IRON CARBOXYMALTOSE ADVERSE DRUG REACTIONS (ADRS): A RETROSPECTIVE CASE SERIES REVIEW OF REPORTS TO THE NEW ZEALAND CENTRE FOR ADVERSE REACTIONS MONITORING (CARM)

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INTRODUCTION

Iron deficiency anaemia is a common condition, with potentially significant impacts on a patient's quality of life[1]. There has been an increase in New Zealand primary care prescribing and administration of iron carboxymaltose since the PHARMAC special authority criteria changes in October 2017[2-4]. With this came a parallel increasing trend of Adverse Drug Reactions (ADRs) reported to the CARM. This is a review of the New Zealand specific product ADR data.

AIMS

To retrospectively review and analyse all iron carboxymaltose ADRs reported to CARM, for the period January 2012 to end January 2019, identifying the nature of the reaction, its timing to onset, and the source of the ADR reports.

METHODS

All iron carboxymaltose reports submitted to CARM were analysed to establish their pattern of reaction, time to onset and source of reporter. The descriptions within each report allowed for classification of signs, symptoms and medical conditions, into WHO classification categories. A single case could have multiple reaction terms each potentially falling into different System Organ Class (SOC) categories. Each report was assessed for causality according to international conventions in Pharmacovigilance assessment[5].

For the purposes of this project, "hypersensitivity" included dermatological adverse reaction terms, bronchospasm and symptoms on the anaphylaxis or angioedema spectrum. The Australasian Society of Clinical Immunology and Allergy (ASCIA)[6] definition for anaphylaxis was used in this study. Infusion site reactions, including skin discolouration events, were analysed separately.

RESULTS

There were 128 iron carboxymaltose ADR reports submitted to CARM during the period of January 2012 to end January 2019. During this time, a shift of ADR report sources was noted. Tertiary care teams provided the largest proportion of reports pre-October 2017, with General Practice Nurses and Doctors the primary reporters following the PHARMAC Special Authority Criteria change date.

The majority (79.9%) of ADRs occurred on the day of the iron carboxymaltose infusion *(Table 2)*. ADRs affecting the skin, accounted for the greatest proportion of reports (22.3%), with 4 cases of skin discolouration and 1 of infusion site extravastation. There were also 6 cases of hypophosphatemia reported associated with this medication.

Figure 7 illustrates the distribution of the 73 hypersensitivity events identified. Of these, 7 were classified as "angioedema", and 3 as "anaphylaxis" events. 17 cases were described as "potentially severe" and a further 46 reports were classified as "minor" hypersensitivity events.

Medical Alert Warnings were generated on the National Medical Warning System for 66% of cases, with another 12% of cases resulting in a Danger alert.

Figure 1: *Iron Carboxymaltose ADR Reports to CARM by Year (2012 to end January 2019)*

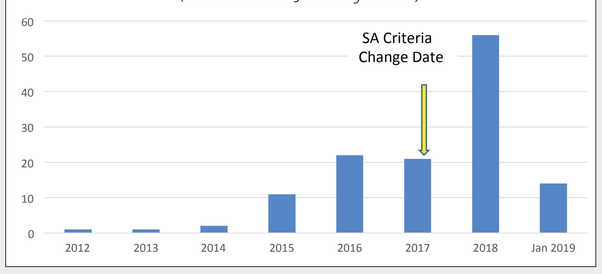

Figure 2: *Iron Carboxymaltose Units Dispensed by Month (Courtesy of Ministry of Health[4])*

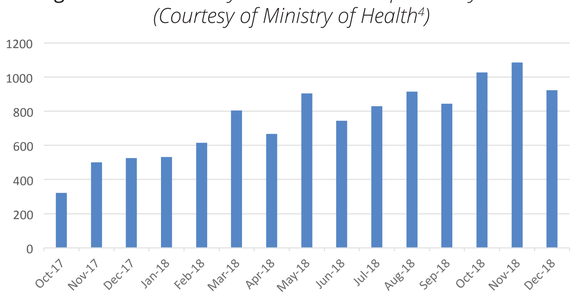

Figure 3: *ADR Report sources pre- and post- SA criteria change (% of total reports for period)*

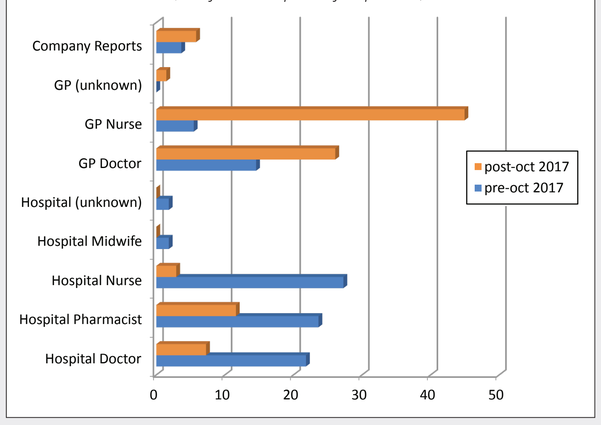

Figure 4: *Descriptive ADR terms by System Order Class (%) (excludes reactions assessed as non-causal)*

