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Research Article

Benefits of Medication Antidote Signals for the Detection of Potential Adverse Drug Reactions over Contemporary Methods of Pharmacovigilance in Hospitalized Children

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Abstract

Objective: To verify the PPVs of ten-medication antidote signals to facilitate in recognizing the probable ADRs and to evaluate their sensitivity to determine the same ADRs with the contemporary method of pharmacovigilance. **Materials and Methods:** The EMR database of King Abdulaziz University Hospital was make use of, from 01 October, 2014 to 30 April, 2015. Children of either sex between the ages 0-15 with recipients of one of the ten medication antidote signals were selected, recipient' data was analyzed to confirm a harm by medical care, patients with no harm were excluded, such an episode is subsequently confirmed as an ADR by the Naranjo's tool. Additionally, contributing factors of ADRs were also evaluated. **Results:** The incidence rate of ADRs detected from MASs was found to be 27.8%. In contrast, voluntarily reported ADRs were observed as meager 0.88% and from progress notes of the patients, it was merely 0.73%. Remarkably, the total number of MASs observed in this study was 864 and 241 were confirmed as ADRs, the propensity of this scrutiny was apparently in the proportion of approximately1:3. Furthermore, ADRs were significantly higher in 0-1 years of age group and higher propensity of ADRs to the extent of 78.4% were observed with intake of 5-6 drugs. Moreover, preventable ADRs were identified in the range of 0-76.1% while severity of ADRs was detected in the range of 0-42.1%. **Conclusion:** Detection of ADRs by voluntary spontaneous reporting is characterized by under-reporting with the ultimate result of jeopardizing the patient safety. The methodology of ADRs detection by medication antidote signal, in this study has revealed the unique opportunity of high detection rate of ADRs with minimum cost, efforts and high precision. Moreover, this method seems to be quite adaptable and practical in view of the widespread availability of computerized medical information.

Key words: Adverse drug reactions, medication antidote signals, positive predictive value, electronic medical record

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The incidence rate of hospitalized-acquired Adverse Drug Reaction (ADRs) seems to be a crucial factor to decide the quality care of the patients. A wide variation in the range of 0.14-21.5% was observed in the incidence of hospitalized-acquired ADRs in pediatric age group during[1] 2002-2012. Interestingly, neonates and infants have a greater propensity to develop ADRs due to several reasons. These reasons range between incapability to converse, inherent inconsistency in relation to pharmacokinetics and pharmacodynamics of drugs, variation of their disease process in comparison to adults, shortage of pediatric formulation, higher incidence of therapeutic failure, off-label use and unavoidable exposure to the drugs due to maternal use during prenatal breastfeeding[2-9].

In view of the fact that, ideal and standard methods for recognition of ADRs are not yet developed. The current approach for detection of ADRs is heavily dependent on spontaneous reporting system[10,11], yet due to its intrinsic constraints[12,13], additional appropriate and efficient methods are still needed to detect ADRs in order to further augment the drug safety[1,14,15]. Furthermore, it needs to be emphasized that, trigger tools method was demonstrated to have 50 times higher capability to identify ADRs in contrast to spontaneous reporting system in hospital acquired ADRs both in adult and pediatric as well[12,16-18]. Moreover, this distinctive approach had been comprehensively acknowledged by pioneers of pharmacovigilance like the Institute for Healthcare Improvement (IHI) and Institute of Medicine for identification of ADRs[19,20]. The concept of trigger or an electronic clue to detect an ADR from the patient's record by using hospital information system was first developed by the Institute of Healthcare Improvement in 1999 in order to improve the patient safety. Basically, trigger tools are meant for detection of ADRs and not the medication errors, moreover not all the positive triggers are identified as ADRs, hence it can be a clue that may have occurred. Furthermore, medication and laboratory value triggers can be automated and easily captured from the information system, subsequent experts review of the patient's record makes it possible to authenticate it as an ADR[17,18].

Moreover, in pharmacoepidemiological studies, quantitative methods for ADRs detection, such as Medication Antidote Signals (MASs) and laboratory signals, find significant acceptance primarily from large clinical databases of Electronic Medical Records (EMRs) of the hospitals[21]. Their advantages are quite remarkable for including large sample size, being practically economical and their lack of personal prejudice[22]. Furthermore, signals obtained from ADRs trigger tools and EMR databases are expected to give a prospect of detecting unknown, uncommon as well as severe ADRs[12,17,21].

The basic essence of this study comprises of determining the Positive Predictive Values (PPVs) of ten Medication Antidote Signals (MASs) and to validate their probability to detect ADRs. Preventable ADRs and severity of ADRs were also recognized. Moreover, comparison of the sensitivity of ADRs was also performed with ADRs detected by other methods like spontaneous reporting ADRs and from the review of progress remarks of the charts of the patient in the database of the hospital. In addition, one more objective of this study is to evaluate the vital contributing factors of ADRs.

MATERIALS AND METHODS

This present study was basically designed to verify the predictive values of ten medication antidotes to perceive the ADRs and to compare their sensitivities with the common methods of pharmacovigilance. Furthermore, vital contributing factors of ADRs such as age, polypharmacy, preventable ADRs and severity of ADRs and additionally, organs and systems involved in ADRs were also studied. The EMR database of pediatric department inpatient of King Abdulaziz University Hospital was made use of from 01 October, 2014 to 30 April, 2015. The information system of the database provides detailed information on the admission notes of the patient, history of the patient, clinician's comments, prescribed drugs and discharge summary.

