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Pharmaco-therapeutic pattern of drug usage in patients with delirium - a study from tertiary care hospital

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ABSTRACT

Background

Research in drug prescription and utilization pattern for any disorder is vital in order to understand the current practice and future modification. Delirium is one of the most common psychiatric emergencies; necessitating early identification and treatment to prevent complications like death and to recover the patient as early as possible to reduce the caregiver burden. Studies from India in this context are few; hence the present study was undertaken at the tertiary care teaching hospital, IGMC&RI, Puducherry.

Methods

A prospective, observational study was conducted over a period of 12 months among the 78 eligible patients admitted in various departments who were referred for psychiatry opinion and management. Data was collected from Patients, their relatives, staff nurses and case records. Parameters like socio-demographic profile, common predisposing and precipitating conditions, biochemical profile and drugs prescribed for them were assessed.

Results

Delirium was most commonly found in males (92.3%), and in alcohol users (74%) and resulting in 15 deaths (mortality for one year - 19.2%). 72 patients (92.3%) received both Benzodiazepines and antipsychotics. Diazepam and Lorazepam were the commonly used benzodiazepines whereas Haloperidol was the most commonly used antipsychotic drug. Lorazepam was used in all patients with deranged liver status. The mean total (oral and parenteral) doses of diazepam, lorazepam and haloperidol used per patient per day were 10.5mg, 7.1mg and 3.2mg respectively.

Conclusion

In the present study both benzodiazepines and antipsychotics were used, mostly together and without much complications. Moreover, these drugs were found to be effective in early improvement of delirium, helping both patients and staffs who care for such uncooperative patients.

Keywords: Delirium, Benzodiazepines, Antipsychotics

INTRODUCTION

Delirium is one of the most common psychiatric emergencies occupying 3-21% of all new admissions and its prevalence shooting up to 41% at any time of hospital stay [1]. The putative risk factors of delirium often play interactive role resulting in etiopathogenesis of delirium as a complex entity [2]. Though alcohol, observed as an important risk factor, isolated alcohol withdrawal delirium is rare and other co morbidities would be present in most of the cases [3]. The implications of these observations do impact upon the management, where several modalities and multiple drugs used, often together. Both pharmacological and non-pharmacological interventions were used for patients with delirium [4]. Among the drugs, anti-psychotics and benzodiazepines are the frontline drugs and studies reported the benefits and risks of each class of drugs [5]. In clinical practice, both drugs are used together in most cases and it is important to keep in mind about the potential complications of combined drug use apart from the advantages of such regime. In this context, we planned to study the pattern of drug usage in patients with delirium in a tertiary care teaching hospital, Puducherry.

METHODS

The study was a prospective observational study, conducted for 12 months in the year 2018.

Study population

The study group consisted of 78 patients, either sex, who were admitted in ICU as well as psychiatry, medicine and surgical wards of Indira Gandhi Medical College and Research Institute, Puducherry and diagnosed as suffering from delirium.

Inclusion criteria

1. Patients of either sex; aged ≥ 18 years.
2. Patients who were diagnosed with delirium

Exclusion criteria

1. No willingness to give consent by the care-givers
2. Patients admitted in Casualty

PROCEDURE

Institutional Ethical Committee approval was taken before conducting the study. Patients admitted to psychiatry, medical, surgical wards and in ICU who fulfill the inclusion and exclusion criteria were selected for the study after obtaining informed, written consent from care-givers (spouse or first-degree relatives). Demographic data and history as per semi-structured proforma were noted from care-givers and staff nurses while biochemical profile was collected from case-sheets of the selected patients. Diagnosis of delirium was ascertained by Confusion Assessment Method. Drug prescription patterns were assessed and analyzed.