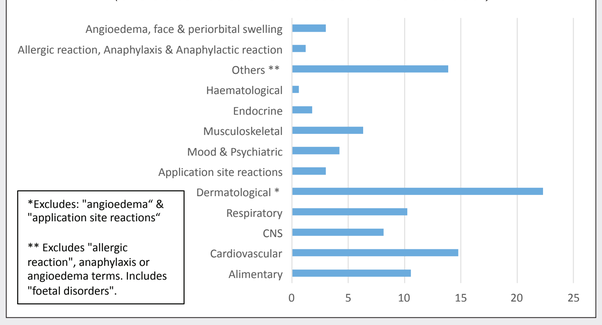

Figure 5: *ADR report distribution by age and gender (n=128)*

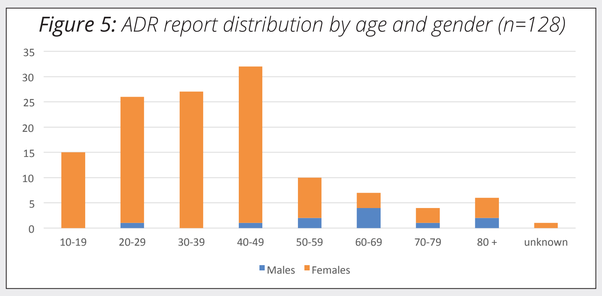

Figure 6: *Distribution of National Medical Warning System Alerts Generated (%)*

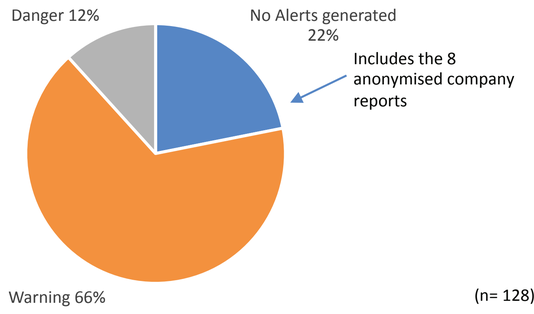

Figure 7: *Sub-analysis of Iron Carboxymaltose Hypersensitivity Spectrum ADR reports (n=73)*

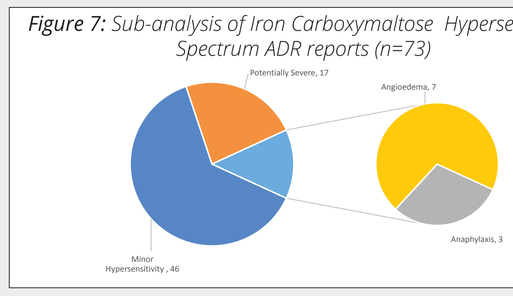

Table 1: *Specific reactions of interest (% of all cases)*

Reaction	Number (% of all cases)
Hypersensitivity spectrum	73 (57%)
Influenza-like-illness symptoms	26 (20.3%)
Infusion site reactions	11 (8.6%)

Table 2: *: Iron carboxymaltose dose to reaction onset timeframe (n=128)*

Dose to ADR onset timeframe	Number (% of all cases)
Same day	102 (79.7%)
Delayed	23 (18%) Next day 8 cases Day 2-7 11 cases Day 8-14 2 cases ≥Day 15 2 cases
Unknown	3 (2.3%)

DISCUSSION

The spectrum of iron carboxymaltose ADRs reported to CARM is similar to those listed on the product datasheet[7]. The majority of these reported ADRs occurred on the day of administration and included events on the hypersensitivity spectrum. The age and gender spread of these New Zealand ADR events, reflected the groups for which this medication is commonly prescribed. The proportions of reports that resulted in Medical Warning and Dangers, is in keeping with the large proportion of hypersensitivity events, which was likely the stimulus for reporting to the CARM. Limitations of this study included the voluntary nature of post-marketing ADR reports received and the potential shortcomings in the descriptive content provided in the reports to CARM.

DISCUSSION

The increase in iron carboxymaltose ADR reports, have mirrored the increase in prescriptions and administrations provided by general practices, since the Special Authority Criteria changes in October 2017. The ADR report profile to CARM suggests that primary care providers should continue to be vigilant about the potential for hypersensitivity events. CARM relies on voluntary reporting of ADRs, and is grateful to primary care medical staff for their contribution of any medication reaction reports to our National and International WHO pharmacovigilance databases.

REFERENCES

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