Selection criteria of medication antidote signals for the study: An organized search was done to get back appropriate articles/studies in the PubMed, Medline, Scopus and Google scholar website search engine to explore the list of common medical antidote signals from relevant articles during the period of 2000-2015. Furthermore, the authentic reference list of important articles was explored to find the suitable MASs to detect ADRs from EMR of our hospital[17,18,23,24]. A multidisciplinary expert panel of two expert clinical pharmacologists and one pediatric consultant prioritizes an initial list comprising 17 MASs. The expert utilized a 5-point Likert scale to estimate their concord or differences, by their response preferences into agreeing, neutral and disagree categories regarding the probability that every signal would be linked with a probable ADR in patients admitted to the hospital. An additional important parameter was also used for the selection of MASs, for every signal random samples of

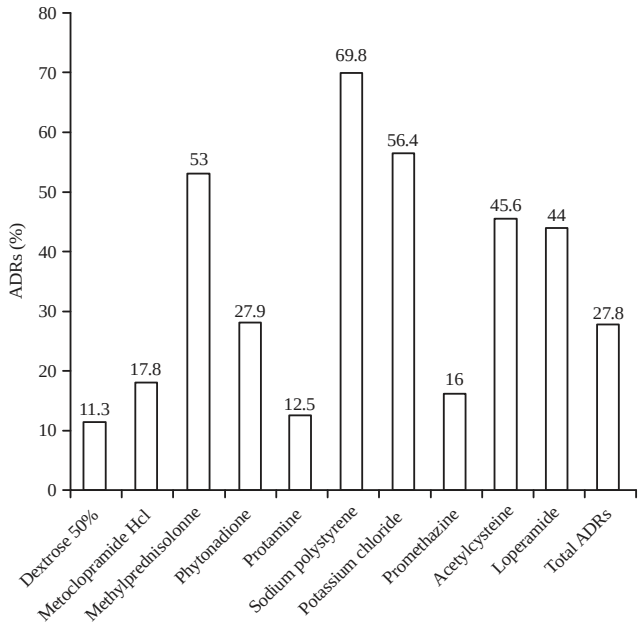

Fig. 1: Medication antidote signals in percentage confirmed as ADRs

50 patients were scrutinized for the existence of ADR. Ten drugs out of 336 commonly employed in inpatient pediatric wards were thus selected as MASs (Fig. 1). The pediatric inpatient database includes 5893 patients with 29794 prescriptions; children of either sex between the ages 0-15 and recipient of at least, one MASs were included in the study, while children with hospitalization of <1 day and prescription with medication errors were excluded.

Basis for identification ADRs from the recipient of MASs: All those patients prescribed with MASs were evaluated by reviewing the patient's data for the recording of a trigger or a clue, which was further analyzed for its symptoms and harm to the patient, e.g., hypokalemia is recognized as a trigger, which develops in some patient, sometimes with no symptom, this is considered as no ADR, however, if the patient develops the symptoms like weakness, cramps, tingling, numbness, nausea and vomiting leading to administration of potassium chloride, then it would be an ADR, according to the definition of World Health Organization, any inadvertent physical harm consequential to or contributed by the medical care could be an ADR, such an episode is subsequently confirmed as an ADR by the most commonly utilized causality assessment algorithm, often described as Naranjo's tool[25], comprising of a concise 10 item questionnaire, the causal correlation is further evaluated as definite, probable, possible or unlikely on precedence to be labeled as an ADR. This was done only by consensus of the expert team. Consequently, Positive Predictive Value (PPV) of each MASs was confirmed.

Moreover, institutional ethical committee approval was acquired prior to conducting this study, all the information of the patient was carefully secured. Before conducting this study, its validity was established by the performance of a pilot study of 50 patients from the EMR database.

Additionally, to compare the sensitivities of ADRs detected by this method with the common methods of pharmacovigilance, a retrospective analysis was done. First for the ADRs reported by voluntary reporting system, then the ADRs were detected from the review of progress remarks of the charts and notes of the patients in the database of the hospital medical records by detecting the relationship of a signal with an episode of an ADR e.g., sodium polystyrene with hyperkalemia.

The assessment of severity of ADRs in clinical epidemiological studies was essentially done in order to determine the basic reason of an ADR[1,26,27]. This was performed by the commonly used methods of Hartwig *et al.*[28] scale. Indeed, the basic essence of pharmacovigilance is the preclusion of ADRs, hence, it is essential to detect preventable ADRs in every epidemiological study[1,26,27]. This was performed by the use of Schumock and Thornton[29] method. It needs to be emphasized that any untoward episode of MASs recipient, was designated as an ADR, preventable ADRs and severity of ADRs were categorized only after fulfilling the criteria of relevant algorithm[25,28,29] additionally to the concurrence of the selected team, comprising of two expert clinical pharmacologists and one pediatric consultant.