RESULTS

Out of 78 patients selected, 72 (92.3%) were males with age ranging from 27 years to 82 years [mean age- 47]. 56 patients recovered completely whereas 15 (19.2%) patients died in the hospital during the study period. Duration of hospital stay ranged from 2 to 30 days (mean - 9.2 days). Alcohol abuse was found in 57 patients who were all males (79% - sex adjusted ratio) and 41 of them had deranged liver function. 25 cases were found to have post-operative delirium (32%). Among those who were operated, 18 were done under general anesthesia. Biochemical profile of patients with key parameters shown in Table.1,

Table. 1

Parameter Measured *	Unit (IU)	Total sample Mean { \pm SD}	Alcoholics Mean { \pm SD}	Non-alcoholics Mean { \pm SD}	Laboratory Reference value
Hb	gm/dl	12.9 [1.75]	12.6 [1.45]	13.2 [1.7]	NA
WBC (TC)	cumm	9500 [2800]	9700 [3550]	9300 [3500]	NA
Bl. Glucose	mg/dl	73 [59.5]	66 [48]	80 [57.5]	70-140
Sr. Urea	mg/dl	23.75 [13.5]	25.5 [10]	22 [13]	15-40
Sr. Cr	mg/dl	0.9 [0.2]	0.9 [0.2]	0.9 [0.2]	0.7-1.2

Sr. Na ⁺	mEq/L	133.7 [4.75]	132 [4.5]	135.4 [4]	135-145
Sr. K ⁺	mEq/L	3.5 [0.77]	3.2 [0.55]	3.8 [0.62]	3.5-5.0
Sr. Bilirubin	mg/dl	1.8 [1.25]	3.1 [1.1]	0.8 [0.25]	0.4-1.2
Sr. Protein	gm/dl	6.1 [0.85]	5.4 [0.7]	6.7 [0.7]	6.3-8.3
Sr. AST	IU/L	111.7 [96.25]	122 [88.5]	101.4 [82.5]	5-40
Sr. ALT	IU/L	79.2 [41.25]	98 [26]	60.4 [25]	5-45
Sr. GGT	IU/L	122 [53]	142 [46]	102 [41]	1-50
Sr. ALP	IU/L	209.8 [197.5]	263.5 [186]	156 [110]	30-125
Sr. Amylase	IU/L	119.5 [468.5]	155 [464.5]	84 [66]	28-100

*Hb –Hemoglobin, WBC (TC) – White Blood Cells (Total Count). Bl. – Blood. Sr. – Serum.

AST -Aspartate transaminase. ALT -Alanine Transaminase. GGT -Gamma-glutamyltransferase

ALP -Alkaline Phosphatase. Bilirubin & Protein – Total. NA – Not Applicable. First Blood sugar level after admission was taken into account as it was a reliable indicator.

76 patients received one or other benzodiazepines. Four patients were on

benzodiazepines alone while two were treated with antipsychotics alone. 72 patients received both antipsychotics and benzodiazepines. Haloperidol was the mostly used antipsychotic. Oral as well as parenteral use was noted for both classes of drugs. Except diazepam which was used exclusively as intravenous route, lorazepam and haloperidol were used as intravenous and intramuscular injections.

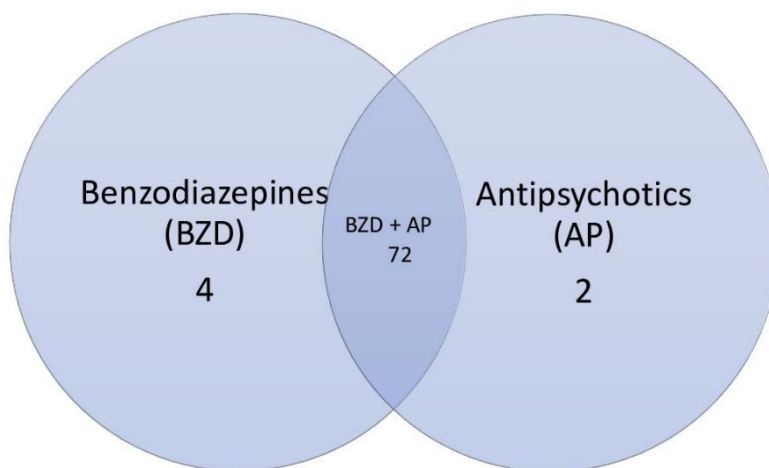


Fig.1. Venn Diagram showing distribution of drugs

Benzodiazepines

Among the benzodiazepines, Lorazepam and Diazepam were used almost equally [41 and 35 respectively]. Both were used orally as well as through parenteral route. Patients with deranged liver function as indicated by elevated liver enzymes and bilirubin (41) were given lorazepam. Patients receiving one type of benzodiazepine orally were given same type of benzodiazepine parenterally.

