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ORIGINAL ARTICLE

Detection of adverse drug reactions by medication antidote signals and comparison of their sensitivity with common methods of ADR detection

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KEYWORDS

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Abstract *Objective:* To determine the PPVs of selected ten medication antidote signals in recognizing potential ADRs and comparison of their sensitivity with manual chart analysis, and voluntary reporting recognizing the same ADRs.

Method: The inpatient EMR database of internal medicine department was utilized for a period of one year, adult patients prescribed at least one of the ten signals, were included in the study, recipient patients of antidote signals were assessed for the occurrence of an ADR by Naranjo's tool of ADR evaluation. PPVs of each antidote signal were verified.

Result: PPV of Methylprednisolone and Phytonadione was 0.28, Metoclopramide and Potassium Chloride – 0.29, Dextrose 50%, Promethazine, Sodium Polystyrene and Loperamide – 0.30, Protamine and Acetylcysteine – 0.33. In comparison of confirmed ADRs of antidote signals with other methods, Dextrose 50%, Metoclopramide, Sodium Polystyrene, Potassium Chloride, Methylprednisolone and Promethazine seem to be extremely significant (P value > 0.0001), while ADRs of Phytonadione, Protamine, Acetylcysteine and Loperamide were insignificant.

Conclusion: Antidote medication signals have definitive discerning evaluation value of ADRs over routine methods of ADR detection with a high detection rate with a minimum cost; Their integration with hospital EMR database and routine patient safety surveillance enhances transparency, time-saving and facilitates ADR detection.

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What is already known about this subject:

- Hospitalized patients are vulnerable to experience ADRs, which frequently conclude in severe ADRs.
- Identification of ADRs contributes to the reduction in morbidity, mortality and economic impact.

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- Constraints in the methods of detecting adverse drug reactions, necessitate exploration for an automated method to revamp drug safety.

What this study adds:

- Antidote signals have discerning evaluation value of ADRs over routine methods, with high detection rate and minimum cost.
- Every fourth evaluation of antidote signal culminates in a confirmed ADR.
- Their integration with hospital EMR database and routine patient safety surveillance enhances transparency, time-saving and facilitates ADR detection.

1. Introduction

Of all the counteractive harm to hospitalized patients, contribution of drugs as a source of adverse drug reactions (ADRs) is highly alarming (Eliasson, 2006; Lopez et al., 2006). They are the subdued cost of drug therapy, in addition, they are coupled with, unconstrained depressing effects on morbidity and mortality of hospitalized patients (Khan, 2013; Wester et al., 2008; Davies et al., 2009) and the top of it, an increase in resource utilization (Bond and Raehl, 2006; Krähenbühl-Melcher et al., 2007; Rodriguez-Monguio et al., 2003). Hospitalized patients are more vulnerable to experience ADRs and quite often concluding in the form of severe ADRs (Khan, 2013; Bavdekar and Karande, 2006). Ubiquitously, judicious identification of ADRs significantly contributes to the reduction of its severity, morbidity and mortality as well as its economic impact (Khan, 2013; Bavdekar and Karande, 2006; Avery et al., 2011). Knowledge of pharmacovigilance is responsible to recognize, appraise, realize and avoid ADRs with the eventual mean to develop secure and rational utilization of medication (Khan, 2013; Avery et al., 2011; Mehta et al., 2008). Contemporary methods of pharmacovigilance have certain limitations reminiscent of under reporting, inability to find the incidence rate, size of the population exposed and biased in collection of drug exposure (Montastruc et al., 2006; Smyth et al., 2012). Pharmacovigilance gives a critical gauge of the burden of drug induced morbidity and about half of ADRs could be avoided with improved prescription care (Khan, 2013; Smyth et al., 2012; Chien and Ho, 2011). Detection of ADRs is a critical task and furthermore worldwide observation methods are heavily dependent on voluntary reporting that is reminiscent of significant underreporting of the factual prevalence of ADRs (Montastruc et al., 2006; Aagaard and Hansen, 2010). In post marketing surveillance, there is a progressive escalation of quantitative methods, such as signal detection of ADRs, principally due to availability of large clinical databases of electronic medical records (EMRs) (Hauben and Bate, 2009). It is characterized by potential strength of abundant sample size, virtually inexpensive and devoid of recall or individual bias, and moreover inpatient EMR data could specifically afford precise diagnosis, exact laboratory and radiological reports, literal dosage, administration time and other noticeable actions throughout hospitalization of patients (Strom and Kimmel, 2006).

