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Donepezil Related Neuroleptic Malignant Syndrome

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Abstract: *The purpose of the paper is to report a case of development of neuroleptic malignant syndrome (NMS), in a 55year old Assamese male patient receiving low dose oral haloperidol 2.5mg/day and Trihexyphenidyl 4mg /day in divided doses which he was tolerating well until after the addition of oral Donepezil 5mg /day following which he developed NMS. Antipsychotics and cholinesterase inhibitor have direct propensity to induce neuroleptic malignant syndrome but it is a very rare event, when given in together they undergo complex interaction to induce NMS and therefore should be chosen very carefully.*

Key word: *Haloperidol, Donepezil, Alzheimer's disease, neuroleptic malignant syndrome*

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I. Introduction

Patients with dementia often present with variety of non cognitive symptoms called as behavioural and psychological symptoms of dementia (BPSD). These symptoms include agitation, aberrant motor behaviour, anxiety, elation, irritability, depression, apathy, disinhibition, delusion, hallucinations, and sleep or appetite changes. It is estimated that upto 90% of all dementia subjects get affected by BPSD over the course of their illness [1]. It is very important to identify BPSD as its management requires a high level of expertise. The task of identifying BPSD becomes even more challenging when the history is not adequate and it becomes almost impossible to differentiate it from independent psychosis. These neuropsychiatric symptoms of dementia are managed with a combination of pharmacological and non pharmacological interventions. A variety of medications are used to treat these symptoms including cholinesterase inhibitors, Memantine, typical and atypical antipsychotics, benzodiazepines, antidepressants and mood stabilisers [2]. A careful selection of drugs becomes very important because of possible drug interactions and precipitation of side effects some of which though rare can prove fatal. One such fatal condition is neuroleptic malignant syndrome (NMS). Here we are reporting a case of a patient withAlzheimer's dementia who was initially diagnosed as a case of psychosis not otherwise specified [3] and was maintained on low dose oral Haloperidol but developed neuroleptic malignant syndrome after initiation of Donepezil.

II. Case Report

A 55 yr old male wandering on the street, unable to tell about his whereabouts was admitted according to the law. At the time of admission he was uncooperative, irritable, had poor self care, was muttering to self, and hadirrelevant speech and perseveration. His vitals were stable,general physical examination revealed pallor and systemic examination was in normal limits. Routine laboratory examination showed Hb-7.8g/dl and other laboratory parameters were within normal range. A CT-scan of brain was done which showed a normal scan.With a provisional diagnosis of psychosis not otherwise specified according to ICD-10, and he was started on oral Haloperidol2.5mg/day which was gradually increased to 7.5mg/day, along with Lorazepam 2mg at night time and Iron supplements.

One month after the start of treatment patient developed tremors and cog wheel type rigidity. The dose of Haloperidol was reduced to 2.5mg/day, an i.m. injection of 50mg of Promethazine was given and oral Trihexyphenidyl at4mg/day was started after which tremor and musculararigidity completelysubsided in two days.

Patient improved but continued to have perseveration in thought, difficulty in sustaining attention and concentration and impaired immediate recall. His MMSE score was 20. Oral Donepezil5mg/day was added to

his treatment. This was ten days after the dose of haloperidol was reduced to 2.5mg /day and two months after the initiation of his treatment in the hospital. On 17th day of starting Donepezil patient developed tremors, had cog wheel rigidity, stooped posture on standing and decreased arm swing while walking. Oral Haloperidol, Trihexyphenidyl and Lorazepam were then stopped and oral Pramipexolewas given as 0.125mg twice a day for three days.Three days laterpatient complained of body ache, he became restless and developed leadpipe type muscular rigidity. He was then started on oral Clonazepam 0.5mg twice daily and oral Trihexyphenidyl 4mg /day in divided doses. By evening the patient developed an axillary temperature of 102° F, tachycardia[pulse =112/minutes], with signs of some dehydration, patient was drowsy and responded only to painful stimuli; hehad severe rigidity in all four limbs and was refusing to take anything orally. All oral medications were stopped, intravenous fluids were given to maintain fluid and electrolyte balance, cold sponging was done and Paracetamol i.m. injection was given to bring down the elevated body temperature, vitals were monitored laboratory investigations were sent. Laboratory tests revealedleucocytosis [TLC= 13,410/cumm] and elevated serum creatine phosphokinase [CPK= 1154 U/L].Patient was able to take oral feed from the next day and therefore he was shifted onto oral Paracetamol from the next day. His temperature normalised after 4 days. However, he still had increased salivation,stooped posture and rigidity in both upper and lower limbs. He was started again oral Pramipexole 0.125mg at night time and in next three days rigidity subsided.

