Original Article

Utilization patterns of central nervous system drugs: A cross-sectional study among the critically ill patients

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ABSTRACT

Introduction: Critically ill patients often receive central nervous system drugs due to primary disorder or complications secondary to multiorgan failure. The aim of the study was to evaluate the current utilization pattern of central nervous system drugs among patients in the medical intensive care unit. **Materials and Methods:** A prospective observational study carried out over a period of 1 year. The relevant data on drug prescription of each patient was collected from the inpatient case record. Drugs were classified into different groups based on WHO–ATC classification. The demographic data, clinical data, and utilization of different classes of drugs as well as individual drugs were analyzed. **Results:** A total of 325 consecutive patients were included for the analysis; 211 (65%) patients were males; 146 patients (45%) were above 55 years of age. Encephalopathy [63(19.38%)] and stroke [62(19%)] were the common central nervous system diagnoses. In a total of 1237 drugs, 68% of the drugs were prescribed by trade name. Midazolam (N05CD08) 142 (43.69%), morphine (N02AA01) 201 (61.84%), and atracurium (M03AC04) 82 (25.23%) were the most commonly used sedative, analgesic, and neuromuscular blocker, respectively. Phenytoin (N03AB02) 151 (46.46%) had maximum representation among antiepileptic agents. **Conclusions:** Utilization of drugs from multiple central nervous system drug classes was noticed. Rational use of drugs can be encouraged by prescription by brand name.

Key words: Central nervous system, critically ill, drug utilization

Introduction

Neurologic disorders are prevalent among the critically ill patients in the intensive care unit (ICU), both as a primary disease as or as a complication of multiple organ dysfunction. Critically ill patients are at a high risk of developing neurologic disorders due to multiple organ failure, advancing age, prescription of psychoactive agents, and malnutrition.[1] Altered sensorium, raised intracranial pressure, cerebrovascular thrombosis, seizures, and bacterial meningitis are the common central nervous system (CNS) disorders noted among the critically ill.[1]

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Critically ill patients, especially those with respiratory failure may require mechanical ventilation, which is uncomfortable because of pain and anxiety. Sedation and analgesia are essential components in the management of these intensive care patients in order to relieve the discomfort and anxiety caused by procedures, such as tracheal intubation, ventilation, suction, and also to minimize agitation and to provide appropriate sleep.[2,3] In addition, CNS drugs are also used to control seizures and treat delirium, depression, and psychotic symptoms among these critically ill patients.[4]

Drug therapy, in critically ill patients, is often complicated by the altered physiology, presence of multiorgan system failure, and multiple medications. Frequently changing disease processes and organ dysfunction result in changes in pharmacokinetic parameters of drugs used in them. Critical illnesses have shown to affect the absorption, distribution, protein binding, metabolism, elimination, and serum concentration of commonly used drugs. The alteration in the pharmacokinetic parameters leads to changes in the pharmacodynamic

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effects of these agents, resulting in either subtherapeutic, supratherapeutic, or toxic effects.[1,4] The use of multiple medications may further increase the risk of drug-related problems, such as adverse drug reactions, interactions, patient noncompliance with treatment, and medication errors. Hence, the appropriate management of these patients is a challenge for the treating physician.

The study of drug prescribing patterns helps to evaluate and suggest modifications in prescribing practices of physicians.[5] This practice ensures rational pharmacotherapy and assures quality medical care to the patients. In the developing countries, drug cost is a major concern for both health care providers and the beneficiaries, and therefore the rational use of drugs plays a pivotal role in cost minimization and optimal utilization of the available funds. The objective of the present study was to evaluate the utilization patterns of CNS drugs among the patients admitted to the medical ICU.