Statistical analysis: Scrutiny of all the patient demographic information was done by means of MedCalc statistical software, version 16.8, while the results were revealed in absolute numbers and percentages. The PPVs were calculated as quotients, by taking the incidences of antidote signals as a numerator and the number of signals as a denominator. The analysis of all the data and sensitivity evaluation of ADRs detected by MASs with ADRs determined by routine methods were done by the use of Fisher's exact test with the objective to test for important relations between the groups ($p<0.05$).

RESULTS

Demographic pattern: This study comprises of 5893 patients taken from EMR database of pediatric department inpatient of King Abdulaziz University Hospital, which includes 46.5% males and 53.5% females. The average duration of hospital stay of these patients was 18 (5-28) days.

ADRs identified by MASs and PPV: It was observed that a total of 336 drugs were used in the patients during the duration of the study; the total number of MASs identified from the EMR database during this period was 864 and 241 were confirmed as ADRs with the corresponding PPV as 0.28. (Table 1).

Relationship of age to ADRs detected by MASs: This study has revealed that ADRs numbers are pretty close, in all the age groups (Average ADRs in male was 112 in female 129) (Fig. 2). However, it is worthwhile to mention that in general, females were slightly more in number in comparison to males. Moreover, the maximum susceptibility to ADRs was identified in 0-1 age group (48 males, 59 females and total 109) (Fig. 2) while the lowest numbers of ADRs were observed in the age group 11-15 (5 males, 9 females and total 14) but strikingly, ADRs in female was significantly higher than those in male in this group ($p<0.05$) (Fig. 2).

Correlation of number of drug intake and ADRs identified by MASs: A significant and remarkable observation of this study has shown strikingly higher propensity of ADRs 78.4% with an intake of 5-6 drugs, ($p<0.05$). While it was 5.8% with 1-2 drugs and 15.8% with 3-4 drugs (Fig. 3).

Sensitivity, specificity and positive predictive values of ten medication antidote signals: The outcomes in this study (Table 1) revealed that sensitivity of acetylcysteine 98, potassium chloride 96.4, sodium polystyrene 96.5 and potassium chloride 96.4 were configured as the highest, while phytonadione 72.9, dextrose 50%, 84.7 and methylprednisolone 89 were represented as the lowest in

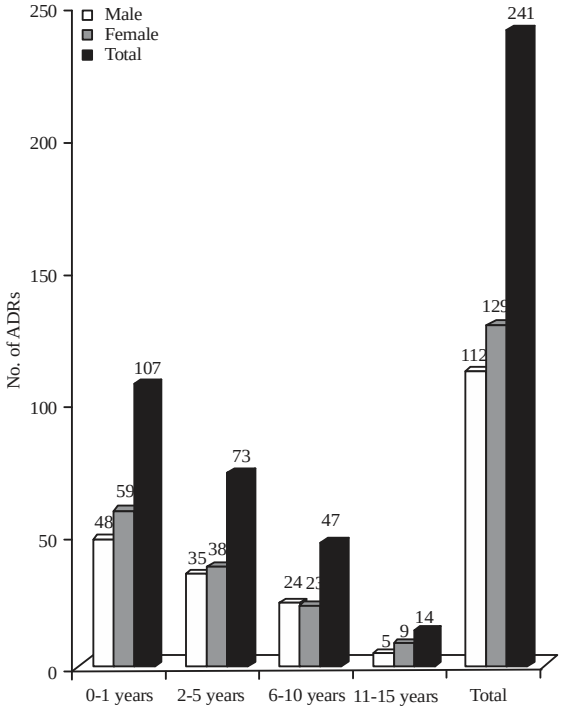

Fig. 2: Age and gender relationship to ADRs detected by medication antidote signals

Table 1: Sensitivity, specificity and positive predictive values of ten medication antidote signals

Antidote signals	Antidote signals confirmed as ADRs	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)
Dextrose 50%	19	89.0 (72.6-98.7)	92.7 (87.4-90.5)	0.30 (0.14-0.52)
Metoclopramide Hcl	41	84.7 (62.5-93.6)	93.3 (91.5-96.2)	0.28 (0.11-0.29)
Methylprednisolone	26	98.0 (37.5-99.8)	97.4 (96.1-98.5)	0.27 (0.10-0.41)
Phytonadione	19	96.4 (94.7-96.8)	83.3 (87.4-92.9)	0.27 (0.14-0.51)
Protamine	01	95.7 (87.3-97.5)	98.6 (96.7-99.3)	0.32 (0.14-0.58)
Potassium chloride	44	94.7 (79.4-96.4)	92.3 (91.2-95.3)	0.29 (0.13-0.47)
Sodium polystyrene	37	96.2 (29.7-98.6)	99.5 (97.3-99.4)	0.28 (0.15-0.53)
Promethazine	22	72.9 (42.6-86.7)	91.7 (91.4-97.2)	0.29 (0.13-0.47)
Acetylcysteine	21	96.5 (87.4-99.2)	87.2 (84.8-87.8)	0.32 (0.16-0.59)
Loperamide	11	94.7 (79.4-96.4)	92.7 (91.3-95.5)	0.29 (0.13-0.47)
Total ADRs	241	92.7 (86.3-95.7)	59.6 (55.4-62.3)	0.28 (0.18-0.47)