In view of the aforementioned recompenses, medication antidote signals are utilized by the healthcare providers as a supplementary mechanism to detect ADRs (Handler et al., 2007). This is also recommended for recognition of ADRs by the Institute for Healthcare, a pioneer in patient safety (Rozich et al., 2003; Takata et al., 2008). Furthermore, clinicians can focus mainly on those antidote medication signals which are more efficacious and precise to identify ADRs rather than evaluating trivial antidote medication signals (Bates et al., 2003). The objectives of this study were to find out the PPVs of selected ten medication antidote signals with the intention of exploring their significance in recognizing potential ADRs. In addition to this, to explore the comparison of the sensitivities of other ADR detection methods which include manual chart analysis, and voluntary reporting, and recognizing the same ADRs by utilization of the hospital EMR database.

2. Method

The inpatient EMR database of internal medicine department of King Abdulaziz University Hospital was utilized from Jan 01, 2013 to Dec 31, 2013. The database consists of 7587 adults, hospitalized patients with 37543 prescriptions. The information system of the database permits to get the information of the admission and discharge notes of the patient, patient's history, drug prescription and clinicians' observations.

2.1. Verification of antidote signals evaluated

A professional group of experts comprising three clinical pharmacologists and one medical internist critically studied and randomly approved ten drugs among the 362 drugs utilized in the hospitals with high frequencies, as antidote medication signals for evaluation, however, selection of antidote signals was based on previous analogous studies (Rozich et al., 2003; Institute for Safe Medication Practices, 2013; Morimoto et al., 2004). All adult patients of either sex were included in the study, who were prescribed at least one of the ten signals (Table 1).

2.2. Potential adverse drug reaction detection procedure

Recipient patients of antidote signals were assessed for the occurrence of an ADR by Naranjo's tool of ADR evaluation

Table 1 List of drugs selected for the study as medication antidotes administered by parenteral route except Loperamide.

Medication antidotes	Signals
Dextrose 50%	Hypoglycemia
Metoclopramide	Nausea and vomiting in relation to drug use
Methylprednisolone	Hypersensitivity skin reaction
Phytonadione	Bleeding with warfarin
Protamine	Heparin induced toxicity
Sodium Polystyrene	Drug induced hyperkalemia
Potassium Chloride	Drug induced hypokalemia
Promethazine	Hypersensitivity skin reaction
Acetylcysteine	Paracetamol toxicity
Loperamide	Antimicrobial induced diarrhea

– a 10-item questionnaire, the strength of a causal relationship is subsequently judged as "definite, probable, possible or unlikely prior to be considered as ADR (Naranjo et al., 1981). PPVs of each antidote signal were verified. Study procedure designed was agreed by the institutional ethics committee. Discretion of information obtained was secured during the study. Suitable study design, thus developed for the detection of antidote medication signal was validated by accomplishing a pilot study of 50 patients from EMR database.

Furthermore, for a comparative analysis of the sensitivity of ADRs detected by antidote signals with common methods of ADR detection, retrospective analysis of the association of a signal with the occurrence of an ADR (Dextrose 50% with hypoglycemia) was carried out from obvious records depicted in the progress remarks of patients' chart and the database of hospital's administration to review ADRs reported by voluntary reporting system. The evaluation of severity of ADRs was done by the utilization of Hartwig's scale (Hartwig et al., 1992), while assessment of preventable ADRs was performed by the method of Schumock and Thornton (1992).