Materials and Methods

The study was carried out at a tertiary care superspecialty teaching hospital in southern part of the Indian subcontinent. The data were collected over a period of 12 months (October 2006 to September 2007). During the study period, all patients admitted to the medical ICU for more than 24 h and who received CNS drugs, were included as study sample. Patients who stayed in the ICU for less than 24 h and those admitted more than once in the ICU during the study period were not included in the study. The study was approved by the institutional ethics committee. The data were collected from the medication orders sheets filled by the physician. All the prescriptions were reviewed prospectively from patients admitted to ICU during the study period. The demographic data [age, gender, and outcome of the patient (improved, died)], clinical data (clinical diagnosis and associated comorbid conditions, length of ICU stay), and all drug prescription details (generic/trade name, route of administration, dose, frequency) were recorded. The data were collected by the first author.

Statistical analysis

The data were subjected to descriptive analysis using Microsoft Excel. The prescribed drugs were identified and placed into 6 classes using the WHO Anatomic Therapeutic Chemical classification system.[6] The total number of the different drugs administered to each patient and exposure rates for each drug class and individual drugs were analyzed and presented as number and percentage. Among the medications prescribed, those that were prescribed from the WHO essential drug list were noted.[7]

Results

The study results provide a detailed overview of the drug utilization pattern of CNS drugs among the patients admitted to medical ICU. During the study period a total of 902 patients were admitted, 325 patients (36%) received CNS drugs and were included as the study sample. The remaining 64% patients admitted to the ICU were not included because they did not receive CNS drugs. Among the 325 patients, male patients were 211 (65%) and female patients, 114 (35%). The majority of the patients were older than 55 years (146; 45%), 110 patients (34%) were between 35 and 55 years and 69 patients (21%) were younger than 35 years. The mean length of stay in the medical ICU was 6.22 ± 3.34 days. Among the 325 patients, 226 (69.53%) patients improved, of whom 30% had disabilities, such as neurologic deficits, hemiparesis, and behavioral abnormalities, 45 (13.84%) patients died, and the outcome of 54 patients was not known because 38 (11.69%) patient were discharged upon request and 16 patients (4.92%) got discharged against medical advice.

The common clinical diagnoses noticed among the patients in ICU were sepsis, acute renal failure, multiorgan dysfunction syndrome, acute respiratory distress syndrome, pneumonia, and lower respiratory tract infections. Among the clinical conditions involving the CNS, encephalopathy 63 (19.38%) and stroke 62 (19.07%) were the frequent CNS disorders observed. Patients with CNS infective conditions, degenerative disease, and structural abnormalities were fewer [Table 1].

Based on the WHO Anatomic therapeutic chemical classification, a total of 1237 drugs from ATC–N (drugs acting on nervous system) were used among 325 patients. It was observed that 68% of the CNS drugs were prescribed by trade name. Forty-two percent of drugs prescribed were from WHO essential drug list. The mean number of CNS drugs received in these patients was 5.22 ± 2.34 drugs. Various drug classes prescribed

Table 1: Most common central nervous system disorders among critically ill patients

Central nervous system disorders	Number (%) *n* =325
Encephalopathy*	63 (19.38)
Stroke†	62(19.07)
Seizure disorders	45(13.84)
Psychiatric disorders‡	42(12.92)
Inflammatory and Infective conditions	36 (11.07)

* Encephalopathy includes: Metabolic, hepatic, hypoxemic, electrolyte imbalance. †Stroke includes: Hemiplegia, paraplegia, intracranial bleed, intracranial and cerebrovascular thrombosis, cerebral infarction. ‡Psychiatric disorders include: delirium, depression, psychosis, anxiety, dissociative personality disorders.

include sedatives, analgesics, neuromuscular blockers, antiepileptics, psychotropic agents, such as antipsychotic agents, antidepressants, and mood stabilizers.

Sedative and analgesics were the frequently prescribed drug classes for patients on ventilators, and therefore they were analyzed. Midazolam (N05CD08) 142 (43.69%) and lorazepam (N05BA06) 116 (35.69%) were the most commonly used sedatives, whereas morphine (N02AA01) 201 (61.84%) was the most common analgesic prescribed. Among the neuromuscular blockers, atracurium (M03AC04) was the most common medication, being received by 82 (25.23%) out of the 325 patients [Table 2].

