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Research Article

INCIDENCE, SEVERITY AND FINANCIAL BURDEN ASSOCIATED WITH SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) THAT ARISE IN CLINICAL TRIALS

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ABSTRACT

Aim: Present study was carried out to assess the incidence of suspected unexpected serious adverse reactions (SUSARS) and assessment of causality, severity and additional financial burden associated with reported suspected unexpected serious adverse reactions.
Materials and Methods: A prospective spontaneous reporting study was conducted over a period of six months in contract research organization at Quest life sciences, Chennai. Who probability scale was used for causality assessment. Reported suspected unexpected serious adverse reactions were classified according to wills & brown classification and assessed for severity using scale developed by hart wig et al. Average cost incurred in treating an SUSARS was calculated.
Results: A total of 49 suspected unexpected serious adverse reactions were reported and evaluated from 149 healthy volunteers showing an overall incidence of 32.89%. About 28 (2.43%) healthy volunteers experienced an suspected unexpected serious adverse reactions and 2 (0.13%) volunteers were hospitalized due to Suspected Unexpected Serious Adverse Reactions. Gastrointestinal system (25.00%) was most commonly involved. Drug class most commonly associated was antimicrobials (79.59%). 69.38% Suspected Unexpected Serious Adverse Reactions were classified as "possible" in view of causality, while 69.38% were found to be "mild" in case of severity. Most volunteers (97.95%) recovered from the Suspected Unexpected Serious Adverse Reactions .79.59% Suspected Unexpected Serious Adverse Reactions were augmented or type A. Average cost incurred in treating an Suspected Unexpected Serious Adverse Reactions was found to be Rs.2653 in India.
Conclusion: Awareness about suspected unexpected serious adverse reactions reporting is still poor amongst contract research professionals in India. Incidence of suspected unexpected serious adverse reactions has to monitor carefully and has to report immediately. The bioethical considerations to be taken into account in determining and implementing health policy and specialties to harmonizing and strengthening drug-safety surveillance measures. Average cost incurred for conducting clinical trial was higher.

Keywords: Suspected Unexpected Serious Adverse Reactions (SUSARS), Prospective Spontaneous reporting, Causality, Severity, Cost.

INTRODUCTION

After the discovery and synthesis of a new drug, and parallel to product development, it undergoes toxicological and pharmacological tests in animals, followed by clinical trials in humans. Although the pre-marketing investigation, preclinical and clinical, of a new medicinal product is carefully performed and critically assessed, it does not always reveal all possible effects, side-effects or adverse reactions. A product which the drug regulatory agency authorizes for marketing still requires intensive post marketing monitoring. Many adverse reactions can be detected only after the medicinal product has been prescribed to, and used by, a large number of patients. This environment, with multiple potential new co-factors of real life, cannot be replicated in clinical trials. The introduction of a new medicinal product, therefore, always carries unknown risks, as numerous instances during the past decades have demonstrated. In this situation the alertness of the prescribing physician and the quality of the operational system for reporting adverse reactions are crucial.

Verification of a new potential and harmful reaction often requires the collection and review of reports from different countries, and these reports must be properly assessed and validated. One major problem has been that concepts of diagnosis and the terms used to designate adverse reactions vary from country to country. European Medicines Agency, Member States and interested parties to draw up and to publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions. This detailed guidance sets out guidance on the collection, verification and presentation and decoding procedures of adverse event/reaction reports arising from clinical trials on medicinal products for human use. In addition, it sets out the responsibilities of the concerned parties. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluation shall be reported to the sponsor according to the reporting requirements within the time periods specified in the protocol.

For trials in high morbidity and/or high mortality disease, where efficacy end-points could also be adverse reactions reported as SUSARs or when mortality or another "serious" outcome (that may potentially be reported as a SUSAR) is the efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised when the blind is systematically broken. Under these and similar circumstances, it may be appropriate to reach agreement with competent authorities in advance concerning serious events that would be treated as disease related and not subject to systematic unblinding and expedited reporting. Modalities for reporting these adverse reactions must be clearly defined in the protocol. For such trials, sponsors are strongly encouraged to appoint an independent Data Monitoring Committee in order to review safety data on the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and operation of a Data Monitoring Committee must be described in the protocol. The Data Monitoring Committee opinion and recommendations should be notified as soon as possible by the sponsor to the competent authority and the Ethics Committee in the concerned Member State where they qualify for expedited reporting

MATERIALS AND METHODS

Data Collection

A prospective spontaneous reporting study approved by the Institutional Ethics Committee (IEC) was conducted over a period of six months from October 2011 to March 2012. The study was coordinated by M.Phil research scholar. Volunteers of either sex in difference of age who are qualified in medical fitness' and got an prior inform concern from the volunteers' about trails were included in the study.

