Medicines & Healthcare products Regulatory Agency

MHRA

Christopher John Woolley
Assistant Coroner,
South Wales Central
The Old Courthouse
Courthouse Street
Pontypridd
CF37 1JW

28 November 2018

Medicines and Healthcare products Regulatory Agency

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Dear Mr Woolley

Reference: 9930

Thank you for sending us the Regulation 28/29 Prevent Future Death report concerning the death of Mrs Deidre Harvey. Further to your agreement to extend the deadline for response to the 3rd December 2018, we have assessed the data in relation to the question you raised for the MHRA:

1. The evidence in this inquest is that Deidre (who was a detained patient under Section 3 MHA) was being given a drug for a physical condition (Lupus) which can build up to toxic levels even at normal doses. The inquest heard that there is no routine checking of Hydroxychloroquine levels at clinical level, even though [redacted] said he thought that clinical monitoring of this drug might be important.

We have further considered your concerns that there may be other dependent persons suffering from lupus (or other conditions for which hydroxychloroquine is prescribed in NHS hospitals in England and Wales) who may also have toxic levels of hydroxychloroquine in their system unbeknown to their carers.

Some symptoms of hydroxychloroquine toxicity can be observed commonly at therapeutic doses as described in section 4.8 of the Summary of Product Characteristics (SmPC) for this drug. Other adverse reactions occur at a lower frequency. Monitoring of toxicity is mainly recommended by way of ophthalmological examinations before treatment initiation and at least every 12 months thereafter. Monitoring of blood levels is currently only recommended in patients with severely compromised renal or hepatic function. However, caution should be applied when using hydroxychloroquine in patients with hepatic or renal disease, and in those taking drugs known to affect those organs.

On 21st November 2018, we sought the advice of the Commission on Human Medicines' Pharmacovigilance Expert Advisory Group (PEAG) on the available data including the information outlined in the report of Mrs Harvey's death. The PEAG advised that in order to ensure that any actions are evidence based, further details on the report would be helpful.

We would therefore be very grateful if you could provide us with further information on the following points, if available:

1. The blood concentration observed in the patient is not clear as in section 4 (page 1) >15 mg/dL and in section 5 (page 4) 25mg/L is stated. Would you be able to confirm the observed concentration?

2. Assuming a blood concentration of 15-25mg/L the patient would have been expected to present with severe hydroxychloroquine toxicity such as headache, visual disturbances, cardiovascular collapse, convulsions, and hypokalaemia. Could you please confirm if any symptoms of overdose were observed in Mrs Harvey?
3. It is stated in the report that Mrs Harvey '*...suffered from several concomitant physical conditions...*' and indicated that she received mood stabilisers and anti-depressants. However, only lamotrigine is specified as a concomitant drug. Would you be able to confirm if lamotrigine was indeed the only concomitant medication? If not, could you provide us with details of any other concomitant drugs Mrs Harvey received as there is a possibility of drug interactions with hydroxychloroquine which may have contributed to the high observed blood levels. In addition, concomitant drugs may explain the patient's hyponatraemia.
4. Hydroxychloroquine is widely distributed in the body and following death redistribution into the circulatory system occurs. It is therefore possible that the observed blood concentration does not reflect the drug level at the time point when Mrs Harvey was still alive. Would you be able to confirm that the observed concentration derived from a post-mortem blood sample? And if so, could you provide information on the time elapsed following her death until the sample was taken?
5. Is there any information on a renal and/ or liver function test for Mrs Harvey?
6. Would you be able to confirm that the patient was compliant in taking her medication?

Thank you for your help with these questions, which will enable us to reach a position on whether regulatory action is required. I look forward to hearing from you.

Yours Sincerely,

Dr Ian Hudson
Chief Executive
Medicines and Healthcare products Regulatory Agency