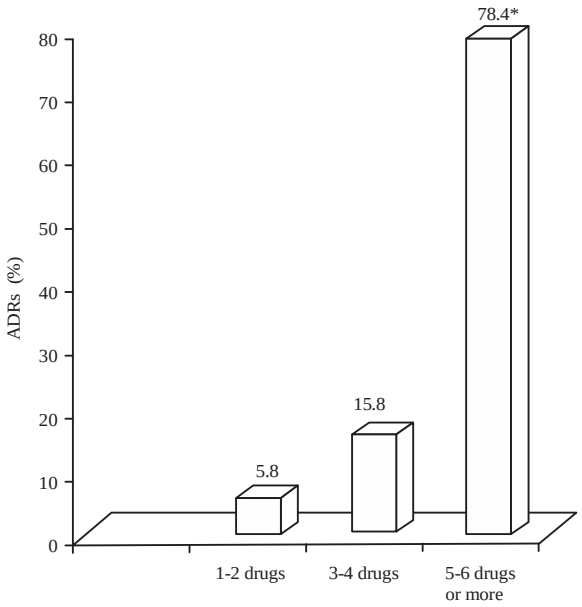

Fig. 3: Correlation of number of drug intake and ADRs identified by MASs, *Within group analysis of less than 5-6 drugs p>0.05

Table 2: Comparison of confirmed ADRs detected by the medication antidote signal method with those detected by voluntarily reported ADRs as well as revealed from the progress notes

Antidote signals	No. of signals confirmed as ADRs n (%)	Voluntarily reported ADRs n (%)	ADRs detected from the progress notes of the patients n (%)	p-value
Dextrose 50%	19 (11.3)	05 (0.08)	02 (0.03)	0.0001*
Metoclopramide	41 (17.8)	07 (0.11)	04 (0.06)	0.0001*
Methylprednisolone	26 (53)	05 (0.08)	06 (0.10)	0.0001*
Phytonadione	19 (27.9)	04 (0.06)	03 (0.05)	0.0001*
Protamine	01 (12.5)	0 (0)	01 (0.01)	0.2500
Sodium polystyrene	37 (69.8)	07 (0.11)	13 (0.21)	0.0001*
Potassium chloride	44 (56.4)	09 (0.15)	05 (0.08)	0.0001*
Promethazine	22 (16)	06 (0.10)	07 (0.11)	0.0001*
Acetylcysteine	21 (45.6)	08 (0.13)	05 (0.08)	0.0001*
Loperamide	11 (44)	02 (0.03)	0 (0)	0.0001*
Total ADRs	241 (27.8)	53 (0.88)	44 (0.73)	0.0001*

*Within group analysis of ADRs detected by medication antidote signals, progress notes and voluntarily reported (p<0.05)

terms of sensitivity. On the contrary, the specificity of medication antidotes (Table 1) was found to be at its peak with protamine 99.5, metoclopramide 98.6 and 97.4, whereas it was at its lowest levels with sodium polystyrene 87.2 and potassium chloride 83.3. As regards average PPVs of antidote signals, it was perceived as 0.28, amongst the ten medication antidotes methylprednisolone, phtonadione and metochlorpropamide has revealed lower values PPVs between 0.28-0.29, while protamine and acetylcysteine has demonstrated the highest PPV of 0.33 (Table 1).

Comparative analysis of sensitivities of ADRs recognized by the MASs method with progress notes and voluntarily reported ADRs: A remarkable difference was observed in a number of ADRs identified by different methods (Table 2). The total number of MASs administered during this study was 864 and 241 were confirmed as ADRs. On the contrary, meager 53 ADRs were reported by spontaneous voluntary reports, while 44 ADRs were detected from the progress reports of the patients. It was further revealed that within-group analysis, ADRs of dextrose 50%, metoclopramide, phytonadione, sodium polystyrene, potassium chloride, promethazine, acetylcysteine and loperamide explicitly exhibited p<0.0001, whereas methylprednisolone demonstrated p<0.001 and protamine was found to be insignificant (Table 2).

Severity of ADRs and preventable ADRs identified by MASs method: The ADRs identified by the MASs method were further revaluated for their severity and this was observed to