WHO definition of an SUSARS was adopted. Spontaneous reporting system was the method followed for monitoring SUSARS. Medical staff, medical post graduates, nursing staff and volunteers were educated and encouraged to report SUSARS by creating awareness

through brief presentations and conducting clinical meetings. SUSARS notification forms were kept in the nursing stations of organization wards and the ICU. M.Phil research scholar students played a crucial role in monitoring the studies and encouraging the physicians to report. Any reaction noted by the student was brought into the notice of the physician, who if convinced enough of the drug cause of reaction filled the notification form. Informed consent was taken from the volunteers for SUSARS before documentation. The demographic details of the volunteers were collected along with the current concern and drug therapy details in a systematically designed volunteers profile form. All relevant data including the drugs volunteers received prior to the onset of reaction, respective dose, and route of administration with frequency, date of onset of reaction and the volunteer's allergic status were noted. In addition to this volunteers medication history and other co-morbidities were identified to assess causality relationship between the suspected drug and reaction. Volunteers were interviewed and the medication order and records were reviewed on daily basis throughout the stay of volunteers in the hospital and In-house clinic. Any drug treatment and/or supportive therapy given for management of the reactions were also noted. The reported SUSARS were classified according to the Wills and Brown classification

Causality assessment of SUSARS was carried out using WHO scale[6-7] which categorizes the causality relationship into certain, probable, possible, unassessable/unclassifiable, unlikely, conditional / unclassified. Severity of SUSARS was graded as per scale developed as mild, moderate and severe. The most common class of drugs causing SUSARS were identified and documented.

Average cost per volunteers was calculated by total amount spent on treating SUSARS divided by the number of volunteers suspected with SUSARS. For analyzing the cost, SUSARS requiring specific drug and supportive therapy were considered. Drugs, laboratory investigation orders, syringes, applicants etc were all calculated per unit per volunteers.

Statistical analysis

Incidences of SUSARS during trail were calculated as percentage of total population included in the study. Z-test was used to compare means. For other variables the chi-squared ($\chi 2$ test) was used. A two-tailed P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 49 SUSARS were reported and evaluated from 149 volunteers (101 males, 48 females)[Fig 1] during the study period. Out of 149 volunteers, 21 (14.09 %) volunteers developed more than one SUSARS. The overall incidence was 32.89%. Female experienced a significantly higher incidence of SUSARS (1.02%) than male (0.49%). Augmented Type A reactions were found to be 39(79.59%) where as 7(14.28%) were Type H hypersensitivity reactions [Table No.1] .

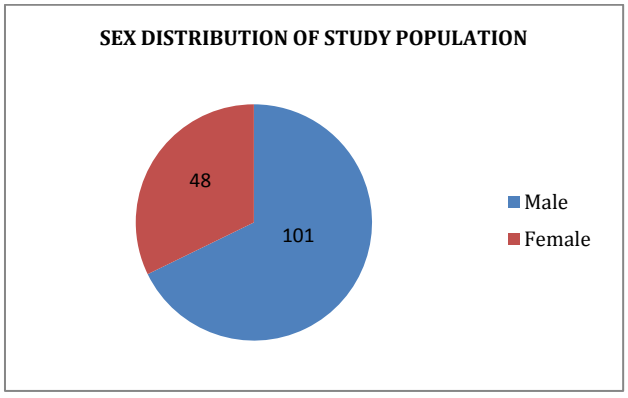

Fig 1: Sex Distribution of Study Population

Table 1: Classification of Suspected ADR's Reaction According To Wills & Brown

Types of ADR	No(%) of SUSARS reported.
Type A (Augmented)	39(79.59%)
Type B (Bugs)	-
Type C (Chemical)	-
Type D (Delivery)	1(2.04%)
Type E (Exit)	-
Type F (Familial)	-
Type G (Genetotoxity)	-
Type H (Hypersensitivity)	7(14.28%)
Type U (unclassified)	2(4.08%)

Assessment of SUSARS is given in [Table No. 2 & Table No.3]. Causality assessment of SUSARS shows out of 49 reported SUSARS 30 (61.22%) were assessed to be "Possible",10 (20.40%) as "Probable" and 9 (18.36%) as "Certain". Reported reactions were found to be "Mild" (34, 69.38%) followed by "Moderate" (26, 33.57%) and "Severe" (2, 4.08%).