Pramipexole was stopped after fourteen days and patient was started on Memantine 5mg/day initially and gradually increased to 10mg /day. A final diagnosis of Dementia in Alzheimer's disease was made according to ICD-10 and patient was discharged on Memantine 10mg/day. There was no change in the MMSE score of the patientfrom its initial value i.e., 20 at the time of discharge and there were no psychotic symptoms.

III. Discussion

In the index case patient developed Neuroleptic Malignant Syndrome after more than two weeks of the addition of 5mg oral Donepezil to the existing treatment i.e., oral Haloperidol 2.5mg/day , and Trihexyphenidyl 4mg/day. Most cases of Neuroleptic Malignant Syndrome develop within 1st week of treatment initiation.Also in this case the patient was already on Ttrihexyphenidyl 4mg/day which is an anticholinergic agent protective against development of NMS. Patient had previously developed extrapyramidal symptoms with7.5mg of haloperidol/ day following which the dose was reduced to 2.5mg/day and Trihexyphenidyl 4mg /day was added to the treatment. Patient also had anaemia which was responding to iron supplements indicating that patient was deficient in iron which is a predisposing factor for development of neuroleptic malignant syndrome. When patient began to develop tremor and rigidity after addition of oral Donepezil, oral Haloperidol and Trihexyphenidyl was stopped and patient was started on Pramipexole for three days and on the third day patient developed neuroleptic malignant syndrome. A complex drug interaction has taken place here. Cholinesterase inhibitors like Donepezil elevate brain acetylcholine level and have potential to cause drug induced extra pyramidal syndrome or worsen drug induced EPS. The potentiation of Haloperidol induced extra pyramidal by cholinesterase inhibitor appear to occur in a synergistic manner.Although the exact mechanism of this synergistic potentiation is not known;Dopamine derived from the substantia nigra negatively regulates the firing of striatal cholinergic interneurons and blocking of D2 receptors is known to facilitate the firing of cholinergic interneuron and enhance the acetylcholine release. Thus Donepezil augments the induction of EPS more potently in presence of Haloperidol than with its single administration. Also both Haloperidol and Donepezil are metabolised CYP3A4 and CYP2D6 and may compete with each other for the enzymes reducing their metabolism and increasing their serum levels. In the index case it is difficult to say whether it was the interaction between Donepezil and Haloperidol that led to the development of Neuroleptic Malignant Syndrome or Donepezil caused NMS all by itself.

There have been case reports of Donepezil causing NMS either by itself and more frequent when given in combination with antipsychotics. A similar case has been reported in an East-Asian female in her mid 50s with history of Schizophrenia for 25 years on Haloperidol decanoate 200mg i.m./month and Fluvoxamine150mg daily and Benztropine0.5mg twice daily developed Neuroleptic Malignant Syndrome when started on Donepezil 5mg/day for the treatment of probable dementia. In this case also there was probability of drug interaction between Haloperidol and donepezilleading to NMS [4]. Another case of a patient with probable Dementia with Lewy Bodyhas been reported todevelop NMS after initiation of treatment with Olanzapine was done [5]. Another case of NMS has been reported in a 78 year old male with 22 year history of Schizoaffective Disorder and a 5 year history of Dementia on oral olanzapine for 10 years and a week after initiation of Donepezil he developed NMS [6]. There is also a case report of a woman with DLB with psychotic symptoms developingNMS twelve days after stopping oral Risperidone and three days after starting Donepezil in the dose of 3mg/day [7].

IV. Conclusion

Neuroleptic malignant syndrome can be precipitated in susceptible individuals treated with antipsychotic and cholinesterase inhibitors. They can cause NMS independently and also as a result of interaction between them. Not much study has been done to explore the ways in which antipsychotics and cholinesterase inhibitors interact to precipitate NMS. Therefore all the patient and medication factors must be considered while giving antipsychotics and cholinesterase inhibitor combination to a patient and patient must be carefully and frequently monitored to detect neuroleptic malignant syndrome as early as possible.

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