Churchill House
35 Red Lion Square
London WC1R 4SG

Tel 020 7092 1500
Email info@rcoa.ac.uk
Web www.rcoa.ac.uk
Twitter @RCoANews

Dr Alison Cave
Chief Safety Officer
MHRA
By email
Copy to: Scottish Medicines Consortium, NHS Scotland

31st August, 2023

Dear Dr Cave,

The current focus on promoting the safer use of opioids in acute pain includes two major aspects that we feel would merit addressing by the MHRA. These two initiatives are supported by the Royal College of Anaesthetists, the Faculty of Pain Medicine, the Centre for Perioperative Care (CPOC), Safe Anaesthesia Liaison Group (SALG), and Medicines Safety Improvement Programme (NHS England). We feel that the reach of these institutions would allow real change to be made in promoting patient safety.

1. An end to the use of modified-release opioids in acute pain

Modified-release opioids have been promoted for many years in enhanced recovery after surgery (ERAS) pathways in the UK, particularly those pathways for hip and knee arthroplasty.
It is now increasingly acknowledged that publications and guidelines advocating perioperative use of modified-release (MR) opioids were not based on good evidence and are not applicable to modern surgical pathways [1].

There is no evidence of improved postoperative pain relief with MR opioids but there is increasing evidence that, not only are MR opioids less effective than immediate-release opioids for managing acute, intermittent pain, but there are increased harms associated with their use [2,3]. These harms include opioid-induced ventilatory impairment (OIVI) and persistent postoperative use (PPOU), where patients continue to use strong opioids many months beyond the immediate postoperative period [4,5].

Consequently, the professional bodies and regulators in several countries have strongly cautioned against the initiation of MR opioids for acute pain [6,7,8,9,10], including requiring changes to manufacturers' product indications [11]. In April this year, the Food and Drug Administration in the United States tightened the indications for MR opioids to "be reserved for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate" [12]. This is now in line with similar recommendations made by the Australian Therapeutic Goods Administration three years earlier [8,9].

Although in the UK the Faculty of Pain Medicine and the Centre for Perioperative Care have issued guidance against MR opioids [10,13], their audience is limited. The message would be stronger with a broader reach if the MHRA followed other international regulatory bodies to strengthen warnings around their use.

2. Limiting pack sizes of opioid medications

Currently in the UK pack sizes are large. The smallest pack size of codeine and dihydrocodeine is 28 tablets, while that of morphine and oxycodone is 56 tablets. The only exceptions to this are one brand of MR morphine (MXL) which has a pack size of 28 and is very expensive, or 5mg tablets of MR oxycodone which is available in a 28-tablet pack [14]. Most hospital pharmacies do not have the time or resources to break packs and dispense smaller quantities.

Similarly, oral solutions of opioids are presented in large volumes, with 100ml being the smallest bottle size available of a 2mg/ml morphine concentration, and 250ml the smallest bottle of oxycodone 1mg/ml solution.

The consequence is that postoperative discharge opioid prescribing is often in excess of patient need, leading to a high community reservoir of unused opioids [15]. The quantity of opioid prescribed on discharge has a strong association with patient-reported opioid consumption [16], which itself leads to a higher risk of OIVI, PPOU and opioid dependence [17]. Further, unused opioids risk diversion and accidental overdose, particularly in children [18].

In June 2020, the Australian Therapeutic Goods Administration required manufacturers of opioids to produce pack sizes of 10 tablets, down from the previous minimum pack size of 20 [19]. This includes all immediate-release opioids (tablets and capsules) including combination products. We ask that the MHRA recommend similar limitations from pharmaceutical companies.

A reduction in bottle size of oral opioid solutions is also important. Further, these oral solutions are commonly dispensed in primary care, making opioid use difficult to monitor or address, and with significant associated risk [20]. There is benefit to keeping oral morphine solution in hospitals, where the Schedule 5 classification requires only one nurse to check it, thus reducing dispensing time to patients. However there is little value of oral solution use in the community, except in rare occasions where swallowing is difficult, so we would support a recommendation against the routine use of oral opioid solutions in primary care.

We are key figures in multidisciplinary national and international opioid stewardship and are looking to improve the safety of opioids for patients in the UK. While much work is already being done, these two aspects require national level change. We applaud the recent release of a MHRA consultation document to make codeine-containing products prescription-only [21] and suggest that it could go even further to promote safe opioid stewardship by considering our two proposals.

Yours Sincerely,

Dr Jane Quinlan, Consultant in Anaesthesia and Pain Management, Oxford University Hospitals; Honorary Senior Clinical Lecturer, University of Oxford

Dr Nicholas Levy, Consultant Anaesthetist, West Suffolk Hospital

Dr Helen Laycock, Consultant in Paediatric Anaesthesia and Pain, Great Ormond Street Hospital; Honorary Clinical Lecturer, Imperial College; Editor of Anaesthesia

Dr Emma Baird, Consultant Anaesthetist, Lancashire Teaching Hospitals; Co-opted Board Member, Faculty of Pain Medicine

Professor Patrice Forget, Clinical Chair in Anaesthesia, University of Aberdeen; Honorary Consultant, NHS Grampian

Mrs Felicia Cox, Nurse Consultant, Pain Management, Guys & St Thomas'; Co-Editor British Journal of Pain; Secretary, IASP Acute Pain Special Interest Group

Professor Roger Knaggs, Associate Professor in Clinical Pharmacy Practice, University of Nottingham; Specialist Pharmacist in Pain Management, Primary Integrated Community Services, Nottingham; President, British Pain Society

Professor Pam Macintyre, University of Adelaide and Emeritus Consultant in Pain Medicine Royal Adelaide Hospital

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