2.3. Statistical analysis

Patient demographic information was scrutinized by the utilization of SPSS data version 19.0 and the results were expressed in absolute number and percentages. Regarding PPVs, they were computed as quotients, where the episodes of an antidote signal recognized as an ADR were taken as the numerator and the number of signals as the denominator. The entire data were analyzed and comparison of sensitivities of the common methods of ADRs with ADRs detected by antidote signals was executed by the utilization of Fisher's exact test for significant association between groups ($P < 0.05$).

3. Results

3.1. Characteristics of study population

(Fig. 1) The total population of patients acquired in this study from the database during a period of one year was 7587, comprising 4022 males and 3565 females, ethnically 6297 were Saudis and 1290 were non-Saudis. The average age of this population was 62 ± 18 years, and the average duration of hospital stay of these patients was determined as 21 (6–35) days.

3.2. Number of antidote medication signals detected

During the period of one year of study 362 drugs were administered to the patients, the total number of antidote medication signals detected was 1019, of them 302 were recognized as ADRs with an average PPV of 0.29.

3.3. Sensitivity, specificity and positive predictive value of each medication antidote signal

(Table 2) The highest sensitivity of antidote signals was observed with Acetylcysteine 100 (30.5–100), Protamine 100 (30.5–100), Potassium Chloride 100 (95.9–100) and the lowest sensitivity was observed with Phytonadione 71.4 (53.7–85.3) and Loperamide 60 (15.4–93.5). This study divulges the overall specificity of antidote medication signals as 58.8 (56.5–61.2), the highest specificity of antidote medication signals was observed with Protamine and Acetylcysteine as 99 (98.3–99.6) and Loperamide 99 (98.2–99.5), while lowest specificity was observed for Sodium Polystyrene 86.1 (83.9–87.9) and Potassium Chloride 77.4 (75.1–79.6). However, specificity of other signals descends in the transitional category, like Dextrose 50%, 94.1 (92.6–95.5), Methylprednisolone 91.4 (89.6–92.9) and Phytonadione 92.1 (90–93.6). Concerning the

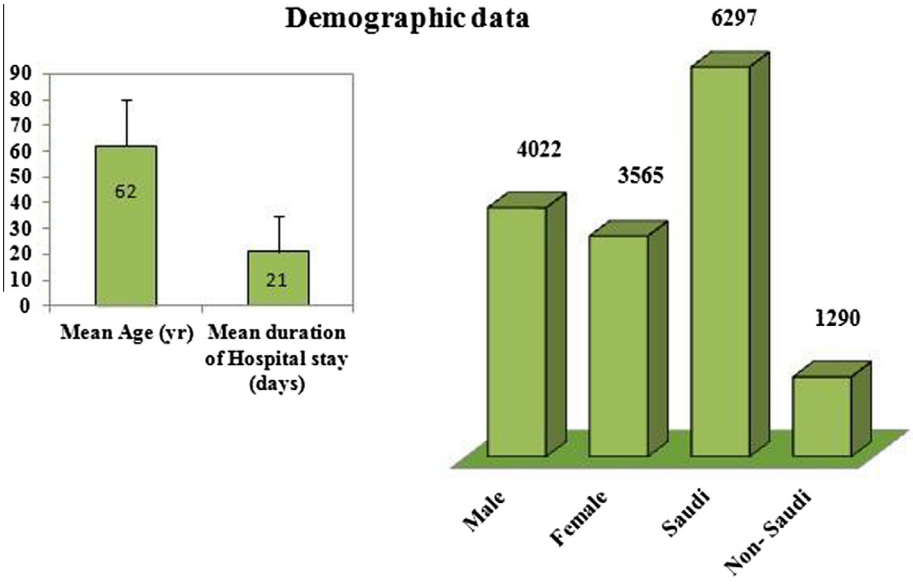

Figure 1 Demographic data of 7589 patients recipient of specific antidote medications.

positive predictive value of antidote signals, this was revealed as in the range of 0.16–0.54, Phytonadione and Methylprednisolone had shown the lowest PPV of 0.28 (0.11–0.43) while Protamine revealed the highest PPV of 0.33 (0.18–0.62).

