Medicines and Healthcare products Regulatory Agency

12 September 2016

Yellow Card collaboration with the National Poisons Information Service

Issue/ Purpose: This paper explores an opportunity for collaboration with the National Poisons Information Service (NPIS) for collection of data on harms associated with overdose of medicinal products.

Summary:
The 2012 pharmacovigilance legislation brought an added focus for reviewing cases of overdose as part of the safety system. In the UK reporting of these cases to the Yellow Card Scheme does happen already, but much of the information on overdose is collected by the NPIS. The cases we do receive have informed signals for regulatory action so it is important for patient safety that we gather better data. VRMM have been in discussions with NPIS around how best to engage with the system used for information on poisons, Toxbase, and the database used to record cases, UKPID. Where there is advice in Toxbase on ADR reporting, this needs to be updated and completion of field mapping will enable cases to be transferred to the MHRA.

At this stage we propose a pilot project where we review UKPID data outside of the usual signal environment to ascertain how best to utilise the data in our pharmacovigilance system and develop clear guidance and costs for moving forward with a fully integrated system.

The Key Performance Indicators for success of this pilot collaboration with NPIS include:

- Identification of high quality ADR data from the UKPID which will feed into to our future signal detection activities.
- Confirmation of new signals generated from both UKPID reports and/or signals identified in a timelier manner when UKPID and Yellow Card reports of overdose are combined in one dataset.
- Generation of a set of clear guidelines for NPIS staff and Yellow Card reporters on reporting harms associated with overdose.

In addition we are working with NHS Improvement on the collection of data through the National Reporting and Learning System and its planned replacement. This includes data on overdose and the work will be informed by this project.

Resource implications:
Within existing VRMM resource. £27,600 exc VAT initial cost for IT platform

EU Referendum implications: None

Timings: If the MHRA Board is in agreement the project would start in November 2016 and complete in March 2017

Action required by the Board: Consider the issue and options presented
Links: NPIS
Author(s): Sarah Vaughan and Mick Foy
Are there any sensitivity issues that would prevent this item being discussed by CET in the presence of staff observers? No
Which of the five themes in the Corporate Plan 2013/2018 does the paper support? Strengthening surveillance
CET Sponsor: June Raine

Yellow Card collaboration with the National Poisons Information Service

1. Issue

This paper explores an opportunity for collaboration with the National Poisons Information Service (NPIS) for collection of data on harms associated with overdose of medicinal products.

2. Background

In June 2012 new pharmacovigilance legislation[1] was adopted in the EU which introduced a broader definition of an adverse drug reaction:

> *For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product'*

The new definition of an ADR has placed a greater focus on our efforts to collect reports of adverse reactions not only when associated with therapeutic use of a medicinal product but also outside its licensed terms of use including harms associated with overdose of a medicinal product.

Current MHRA reporting guidelines encourage healthcare professionals to report all serious suspected ADRs, even if the effect is well recognised. We are particularly interested in receiving Yellow Card reports of suspected ADRs:

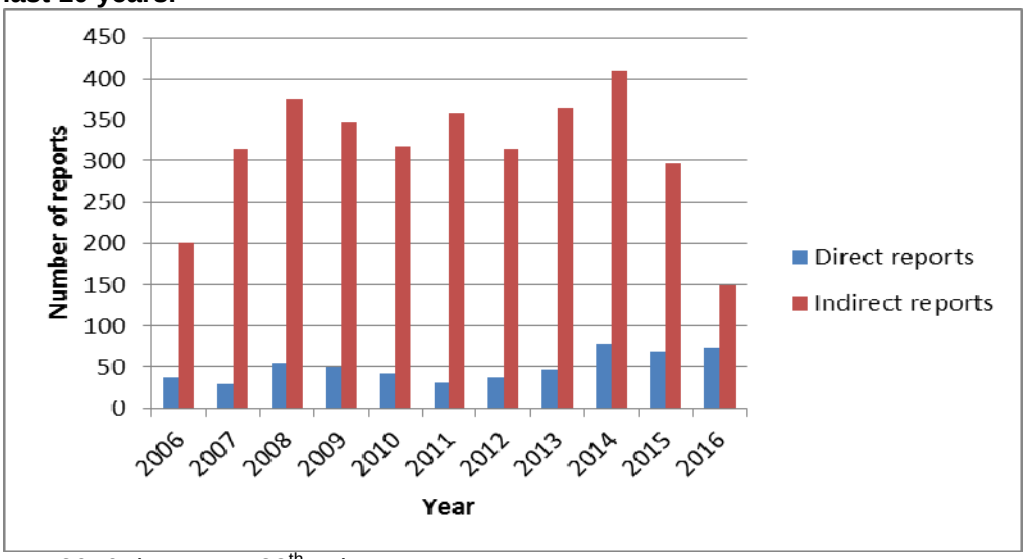
- In children
- In patients aged over 65
- To biological medicines and vaccines
- Associated with delated drug effects and interactions
- To complementary remedies such as homeopathic and herbal products

