Department of Health & Social Care

[redacted]
Minister of State for Health

39 Victoria Street
London
SW1H 0EU

Our ref: [redacted]

Ms Nadia Persaud
Area Coroner
East London Coroner's Court
Queens Road
Walthamstow
E17 8QP

By email: [redacted]

08 August 2024

Dear Ms Persaud,

Thank you for the Regulation 28 report to prevent future deaths of 15 May 2024 about the death of Mr Gary David Ash. I am replying as Minister of State for Health (Secondary Care).

Firstly, I would like to say how saddened I was to read of the circumstances of Mr Ash's death, and I offer my sincere condolences to their family and loved ones. The circumstances your report describes are concerning and I am grateful to you for bringing these matters to my attention.

The report raises concerns over:

- Management of the condition neuroleptic malignant syndrome, including the inappropriate, off licence, use of Dantrolene;
- The role of Dantrolene in the development of pulmonary oedema in the presence of intravenous fluid overload;
- The potential interaction between Dantrolene and Labetalol in relation to the reduction of cardiac contractility;
- The lack of knowledge around the diagnosis of serotonin syndrome and the risk of it developing following the combined use of Fentanyl and Ondansetron as part of anaesthesia.

In preparing this response, Departmental officials have made enquiries with the Medicines and Healthcare products Regulatory Agency (MHRA), NHS England and the Care Quality Commission (CQC).

In your report, you raised a concern regarding the lack of knowledge around the diagnosis of serotonin syndrome and the risk of it developing, following the combined use of Fentanyl and Ondansetron as part of anaesthesia.

The Medicines and Healthcare products Regulatory Agency (MHRA) is an Executive Agency of the Department of Health and Social Care (DHSC) with responsibility for the regulation of medicinal products in the UK. The MHRA ensures that medicines are efficacious and

acceptably safe, and that any possible side effects which have been recognised to occur with use of a medicine are appropriately described in the authorised product information.

Information from MHRA advises that serotonin syndrome and neuroleptic malignant syndrome (NMS) share similar symptoms, and as a result serotonin syndrome has generally been under-diagnosed. Serotonin syndrome is caused by the increased activation of serotonin receptors found in nerve synapses (in which nerve cells connect with other nerve cells), whereas NMS is more closely associated with dopamine activity. Diagnosis of serotonin syndrome was not universally harmonised until 2003 with the introduction of a set of diagnostic criteria known as Hunters Serotonin Toxicity Criteria. The diagnostic criteria include altered mental status, neuromuscular excitation and dysfunction of the autonomic nervous system which controls body systems including the heart, respiratory and urinary systems. These effects can typically occur rapidly within 1 to 6 hours after exposure to a relevant trigger. A similar feature of NMS relating to rigidity is reported only to occur several days after exposure to medication. It can be more difficult to diagnose serotonin syndrome in a patient under general anaesthesia because the signs and symptoms are similar to other perioperative conditions.

The MHRA has also provided information regarding Serotonin Syndrome warnings in medicinal product information. The Summary of Product Characteristics (SmPC) is a summary of a medicinal product's properties and the conditions for use, written for healthcare professionals and is available online on the MHRA website and in the Electronic Medicines Compendium (EMC). The use of opioids such as fentanyl and the risk of serotonin syndrome when used concomitantly with serotonergic medicines is known and highlighted within the fentanyl Summary of Product Characteristics (SmPC).

The warning was added to the SmPC for fentanyl medicinal products across Europe including in the UK by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) in 2015. Whilst the warning does not specifically refer to a potential for interaction between fentanyl and ondansetron, it should be noted that ondansetron is a serotonin receptor blocker and will prevent the binding of serotonin to its receptor resulting in excess synaptic serotonin. This makes an interaction between fentanyl and ondansetron potentially biologically plausible.