3.4. Objective analysis and comparison of ADRs sensitivities, perceived by diverse methods

(Table 3) From the total 1019 antidote signals 302 were identified as ADRs by Naranjo's tools of ADR evaluation, 41 ADRs were recognized from patients' progress remarks, while 23 ADRs were authenticated as voluntarily reported. In comparison of confirmed ADRs of antidote signals with other methods (within the group analysis), ADRs of Dextrose 50%, Metoclopramide, Sodium Polystyrene, Potassium Chloride, Methylprednisolone and Promethazine seem to be extremely significant (P value > 0.0001), while ADRs of Phytonadione, Protamine, Acetylcysteine and Loperamide were found to be insignificant.

3.5. Preventable ADRs and Severity of ADRs from antidote medication signals confirmed as ADRs

This study revealed the severity of ADRs in the range of 4.7–26.3%; most of them were related to the administration of Dextrose 50% and minimum with Promethazine (Fig. 2). Regarding preventable ADRs, Protamine, Acetylcysteine and Loperamide seem to be associated with maximum preventable ADRs–66.6%, while minimum preventable ADRs were depicted with the utilization of Sodium Polystyrene as 26% (Fig. 2).

4. Discussion

Pharmacovigilance is an indispensable constituent of patient care and surveillance and therefore excellent assertive pharmacovigilance methods are required to enhance the crucial aspect of drug safety with the prime aim of avoiding potential ADRs (Khan, 2013; Pal et al., 2013). The current lifecycle approach for various therapeutic agents necessitates a customary safety monitoring and contemporarily this is best managed by a

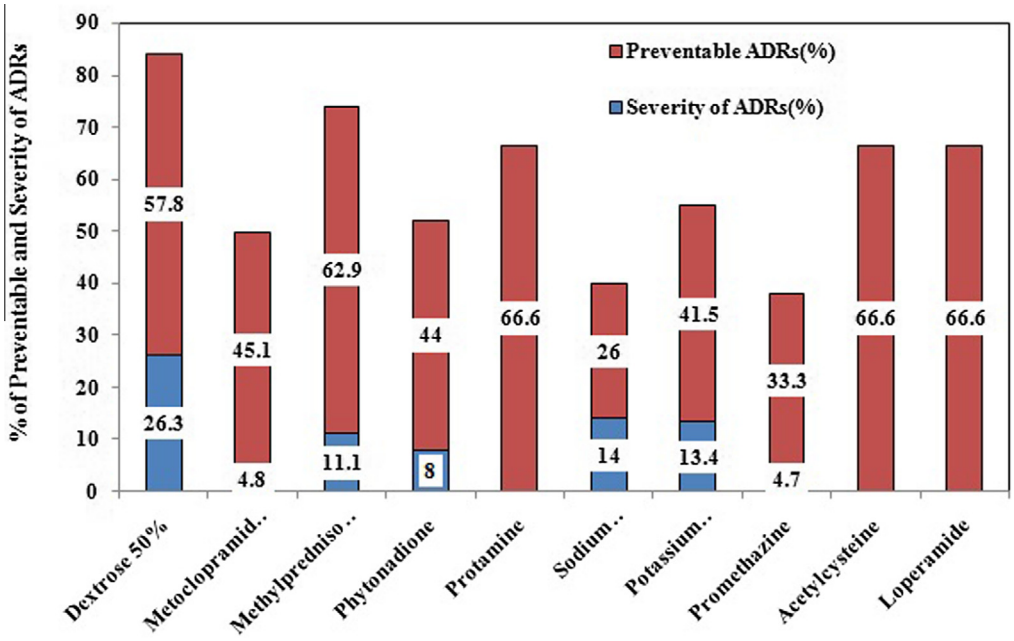

Figure 2 Bar diagram depicting the preventable ADRs and severity of ADRs detected by antidote medication signals confirmed as ADRs.