These guidelines do not explicitly state adverse reactions associated with overdose. Yellow Card reports of ADRs in overdose are currently received by the MHRA but numbers are low. As of the 28th July 2016, the MHRA has received 5706 UK spontaneous ADR reports that contain a reaction within the High Level Term (HLT) "Overdoses NEC" (not elsewhere classified) or Preferred Term (PT) "Accidental overdose". In 2015, 0.9% of reports received overall were associated with the overdose terms mentioned above.

Figure 1 below shows the volume of cases received over the past 10 years directly through the Yellow Card Scheme from both healthcare professionals and members of the public and from Marketing Authorisation Holders as part of their pharmacovigilance responsibilities.

[1] Directive 2010/84/EU

Figure 1: The number of UK spontaneous ADR reports received per year associated with the HLT 'Overdoses NEC' or PT 'Accidental Overdose' for the last 10 years.



*2016 data up to 28th July

3. Current processes for assessment of safety concerns relating to overdose

Although reporting volumes for ADRs arising from overdose are low, the MHRA have nevertheless identified a number of signals relating to overdose from spontaneous ADR data. Up to the end of 2015 forty signal case folders have been created and reviewed as part of a safety concern associated with overdose or where overdose cases have been included as part of a wider safety review.

One example of a medicinal product where a number of signals have been investigated in recent years relating to product misuse is the opioid fentanyl. These signals included reports of accidental overdose, which resulted in regulatory action to increase visibility of the patches, and fatalities associated with deliberate misuse of fentanyl patches and application of heat.

A number of issues relating to risk of overdose have been communicated in Drug Safety Update (DSU), with important advice for healthcare professionals for example the toxic effects of colchicine in overdose (Nov 2009),[2] and risk of accidental overdose with intravenous paracetamol (July2010), triggered after spontaneous Yellow Cards were received in association with infants and neonates.[3]

When assessing the risk of overdose associated with a medicinal product a variety of other data is evaluated in VRMM alongside the spontaneous data generated by the Yellow Card Scheme. Overdose can be identified in a medicinal product's Risk Management Plan (RMP) as a potential or identified risk and any safety data is then

[2] https://www.gov.uk/drug-safety-update/colchicine-extremely-toxic-in-overdose
[3] https://www.gov.uk/drug-safety-update/intravenous-paracetamol-perfalgan-risk-of-accidental-overdose

assessed periodically in Periodic Safety Update Reports. Where there is a particular concern regarding overdose a Post Authorisation Safety Study (PASS) can be requested or initiated by the MAH. For example with Espranor (buprenorphine) a Drug Utilisation study is underway for a novel formulation. The concern is that the novel formulation may make overdose more likely.

4. NPIS

The NPIS is a national service commissioned by Public Health England that provides expert advice to health professionals on all aspects of acute and chronic poisoning. The service comprises four individual Units, based in Birmingham, Cardiff, Edinburgh and Newcastle. Each Unit is staffed by Consultant Clinical Toxicologists and Specialists in Poisons Information (SPI). Information is provided using 2 platforms; Toxbase and telephone enquiries.

Toxbase is the primary clinical toxicology database of the NPIS and as an online resource is often the first point of reference for UK healthcare professionals. In 2014/15 there were 628,740 TOXBASE user sessions[4] .

Within Toxbase there is a page providing information on Yellow Card reporting which provides a link to the Yellow Card reporting website and describes the current MHRA guidelines for submitting a report. Work has been carried out over the past year to create a link to the Yellow Card reporting website from each page for pharmaceutical products. The wording on these pages however describes reporting of 'ADRs from normal use'.