Among the other CNS drugs, phenytoin (N03AB02) 151 (46.46%) was the most commonly prescribed antiepileptic and haloperidol (haloperidol 25 (7.69%) most commonly used antipsychotic agent [Table 3].

During the ICU stay, the adverse effects associated with CNS drugs were ketamine-induced bradycardia, lithium-induced encephalopathy, and ataxia, risperidone-induced orofacial dyskinesia and seizures, sodium valproate-induced encephalopathy, and carbamazepine-induced syndrome of inappropriate antidiuretic hormone.

Discussion

The results of the present study give a detailed overview of the utilization patterns of CNS drugs among the seriously ill patients of medical ICU. It was observed that more male patients were admitted to the ICU in comparison to female patients. The common CNS conditions observed were encephalopathy (19.38%) secondary to electrolyte imbalance, hepatic cause, and metabolic and hypoxic etiologies followed by stroke. Factors associated with encephalopathy include primary cerebral disorders, such as stroke, trauma, and meningitis, or systemic derangements, including sepsis, organ failure, and exposure to pharmacologic agents and toxins. There is mounting evidence that cerebral dysfunction persists beyond the acute phase of critical illness resulting in impairments in cognitive ability, suggesting occult brain injury. Preventive and therapeutic interventions are cornerstones in the management of encephalopathy.

Of the 1237 drugs from ATC–N (drugs acting on nervous system) utilized among 325 patients, it was observed that 68% of the drugs were prescribed by brand name. Clinicians should practice generic prescription by which equally efficacious drugs could be given at a low cost and also encourage rational use of drugs.

Table 2: Utilization of sedatives, analgesics, and neuromuscular blockers in the ICU

Drug class	Drug	ATC code	Number (%) of patients (*n* = 325)
Sedatives	Midazolam	N05CD08	142 (43.69)
	Lorazepam	N05BA06	116 (35.69)
	Propofol	N01AX10	40 (12.30)
	Chlordiazepoxide	N05BA02	10 (3.07)
	Diazepam	N05BA01	3 (0.92)
Analgesics	Morphine	N02AA01	201 (61.84)
	Fentanyl	N01AH01	80 (24.61)
	Tramadol	N02AX02	76 (23.38)
	Pethidine	N02AB02	64 (19.69)
	Paracetamol + dextropropoxyphene	N02BE02	18 (5.53)
	Ketamine	N01AX03	9 (2.76)
Neuromuscular blockers	Atracurium	M03AC04	82 (25.23)
	Baclofen	M03BX01	13 (4)
	Pancuronium	M03AC01	6 (1.84)
	Vecoronium	M03AC05	3 (0.92)
	Rocuronium	M03AC03	3 (0.92)

Table 3: Utilization patterns of other central nervous system drugs among medical ICU patients

Drug class	Drug	ATC code	Number (%) of patients (*n* =325)
Antiepileptics	Phenytoin	N03AB02	151 (46.46)
	Diazepam	N05BA01	12 (3.69)
	Clobazam	N05BA09	12 (3.69)
	Phenobarbitone	N05CA04	11 (3.38)
	Carbamazepine	N03AF01	10 (3.07)
	Clonazepam	N03AE01	6 (1.84)
	Gabapentin	N03AX12	5 (1.53)
	Valproic acid	N03AG01	2 (0.61)
Antiedema drugs	Mannitol	B05BC01	77 (23.69)
	Acetazolamide	S01EC01	12 (3.69)
	Glycerol	A06AG04	6 (1.84)
Antipsychotics	Haloperidol	N05AD01	25 (7.69)
	Trazodone	N06AX05	16 (4.92)
	Risperidone	N05AX08	12 (3.69)
	Citalopram	N06AB04	6 (1.84)
	Quetiapine	N05AH04	3 (0.92)
	Prochlorperazine	N05AB04	2 (0.61)
Antidepressants	Imipramine	N06AA02	8 (2.46)
	Fluoxetine	N06AB03	6 (1.84)
	Duloxetine	N06AX21	2 (0.61)
Antiparkinsonian drugs	Levodopa + carbidopa	N07CA02	8 (2.46)
Miscellaneous: CNS stimulant	Piracetam	N06BX03	16 (4.92)
Immunoglobulin	Immunoglobulin (IgG)	J06BA02	8 (2.46)