Table 2 Depicting 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)
Acetylcysteine	03	100 (30.5–100)	99.1 (98.3–99.6)	0.33 (0.18–0.62)
Dextrose 50%	19	82.6 (61.2–94.9)	94.1 (92.6–95.5)	0.30 (0.16–0.54)
Methylprednisolone	27	90 (73.4–97.8)	91.4 (89.6–92.9)	0.28 (0.11–0.43)
Metoclopramide	62	93.9 (85.2–98.3)	98.2 (97.2–98.9)	0.29 (0.13–0.47)
Phytonadione	25	71.4 (53.7–85.3)	92.1 (90 93.6)	0.28 ((0.11–0.43)
Potassium Chloride	89	100 (95.9–100)	77.4 (75.1–79.6)	0.29 (0.13–0.47)
Promethazine	21	95.5 (77.1–99.2)	93.6 (91.9–94.9)	0.30 (0.16–0.54)
Protamine	03	100 (30.5–100)	99 (98.3–99.6)	0.33 (0.18–0.62)
Sodium Polystyrene	50	94.3 (84.3–98.7)	86.1 (83.9–87.9)	0.30 (0.16–0.54)
Loperamide	03	60 (15.4–93.5)	99 (98.2–99.5)	0.30 (0.16–0.54)
Average (SD)	30.2 (28.5)	93 (89.7–95.5)	58.8 (56.5–61.2)	0.29 (0.16–0.54)

Table 3 Comparison of the sensitivities of common methods of ADR detection with ADRs detected by antidote signals.

Antidote signals	Antidote signals confirmed as ADRs©	Voluntarily reported ADRs (%)	Obvious ADRs recognized from progress notes of the patients (%)	*P-value
Dextrose 50%	19	0 (0)	04 (21)	0.0001***
Metoclopramide HCl	62	04 (6)	07 (11)	0.0001***
Methylprednisolone	27	03 (11)	06 (22)	0.0017**
Phytonadione	25	10 (40)	04 (16)	1.0000§
Protamine	03	0 (0)	01 (33)	0.2500§
Sodium Polystyrene	50	03 (6)	15 (30)	0.0001***
Potassium Chloride	89	0 (0)	07 (8)	0.0001***
Promethazine	21	01 (5)	07 (33)	0.0001***
Acetylcysteine	03	0 (0)	01 (33)	0.2500§
Loperamide	03	02 (67)	0 (0)	0.1165§
Total ADRs	302	23 (8)	52 (17)	0.0001***

© ADRs confirmed using the agreement of Naranjo's scale causality assessment tool.
* *P*-value was determined by Fischer exact test, within the group analysis of ADRs detected by medication antidote signals, review charts and voluntarily reported.
** Very significant.
*** Extremely significant.
§ Not statistically significant.

spontaneous reporting system (Alj et al., 2007; Härmark and van Grootheest, 2008). Nevertheless, this highly accepted method has inherent limitations (Hazell and Shakir, 2006; Khan et al., 2012). It is highly imperative to incorporate supplementary methods to scrutinize medicine safety (Lopez et al., 2006; Rodriguez-Monguio et al., 2003). Trigger tools method had revealed to be quite superior to voluntary reporting system with a 50 fold higher ability to detect ADRs both in hospitalized adults and pediatric patients (Rozich et al., 2003; Khan et al., 2012; Resar et al., 2006; Sharek et al., 2006). This approach had received recommendation of both Institute for heaithcare improvement (IHI) and Institute of Medicine for the detection of hospital acquired ADRs (Institute of Medicine Report, 2004; Institute for Healthcare improvement, 2009).

Signals produced by the ADRs trigger tools and obtained from electronic medical record database are deemed to provide the opportunity not only for the detection of unknown, rare and severe ADRs; but also have additional benefits of high detection rate with minimum cost (Hauben and Bate, 2009; Rozich et al., 2003; Khan et al., 2012).