Maximum oral dose was observed within 48 hours after admission (mean – 38.6hrs) for Diazepam group. Maximum dose was observed within 36 hours after admission (mean – 28.4hrs) for Lorazepam group.

Mean dose per patient per day, starting dose, maximum dose and mean dose of benzodiazepines prescribed at the time of discharge were given in Table.2

Table.2

Drug	Mean dose/patient/day (in mg)	Mean starting dose (first 24 hours) (in mg)	Maximum daily dose (mean) (in mg)	Mean dose at discharge (in mg)
Diazepam (Oral)	12.4	8.6	22.5	5
Diazepam (Parenteral)	8.6	15.96	17.5	-
Lorazepam (Oral)	7.8	6.2	12	3.6
Lorazepam (Parenteral)	6.4	8.1	10	-

Each vial of diazepam contained 5mg/ml and the mean dose of each injection of diazepam was 4.2mg. Mean frequency of injection of diazepam was 3.8 times in 24 hours for first 72 hours and 1.8 after that. Each 2ml vial of lorazepam contained 2mg/ml and the mean dose of each injection of lorazepam was 1.8mg. Mean frequency of injection of Lorazepam was 4.5 times for 24 hours in first 3days and 3.2 in subsequent days. The mean time lag of first injection from the time of admission for diazepam was 1.2 hrs and for Lorazepam was 1.6 hrs.

In the diazepam group, 12 patients received only parenteral forms for first 72 hours, followed by both oral and parenteral routes in subsequent days. In Lorazepam group, 9 patients received only parenteral forms for first 72 hours, followed by both oral and parenteral routes in subsequent days. Mean frequency of parenteral diazepam per patient for the entire duration of stay was 12.4, while it was 14.6 for Lorazepam. Mean hours necessitating parenteral use of diazepam for all patients based on stratified analysis was found to be 88 for diazepam while it was 92 for Lorazepam. [i.e., mean number of days parenteral benzodiazepines used for all patients – Diazepam 3.6 days; 3.8 days for Lorazepam].

Antipsychotics

Haloperidol was the only drug used as parenteral form of antipsychotic for 74 patients. It was given

always with the combination of promethazine as 1: 10 dose ratio [1mg haloperidol mixed with 10 mg of promethazine]. The routine use of this combination was to prevent any acute extra pyramidal side effects like dystonia due to haloperidol alone. Each promethazine vial contains 25mg/ml. The mean time lag of first injection from the time of admission for haloperidol was 2.2 hours.

Each 2ml vial of Haloperidol contained 5mg/ml and the mean dose of each injection of Haloperidol was 1.2mg for each patient. Mean frequency of injection of haloperidol was 3.6 times in 24 hours for the first 72 hours and 2.4 in subsequent days. Mean frequency of parenteral haloperidol used per patient for the entire duration of stay was 14.2. Mean hours necessitating parenteral use of haloperidol for all patients based on stratified analysis was found to be 108 hours. [i.e., each patient 4.5 days were on haloperidol injection]

Among oral antipsychotics, haloperidol was used in 58 patients while risperidone and olanzapine were used for 14 and 2 patients respectively. Oral antipsychotics were started after mean lag period of 28 hours. Both oral and parenteral antipsychotics used in 74 patients. Those who received parenteral haloperidol were gradually switched to oral haloperidol based on daily assessment. Doses of oral antipsychotics are depicted in Table.3.

