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Editorial

Fluid warmers, aluminium and what the regulator did

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The Medicines and Healthcare products Regulatory Agency (MHRA) is an arms-length government organisation responsible for overseeing the regulation of medical devices used in the UK. The regulatory system is in place to contribute to the overall need to protect public health and increase patient safety, while facilitating the safest access to medical devices used in the treatment and care of patients.

This editorial will help to demonstrate this process in action and allow readers to better understand how MHRA works and show how we sometimes have to balance conflicting issues between continuity of care and safety. To illustrate this, we will explore how we approached a difficult problem presented to us earlier in the year regarding a certain type of fluid warming device.

As all anaesthetists know, fluid warming devices are essential to ensure intravenous (i.v.) fluids used in treating patients, such as electrolyte solutions, blood and blood products, are warmed before administration, as part of the overall strategy to prevent hypothermia [1]. This is important for all patients but is particularly important in neonatal and paediatric populations. These medical devices are established technology and are in use throughout UK clinical practice, as well as in global healthcare systems.

In January 2019, MHRA was informed through its network of clinicians of work being done which suggested a particular fluid warming device (enFlow®; Vyaire Medical Inc, Mettawa, IL, USA) was potentially releasing higher than expected levels of aluminium when used to warm certain types of fluids. This 'soft signal' immediately triggered an investigation by MHRA into the medical device concerned. This investigation, in collaboration with other European Union member states, confirmed the conclusions of the study by Perl et al. which reported the uncoated aluminium plates used in the enFlow fluid warmer can lead to administering higher than expected concentrations of aluminium when using certain electrolyte solutions [2].

Following these rapid investigations and in consultation with the manufacturer, MHRA published a Medical Device Alert (MDA) [3] to notify UK healthcare professionals of this potential risk. This involved preparing a carefully considered message to try to balance the need to protect patients from an, as yet, unquantified risk vs. the absolute need for fluid warming in situations such as acute resuscitation. It was deemed to be particularly important to achieve this balance in this case, because we were aware not all hospitals could easily source alternative devices quickly and we could not ensure devices from other manufacturers were unaffected. In our deliberations, we decided quickly the overriding clinical need for fluid warming should take precedence over considerations of risk of aluminium release. This was in part because these devices have been in service for 10 or more years, with no safety signal being flagged by the clinical community or manufacturers and fluid warming can be life-saving.

As is normal in such circumstances, part of the process for determining MHRA's recommendation involved consulting with the relevant clinical and in this case, toxicology experts, to agree on the most appropriate communication to healthcare professionals. The continuing investigation also revealed a similar risk could exist with

blood products and MHRA required further testing to be undertaken to better understand the potential risks. This additional testing ultimately led to the withdrawal of the device by the manufacturer; MHRA supported this action in the form of a second MDA [4]. The study by Taylor et al. in this edition of Anaesthesia further reinforces the need for caution and the rationale for the withdrawal of the device from the market [5]. The authors of the study also concluded the actual risk of exposure could not be characterised at this time. MHRA was already of this opinion and this had led to the formation of an independent Expert Advisory Group which was asked to consider questions regarding the potential for clinical effects of exposure to this additional aluminium. Until this group has considered all the evidence and reported, the potential risk imposed by the additional exposure from these devices is unclear. This is particularly true because aluminium is a metal ubiquitous in the environment, which most individuals are exposed to daily, through the air which they breathe and their diet [6]. We know humans have developed protective mechanisms in our gut to help reduce excessive uptake of aluminium, much as it does with some other potentially harmful substances. Also, our overall net positive daily balance of aluminium is compensated for by renal excretion. This is clearly a different set of circumstances to patients who are having i.v. infusions. Therefore, in groups at particular risk, such as those with renal impairment [7], higher than recommended levels of aluminium may accumulate in the systemic circulation. This is why patients with renal failure on dialysis, for example, have their aluminium levels monitored, even though measures taken over the past few years have reduced the exposure of dialysis patients to aluminium [8].

There have been some attempts to study aluminium exposure, because there are other issues to consider such as industrial exposure in workers in certain industries and there are circumstances in which signs of toxicity may occur. According to a European Union Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) review, daily aluminium exposure regularly exceeds recommended levels even in non-industrial settings [9].

It is hoped the Expert Advisory Group will undertake and complete their review, including reporting their findings to MHRA, within the next few months and will help to guide any possible future MHRA regulatory action. As well as this, MHRA are working with all manufacturers of fluid warming devices available in the UK to determine if any similar risks exist with their devices and additionally MHRA has been collaborating with other regulators within the European Union and globally.

The future of medical device regulation

This issue has demonstrated how MHRA can act even more effectively and respond rapidly to a potential safety concern brought to our attention by the clinical community. What remains for discussion is how we can, as a community already invested heavily in patient safety, go further in protecting public health and patient safety in a more proactive way. It may be scientists, researchers and publishers should work more closely with regulators and/or manufacturers when they undertake work of this nature, because it may be possible to inform the need for action much sooner if there are suspicions of a problem which could affect patient safety. The latter is most important, because there are balances to be struck between issues which include the need to protect patients, professional responsibilities of doctors and other healthcare professionals, academic in-confidence and whistleblowing, which need to be addressed if we are to progress.

With existing medical devices, we can look back to the regulatory environment which existed in the 2000s when devices such as the enFlow fluid warmer were placed on the market. The regulatory landscape was similar, but the emphasis on testing was different due to the scientific environment of the time. Since then, there has been a shift in the focus on chemical assessment within the international standard on biological safety to include more emphasis on leachables and extractables [10]. This is because, previously, these devices were classified as low-risk under the medical device classification system, but with a greater understanding of the potential for release of certain compounds from some medical devices it is now known they can carry a higher toxicological risk. It is therefore necessary to review the classification system to decide if changes should be made to address the issue highlighted by this case, and due to this MHRA is currently discussing this matter as a leading member of a European taskforce.

With a return to working in the field of standards, such as those of the International Standards Organisation and of the British Standards Institute in the past few years, MHRA has taken the initiative to ensure this new emphasis is applied to all assessments of medical devices. MHRA has collaborated with and invested in scientists who have a clear understanding of toxicological issues and a member of the Devices Clinical Team was appointed as the chair of the UK committee responsible for contributing to the international committee for standards relating to biological evaluation of medical devices.

This co-incides with the new Medical Device Regulations (MDR) [11] which MHRA have been

instrumental in developing over the past 8 years. Amongst the key elements introduced is an increased emphasis on pre-market provision of biological safety testing and pre-clinical evaluation data for clinical investigation applications and requirements to make available postmarket safety data to Notified Bodies and Competent Authorities on a regular basis. For new medical devices and those being represented for conformity assessment in the future, the work on the standards committee will complement the strengthened regulatory system of the MDR.

In conclusion, as a regulator we feel it is essential for public health and patient safety that all stakeholders work together, keeping the patient at the centre of this activity. Emerging safety concerns and signals when escalated by clinicians, scientists and industry through existing reporting channels, as this example has demonstrated, leads to fast and effective assessment of risk and implementation of actions to protect patients.

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