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Short communication

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Medication errors (MEs) in children are frequent and associated with increased risk of harm [1,2]. Incident reporting of errors is considered a key element in strategies to reduce MEs [3]. Traditionally, analyses of ME reports involve narrative descriptions and frequency counts which may cause important errors to be overlooked or may entail an element of subjectivism [2,4]. A formal approach to analysis of ME reports could involve disproportionality principles used in pharmacovigilance, for example the proportional reporting ratio (PRR) [5]. In large databases, PRRs may help identify potential safety targets which would go unnoticed when using frequency counts [6].

We aimed to explore the utility of disproportionality analysis of medication errors involving hospitalized children.

Method

A retrospective analysis of MEs involving hospitalized children reported to the national mandatory incident reporting system, the Danish Patient Safety Database, was conducted. ME reports were submitted from January 2010 to December 2014 and included both near misses, that is errors intercepted before reaching the patients and errors reaching the patients, involving inpatients aged <18 years in different hospital settings. Prior to the analysis, MEs were categorized according to ME type based on a modified version of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy of MEs and the medication involved (WHO's Anatomical Therapeutic Chemical (ATC) classification system 5th level) [7,8].

The calculation of PRRs is a hypothesis-generating method originally proposed by Evans *et al.* [6]. This method is primarily used in pharmacovigilance to describe the association between medication use and resulting adverse drug reactions. For a given large set of reports, the method calculates the number of expected reports for a particular combination of a medication and an event, given the overall observed frequency of reports for this medication and for this event in the entire dataset. The PPR is then the ratio between the number of observed and expected reports. As a theoretical example, we can calculate the association of paracetamol and wrong dose errors expressed as PRR (table S1). Compared to other reports of all other medications involving dosing errors, the PRR of paracetamol-'wrong dose' is 1.5, indicating an increased prevalence of reporting involving this medication–event pair compared to all other medications.

We calculated PRRs for all medication–event pairs using ME type as the event. A signal was arbitrarily defined as a PRR ≥2, a number of cases ≥3 and a *p*-value <0.05 according to Evans *et al.* (2001) [6]. The size of the PRR reflects the strength of the signal. PRR ≥2 was chosen to highlight medication–event pairs with a higher reporting rate than expected. The null (or expected) value for PRR is one, that is the value when there is no association.

p-Values were calculated by exact Poisson distributions, using the expected count as the Poisson parameter, λ. We ranked the signals according to the excess number of reports, that is the numerical difference between the observed and expected number of reports.

Results

In total, 43 signals were identified from 2071 reported MEs involving 620 different medication–event pairs (table 1). High PRR values were observed for terbutaline-wrong dosage form (PRR = 36.6), metoclopramide-wrong patient (PRR = 20.4), pantoprazole-wrong patient (PRR = 18.7) and sulphamethoxazole and trimethoprim-wrong duration (PRR = 18.7). Top ranking pairs (excess ≥6) included gentamicin-wrong time (excess = 19.3), acetylcysteine-wrong rate (excess = 8.1) and amoxicillin-wrong medication (excess = 6.9).

Discussion

Several medication–event pairs were identified through disproportionality analysis of ME reports involving hospitalized children submitted to a large national reporting system. These pairs were likely to have been unrecognized by traditional

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Table 1.

Analyses of proportional reporting ratio (PRR) for 2071 reports of medication errors involving hospitalized children. Medication–event combinations were ranked according to the excess, that is, the numerical difference between observed and expected reports.