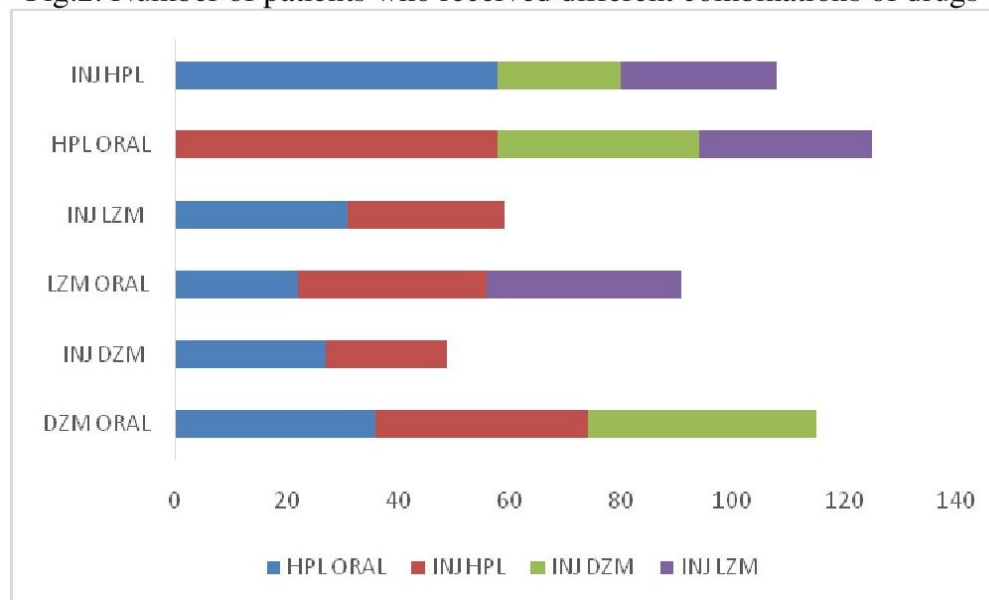
Table.3

Drug	Mean dose/patient/day (in mg)	Mean starting dose (per day for first 72 hours) (in mg)	Maximum daily dose (mean) (in mg)	Mean dose at discharge (in mg)
Haloperidol (Parenteral)	4.2	4.32	8.5	-
Haloperidol (Oral)	2.2	2.6	2.8	1.8
Risperidone	1.4	1.8	2.2	0.8
Olanzapine	3.8	3.2	4.5	3.2

Polypharmacy was noted in the form of usage of both benzodiazepines and antipsychotics. Parenteral diazepam and oral haloperidol together were used in 27 patients while parenteral Lorazepam and oral

haloperidol were used in 31 patients. Bar diagram in Fig. 2 shows the number of patients received the multiple drugs.

Fig.2. Number of patients who received different combinations of drugs



HPL- Haloperidol, DZM- Diazepam, LZM- Lorazepam

DISCUSSION

Delirium is a multifactorial condition for which benzodiazepines and antipsychotics are frontline drugs. The division of exclusive alcohol withdrawal delirium and other types of delirium is arbitrary from practical point of view since most patients have alcohol as well as other risk factors together [6]. Perhaps, hepatic status could be used as a guide for choosing benzodiazepines. In our study, males outnumber females reflecting the etiological factors like alcohol which were almost always seen in males. Mean age is less in our study when compared to west

but Shivanandh *et al* observed similar findings in Indian setting [8].

Though all subclasses of benzodiazepines were equally effective in treating delirium, availability and pharmacokinetic profile of each drug determine the choice. Long acting drugs like diazepam carry the risk of prolonged action like sedation due to active metabolites, especially in patients with alcoholic liver disease. But they offer smooth course due to less chance of rebound symptoms. In our study, moderate doses of diazepam were used, both orally and intravenously, without dreaded complications like respiratory depression [9].

Benzodiazepines like lorazepam would be preferred in patients with severe liver dysfunction due to their inactive metabolites. On the other hand, they should be tapered slowly to counter relapse of symptoms and the same was observed in our study. Few studies reported worsening of delirium with lorazepam, but rigorous adherence to treatment protocol might avoid this phenomenon [10].

The doses of drugs used were in concordance with many other studies though some studies reported higher doses of both benzodiazepines and antipsychotics [11]. No significant side effects for haloperidol noted, rather improvement of symptoms was observed even in postoperative patients as in line with other studies [12,13,14]. Combined use of haloperidol with benzodiazepines was found effective and no added side effects were noted in our study as it was seen in many others [15]. Newer antipsychotics like risperidone and olanzapine were used less commonly which could be due to

widespread unavailability of these drugs as parenteral forms for immediate action. Nevertheless, it is prudent to study these drugs in future so as to reduce high dose of haloperidol usage with its attendant risks [16,17,18].

Conclusion

Irrespective of etiology of delirium, combined use of Benzodiazepines and Antipsychotic drugs had been found in the study. Role of newer antipsychotic drugs needs further studies to throw more light on their efficacy and safety.

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