Utilization Profile of Gastrointestinal Medications among the Critically Ill Patients of A Tertiary Care Hospital

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ABSTRACT

Pharmacotherapy in critically ill is complicated by altered physiology, presence of multi organ system failure and utilization of multiple medications. The present study assessed the utilization pattern of gastrointestinal drugs among the inpatients of the intensive care unit. This prospective study was carried out in medical intensive care unit (ICU) of a tertiary care hospital. Case records of all inpatients of ICU were reviewed over a period of 12 months. The demographic data, clinical data, and drug details were recorded. Descriptive statistics was carried out, values are expressed as percentage, mean $\pm$ SD and range. Of the 728 inpatients, a total of 695 patients received gastrointestinal drugs. Male to female ratio was 1:9. The mean age was 49.21 ± 15.84 years with a range of 18-90 years. Drugs for gastrointestinal system and drug metabolism (ATC-A) (23.3%) were most commonly utilized drug class of all the drugs prescribed in the ICU. Among the anti-peptic ulcer agents, pantoprazole (A02BC02) (87%) and ranitidine (A02BA02) (9.7%) were the frequently prescribed drugs. Metoclopramide (A03FA01) (19.5%) was the most frequent prokinetic agent and ondansetron (A04AA01) (15%) anti-emetic agents. Lactulose (A06AD11) (11.7%) was the most common laxative given while Glycopyrrolate (A03BA01) (6.3%) most frequent anti-secretory agent prescribed. Gastrointestinal drugs were the widely prescribed drug class among the critically ill prescribed both as prophylactic as well as therapeutic indications. Proton pump inhibitors were the acid suppressant therapy of choice, which require revision based on its recent findings on safety and efficacy in critically ill.

Keywords: Anti-Peptic Ulcer Drugs, Drug Utilization, Critically Ill

INTRODUCTION

Gastrointestinal (GI) problems are common and often associated with adverse outcomes among the critically ill patients.[1,2] Diverse gastrointestinal complications (decreased bowel sounds, delayed gastric emptying, constipation and diarrhoea) are common among the mechanically ventilated patients [3] .In the critically ill patients most of the gastrointestinal complication are consequence of the primary systemic disease or associated multiple comorbidities. GI emergencies such as bleeding, diarrhea, hepatitis, hepatic failure are frequent indications for admission to intensive care unit (ICU) and also common among hospitalized ICU patients'. The clinical presentation of these GI disorders among these patients is often not typical which result in delay in the diagnosis and initiation of appropriate management which could contribute to increased morbidity and mortality.

Drug therapy in critically ill is complicated by altered physiology, multi organ failure and altered pharmacokinetic parameters.[4] Data on drug safety and efficacy for the use among the critically ill is inadequate due to limited number of large scale multicentric randomized controlled trials. Drugs developed and approved for use in the normal population is eventually used among the ICU patients with their altered pharmacokinetics. Drug utilization studies are useful, inexpensive tool for evaluation of current prescribing patterns to suggest modifications to achieve rational and cost effective therapeutic practices in health care.[5] Several methods of drug utilization studies have been used internationally and regionally such as the methods used for qualitative studies to identify differences in use in different countries, studies on prescription habits, patient compliance, drug effects, patients knowledge about drugs, ad hoc studies descriptive studies, determinants of drug utilization and impact of drug use and consumption studies.[5] Studies on prescription habit focuses on analysing the pattern of drug use among patient categories such as age, gender, diagnosis etc.

Several studies have been reported on the overall drug utilization pattern in the intensive care unit, [6,7] some reports have focussed on specific drug categories such as antimicrobials or (Shankar), sedatives, analgesics and neuromuscular blockers. [8,9] Overall drug utilization rate in the medical ICU has been high as documented in previous literature. Utilization of gastrointestinal drugs in the outpatient setting have been reported.[10] However, the drug utilization review of the gastrointestinal drugs among the critically ill patients is infrequently reported. Hence, the present study aimed to assess the current gastrointestinal drug prescribing pattern and gastrointestinal adverse effects among the inpatients of medical ICU.