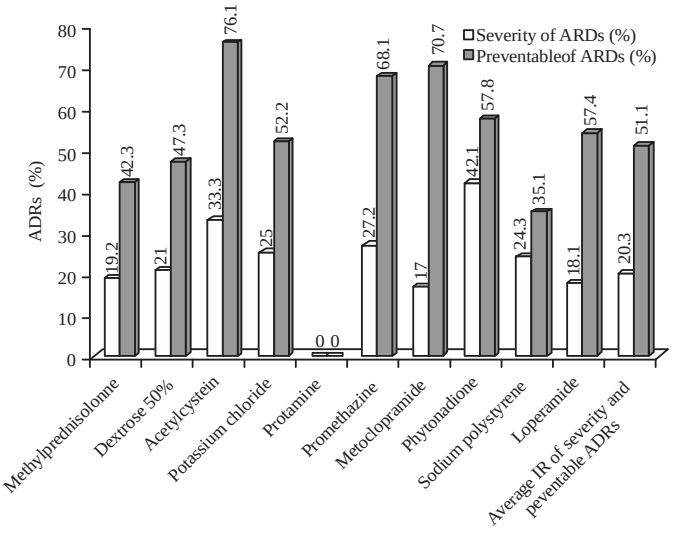

Fig. 4: Relationship of preventable ADRs and severity of ADRs identified by MASs

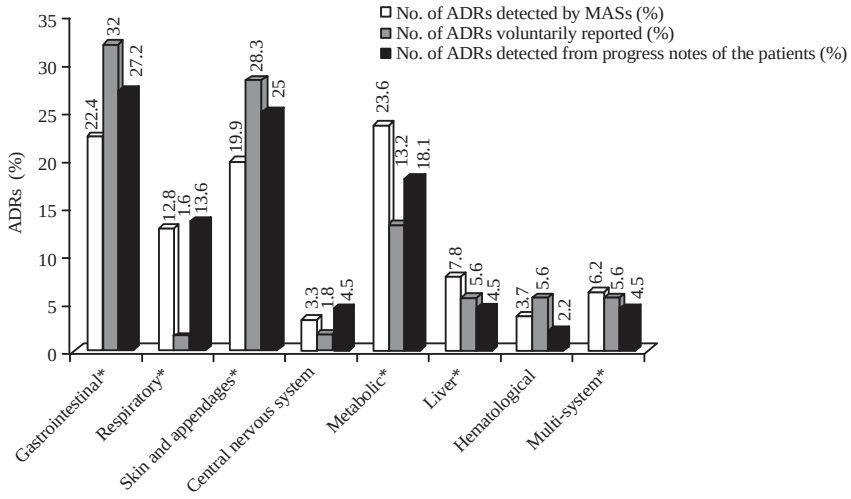

Fig. 5: Incidence of organs and systems involved in ADRs identified by different methods, *p-value by Fischer exact test within the group analysis of ADRs detected by medication antidote signals, progress notes and voluntarily reported

be highest (42.1%) with phytonadione and lowest with protamine (Fig. 4). Whereas the highest degree of preventable ADRs was demonstrated as 76.1% with acetylcysteine and no preventable ADRs was seen with protamine (Fig. 4).

Organs and systems involved in ADRs identified by different methods: Comparative analysis of the organs and systems limplicated in the ADRs detected by all the three methods has revealed strikingly high implication of the gastrointestinal system, followed by skin, respiratory and metabolic systems, $p<0.05$ (Fig. 5). Conversely, the involvement of the central nervous system, liver, hematological system and multi-system were observed to be comparatively quite infrequent and statistically not significant.

DISCUSSION

The distinctive approach of pharmacovigilance incorporates a major role in patient safety and the majority of healthcare providers are principally dependent on spontaneous reporting, which detects just a fraction of ADRs and consequently, the reality of the dilemmas associated with safety continues to be concealed[10-13]. Furthermore, pharmacovigilance is not just to count the bodies but to

identify the ADRs to facilitate and improve the management of patient and circumvent the further impending ADRs. Nevertheless, the detection of the magnitude of ADRs is also essential. This is revealed and highlighted in our study by using a well-planned intensive monitoring method like MASs for ADRs detection and their comparative analysis with the routine methods. Thus, the incidence rate of ADRs in this study by the MASs method was found to be 27.8% (Fig. 1, Table 2). This was undoubtedly and exceedingly remarkable in contrast to voluntarily reported ADRs as meager 0.88% and ADRs detected from progress notes of the patients merely as 0.73% (Table 2). Moreover, the sole contributory factor of inability to provide adequate measures en route to the patient safety is improper and misleading in providing information of the incidence rate of ADRs[1,30]. This highlights and focus the significance of MASs in an assortment of ADRs over the established methods of ADRs reporting as consistent with other similar and recent studies[17,19,21,23,31-33]. Furthermore, there is an imminent requirement to integrate the complementary methods of pharmacovigilance considering the inherent shortcomings of the conventional methods[1,12-15]. This is evidently reported in recent studies that the trigger tools method has the ability to recognize ADRs by 50 times higher than the contemporary method and therefore highly recommended[16-19].

In addition, it needs to be comprehended that depending on the different hospital settings, the selection of medication antidote is decided for the detection of ADRs[33]. The outcome of our study revealed that the average PPVs of the ten selected MASs was 0.28 (0.18-0.47) (Table 1), which emerges to be relatively consistent with other recent studies[23,31,33-35]. Remarkably, eight of the ten MASs selected in our study revealed PPVs in close approximation to several other recent studies[17,31,33,35-37]. It was moreover significant to find in our study that MASs commonly employed in metabolic disorders like potassium chloride and sodium polystyrene, detect a very high number of signals which are identified as confirmed ADRs and their PPVs were at similarity with the findings of other recent studies[18,33-35] (Table 1). Interestingly, another significant observation of this study is that the frequency of ADRs detection, the number of total MASs observed from the EMR database in this study was 864 and 241 were confirmed as ADRs, the propensity of this scrutiny is apparently in the proportion of approximately1:3 (Table 2). Conversely, this study further reveals that when compared with ADRs detection by other methods, nine of the ten medication antidotes were found to be more effective and significant in the detection of ADRs (Table 2). These observations further sustain the discernment that MASs possess the capability of more effectively detecting the ADRs from EMRs. Their utility to track ADRs from EMRs can be utilized for evidence-based prevention of ADRs both in/outpatient of the hospitals[23,24,38].

