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TO ANALYSE PATTERN, PROFILE AND SERIOUSNESS OF ADRs OF CNS ACTING DRUGS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Adverse drug reactions contribute to poorer patient outcomes and additional burden to the patients regarding hospitalization and increase in treatment cost. ADRs negatively affects the patient's quality of life and confidence in taking the prescribed medication, hence it leads to poor treatment outcome. **Aim:** To analyse the Pattern, Profile and Seriousness of ADRs of CNS acting Drugs in a tertiary care teaching hospital in Erode. **Methodology:** It is a Retrospective, observational, record-based study conducted at tertiary care hospital in Erode. The Study period includes the ADR reports from 06.01.2014 to 02.12.2019 will be studied. The Sample Size of the study depends on the number of ADRs reports from the patient's case sheet of the hospital during the above-mentioned period. All the ADR Reports of CNS acting Drugs during the specific period will be included. Complete details of ADR reports were collected from the patient's case sheet and documented. Inclusion criteria includes any reported ADRs of CNS acting Drugs in Patients case sheet, ADR reported by healthcare professionals – Doctors, Nurses, Clinical Pharmacists and Pharmacist, ADRs reported in CDSCO-IPC suspected ADR reporting form, ADR reports which are duly completed. **Report:** 105 ADRs reported during the study period which include 42.8% male and 57.14% Female. Middle age population was most commonly affected with ADRs (56.19%). followed by 27.61% were Older Adult, 11.42% were Young Adult. Among the total ADRs reported the majority of the ADRs reported were Hypersensitivity Reaction(40%), followed by Hyponatremia (10.47%),

Steven Jhonson Syndrome (6.66%), Nausea and Vomiting (6.66%). According to the WHO-UMC Scale, majority of the serious ADRs were categorized as Probable (70.49%) followed by Possible (29.52%) and no ADRs were reported under Unlikely and Definite. The most common affected body system was skin/soft tissue (54.28%), followed by Blood (17.14%), CNS (15.23%), GIT (10.47%), CVS (1.90%) and Respiratory (0.95%). **Conclusion:** Adverse Drug Reactions are a rising concern in the day today life of medical profession. The present study found that skin/soft tissue was the most commonly affected organ systems owing to ADRs caused by CNS acting drugs. The most frequently reported ADRs was hypersensitivity reaction which is induced by different class of drugs such as midazolam, pentazocine, sodium valproate, phenytoin, lorazepam, carbamazepine, levetiracetam and tramadol.

KEYWORDS: ADRs, CNS acting, CDSCO-IPC.

INTRODUCTION

A Central Nervous System acting Drugs include General Anaesthetics (E.g: Thiopentone Sodium, Propofol, Etomidate, Fentanyl etc.), Sedative and Hypnotics (E.g: Diazepam, Flurazepam, Lorazepam, Nitrazepam, Alprazolam, Zolpidem etc.), Antiepileptic Drugs (E.g.: Phenobarbitone, Phenytoin, Fosphenytoin, Carbamazepine, Levetiracetam etc..), Antiparkinsonian Drugs (E.g.: Levodopa, Carbidopa, Selegiline etc.), Antipsychotic Drugs(E.g.: Haloperidol, Aripiprazole, Olanzapine, Quetiapine etc.), Antidepressant and Anxiolytic Agents (E.g.: Sertraline, Escitalopram, Lorazepam etc.), Mood Stabilizers (E.g.: Lithium Salts, Carbamazepine, Gabapentin, Clozapine, Risperidone etc.), CNS Stimulants and Cognition Enhancers (E.g.: Methyl phenidate, Dimethyl phenidate, Memantine etc.), Opioid Analgesics and Antagonists (Eg: Tramadol, Morphine, Fentanyl etc.)

Polypharmacy is one of the leading causes of adverse drug reactions (ADRs) in patient taking CNS acting drugs.[1] WHO defines an adverse drug reaction as any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.[2] The ADR may leads to hospitalization, prolongation of hospital stay, causes congenital malformation, results in persistent or significant disability or incapacity, is life- threatening or results in death.[2]

Adverse drug reactions (ADRs) are known to be the significant cause of morbidity and mortality in both inpatients and outpatients settings.[3] The association of CNS acting

medications with ADRs is common and can occur even at the normal doses used in the management of acute and maintenance phases of various disorders.[4] These ADRs can impair quality of life, may lead to poor adherence to medications, cause physical morbidity, issue stigma, and in extreme cases, can be fatal.[5] In this study we are trying to analyze the pattern and profile of ADRs among patients receiving CNS acting drugs. This may help us to identify individuals predisposed for ADRs and to develop interventions for prevention of adverse reactions.