Table 2: Assessment of SUSARS In Terms Of Causality

Causality parameters (who scale)	No. (%) of SUSARS reported
Certain	9 (18.36%)
Probable	10 (20.40%)
Possible	30 (61.22%)

Table 3: Assessment of SUSARS In Terms Of Severity

Level of severity (hartwig scale)	No (%) of SUSARS reported
MILD	34(69.38%)
MODERATE	26(33.57%)
SEVERE	2(4.08%)

In majority of SUSARS (97.95%) "Complete recovery" was achieved, Life threatening reactions were reported in 1 volunteers (2.04%) which were recovered later [Fig 2].

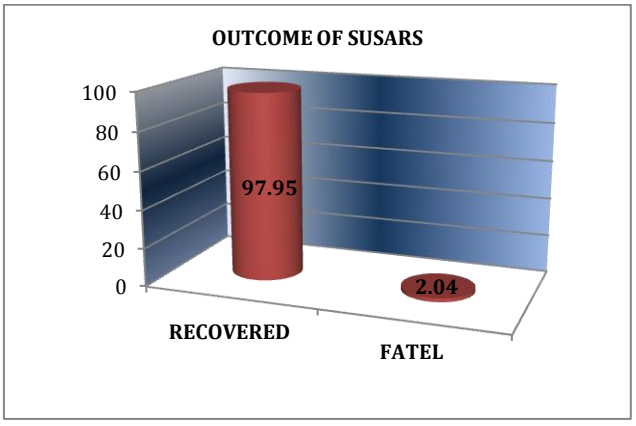

Fig 2: Outcome of SUSARS

The drug class most commonly associated with SUSARS was Antimicrobial (79.59%) followed by NSAIDS (14.28%) while least affected class was found to be Steroids (2.04%) [Table No 4]. Accordingly, the organ systems most commonly affected by an SUSARS was the gastrointestinal system (25%) followed by the Skin (24%) and Endocrine/ Metabolic system (13%) [Fig 3].

Table 4: Drug Class Most Commonly Associated With SUSARS

Drug class	No. (%) of ADRs reported
Antimicrobials	39 (79.59%)
NSAIDs	7(14.28%)
Cardiovascular agent	2 (4.08%)
Steroids	1 (2.04%)

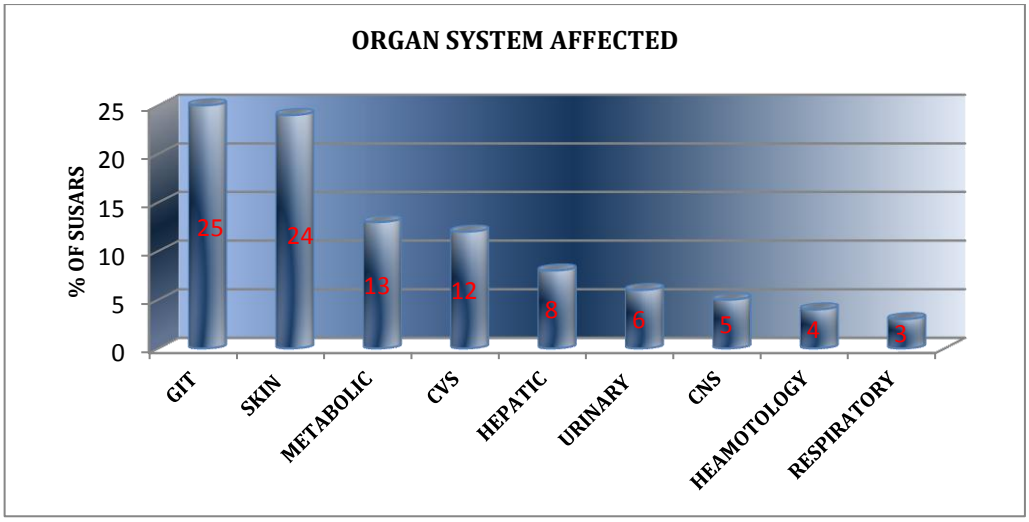

Fig 3: Organ Systems Most Commonly Associated With SUSARS

Reporting of SUSARS was dominated by the staff nurses [Fig 4] (41.96%). This was followed by Quality assurance who reported about 34.97% SUSARS. Physician reporting was found to be 13.29% whereas patients were responsible for 7% reporting.