Medication	Event	Observed number of reports	Expected number of reports	PRR	*p*-value	Excess number of reports
Gentamicin (J01GB03)	Wrong time	29	9.7	3.0	<0.0001	19.3
Acetylcysteine (V03AB23)	Wrong rate	9	0.9	9.8	<0.0001	8.1
Amoxicillin (J01CA04)	Wrong medication	9	2.1	4.3	<0.0001	6.9
Caffeine (N06BC01)	Dose omission	9	3.1	2.9	0.0014	5.9
Solutions for parenteral nutrition combinations (B05BA10)	Wrong medication	7	1.5	4.6	0.0002	5.5
Gentamicin (J01GB03)	Wrong duration	8	2.7	3.0	0.0017	5.3
Ceftriaxone (J01DD04)	Wrong medication	7	2.2	3.2	0.0021	4.8
Metoclopramide (A03FA01)	Wrong patient	5	0.2	20.4	<0.0001	4.8
Sodium bicarbonate (B05XA02)	Wrong medication	6	1.5	4.0	0.0010	4.5
Dexamethasone (H02AB02)	Wrong time	6	1.6	3.8	0.0012	4.4
Electrolytes with carbohydrates (B05BB02)	Wrong medication	6	1.6	3.7	0.0015	4.4
Electrolytes (B05BB01)	Wrong medication	7	2.7	2.6	0.0063	4.3
Pantoprazole (A02BC02)	Wrong patient	4	0.2	18.7	<0.00701	3.8
Sulphamethoxazole and trimethoprim (J01EE01)	Wrong duration	4	0.2	18.7	<0.0001	3.8
Vancomycin (J01XA01)	Wrong route of administration	4	0.3	14.8	<0.0001	3.7
Diazepam (N05BA01)	Dose omission	5	1.4	3.7	0.0028	3.6
Sodium phosphate (A06AG01)	Wrong duration	4	0.6	6.8	0.0004	3.4
Sodium phosphate (A06AG01)	Wrong patient	4	0.7	5.9	0.0007	3.3
Diclofenac (M01AB05)	Wrong dosage form	4	0.7	5.5	0.0009	3.3
Methotrexate (L01BA01)	Wrong time	5	1.9	2.7	0.0120	3.1
Terbutaline (R03AC03)	Wrong dosage form	3	0.1	36.6	<0.0001	2.9
Multivitamins and trace elements (A11AA04)	Dose omission	4	1.1	3.6	0.0057	2.9
Cytarabine (L01BC01)	Wrong time	4	1.2	3.4	0.0071	2.8
Ibuprofen (M01AE01)	Wrong patient	4	1.2	3.3	0.0076	2.8
Furosemide (C03CA01)	Unauthorized medication	3	0.2	15.2	<0.0001	2.8
Morphine (N02AA01)	Wrong rate	5	2.2	2.2	0.0267	2.8
Clonidine (N02CX02)	Wrong route of administration	3	0.2	12.4	0.0001	2.8
Hepatitis B immunoglobulin (J06BB04)	Wrong time	3	0.3	10.2	0.0002	2.7
Fentanyl (N01AH01)	Wrong rate	3	0.3	8.9	0.0004	2.7
Paracetamol (N02BE01)	Unauthorized medication	4	1.4	2.9	0.0128	2.6
Calcium levofolinate (V03AF04)	Wrong time	3	0.4	7.7	0.0007	2.6
Piperacillin and enzyme inhibitor (J01CR05)	Wrong patient	3	0.4	7.0	0.0010	2.6
Voriconazole (J02AC03)	Dose omission	3	0.5	6.1	0.0017	2.5
Lomustine (L01AD02)	Wrong medication	3	0.6	5.1	0.0030	2.4
Sodium bicarbonate (B05XA02)	Dose omission	4	1.6	2.5	0.0241	2.4
Potassium chloride (B05XA01)	Wrong medication	4	1.6	2.5	0.0254	2.4
Electrolytes with carbohydrates (B05BB02)	Dose omission	4	1.7	2.3	0.0316	2.3
Cefuroxime (J01DC02)	Wrong duration	4	1.8	2.3	0.0342	2.2
Meropenem (J01DH02)	Wrong patient	3	0.8	3.8	0.0089	2.2
Fluticasone (R03BA05)	Wrong medication	3	0.8	3.7	0.0097	2.2
Calcium folinate (V03AF03)	Wrong time	3	0.9	3.4	0.0126	2.1
Heparin (B01AB01)	Wrong medication	3	1.2	2.6	0.0308	1.8
Prednisolone (H02AB06)	Wrong medication	3	1.3	2.3	0.0413	1.7

methods involving frequency counts and review of narrative descriptions [2].

To our knowledge, no study has previously explored the use of disproportionality analysis of ME reports in children or hospital settings. However, PRRs have been used to identify medication–event pairs involving ME reports from nursing homes [10].

The ME reports have previously been described using frequency counts and narrative descriptions [2]. Using frequency

counts, medications including gentamicin, acetylcysteine, morphine, cefuroxime, diclofenac, ibuprofen and carbohydrates were identified to be involved in the majority of reports. However, the large dataset involving 620 different medication–event pairs prevented us from noticing most of the medication–event pairs identified using PRRs.