AIM AND OBJECTIVES

Aim: To analyse the Pattern, Profile and Seriousness of ADRs of CNS acting Drugs in a tertiary care teaching hospital in Erode.

Primary objectives

1. To study the pattern and profile of CNS acting Drugs.
2. To assess the seriousness of ADRs.

Secondary objectives

1. To assess the severity of ADRs using relevant assessment scale.
2. To assess the outcome ADRs through WHO criteria.

METHODOLOGY

It is a Retrospective, observational, record-based study conducted at tertiary care hospital in Erode. The Study period includes the ADR reports from 06.01.2014 to 02.12.2019 will be studied. The Sample Size of the study depends on the number of ADRs reports from the patient's case sheet of the hospital during the above-mentioned period. All the ADR Reports of CNS acting Drugs during the specific period will be included. Complete details of ADR Reports were collected from the patient's case sheet and documented. The collected data will be entered in Microsoft excel worksheet and the analyses using Simple Descriptive Statistics.

Inclusion criteria

1. Any reported ADRs of CNS acting Drugs in Patients case sheet.
2. ADR reported by healthcare professionals – Doctors, Nurses, Clinical Pharmacists and Pharmacist.
3. ADRs reported in CDSCO-IPC suspected ADR reporting form.
4. ADR reports which are duly completed.

Exclusion criteria

1. Incomplete ADR reports.
2. ADR reports by non-health care professionals.
3. ADR reports by patients.

Study procedure

A retrospective, observational, record-based study will be carried out using the data collected from the patient's case reports from 06.01.2014 to 02.12.2019. The study will be carried out in a tertiary care hospital in Erode, Tamil Nadu. The data regarding age, sex, gender, details of the adverse drug reaction, status of recovery, seriousness of reaction, details of the drugs, causality assessment and outcome of reaction will be collected.

SERIOUSNESS OF ADR

The criteria for serious ADR have been specified by WHO and US Food and drug administration (FDA) and are adopted by CDSCO in suspected ADR reporting form.[6] It includes any untoward medical occurrence at any dose that,

- Results in Death
- Life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability or incapacity
- Required intervention to prevent permanent disability
- Results in congenital abnormality

OUTCOME OF ADR

In the current study outcome of reaction is categorized as per CDSCO – IPC suspected ADR reporting form. Outcome is categorized as,

1. Recovered
2. Recovering
3. Not recovered
4. Recovered with sequelae
5. Fatal
6. Unknown.

ETHICAL CONSIDERATIONS

The study is conducted only after obtaining approval from the Institutional Ethics Committee.

RESULTS AND DISCUSSION

Table 1: Gender wise distribution data.

Sl No	Gender	Number (n=105)	Percentage (%)
1	Male	45	42.8%
2	Female	60	57.14%

105 ADRs reported during the study period which include 42.8% male and 57.14% Female. The majority of the population consist of Female.

Table 2: Age wise distribution.

Sl no.	Age Wise Distribution	Number (n=105)	Percentage (%)
1	Young Child	1	0.95%
2	Child	2	1.90%
3	Adolescent	2	1.90%
4	Young Adult	12	11.42%
5	Middle Age	59	56.19%
6	Older Adult	29	27.61%

Out of 105 Reported ADRs 56.19% were Middle Age followed by 27.61% were Older Adult, 11.42% were Young Adult, 1.90% were Adolescent, Child constitute about 1.90% and the least were Young Child (0.95%).

Table 3: ADR distribution data.