Definitions:

Drug utilization study: Drug utilization study is a component of medical audit that does monitoring and evaluation of the drug prescribing patterns and suggests necessary modifications in prescribing practices to achieve rational therapeutic practice as well as cost effective health care.[5]

Adverse drug reaction (ADR): A reaction which is noxious and unintended and which occurs at doses normally used in humans for prevention, diagnosis or therapy of disease, or for the modification of physiological functions. [11]

Defined daily dose (DDD): It is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. [12]

World Health Organization (WHO) causality definitions[13]**:**

Certain ADR. A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs. The response to dechallenge should be clinically plausible.

Probable ADR. A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, likely to be attributed to concurrent disease or other drugs and follows clinically reasonable response on dechallenge.

Possible ADR. A clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other' drugs. Information on dechallenge may be lacking or unclear. [13]

Methods

Study design: This was a prospective cross-sectional study carried out among inpatients of the medical ICU.

Study setting: The study was carried out in the 15 bedded medical intensive care unit tertiary care hospital in South India.

Study population: The medical records of all inpatients of the ICU were evaluated over a period of twelve months.

Inclusion criteria: All patients admitted to the medical ICU for more than 24 h and who received gastrointestinal drugs, were included as study sample.

Exclusion criteria: Patients who stayed in the ICU for less than 24 h and those admitted more than once in the ICU

during the study period was not included in the study.

Data collection: The ethical approval was obtained by the institutional ethics committee before the start of the study. A specially designed validated questionnaire was used as the research instrument to collect the relevant data. The questionnaire included, the demographic data (age, gender and length of stay), clinical data (Clinical diagnosis and associated co-morbid conditions), and all drug prescription details (generic/trade name, route of administration) and adverse drug reaction details (type of reaction, implicated drug, causality assessment) were recorded. The data were collected from the prescription/medication orders sheets in the medical ICU filled by the physician. Individual prescriptions were analyzed prospectively from patients admitted to medical ICU during the study period. World Health Organization-Anatomic Therapeutic Chemical classification system (WHO-ATC) was used to classify drug classes and individual drugs.[12] The **DDD/100 bed-days** was calculated using the following formula:

DDD/100 bed-days = Drug consumption in the study period (mg) x 100 / DDD (mg) x period of study x bed strength x average occupancy

The present study was carried out for a time period of 365 days. There were a total of 15 beds in the medical ICU and the average occupancy index was 0.8.

Statistical analysis: Descriptive statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS version.18). The total number of the different drugs administered to each patient and drug exposure rates for each drug class and individual drugs were analyzed and values are expressed as percentage, mean $\pm$ SD and range. Among the medications prescribed, those that were prescribed from the WHO essential drug list were noted.

Results and Discussion

This study provides the detailed overview of the gastrointestinal medications utilized among the critically ill patients admitted to the medical ICU. During the study period, 728 inpatients of the ICU were selected as the study population. A total of 706 (97%) patients received gastrointestinal drugs (ATC-A) of the 728 patients admitted to the medical ICU. Male to female ratio was 429 to 266. The mean and standard deviation (SD) for age was 49.21±15.84 years with a range of 18-90 years. The mean and SD among males was 49±15.7 years and among females 49.6±16 years. The mean length of stay in the medical ICU was 7.4±4.3 days and a range of 3-15 days. The demographic characteristics of the Medical ICU patients are detailed in table 1.

Table1. Characteristics of patients admitted to the medical intensive care unit

Item	Characteristics	No (%) n=706
Gender	Male	429 (60.7)
	Female	266(39.3)
Age (In years)	Mean $\pm$ SD	49.2±15.8
	Range	18-90
Length of stay	Mean $\pm$ SD	7.4±4.3 days
	Range	3-15 days

The common clinical gastrointestinal diagnoses in patients admitted to the medical ICU were; hepatic encephalopathy (62), alcoholic liver disease (acute and chronic)(56), acute gastroenteritis with dyselectrolytemia (35), hepatitis (28), upper gastrointestinal bleeding (20).