The disproportionality analysis used in this study is almost exclusively used in pharmacovigilance. Within safety monitoring of medications, the general principle of the method was to address medication drug reactions associated with consumption of certain medicines, which could ultimately lead to withdrawal of a medication from the market [6]. In relation to incident reporting, disproportionality analysis should be seen as a supplementary tool to help identify events in large databases, which can be targeted through quality improvement [10]. For example, the large number of excess reports on gentamicin and wrong time of administration in our study may suggest that a clinical/organizational follow-up is warranted to reduce this number. Possibly, the organization concerning intravenous medication administration is too vulnerable towards distractions in Danish paediatric hospitals. Further, signals concerned with wrong infusion rate of acetylcysteine and prescribing of a wrong drug (amoxicillin instead of phenoxymethylpenicillin to treat pneumonia) indicate the need for improved communication and training of frontline staff about existing medication guidelines to ensure appropriate medication prescribing and administration. In national incident reporting systems, PRRs may prompt further investigation of potential safety targets and facilitate the development of strategies to reduce MEs. Factors to determine which signals to investigate further involve the strengths of the signal, the potential or actual harm of the medication error events and the potential to prevent the errors from occurring [6].

It should be noted that PRRs involving ME reports, like those PRRs involved in traditional pharmacovigilance, should not be interpreted as measures of association, that is, something similar to the relative risk or incidence rate ratio. It rather reflects the extent to which these medication–event combinations are striking, strange or conspicuous to the clinicians involved in reporting [6].

A strength of the disproportionality analysis is its simplicity and efficiency in processing, even for large datasets. In addition, the calculated PRR is robust towards general underreporting for the given medication and general under-reporting for the given event [6]. However, our ranking of the medication–event combination may to some extent be affected by general under-reporting. If there were a generally low reporting rate for a given medication or an event, we would observe fewer reports involving these. While the PRR would be unaffected, these medication–event combinations would be unlikely to generate high values of the 'excess' that we used for ranking. On the contrary, healthcare professionals may tend to report certain types of events such as ten times overdosing errors or potential or actual serious MEs causing reporting bias. This is supported by reports from another spontaneous reporting scheme [11].

Conclusion

Medication error reports among hospitalized children can meaningfully be subjected to pharmacovigilance-type analyses, such as the PRR, which may provide guidance to identify problems in the handling of medication.

References

1 Manias E, Kinney S, Cranswick N, Williams A. Medication errors in hospitalised children. J Paediatr Child Health 2014;**50**:71–7.
2 Rishoej RM, Almarsdóttir AB, Christesen HT, Hallas J, Kjeldsen LJ. Medication errors in pediatric inpatients: a study based on a national mandatory reporting system. Eur J Pediatr 2017;**176**: 1697–705.
3 Institute of Medicine (US) Committee on Quality of Health Care in America. In: Kohn LT, Corrigan JM, Donaldson MS (eds). To Err is Human: Building a Safer Health System. [Internet] National Academies Press (US), Washington, D.C., 2000; http://www.ncbi. nlm.nih.gov/books/NBK225182/.
4 Cohen MR. Medication Errors, Vol. **1999**. American Pharmaceutical Association, Washington, D.C., 2007.
5 Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJW, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther 2007;**82**:157–66.
6 Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001;**10**:483–6.
7 NCC, MERP. Taxonomy of Medication Errors. [Internet] http:// www.nccmerp.org/sites/default/files/taxonomy2001-07-31.pdf. 1998 (last accessed on 6 August 2017).
8 WHOCC. Structure and principles. [Internet] http://www.whocc.no/atc/ structure_and_principles/. 2011 (last accessed on 25 November 2015).
9 van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 2002;**11**:3–10.
10 Hansen RA, Cornell PY, Ryan PB, Williams CE, Pierson S, Greene SB. Patterns in nursing home medication errors: disproportionality analysis as a novel method to identify quality improvement opportunities. Pharmacoepidemiol Drug Saf 2010;**19**:1087–94.
11 Flynn EA, Barker KN, Pepper GA, Bates DW, Mikeal RL. Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities. Am J Health Syst Pharm 2002;**59**:436–46.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Theoretical example of a PRR calculation (paracetamol and wrong dose).