Sl No.	Reaction	Number (n=105)	Percentage (%)
1	Pancreatitis	1	0.95%
2	Hyperammonaemia	2	1.90%
3	Mouth Ulcer	1	0.95%
4	Pill Roll Tremor	1	0.95%
5	Febrile Neutropenia	1	0.95%
6	Hyperglycaemia	1	0.95%
7	Hyponatremia	11	10.47%
8	Bradykinesia	2	1.90%
9	Parkinsonian Symptoms	2	1.90%
10	Urticaria	5	4.76%
11	Dystonia	2	1.90%
12	Hypersensitivity reaction	42	40%
13	Jerking movement and up rolling of eyes	1	0.95%
14	Facial puffiness and oedema	1	0.95%
15	Increased sleep	2	1.90%

16	Increased psychomotor activity	3	2.85%
17	Drowsiness and fainting	2	1.90%
18	Nausea and Vomiting	7	6.66%
19	periorbital oedema	1	0.95%
20	Transaminase elevation	2	1.90%
21	Arrhythmia	2	1.90%
22	Ichthyosis	1	0.95%
23	Steven Johnson Syndrome	7	6.66%
24	Constipation	1	0.95%
25	Ataxia	1	0.95%
26	Increased Appetite	1	0.95%
27	Hypothyroidism	1	0.95%
28	Shortness of Breath	1	0.95%

Among the total ADRs Reported, the majority of the ADRs reported were Hypersensitivity Reaction(40%), followed by Hyponatremia (10.47%), Steven Johnson Syndrome (6.66%), Nausea and Vomiting (6.66%) and the least include Shortness of Breath (0.95%), Hypothyroidism (0.95%), Increased Appetite (0.95%), Ataxia (0.95%), Constipation (0.95%), Ichthyosis (0.95%), Periorbital oedema (0.95%), Facial puffiness and oedema (0.95%), Jerking movement and up rolling of eyes(0.95%), Mouth Ulcer(0.95%), Pill Roll Tremor(0.95%), Febrile Neutropenia (0.95%)and Hyperglycaemia(0.95%).

Table 4: Immutability score of ADRs monitored.

Sl No.	Casuality	Number (n=105)	Percentage (%)
1	Unlikely	0	0
2	Possible	31	29.52%
3	Likely/Probable	74	70.49%
4	Definite	0	0

According to the WHO-UMC Scale, majority of the serious ADRs were categorized as Probable (70.49%) followed by Possible (29.52%) and no ADRs were reported under Unlikely and Definite.

Table 5: Most common ADRs system wise.

Sl No.	System Wise Distribution	Number (n=105)	Percentage (%)
1	Skin /Soft Tissue	57	54.28%
2	Blood	18	17.14%
3	CNS	16	15.23%
4	GIT	11	10.47%
5	CVS	2	1.90%
6	Respiratory	1	0.95%

Sl no.	System	ADR	Drugs	Most Common ADR	Most Common Drug
1	GIT	Pancreatitis	Divalproex Sodium	Nausea and Vomiting	Tramadol
		Mouth Ulcer	Chlordiazepoxide		
		Nausea and Vomiting	Tramadol		
		Constipation	Tramadol		
		Increased Appetite	Sodium Valproate		
2	CNS	Pill Roll Tremor	Levosulpiride	Increased Psychomotor Activity	Risperidone
		Bradykinesia	Risperidone		
			Lithium		
		Parkinsonian Symptoms	Clozapine		
			Risperidone		
		Dystonia	Quetiapine		
			Risperidone		
		Jerking movements and up rolling eyes	Fosphenytoin		
		Increased Sleep	Promethazine		
			Haloperidol		
		Increased Psychomotor Activity	Haloperidol		
			Lorazepam		
			levodopa+carbidopa		
		Drowsiness and Fainting	Phenytoin		
			Lorazepam		
		Ataxia	Phenytoin		
3	Skin/Soft Tissue	Urticaria	Phenytoin	Hypersensitivity Reaction	Phenytoin and Tramadol
			Carbamazepine		
			Tramadol		
		Hypersensitivity Reaction	Midazolam		
			Pentazocine		
			Sodium Valproate		
			Phenytoin		
			Lorazepam		
			Carbamazepine		
			Levetiracetam		
			Tramadol		
		Facial puffiness and oedema	Fosphenytoin		
		Periorbital oedema	Midazolam		
		Ichthyosis	Lamotrigine		
		Steven Johnson Syndrome	Phenobarbitone		
			Phenytoin		
			Oxcarbazepine		
			Quetiapine		
4	Blood	Hyperammonaemia	Sodium Valproate	Hyponatremia	Sertraline,

		Hyperglycaemia	Quetiapine		Escitalopram, Zolpidem, Lorazepam and Mirtazapine
		Hypothyroidism	Lithium		
		Transaminase Elevation	Phenytoin		
		Febrile Neutropenia	Phenytoin		
		Hyponatremia	Oxcarbazepine		
			Sertraline		
			Escitalopram		
			Zolpidem		
			Lorazepam		
			Mirtazapine		
5	CVS	Arrhythmia	Propofol	Arrhythmia	Propofol and Fentanyl
			Fentanyl		
6	Respiratory	Shortness of Breath	Tramadol	Shortness of Breath	Tramadol

The most common affected body system was skin/soft tissue (54.28%), followed by Blood (17.14%), CNS(15.23%), GIT(10.47%), CVS(1.90%) and Respiratory (0.95%).