Sedation and analgesia are important to ensure patient comfort from psychological and physical point of view, thus reducing stress which leads to profound changes in the fluid and electrolyte balance, mobilization of substrates from energy source, and neurohormonal milieu.[8] In the present study, morphine sulfate (61.84%) was the most commonly utilized analgesic followed by fentanyl (24.61%). This finding was similar to previous studies carried out by Soliman *et al*,[8] Biswal *et al*,[9] and Bobek *et al*.[10] Morphine is the principal sedative agent preferred in ICU due to its potency, improved patient ventilator synchrony, and availability of effective antagonist.[11]

Midazolam (43.69%), the most frequently used sedative followed by lorazepam (35.69%). Our findings were comparable with earlier reports from Europe,[8] India,[9] and United States.[10] Midazolam, due to its rapid onset of effects, faster redistribution and quicker elimination, is an appropriate choice for short-term sedation.[12] Lorazepam has an intermediate duration of action due to low lipid solubility; it is recommended for long-term maintenance of sedation in the chronically critically ill patients.[12]

Pancuronium was the most frequently utilized neuromuscular blocker in an earlier study[10] in ICU setup, while atracurium was preferred in our study; probably because atracurium follows Hofmann elimination, so can be used safely in patients with renal failure.[13]

Older intravenous antiepileptic agents, such as phenytoin (46.46%) were preferred in the present study. This finding was in concordance to an earlier study from India.[9] Phenytoin was used mainly for seizure prophylaxis and maintenance therapy. Phenytoin, due to its saturation kinetics, drug interactions, and adverse effects can be replaced by newer antiepileptic agents.[14] Studies carried out on the use of the newer agents, such as levetiracetam and lacosamide suggest that newer agents are better tolerated.[15,16]

Stroke is associated with morbidity and mortality mainly due to raised intracranial pressure (ICP) and its consequences in the acute stage.[17] Osmotic agents (glycerol, mannitol) and diuretics are often used to reduce raised ICP.[18,19] In the present study, 23.69% of the patients received mannitol. A previous report from India looking into the prescribing pattern of antiedema therapy in ICU showed that there was no uniformity among physicians in prescribing antiedema therapy.[20]

Delirium is one of the common psychiatric illness common in the ICU, occurring in 20%–80% of patients, with the highest proportions seen in mechanically ventilated patients.[21] Haloperidol was prescribed to 25 patients, whereas risperidone was prescribed to 12 patients. Although atypical antipsychotics are found to be equally efficacious and associated with lesser incidence of extrapyramidal effects, utilization of atypical antipsychotics are limited in the ICU, primarily due to fewer studies comparing them.[22,23] Haloperidol, a high-potency neuroleptic, offers greater advantage due to additional sedative effect.[22, 23]

Depression, in ICU patients, results from the psychological toll of serious illness as well as the physiologic derangements caused by illnesses and treatments. The percentage of antidepressant prescriptions noticed in the study was 5%. Previous data suggest that establishing the diagnosis of depression in critically ill is often difficult.[24]

Although drug therapy is the most cost-effective method of minimizing mortality and morbidity in critically ill patients, drug therapy itself can be a major cause of increased cost, morbidity, and mortality in these patients.[25] The purpose of inpatient-based prescription audit has advantage of minimizing the "drop-outs" as patients had to purchase and take the prescribed drugs and limitation of the study included smaller sample size, study of only a single ICU for a specific 12-month time period and qualitative assessment of drug utilization was not performed. In conclusion, the utilization of drugs from multiple CNS drug classes was noticed and rational use of drugs can be encouraged by prescription by brand name.

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