

Prolonged haloperidol induced Parkinsonism in a patient with cirrhosis

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Introduction

Haloperidol is a high potency typical antipsychotic agent having an increased propensity to cause drug induced extrapyramidal symptoms (EPS). Prolonged drug induced Parkinsonism with haloperidol use has been reported a few times in world literature^{1,2}. We describe here a patient who had haloperidol induced Parkinsonism for about seven weeks after discontinuation of the drug.

Case report

A 56 year old lady was admitted to Teaching Hospital Kandy with an acute confusional state which was retrospectively diagnosed as an episode of steroid induced psychosis. On

physical examination, patient did not have rigidity, bradykinesia or any other features of Parkinsonism. Haloperidol lactate 10 mg was given intramuscularly to calm the patient and it was followed by oral haloperidol 1.5 mg and benzhexol 2 mg twice a day. Investigations done while she was taking in-ward treatment revealed that she is having cirrhosis (Macronodular cirrhosis in liver biopsy). She was not on any other medication which was likely to give rise to EPS.

She was reviewed in the clinic one month afterwards. Neurological examination revealed symmetrical rigidity of all four limbs. Both lead-pipe and cogwheel rigidity was clearly seen. Facial expression and gait were normal. No resting tremors were seen. A mild bradykinesia

was noted. Serum caeruloplasmin, 24-hours urinary copper excretion, antidouble-stranded DNA antibodies, serum ferritin, contrast CT and MRI scan of brain and an EEG did not reveal any abnormalities. Haloperidol was stopped suspecting antipsychotic induced Parkinsonism.

Patient was reviewed in the clinic every fortnightly for one month and in three weeks thereafter. Seven weeks after stopping haloperidol the patient was completely free of rigidity and bradykinesia. At the time of writing she is attending the clinic regularly for nearly ten months after the disappearance of parkinsonian signs and is clinically well except for mild ankle oedema.

Discussion

The temporal relationship between starting of haloperidol and appearance of parkinsonian signs and the absence of any evidence from clinical findings or investigations to suggest an alternative diagnosis (e.g. basal ganglia infarction, cerebral lupus) confirms that this clinical observation is very likely to be due to haloperidol induced EPS. Complete disappearance of the signs reinforces this possibility, excluding the possibility of this being idiopathic Parkinson's disease which is progressive in nature.

One explanation for prolonged Parkinsonism in our patient at low normal haloperidol doses may be poor hepatic clearance. Haloperidol is extensively metabolized in liver and has a moderate hepatic extraction ratio³. In addition haloperidol is a drug with a narrow therapeutic window. If such drugs are to be given to cirrhotic patients, maintenance dose needs to be reduced and sometimes portosystemic shunts may necessitate reduction in initial dose also⁴. Therefore, in our case, low normal haloperidol dosage may have given rise to high sometimes even toxic serum haloperidol levels. Therapeutic monitoring of serum haloperidol levels was not done as facilities were not available locally.

Another possibility is the inter-individual variation resulting from pharmacogenetic differences. CYP2D6 is an isoform of cytochrome P450 (CYP450) system involved in

haloperidol metabolism. It has been shown that EPS with haloperidol occurred more in poor metabolizers (PMs) for CYP2D6 than extensive metabolizers (EMs) having schizophrenia³. Llerena and colleagues demonstrated that PMs for CYP2D6 had significantly longer plasma half life of haloperidol than EMs⁵. Further, independent of the CYP2D6 polymorphism, a higher metabolic ratio (i.e. reduced haloperidol / haloperidol ratio) is seen in most Caucasians compared with majority of Orientals³.

Parallel with the EPS due to blockade of dopamine D₂ receptors in basal ganglia, blockade of D₂ receptors in the anterior pituitary causes elevation of prolactin levels in blood. Nishikawa and colleagues describe two cases of prolonged haloperidol induced Parkinsonism with hypokinetic EPS persisting even after prolactin levels return to normal¹. Thereby they argue the pathophysiology behind this long lasting EPS is not dopamine receptor blockade by neuroleptics but possibly reversible cytotoxicity in dopaminergic neurons.

In our patient most likely a combination of these factors i.e. poor hepatic clearance, genetic polymorphism of CYP2D6 or Asian race may have given rise to this prolonged antipsychotic-induced Parkinsonism.

The understanding that haloperidol-induced Parkinsonism can last for several weeks to months after discontinuing the drug is important for the clinician. So that he / she will not be in a hurry to diagnose incurable Parkinson's disease in a patient with this prolonged manifestation of a reversible adverse drug reaction.

References

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