The propensity with which this study remarkably revealed substantial comparison of PPVs for almost all the medication antidotes in concordance to the results of past studies (Handler et al., 2007; Rozich et al., 2003), significantly demonstrated its prime utility in the prompt detection of ADRs. Furthermore, importance of effectiveness of signals, their specificity and sensitivity in the detection of ADRs from EMR database was highlighted in a recent study (Park et al., 2011), similar reflections were observed in our study with high sensitivity of seven medication antidotes and high specificity of eight medication antidotes acquired from EMR database.

It needs to be emphasized that, utilization of medical antidotes to identify potential ADRs in hospitalized patients, distinctly vary between the multiple discipline of hospitals like general wards, medical, pediatric and surgical ICUs as well as nursing home settings (Handler et al., 2007). In comparison to the other medication antidotes, the frequency of ADR detection of Protamine, Acetylcysteine and Loperamide, in our study was found to be low (Table 2), due to infrequent use in general wards of internal medicine, notwithstanding their PPVs are quite comparable to the results of other studies (Handler et al., 2007; Jha et al., 2001).

The average PPVs of the ten medication antidotes selected in our study was found to be 0.29 (0.16–0.54), this is in quite close approximation with other similar studies (Handler et al., 2007; Takata et al., 2008). The PPVs of Dextrose 50% in our study was revealed as 0.30 (0.16–0.54), this seems to be quite consistent with the findings of a systematic review of 12 studies with ten medications and seven antidotes and other studies (Handler et al., 2007; Lewis et al., 2004; Rea et al., 2007), depicting PPVs of 0.33 (0.27–0.27). The PPVs for Phytonadione perceived in our study was 0.28 (0.11–0.43), which is at parity with other studies including the 3 studies of a systematic review, in the range of 0.02–0.30 (Handler et al., 2007; Hartis et al., 2005). Promethazine in our study excludes its utilization in the patients as sedative–hypnotic and by oral route, which makes its indication more specific for allergic reactions, its PPVs were determined as 0.30 (0.16–0.54), and in several studies, remarkable comparative PPVs of antihistaminics were observed in a similar range (Handler et al., 2007; Jha et al., 2001).

Hyperkalemia and hypokalemia observed in hospitalized patients exclusively after medications are quite evident by the utilization of Sodium Polystyrene and Potassium Chloride to avert the development of cardiac arrhythmias. The PPV of Sodium Polystyrene depicted in our study was 0.30 (0.16–0.54) and the PPV of Potassium Chloride was 0.29 (0.13–0.47); furthermore, it was fairly noticeable that their number of signals confirmed as ADRs was also quite high, while comparative PPV of Sodium Polystyrene in another study was revealed in the range of 0.06–0.12 (P-value < 0.5) and PPVs of Potassium Chloride in 2 studies were shown as 0.03–0.03 (P-value < 0.5), nevertheless both the values were slightly lower than our findings (Handler et al., 2007).

Moreover, it was notable that due to most common use in our hospital, we selected Methylprednisolone as a medication antidote in contrast to oral and topical steroids utilized in two studies of systematic review (Handler et al., 2007), and the

PPV of our study in the range of 0.11–0.43 was a comparative reflection of their observation. It needs to be emphasized that, signals of Metoclopramide, Acetylcysteine and Loperamide were considered only after authentication of their utilization for drug induced ADRs. Metoclopramide was commonly utilized as anti-emetic, demonstrated its PPV as 0.29 (0.13–0.47) in our study, which was evidently lower than the PPVs of anti-emetic drugs 1.55 (0.80–2.69) observed in a study (Takata et al., 2008). However, this disparity was statistically insignificant (P-value < 0.5). Finally, the only antidote administered by the oral route in this study was Loperamide, and the observed PPV was 0.26 (0.11–0.34), which seems to be discreetly higher than that observed in the three recent studies (Handler et al., 2007), depicting PPV in the range of 0.09 (0.06–0.13), although the difference was statistically not significant (P-value < 0.5).