Individual advice on more serious or complex cases is available via the NPIS 24-hour national telephone support service. This consists of a network of SPI staff based at the four provider Units. All calls are logged and available for each of the NPIS units for the provision of easily accessible national data on the activity of the service and the patterns of enquiries received. These calls are all stored in the UK Poisons Information Database (UKPID) since 2007. In 2014/15 46,711 telephone enquiries relating to patients were answered by the NPIS

Benefits of collaborating with NPIS

Working with NPIS on an ADR reporting initiative would bring a number of benefits.

i. The data collected through the NPIS telephone enquiry service offers a valuable additional data pool for our vigilance activities and our ability to identify safety concerns associated with medicinal products both within their licensed use and outside of it, thereby enhancing our ability to perform our public health role in monitoring the safe use of medicines. Improved data coming into the MHRA will better inform the outputs for healthcare professionals with regards to clinical treatment of patients.

ii. There is little opportunity to be able to access this type of spontaneous data on harms associated with overdose from any other data sources. Harms with overdose are coded in ICD-10 in Hospital Episode Statistics however this is not granular enough to be able to monitor overdose with specific products and there is limited data on overdose currently in CPRD. This project will offer us the opportunity to analyse the clinical nature of ADRs associated with

[4] NPIS Annual Report 2014-15

overdose from spontaneous ADR cases upon which we carry out our signal detection activities. Such signal detection is important as overdose is often a key potential or known risk in a medicine's RMP and inclusion of these types of reports will enable us to identify trends in overdose reporting both from accidental and intentional overdose cases. This will complement other data sources such as HES and CPRD currently used by the Agency for signal validation and enable us to create a generate a more holistic approach to signal management relating to harms associated with overdose.

iii. UKPID data will offer insight into harms associated with overdose not frequently reported through the Yellow Card for example intention overdose in association with chloroquine purchased through the internet, which is currently brought to our attention by other means such as Coroner's reports or intelligence shared with us from IE&S division.

iv. This initiative aims to create a more complete flow of information between NPIS and MHRA whereby the information received by NPIS contributes to signal detection and assessment at the MHRA which in turn will inform the recommendations and advice provided to healthcare professionals in NPIS's Toxbase. MHRA have worked with NPIS on a number of previous initiatives and such collaboration has been very beneficial for example in the development of standardised and harmonised warnings in the treatment and management of overdose for a number of medicines in 2001 as well as help on particular safety issues on a case by case basis.

5. Proposal

Our proposal covers two aspects of ADR reporting:

(i) To amend the wording in Toxbase with regards to adverse reactions to talk about any ADRs relating to drug exposure and not just within the licensed use of a medicine.

This is a relatively low cost activity and would rely on NPIS staff amending the relevant Toxbase pages although due to the number of pharmaceutical product pages in Toxbase and the demand on NPIS staff resource to do this, it is likely to have to be carried out in a phased approach.

Any update to the wording for ADR reporting would also need to be mirrored by updates to the MHRA published guidance on ADR reporting for consistency and to avoid confusion amongst reporters.

(ii) To develop an integrated Yellow Card reporting function within NPIS database (UKPID) for their SPI staff to be able to report the cases received via their telephone enquiry service directly to MHRA's Yellow Card database.

The NPIS receive and log enquiries relating to ADRs both from traditional use of medicines as well as overdose and medication error. These calls are logged in the specially designed secure common national database, UKPID. This database currently runs on OpenInsight 8.0.8 by Revelation Software.

An initial comparison of UKPID data fields with the required data fields for a Yellow Card report has shown compatibility in the data collected. Clinical features of the overdose are coded using WHO-ART for which a mapping to MedDRA terminology is already available. A complete mapping exercise for all the remaining fields within UKPID to the Yellow Card Information Standard[5] is now required to enable data transfer between UKPID and MHRA. This mapping will be carried out by MHRA staff and passed to the UKPID software developers who have been asked to provide an approximate cost for the subsequent technical integration work.

Following deployment of direct electronic reporting from UKPID, cases will be automatically populated into the MHRA's ADR database and require minimal case processing in line with other electronic healthcare records for which the MHRA already has direct integration of Yellow Card reporting including 2 GP and 2 hospital software systems.