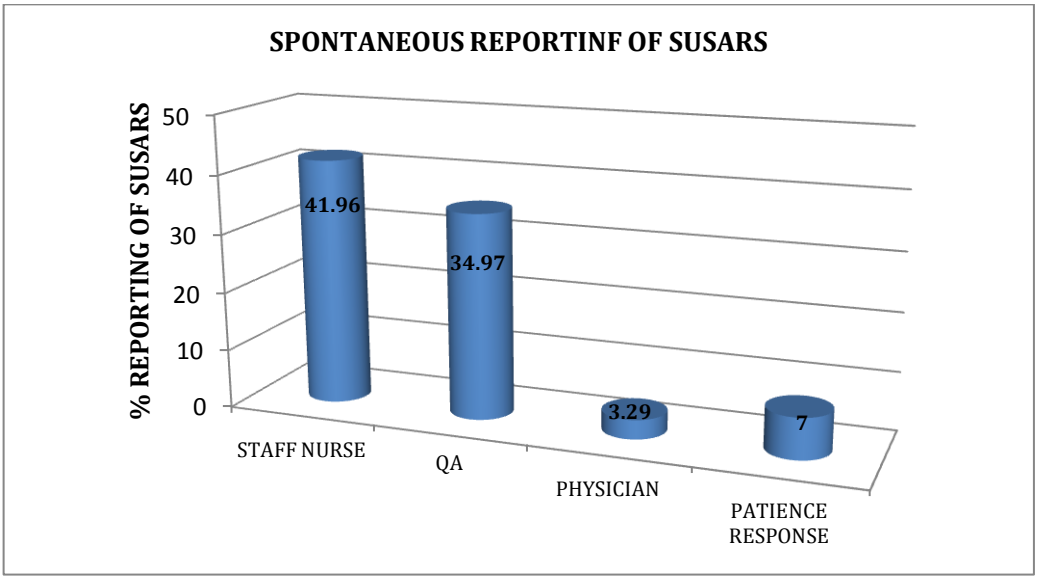

Fig 4: Spontaneous Reporting Of SUSARS

Total cost incurred in managing all SUSARS reported was Rs 130000. The average cost incurred during "SUSARS related hospitalization" was found to be higher than "SUSARS occurred in In-house" i.e. Rs. 8000 and Rs. 918 respectively. The average cost involved in treating SUSARS per patient was found to be Rs 2653 [Table No.5].

Table 5: Cost Incurred In Managing SUSARS

Category of SUSARS	Total no volunteers	Total cost incurred in Rs	Avg cost per patient in Rs
SUSARS treated in In-house Clinic	37	34000	918.91
SUSARS treated in Hospitalized	12	96000	8000

DISCUSSION

Overall incidence of SUSARS in our study was found to be 32.89%% of volunteers experienced an SUSARS after drug administered. This finding is similar to the reports generated from other Indian studies for adverse drug reaction in Indian hospitals[8-10]. This can be attributed to the fact that the study was conducted over pilot and pivotal study in CRO's and duration of the study was short of just six months.

Different epidemiological studies have indicated the female predominance in SUSARS with no known underlying explanation for the occurrence. Our study results reveal similar higher prevalence in female gender (1.02%) compared to the male (0.49%) [11]

Severe reactions (4.08%) were those which required intensive medical care, permanent harm, or leading to death directly or indirectly, though no fatality was observed in the study. They required advanced treatment procedures and greater financial expenditure from the CRO'S. Moderate reactions (33.57%) did require immediate cessation of the causative drug therapy, substitution with alternative drug and also treatment to the reaction. Mild reactions (69.38%) did not require any change in prescribed drugs, no extended hospitalization. Severity assessment was done according to Hartwig et.al criterion and study results were comparable with similar assessment in previous studies[12-13]

Outcome of the reaction showed 97.95% SUSARS were "fully recovered" which shows better management of drug therapy SUSARS encountered in the study were Diahorea and Purpuric rash (suspected for Steven Johnson Syndrome) which were recovered later.

The average cost per patient incurred for managing each SUSARS was found to be Rs 2653.

Average cost of hospitalized SUSARS per patient was found to be Rs.8000 whereas for SUSARS related In-house per patient was Rs. 918.91 which indicates that average cost for treating SUSARS leading to admission was higher.

CONCLUSION

Geriatrics and females were most affected with SUSARS. Antimicrobial drugs being mostly affecting class of drugs. Average cost incurred for treating SUSAR leading to admission was higher than treatment In In-house Clinic. There is need for establishing separate SUSARS monitoring centre at every CRO'S. Also, more original studies need to be conducted in Indian CRO'S to know the exact prevalence of SUSARS occurred during clinical trials.

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