Drugs for gastrointestinal system and drug metabolism (ATC-A) (23.3%) were most commonly utilized drug class of all the other drug classes in this

study. Among the previous drug utilization studies carried in ICU setting, Biswal et al,[6] documented antimicrobials as the commonest therapeutic class administered in their study.

About 68% of the gastrointestinal drugs belonged to WHO essential drug list. The various gastro intestinal drug classes included anti-peptic ulcer agents, anti-secretory, anti-emetics, laxatives and antispasmodic medications. The utilization pattern of the gastrointestinal drugs and the DDD/100 bed-days of the most commonly prescribed groups of drugs are shown in table-2. From the

results of the present study, prescriptions of gastrointestinal drugs for both prophylactic as well as therapeutic indication were observed. Critically ill patients are at a higher risk for gastrointestinal complications such as stress ulcers, vomiting and constipation necessitating aggressive prophylactic and therapeutic management. Anti-ulcer agents, antiemetics and laxatives were the commonly used prophylactic medication in our study indicating Previous reports also have documented the role of prophylactic gastrointestinal medications in critically ill.[14-16]

Table.2 Drug utilization pattern of gastrointestinal drugs in the medical intensive care unit

Drug class	Drug	ATC code	DDD/100 bed days	Number	Percentage
Antiulcer agents	Pantoprazole	A02BC02	138	607	86
	Ranitidine	A02BA02	9.96	68	9.6
	Al(OH)3+ Mg(OH)2	A06AD10	-	16	2.2
	Omeprazole	A02BC01	2.2	10	1.4
	Sucralfate	A02BX02	1.71	10	1.4
Prokinetic	Metoclopramide	A03FA01	24.8	136	19.3
Anti-emetics	Ondansetron	A04AA01	1.8	105	14.9
	Promethazine	R06AD02	1.8	20	2.8
	Domperidone	A03FA03	2.73	12	1.7
Laxative	Lactulose	A06AD11	100.8	82	11.6
	Ispagula	A06AC51	-	7	1
	Bisacodyl	A06AB02	1.36	6	0.9
Anti secretory	Glycopyrrolate	A03AB02	5.37	44	6.2
Antispasmodic	Hyosine bromide	A04AD01	-	5	0.8

Among the anti-peptic ulcer agents, higher number of patients received pantoprazole (A02BC02) 607 (86%) followed by ranitidine (A02BA02) 68 (9.6%). The major route of administration of acid suppression therapy was intravenous route. This finding was inconsistent with earlier Indian study,[6] and American study, [17] where in H_2 receptor antagonists were the most frequently prescribed. The risk of stress ulcers is very high among the patients admitted to the ICU. Treatment of stress ulceration begins with prevention. The American Society of Health-System Pharmacists (ASHP) guidelines have been put forward for stress ulcer prophylaxis in critically ill patients. [18] Proton pump

inhibitors were preferred since they are well tolerated and more potent in comparison to the H_2 receptor antagonists. [19] The medications currently recommended for stress ulcer prophylaxis are antacids, sucralfate, H_2 receptor antagonists, and PPIs. A recent meta-analysis by Lin et al concluded that there is no significant difference between PPIs or H_2 receptor antagonists in rates of stress-related upper gastrointestinal bleeding among the critically ill patients. [20] Considering the safety profile of PPIs and H_2 receptor antagonists among the ICU patients on stress ulcer prophylaxis Miano et al reported that (9.3%) in the pantoprazole group developed nosocomial pneumonia

while, only (1.5%) in the ranitidine group developed nosocomial pneumonia.[21] Thus, inappropriate and unnecessary prescribing of pantoprazole in ICU can result can lead to unintended consequences such as adverse drug reactions, increase in drug costs for the patient and health care system. Furthermore, there is insufficient data on the intravenous use of PPI among the critically ill patients which the major route of administration in these patients.