In 2014/15 46,711 telephone enquiries were received by NPIS, approximately 70% of these related to pharmaceutical products and nearly 90% of those cases (approximately 29,500 cases) were associated with adverse effects making them viable as suspected ADR reports which could be entered into the MHRA ADR database as valid cases.

The number of these cases which would be transferred to the MHRA through integrated reporting would be determined by the SPI staff handling the calls and would require development of guidance for key criteria for which cases we would want to receive.

As the volume of cases to be received cannot be predicted (up to a maximum of nearly 30,000 cases based upon 2014/15 UKPID data) it will be necessary to restrict these cases in the MHRA signalling software in order to prevent any risk to current signalling processes. The cases will be cumulatively analysed in order to determine whether overdose data is scientifically distinct from ADR data arising from therapeutic use and should be handled differently with regards to signal thresholds and use of disproportionality scores. In addition there is a need to determine whether the potential volume of NPIS cases could mask other signals in the current MHRA ADR dataset if subsequently included in the MHRA's ADR database. Two options are outlined below as to how this could be handled.

6. Options Appraisal

Option 1:
Integration of electronic reporting to commence immediately upon development and deployment of the required technology. A 6 -12month pilot will be run enabling automatic transfer of cases from UKPID by the SPI staff into the MHRA's ADR database. Cases will flow through to our Empirica Signal software on a nightly basis as per the MHRA's current Extract, Transform and Load (ETL) process. Updates to Empirica production software will be required to exclude cases from UKPID. These

[5] YC NHSIB
http://webarchive.nationalarchives.gov.uk/+/http://www.isb.nhs.uk/documents/isb-1582/amd-28-2012/index_html

cases will be excluded from current signalling processes for usual ADR data and separate statistical data mining runs will be set up to evaluate the UKPID data.

Timeframe:

- 3 months to build, test and integrate Yellow Card within UKPID
- Simultaneous 3 month process to update Empirica signalling software
- 6-12 months pilot of direct reporting to assess the impact on MHRA signalling processes and determine the value of the data.

Advantages:

- Data can be analysed real time as the reports come in to mirror current signal generation activities.
- Up front work of integration of Yellow Card into UKPID which with experience we can then refine our requirements for transmission of cases by SPI staff.

Disadvantages:

- No advance knowledge of what is reported to NPIS such as the spread of reports across pharmaceutical products, the range of WHO-ART terms used to describe the reactions experienced or the level of detail provided in the cases.
- Costly changes to current Empirica software in the production environment which will then require further revisions as a result of the outcome of the pilot.
- The time taken to run the pilot will depend on the number of cases received each week in order for a sufficient volume to be collected upon which to base our analysis of the data.

Cost:

- Quote for technical integration work still to be provided by UKPID software developer
- Required changes to Empirica software: £32,500 exc VAT
- Further changes will also be required to Empirica software in light of the outcome of this pilot

Option 2: Preferred Option

A retrospective approach to explore the UKPID data in a separate system outside the Empirica software. Each of the four poison centres currently use an automatic export process to transfer structured comma-separated-values (CSV) files into the national UKPID and therefore this format should be relatively easy for NPIS to provide an anonymised extract to us. UKPID has data going back to 2007 and therefore we could request either the complete dataset for review or a sample of the past few years to evaluate the content of the cases – including the validity of the cases (for ADR reporting purposes), the spread across pharmaceutical products and events reported as clinical features described in these cases. We would then map the drugs and events reported along with the dates of the incidents to compute counts of cases at time points in the past which can be compared to the counts already generated from our Yellow Card ADR data at the same point in time. This represents a more

cautious approach to the pilot with less associated risk as no changes will be made to our live production environment for Empirica software.

Time frame:

- 4 months from the point of obtaining the UKPID data to carry out the retrospective review.

Following on from the conclusions of this review, the integration of electronic reporting within UKPID will take 3 months to build, test and deploy, this will be carried out in conjunction with any revisions required to our Empirica signalling software.

Benefits:

- This would enable us to confirm the additional value of this data above what we currently have in our ADR dataset and whether the data is sufficiently distinct to require separate signal detection process or can be managed according to existing signalling processes.
- The retrospective comparison of drug-event pairs with and without the benefit of the additional UKPID cases would allow us to assess whether there would have been earlier signalling of identified safety concerns.
- Having access to a larger volume of retrospective cases will give us a better change to observe rare events that would be of specifically high signal detection value.
- Lower initial cost (assumption that extract of UKPID csv files is a smaller cost than building the technical integration of Yellow Card within UKPID)
- Analysing the current data within UKPID would help inform development of new reporting requirements in relation to overdose from both SPIs in the NPIS and broader Yellow Card guidelines for healthcare professionals reporting directly.