Table 6: Reaction distribution data.

Sl No.	Reaction	Number (n=105)	Percentage (%)
1	Serious	46	43.80%
2	Not Serious	59	56.19%

Out of 105 Reported ADRs 43.80% were serious ADRs which leads to hospitalization or prolonged hospital stay and 56.19% ADRs reported were not serious.

Table 7: Seriousness of the reaction.

Sl No.	Seriousness of the reaction	Number (n=46)	Percentage (%)
1	Death	0	0.00%
2	Life Threatening	0	0.00%
3	Hospitalization-Initial or Prolonged	46	100%
4	Disability	0	0.00%
5	Required Intervention to prevent permanent impairment/damage	0	0.00%

Among the total ADRs reported 43.80% were serious adverse drug reactions which lead to hospitalization and prolonged hospital stay were of 100%.

Table 8: Outcomes of the reaction.

Sl No.	Outcomes	Number (n=105)	Percentage (%)
1	Fatal	0	0.00%
2	Continuing	2	1.90%
3	Recovering	46	43.80%
4	Recovered	57	54.28%
5	Unknown	0	0.00%
6	Other	0	0.00%

Among the total ADR reports majority of the ADRs outcomes were Recovered (54.28%) followed by Recovering (46%) and continuing (1.90%).

Table 9: Dosage form distribution data.

Sl No.	Dosage Form	Number (n=105)	Percentage (%)
1	Tablet	76	72.38%
2	Syrup	1	0.95%
3	Injection	28	26.66%

Dosage Form received by study population were documented and depicts that tablets were most commonly reported with ADR(72.38%), followed by Injection (26.66%) and syrup (0.95%).

DISCUSSION

It is a retrospective study with 105 ADR Reports. Previous studies have shown that a larger percentage of ADRs were reported from the geriatric and the paediatric populations, which had no similarity with our results.[7] In our study middle age population was most commonly affected with ADRs (56.19%), this is quite similar to study conducted by Anita G et al.[8] A slight female preponderance was observed in this study; which is not conformity with previous studies.[9-11] However, Agaard et al. Reported 60% ADRs in female.[12] and Doshi et al. showed that both genders were equally affected.[13] In this study Skin/soft tissue constituted the most common system affected with ADR. Our observations are synonymous with Agaard et al.[12] Out of its Steven Johnson Syndrome was the most frequently reported ADRs. Among the total ADRs Reported, the majority of the ADRs reported were Hypersensitivity Reaction(40%), followed by Hyponatremia (10.47%), Steven Johnson Syndrome (6.66%), Nausea and Vomiting (6.66%). Neurological ADRs too had been on the top of the list of ADRs in previous studies[14] but in our study it constitute about 15.23%.

Majority of the ADRs were categorized as Probable (70.49%) based on the causality assessment, which was similar to the results of another study.[15-17] As far as the total ADRs reported 43.80% were serious adverse drug reactions which lead to hospitalization and prolonged hospital stay were of 100% as compared to other studies which did not show such a higher percentage.[15] Out of 105 ADR reports majority of the ADRs outcomes were Recovered (54.28%).

Dosage Form received by study population were documented and depicts that tablets were most commonly reported with ADR(72.38%), followed by Injection (26.66%) and syrup (0.95%). The oral route was responsible for the ADR causation compared to the intravenous/intramuscular route. This was conceding with the findings of a study done by Sharma et al.[18]

CONCLUSION

Adverse Drug Reactions are a rising concern in the day today life of medical profession. The present study found that skin/soft tissue was the most commonly affected organ systems owing to ADRs caused by CNS acting drugs. The most frequently reported ADRs was hypersensitivity reaction which is induced by different class of drugs such as midazolam, pentazocine, sodium valproate, phenytoin, lorazepam, carbamazepine, levetiracetam and tramadol.

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