A warning is also included in the patient information leaflet provided with all fentanyl medicines advising patients to inform their healthcare professional if they are taking any antidepressants, especially those similar to serotonergic medicines including SSRIs, SNRIs or MAOIs. Patients who are using fentanyl patches are also advised to tell their doctor if they are going to have an operation. This enables health care professionals to be aware of possible signs of serotonin syndrome which can be more difficult to diagnose in a patient under general anaesthesia.

The risk of serotonin syndrome when used in combination with serotonergic drugs is also highlighted in the SmPC for ondansetron.

One SmPC (PL 04569/0656) for ondansetron that was harmonised with its licence in Ireland in June 2020, contains the additional warning:

There are also reports of serotonin syndrome when ondansetron is used concomitantly with opioid/opiate medicines, e.g. buprenorphine.

The British National Formulary (BNF) is a joint publication of the British Medical Association and the Royal Pharmaceutical Society and aims to provide prescribers, pharmacists, and other healthcare professionals with up-to-date information about the use of medicines. Information is drawn from the manufacturers' product literature, medical and pharmaceutical literature, UK health departments, regulatory authorities, and professional bodies and advice is constructed from clinical literature and reflects, as far as possible, an evaluation of the evidence from diverse sources.

The BNF also takes account of authoritative national guidelines and emerging safety concerns, in addition, to receiving advice on all therapeutic areas from expert clinicians to ensure that the BNF's recommendations are relevant to practice.

The interaction between fentanyl and ondansetron is included in the BNF under interactions for both ondansetron and fentanyl Ondansetron | Interactions | BNF | NICE.

The MHRA's Yellow Card Scheme primarily acts as an early warning system for the identification of previously unrecognised adverse reactions and also provides valuable information on recognised ADRs, allowing the CHM and MHRA to identify and refine the understanding of risk factors that may affect the clinical management of patients.

Up to 21 May 2024, two Yellow Card reports of suspected serotonin syndrome with concomitant use of fentanyl and ondansetron are on the MHRA Yellow Card database. However, neither report provides sufficient information to enable confirmation that the serotonin syndrome resulted from a fentanyl-ondansetron interaction in either patient. The MHRA will continue to undertake signal detection on its database of reports.

Getting It Right First Time (GIRFT) is a national programme designed to improve the treatment and care of patients through in-depth review of services, benchmarking, and presenting a data-driven evidence base to support change. GIRFT is part of an aligned set of programmes within NHS England.

The GIRFT Pre op team have advised that due to the limited information on what anaesthetic was used, what happened and the time scale of the event, it would be difficult to comment. They have also advised that Serotonin syndrome and malignant hyperpyrexia (MH) are both rare. These conditions have similar symptoms. When they precipitate a life-threatening crisis there is no simple test available to make a certain diagnosis. It can be made retrospectively for MH.

I understand that the Barking, Havering and Redbridge University Hospitals NHS Trust contacted Mr Ash's next of kin last year, which outlined the progression of actions at that point.

Further to this, NHS England has contacted the Trust for any further developments. The Trust has stated that at the time of this incident, they did not have dedicated deep sedation lists for endoscopy. This has now changed, and it now offers deep sedation only for these procedures. There are regular deep sedation lists which are in place since this incident. This is provided by anaesthetists who have the required expertise. There is a deep sedation standard operating procedure in place to ensure this procedure is conducted safely. Additionally, the consent process is more robust and learning from this incident was shared across the division.

Following receipt of the Prevention of Future Deaths report for Mr Ash, the CQC also contacted Barking Havering and Redbridge University Hospitals NHS Trust to follow up the concerns raised. The Trust provided an action plan which addressed 22 specific points. The majority of actions related to improvements in clinical governance, such as policies and processes, and these have been completed. There are some actions that remain in progress, and the CQC has, I understand asked the Trust for a further update.

The wider questions regarding assurance will be explored through the CQC's ongoing engagement with the Trust and the CQC will continue to monitor their progress.

I hope this response is helpful. Thank you for bringing these concerns to my attention.

Yours sincerely,

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MINISTER OF STATE FOR HEALTH