Lactulose (A06AD11) 82 (11.6%) was the most common laxative prescribed among the critically ill patients in the present study consistent with results of previous study from an Indian setting,[6] as well as Masri et al,[22] from United Arab Emirates. Incidence of constipation in critically ill patients is reported to be as high as 83%.[23] The impact of constipation in critically ill patients is largely unidentified, but observational studies have reported prolonged length of stay and increased mortality in these patients. [24] Masri et al,[22] and Van der Spoel et al,[25] documented that the use of lactulose can efficiently prevent and treat constipation among critically ill. However, there are no clear published guidelines or data available on prevention and treatment of this commonly occurring problem in critically ill patients.

In addition to the critical illness contributing to the poor gastrointestinal motility, a wide range of medications prescribed in the ICU such as inotropes, opioids, calcium-channel blockers, anticholinergics and proton-pump inhibitors also impair gastric motility. Metoclopramide (A03FA01) 136(19.3%) was the most frequent prokinetic agent. This finding was in line with Biswal et al study.[6] Metoclopramide in addition to its central dopamine antagonism is also a prokinetic agent which further contributes to the antiemetic property. Metoclopramide increases the rate of luminal passage as well as the force of contraction. The sedative effects associated with metoclopramide have added benefit to patients with ICU agitation and the most worrisome adverse effect is extrapyramidal effects.[26] Though metoclopramide is widely utilized as prokinetic agent in the ICU and accepted in the Intensive care unit feeding recommendations for use, the evidence of its effectiveness among the critically ill is limited due to lack of large-scale randomised controlled trials [27]

Nausea and vomiting is a common and distressing complication for patients with critical illness, and Ondansetron (A04AA01) 105(14.9%) was the frequently utilized anti-emetic agent in the medical ICU Ondansetron was preferred in the ICU setting probably due to better efficacy and safety profile in comparison to dopamine antagonists.

Glycopyrrolate (A03BA01) (6.3%) was the most common antisecretory agent utilized and the primary indication among the critically ill is to reduce the upper airway secretions especially patients on mechanical ventilation.

The common drug induced gastrointestinal disorders encountered in patients in the ICU along with the drugs attributed to the adverse drug reaction have been detailed in table 3. The rare adverse effects observed were leflunamide induced hepatic encephalopathy and Anti tubercular therapy (ATT) induced hepatic encephalopathy. Majority of the gastrointestinal ADRs detected in this study are well documented and known ADRs. The two rare and serious adverse effects observed were leflunamide induced hepatic encephalopathy and ATT induced hepatic encephalopathy. Leflunamide induced elevated liver function tests have been reported in the past.[28] The European Agency for the Evaluation of Medicinal Products (EMEA) published a warning regarding the potentially serious hepatic toxicity associated with leflunomide, and has been of concern since then.[29]

Table 3. Gastrointestinal adverse drug reaction profile in the medical ICU

Adverse drug reaction	Number	Implicated drug	Causality
Drug induced hepatitis	5	Antitubercular drugs Valproic acid Phenytoin	Probable
Drug induced upper gastrointestinal tract bleeding	4	Non-steroidal anti-inflammatory drugs Warfarin	Probable
Drug induced diarrhea	4	Amoxicillin clavulanate Ceftriaxone	Probable
Hepatic encephalopathy	2	Leflunamide Antitubercular drugs	Probable

Conclusion

Gastrointestinal drugs were the widely prescribed drug class among the critically ill prescribed both as prophylactic as well as therapeutic indications. PPIs were the acid suppressant therapy of choice, which require revision based on recent findings on safety and efficacy of PPI in critically ill. Periodic drug utilization review and surveillance evaluating the current utilization pattern can assist in formulating and modifying ICU treatment protocols and guidelines in this special population. Furthermore, there is a need to greater number of multicentric randomized controlled trials for use of various gastrointestinal medications among the critically ill patients to add to the available evidence. Health care professionals of the ICU play an integral role in minimizing the inappropriate and unnecessary use of medications and promote rational use of drugs and maintain optimal patient care.

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