Evidently, consistent with the findings of systematic review (Handler et al., 2007), this study reveals that, considering the PPV of Methylprednisolone and Phytonadione, Metoclopramide, Potassium Chloride, Dextrose 50%, Promethazine, Sodium Polystyrene and Loperamide seem to be quite realistic in recognition of potential ADRs in hospitalized patients in general wards. Additionally, it is also notable from this study that relatively every fourth evaluation of antidote signal culminates in a confirmed ADR.

Secondly, our results of comparative analysis of ADRs by different methods (Table 3), with quite fairness have depicted the superiority of seven out of ten antidote signals over other methods like chart review and voluntary reporting methods. Distinctly this reiterates and reinforces the perception that medication antidote signals characterize the most robust method to assess the EMR database for detection of ADRs. Furthermore, potential benefits are inconsequential if this method fails to improve the quality of healthcare with reduction of healthcare costs. Such method amazingly reduced healthcare cost by $760,000 per year in a teaching hospital (Kaushal et al., 2006). Their ability to identify ADRs is substantially greater than the well known established methods and this could, not only form the basis for tracking ADRs from EMR database, but also provides the groundwork for evidence based prevention method to reduce the risk of ADRs to our inpatients (Takata et al., 2008; Park et al., 2011; Szekendi et al., 2006).

Finally, determination of preventable ADRs in all epidemiological studies appears to be crucial with the aim of reinforcing the rationality of drug therapy and eventually augmenting drug safety (Khan, 2013; Chien and Ho, 2011). Furthermore, this vital aspect is additionally strengthened by including assessment of severity of ADRs in any study, to facilitate recognition of critical areas by healthcare professionals for appropriate intervention to vitalize pharmacovigilance (Khan, 2013; Khan et al., 2012). Aforementioned statements were apparently fulfilled in our study with the detection of preventable ADRs by antidote signals in the range of 26–66.6% (Fig. 2). Other similar studies have also revealed the median preventability of ADRs in hospitalized patients in the range of 35–46% (Krähenbühl-Melcher et al., 2007; Mehta et al., 2008), and the range of severity of ADRs perceived by antidote signals in our study was 4.7–26.3%, (Fig. 2) almost identical with nine studies of hospitalized adult patients in a recent systematic review (Khan, 2013). In consequence of the above findings it seems to be quite comprehensible that assessment of these vital components of ADRs is indispensable for drug safety. Therefore, effective emphasis and alertness of these factors would play an important role in reducing the burden of ADRs, reduction of health care cost with enhanced quality care of the patients (Khan, 2013; Rodriguez-Monguio et al., 2003).

The number of signals detected by Acetylcysteine, Protamine and Loperamide, was observed to be very less in this study, however the reason could be their infrequent use in general wards in comparison to ICU setting, whereas selection criteria were based on high frequency utilization in hospitals, nevertheless antidote signals were randomly selected. Furthermore, utilization of antidote signals incorporates data study of every patient, this is not feasible for conducting large epidemiological studies, nevertheless hospital EMR database could make it practicable.

Conversely, our study seems to be significant in affording inclusive acquaintance on the importance of medication antidote signals in detecting hospital acquired ADRs in adults. Furthermore, comparison of ADRs detected by antidote medication signals with multiple data sources may facilitate ADR detection rates, in view of the fact that still; definitive standards for identification of ADRs are yet to be established. The comprehensive information of individual antidote signal could be utilized by healthcare team in hospitals, to be incorporated in their system in order to magnify ADR detection strategies, further studies are required to improvise and augment the performance characteristics of individual medication antidote signal.

5. Conclusion

- Antidote medication signals have definitive discerning evaluation value of ADRs over routine methods of ADR detection.
- Relatively every fourth evaluation of antidote signal culminates in a confirmed ADR.
- They are also characterized by a high detection rate with minimum cost; their integration with hospital EMR database can further enhance their transparency and time effectiveness.
- Hence, they are recommended to be incorporated in the routine patient safety surveillance system to facilitate ADR detection.

Disclosure

There is no conflict of interest in this study.

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