In this study, only one antidote, i.e., protamine was observed to be deficient in detecting the signals, which could be due to their sporadic utilization in general wards in contrast to the intensive care units and seems to be, an imprecision in selection by the experts of this study (Table 2). An additional, shortcoming of such studies is the requirement of a huge data study for every patient. This is virtually not realistic for performing big epidemiological studies, yet this can be fairly accomplished in the current scenario due the availability of hospital EMR database, which has the prospective potency of adequate sample size, being economical and having no likelihood of prejudice[17,22,24].

In addition, like most of the clinical epidemiological studies, we have also focused in this study on observing the vital contributing factors for ADRs such as age and polypharmacy, preventable ADRs and severity of ADRs and organ and systems involved in ADRs. This provides better insights for specific measures required to avert impending ADRs[1,26,27]. The susceptibility of ADRs was observed significantly higher in the age group 0-1 year, in comparison to other pediatric age groups (Fig. 2). This propensity is elucidated by various factors such as differences in physiological functions, body weight, non-availability of important pediatric formulation and off-label use of drugs[7-9,39,40].

In our study, polypharmacy has also proved to be a noteworthy contributing factor for augmented incidence of ADRs (Fig. 3). Correlation of a number of drug intakes and ADRs identified by MASs were demonstrated statistically significant susceptibility for ADRs with the intake of 5-6 drugs ($p<0.05$). This additive and reciprocal risk factor and important predictor of ADRs needs to be avoided by the clinicians, if not essential[26,41,42]. Identification of preventable ADRs emerges as a sheet anchor for all pharmacoepidemiological studies, because it strengthens the judicious use of drugs which ultimately enhances the drug safety[1,3,26]. This vital aspect was accomplished in our study with the identification of preventable ADRs by medication antidote signals. They were found to be in the range of 0-76.1% (Fig. 4), that seems to be quite confirmative with other studies[41,43,44]. Additionally, to ascertain that the severity of detected ADRs plays an important role to assist in finding of the significant location by healthcare providers for the desired intercession in order to revitalize Pharmacovigilance[27,45]. Hence, this essential facet was also looked after in our study and this has revealed

severity in the range of 0-42.1% (Fig. 4), a systematic review comprised of 34 studies of severity of ADRs depicted a range of 0-66%[26] and other recent studies revealed the severity of ADRs in the range of 2.1-23%, such scenario explicitly extends the hospital stay of these patients and escalates the economic burden on healthcare providers[1,46].

It is an illustrious fact that body defense mechanism of hospitalized children is obviously weaker and suppressed in comparison with non-hospitalized individuals. Moreover, this situation augments the necessity of utilization of multiple medications and under these circumstances, the inherent properties of drugs to produce augmented or bizarre ADRs and potential drug-drug interaction is quite fairly anticipated. Indeed, this can affect an organ, a system or multiple systems. Moreover, this study also demonstrated strikingly high implication of gastrointestinal system in ADRs, followed by skin, respiratory and metabolic systems and our results are fairly consistent with reports of several similar recent studies[26,44,46-48] (Fig. 5).

Undoubtedly, strong measures of pharmacovigilance are one of the key factors to reduce the incidence of hospital acquired ADRs[1,3,49]. The present study strongly provides an unambiguous substantiation of medication antidote signals to identify ADRs in hospitalized children. However, this technique is characterized by the intrinsic setback of making large false positive results[27]. The present scenario of the absence of a definitive standard for identification of ADRs can be overcome by the utilization of global trigger tools and MASs to detect ADRs and compare their efficacy with routine methods from multiple data resources. It needs to be stressed that, comprehensive information generated by the individual medication antidote could be integrated by the healthcare providers in their scheme, to promote the essential aspect of pharmacovigilance.

Finally, cognizance and application of the MASs method might be used to enhance target diseases known to be associated with high rates of adverse reactions (e.g., diabetes). It can also strengthen the coherence of drug therapy as well as improve the clinician's efforts on optimizing patient management.

CONCLUSION

This study highlights that incorporating the methodology of antidote signal evaluations with hospital EMR database provides a bright prospect of detecting the ADRs, which are not likely to be captured by the routine voluntary spontaneous reporting system. It also affords a unique opportunity for a high detection rate of ADRs with minimum cost, efforts and high precision.

