a 13-year old boy was hospitalised in the ICU at Toulouse University Hospital for impaired consciousness having been treated preventively with ivermectin for suspected scabies. Having eliminated all the usual causes of coma, the physicians had his blood analysed by INRAE research scientists specialised in using this drug: they found normal levels of ivermectin, so straight away it was possible to exclude the possibility of an overdose. The patient finally recovered consciousness and was able to return home after 48 hours. However, the research was pursued and the biology team at Montpellier University Hospital sequenced the boy's P-glycoprotein (P-gp) gene. P-gp is a pump that enables the efflux of toxins and drugs such as ivermectin, thus protecting the brain. In this case, the gene displayed two different mutations, each inherited from one of the parents. These "nonsense" mutations generate two incomplete copies of the protein and lead to a loss of its function. Because P-gp was no longer playing its barrier role, ivermectin entered the brain of this patient and became toxic. This is the first case of non-functional P-gp to have been described in humans.

The mutations discovered here are extremely rare in the general population and it is only thanks to a concerted and multidisciplinary approach combining clinical, pharmacological, biological and bioinformatics skills that it was possible to make a relatively early diagnosis in this boy, who will thus benefit

from appropriate monitoring concerning the prescription of medications, and particularly those that are carried by P-gp.

This work demonstrates the usefulness of pharmacogenetics – or study of the influence of genes on an individual's response to medication – which is still too rarely envisaged in clinical practice before the initiation of drug therapy.

[1] An infectious, tropical parasitic disease (also called river blindness) that is caused by a worm entering the skin and reaching the eyes; it is transmitted to humans through the bite of a small blackfly.

[2] An infectious, tropical parasitic disease that affects the lymphatic system, transmitted to humans by mosquitoes.

[3] Proteins in the membrane of brain cells that enable ion transport.

Reference

E. Baudou, A. Lespine*, G. Durrieu, F. André, P. Gandia, C. Durand, S. Cunat*. *Serious Ivermectin Toxicity and Human ABCB1 Nonsense Mutations.* New England Journal of Medecine 383;8; August 20, 2020; DOI: 10.1056/NEJMc1917344
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