Disadvantages:

- This review would need to be conducted prior to any integration of electronic Yellow Card into UKPID and would delay receipt of any ‘new’ cases of harm associated with overdose from NPIS into the MHRA’s ADR database.

Cost:

- Quote for export of UKPID csv files still to be provided by UKPID software developer
- Server hosting and analysis software: £27,600 exc VAT
- Further changes will also be required to Empirica software in light of the outcome of this pilot

7. Risks

i. Following integration of electronic reporting from UKPID into the MHRA ADR database, the increased volume in ADR reporting will need to be monitored

and managed to prevent any impact on the Agency's key performance indicators for the processing of ADRs onto the MHRAs ADR database and consequent initial review for potential signals.

ii. The data received through integrated reporting from NPIS will only represent a small subset of cases relating to harm from overdose of medicinal products. Consideration will also therefore need to be given to direct reports received through the Yellow Card Scheme and data received through the National Reporting and Learning system direct from local risk management systems within hospitals.

8. Resource

For both options the following involvement will be required from existing VRMM staff:

- 1 member of staff (SEO grade) will be required to input into the initial mapping and testing work for integration of the Yellow Card reporting mechanism. Currently this falls within the role of the Pharmacovigilance Coordinators in VIRG
- 1 Signal Assessor (EO/HEO grade) to manage the associated volumes of cases received and monitor the quality of information within the UKPID cases.
- 1 pharmacoepidemiologist within BMRG to analyse signal thresholds and create data mining runs to enable comparison of drug-event pairs from UKPID data with MHRA Yellow Card data along with input from Commonwealth Informatics (Empirica Signalling software suppliers) and the Signal Management Unit Manager.

9. General reporting guidance for ADRs associated with overdose.

Review of MHRA reporting requirements for harms associated with overdose is required with adoption of either suggested options. Option 1 for a pilot of direct reporting from UKPID will need to coincide with development and communication of guidance for healthcare professionals and members of the public for direct Yellow Card reporting of harms associated with overdose to avoid confusion to reporters to the Scheme. With option 2 any changes to MHRA reporter guidance can be developed in light of our increased understanding of the nature of this data source following our review of the retrospective data.

It is proposed a small multidisciplinary working group is established to conduct this review over a 3 month period. Any changes to MHRA reporting guidelines can be promoted as part of Yellow Card communication campaigns currently being planned for 2017.

10. Success Criteria

The Key Performance Indicators for success of this pilot collaboration with NPIS include:

- Identification of high quality ADR data from the UKPID which will feed into to our future signal detection activities.
- Confirmation of new signals generated from both UKPID reports and/or signals identified in a timelier manner when UKPID and Yellow Card reports of overdose are combined in one dataset.

- Generation of a set of clear guidelines for NPIS staff and Yellow Card reporters on reporting harms associated with overdose.

In addition we are working with NHS Improvement on the collection of data through the National Reporting and Learning System and its planned replacement. This includes data on overdose and the work will be informed by this project.

11. Timescales

For option 1; due to the amount of investigation work with regards to mapping between the systems and associated costs still to be completed, the provisional date for a pilot is the start of next financial year April 2017 with funding to be agreed in advance.

For option 2; as the complexity of extracting UKPID data is anticipated to be less than the initial work to develop integrated Yellow Card reporting an earlier start time to progress this review could begin from November 2016 with recommendations expected to be available by March 2017.

Subject to the proposed recommended option being agreed by the Board, the proposal will be taken through the necessary governance channels, including IMGB, for procurement and agreement of associated costs.

Updates on progress can be provided on a quarterly basis.

12. Actions for MHRA Board

The Board are asked to:

- Consider the issue and options presented and support the proposed collaboration with the National Poisons Information Service.
- Note our recommendation to pursue the plan outlined in option 2.
- Support the creation of a small multidisciplary team to review reporting guidelines for harms associated with overdose over a 3 month period.

VRMM
August 2016