REFERENCES

1. Khan, L.M., 2013. Comparative epidemiology of hospital-acquired adverse drug reactions in adults and children and their impact on cost and hospital stay-a systematic review. Eur. J. Clin. Pharmacol., 69: 1985-1996.
2. Demoly, P. and J. Bousquet, 2001. Epidemiology of drug allergy. Curr. Opin. Allergy Clin. Immunol., 1: 305-310.
3. Chien, J.Y. and R.J.Y. Ho, 2011. Drug delivery trends in clinical trials and translational medicine: Evaluation of pharmacokinetic properties in special populations. J. Pharmaceut. Sci., 100: 53-58.
4. Rawlins, M.D., 2004. NICE work-providing guidance to the British National Health Service. New Engl. J. Med., 351: 1383-1384.
5. Castro-Pastrana, L.I. and B.C. Carleton, 2011. Improving pediatric drug safety: Need for more efficient clinical translation of pharmacovigilance knowledge. J. Popul. Therapeut. Clin. Pharmacol., 18: e76-e88.
6. Napoleone, E., 2010. Children and ADRs (adverse drug reactions). Ital. J. Pediatr., Vol. 36. 10.1186/1824-7288-36-4
7. Impicciatore, P., I. Choonara, A. Clarkson, D. Provasi, C. Pandolfini and M. Bonati, 2001. Incidence of adverse drug reactions in paediatric in/out-patients: A systematic review and meta-analysis of prospective studies. Br. J. Clin. Pharmacol., 52: 77-83.
8. Leeder, J.S., 2003. Developmental and pediatric pharmacogenomics. Pharmacogenomics, 4: 331-341.
9. Lindell-Osuagwu, L., M.J. Korhonen, S. Saano, M. Helin-Tanninen, T. Naaranlahti and H. Kokki, 2009. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J. Clin. Pharm. Therapeut., 34: 277-287.
10. Alj, L., M.D.W. Touzani, R. Benkirane, I.R. Edwards and R. Soulaymani, 2007. Detecting medication errors in pharmacovigilance database: Capacities and limits. Int. J. Risk Saf. Med., 19: 187-194.
11. Harmark, L. and A.C. van Grootheest, 2008. Pharmacovigilance: Methods, recent developments and future perspectives. Eur. J. Clin. Pharmacol., 64: 743-752.
12. Khan, L.M., S.E. Al-Harthi, O.I. Saadah, A.B. Al-Amoudi and M.I. Sulaiman *et al*., 2012. Impact of pharmacovigilance on adverse drug reactions reporting in hospitalized internal medicine patients at Saudi Arabian teaching hospital. Saudi Med. J., 33: 863-868.
13. Hazell, L. and S.A. Shakir, 2006. Under-reporting of adverse drug reactions. Drug Saf., 29: 385-396.
14. Lopez, A.D., C.D. Mathers, M. Ezzati, D.T. Jamison and C.J. Murray, 2006. Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. Lancet, 367: 1747-1757.
15. Rodriguez-Monguio, R., M.J. Otero and J. Rovira, 2003. Assessing the economic impact of adverse drug effects. Pharmacoeconomics, 21: 623-650.

16. Sharek, P.J., J.D. Horbar, W. Mason, H. Bisarya and C.W. Thurm *et al*., 2006. Adverse events in the neonatal intensive care unit: Development, testing and findings of an NICU-focused trigger tool to identify harm in North American NICUs. Pediatrics, 118: 1332-1340.
17. Rozich, J.D., C.R. Haraden and R.K. Resar, 2003. Adverse drug event trigger tool: A practical methodology for measuring medication related harm. Qual. Saf. Health Care, 12: 194-200.
18. Resar, R.K., J.D. Rozich, T. Simmonds and C.R. Haraden, 2006. A trigger tool to identify adverse events in the intensive care unit. Joint Commission J. Qual. Patient Saf., 32: 585-590.
19. Aspden, P., J.M. Corrigan, J. Wolcott and S.M. Erickson, 2004. Patient Safety: Achieving a New Standard for Care. National Academy Press, Washington, DC., USA., ISBN-13: 9780309090773, Pages: 350.
20. Classen, D.C., R. Resar, F. Griffin, F. Federico and T. Frankel *et al*., 2011. 'Global trigger tool' shows that adverse events in hospitals may be ten times greater than previously measured. Health Affairs, 30: 581-589.
21. Hauben, M. and A. Bate, 2009. Decision support methods for the detection of adverse events in post-marketing data. Drug Discovery Today, 14: 343-357.
22. Strom, B.L., 2006. Pharmacoepidemiology. 4th Edn., John Wiley & Sons, New York, USA., ISBN-13: 9780470866832, Pages: 910.
23. Takata, G.S., W. Mason, C. Taketomo, T. Logsdon and P.J. Sharek, 2008. Development, testing and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. Pediatrics, 121: e927-e935.
24. Szekendi, M.K., C. Sullivan, A. Bobb, J. Feinglass, D. Rooney, C. Barnard and G.A. Noskin, 2006. Active surveillance using electronic triggers to detect adverse events in hospitalized patients. Qual. Saf. Health Care, 15: 184-190.
25. Naranjo, C.A., U. Busto, E.M. Sellers, P. Sandor and I. Ruiz *et al*., 1981. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther., 30: 239-245.
26. Smyth, R.M.D., E. Gargon, J. Kirkham, L. Cresswell, S. Golder, R. Smyth and P. Williamson, 2012. Adverse drug reactions in children-a systematic review. PLoS ONE, Vol. 7. 10.1371/journal.pone.0024061
27. Davies, E.C., C.F. Green, S. Taylor, P.R. Williamson, D.R. Mottram and M. Pirmohamed, 2009. Adverse drug reactions in hospital in-patients: A prospective analysis of 3695 patient-episodes. PLoS ONE, Vol. 4. 10.1371/journal.pone.0004439
28. Hartwig, S.C., J. Siegel and P.J. Schneider, 1992. Preventability and severity assessment in reporting adverse drug reactions. Am. J. Health-Syst. Pharm., 49: 2229-2232.
29. Schumock, G.T. and J.P. Thornton, 1992. Focusing on the preventability of adverse drug reactions. Hosp. Pharm., 27: 538-538.
30. Krizek, T.J., 2000. Surgical error: Ethical issues of adverse events. Arch. Surg., 135: 1359-1366.
31. Handler, S.M., J.T. Hanlon, S. Perera, M.I. Saul and D.B. Fridsma *et al*., 2008. Assessing the performance characteristics of signals used by a clinical event monitor to detect adverse drug reactions in the nursing home. Proceedings of the American Medical Informatics Association Annual Symposium, November 8-12, 2008, Washington, DC., USA., pp: 278-282.
32. Bates, D.W., R.S. Evans, H. Murff, P.D. Stetson, L. Pizzifferi and G. Hripcsak, 2003. Detecting adverse events using information technology. J. Am. Med. Inform. Assoc., 10: 115-128.
33. Handler, S.M., R.L. Altman, S. Perera, J.T. Hanlon and S.A. Studenski *et al*., 2007. A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. J. Am. Med. Inform. Assoc., 14: 451-458.
34. Kane-Gill, S.L., C.J. Bellamy, M.M. Verrico, S.M. Handler and R.J. Weber, 2009. Evaluating the positive predictive values of antidote signals to detect potential Adverse Drug Reactions (ADRs) in the medical Intensive Care Unit (ICU). Pharmacoepidemiol. Drug Saf., 18: 1185-1191.
35. DiPoto, J.P., M.S. Buckley and S.L. Kane-Gill, 2015. Evaluation of an automated surveillance system using trigger alerts to prevent adverse drug events in the intensive care unit and general ward. Drug Saf., 38: 311-317.
36. Lewis, K.S., S.L. Kane-Gill, M.B. Bobek and J.F. Dasta, 2004. Intensive insulin therapy for critically Ill patients. Ann. Pharmacother., 38: 1243-1251.
37. Jha, A.K., G.J. Kuperman, E. Rittenberg, J.M. Teich and D.W. Bates, 2001. Identifying hospital admissions due to adverse drug events using a computer-based monitor. Pharmacoepidemiol. Drug Saf., 10: 113-119.
38. Park, M.Y., D. Yoon, K. Lee, S.Y. Kang and I. Park *et al*., 2011. A novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database. Pharmacoepidemiol. Drug Saf., 20: 598-607.
39. Kearns, G.L., S.M. Abdel-Rahman, S.W. Alander, D.L. Blowey, J.S. Leeder and R.E. Kauffman, 2003. Developmental pharmacology-drug disposition, action and therapy in infants and children. New Engl. J. Med., 349: 1157-1167.
40. Aagaard, L., A. Christensen and E.H. Hansen, 2010. Information about adverse drug reactions reported in children: A qualitative review of empirical studies. Br. J. Clin. Pharmacol., 70: 481-491.
41. Priyadharsini, R., A. Surendiran, C. Adithan, S. Sreenivasan and F.K. Sahoo, 2011. A study of adverse drug reactions in pediatric patients. J. Pharmacol. Pharmacother, 2: 277-280.
42. Juarez-Olguin, H., G. Perez-Guille and J. Flores-Perez, 2007. Pharmacovigilance and pharmacoepidemiology of drugs in a Mexican pediatric hospital. A proposed guide. Pharm. World Sci., 29: 43-46.
43. Temple, M.E., R.F. Robinson, J.C. Miller, J.R. Hayes and M.C. Nahata, 2004. Frequency and preventability of adverse drug reactions in paediatric patients. Drug Saf., 27: 819-829.

44. Baniasadi, S., F. Fahimi and G. Shalviri, 2008. Developing an adverse drug reaction reporting system at a teaching hospital. Basic Clin. Pharm. Toxicol., 102: 408-411.
45. Bavdekar, S.B. and S. Karande, 2006. National pharmacovigilance program. Indian Pediatr., 43: 27-32.
46. Khan, L.M., S.E. Al-Harthi and O.I. Saadah, 2013. Adverse drug reactions in hospitalized pediatric patients of saudi arabian university hospital and impact of pharmacovigilance in reporting ADR. Saudi Pharm. J., 21: 261-266.
47. Hawcutt, D.B., P. Mainie, A. Riordan, R.L. Smyth and M. Pirmohamed, 2012. Reported paediatric adverse drug reactions in the UK 2000-2009. Br. J. Clin. Pharmacol., 73: 437-446.
48. Buajordet, I., F. Wesenberg, O. Brors and A. Langslet, 2002. Adverse drug events in children during hospitalization and after discharge in a Norwegian university hospital. Acta Paediatrica, 91: 88-94.
49. Avery, A.J., C. Anderson, C.M. Bond, H. Fortnum and A. Gifford *et al*., 2011. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': Literature review, descriptive and qualitative analyses and questionnaire surveys. Health Technol. Assess., 15: 1-234.