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AGRANULOCYTOSIS AND CARDIAC TOXICITY - SERIOUS SIDE EFFECTS OF CLOZAPINE

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ABSTRACT

Clozapine is probably the most effective antipsychotic. Treatment with clozapine is proved to decrease frequency of suicidal behavior. It is related to decrease in use of psychoactive substances and decrease in frequency and intensity of aggressive behavior among patients. It decreases the risk of rehospitalization and relapse. However because of serious, potentially fatal side effects like agranulocytosis or cardiac toxicity, use of clozapine is limited to schizophrenia symptoms partially or fully resistant to treatment with other antipsychotic drugs, or accompanied by persistent suicidal or self-injurious behavior.

INTRODUCTION

The introduction of the dibenzodiazepine antipsychotic agent clozapine (8-chloro-11[4-methyl-1-piperazinyl]-5h-dibenzo-[b,e][1,4] diazepine) was a significant development in the pharmacotherapy of schizophrenia. [1] Clozapine is an atypical antipsychotic medication.[2] unlike classic neuroleptic agents, it does not cause parkinsonism, dystonia,[8] or tardive dyskinesia, nor elevate prolactin levels.[1] It is more effective than conventional neuroleptics in reducing symptoms of patients with both treatment-resistant and nonresistant schizophrenia.[3] Clozapine is on the WHO model list of essential medicines, which lists the most effective and safe medicines needed in a health system.[4] It also has been associated with reduced or delayed risk of suicide attempts, which led to the precedent-setting approval by the US Food and Drug Administration (FDA) for this effect in 2003.[5]

The therapeutic efficacy of clozapine is mediated through antagonism of the dopamine type 2 (D_2) and serotonin type 2a ($5\text{-}HT_{2a}$) receptors. Clozapine also binds to D1, D3, and D5 receptors, and has a high affinity for the D4 receptor, but the implications of these binding activities are unclear. It interacts also at histamine (H_1), acetylcholine muscarinic (M_1) and serotonin ($5\text{-}HT_{2a}$, $5\text{-}HT_{2c}$, $5\text{-}HT_6$ and $5\text{-}HT_7$) receptors and α_1 adrenoceptors.[5]

With the exception of clozapine, careful systematic reviews and meta-analyses have not found convincing evidence that any of the antipsychotics are more effective than others for positive symptoms in acute schizophrenia.[6] Although clozapine is proved to be more effective in treatment of schizophrenic symptoms than majority of drugs (including amisulpride, olanzapine, haloperidol, quetiapine, aripiprazole)[7], primary indications for its use in patients with schizophrenia or schizoaffective disorder are only schizophrenia symptoms partially or fully resistant to treatment with other antipsychotic drugs, or accompanied by persistent suicidal or self-injurious behavior. It is so, because of multiple, potentially dangerous side effects of clozapine like agranulocytosis or cardiac toxicity.

SIDE EFFECTS

Clozapine may cause side effects, some of which are serious and potentially fatal. Common side effects do not seem to be very dangerous for patient's, however they can be arduous. They include constipation, bed-wetting, night-time drooling, muscle stiffness, sedation, tremors, orthostatic hypotension, hyperglycemia, and weight gain.

Clozapine carries five black box warnings, including warnings for agranulocytosis, seizure disorder, myocarditis, increased mortality in elderly patients with dementia-related psychosis and other adverse cardiovascular and respiratory effects.[8] In our review we are going to present briefly some of serious side effects of clozapine – agranulocytosis and cardiac toxicity.

AGRANULOCYTOSIS

Clozapine carries a black box warning for drug-induced agranulocytosis. Clozapine-induced agranulocytosis selectively affects precursors of polymorphonuclear leukocytes in the bone marrow and can be reversed without hematologic sequelae if treatment is stopped promptly However the risk of potentially fatal agranulocytosis is the main factor limiting its use.[1]

The exact mechanism of clozapine induced agranulocytosis remains unclear. It has been postulated that clozapine is metabolised to a nitrenium ion. The binding of this ion to neutrophils may result in agranulocytosis. Also antineutrophil antibodies may be involved in mediating agranulocytosis. Genetic predisposition is considered as well. Some human leucocyte antigen (HLA) alleles, for example the HLA B38 phenotype in Ashkenazi Jews, have been shown to be associated with clozapine induced agranulocytosis.[9]

Clozapine induced agranulocytosis is estimated to occur in 1 to 2 percent of treated patients.[1] Neutropenia is seen in about 3%.[9] The risk of agranulocytosis increases with age and is higher among women. The occurrence of agranulocytosis is a substantial hazard of the administration of clozapine, but this hazard can be reduced by monitoring the white-cell count. The risk of developing agranulocytosis is also the highest within initial three months of treatment, and decreases substantially thereafter, to less than 0.01% after one year. [1] Therefore, according to US labeling : prior to initiating treatment, obtaining a baseline Complete Blood Count (CBC), including the Absolute Neutrophil Count (ANC) is recommended. The ANC must be ≥1,500/mm^3 for the general population in order to initiate treatment. An exception is made for patients with benign ethnic neutropenia, who are subject to a lower ANC level. During the first 6 months of treatment, the ANC need to be monitored weekly. If the ANC remains ≥1,500/mm^3, the monitoring frequency can be reduced to every 2 weeks for the next 6 months. If the remains ≥1,500/mm^3 for the second 6 months of continuous therapy, the ANC monitoring frequency can be reduced to once every 4 weeks.[2] In the United Kingdom and Ireland, weekly CBC monitoring is mandatory for the first 18 weeks, after which it is done fortnightly until the end of the first year, and every four weeks thereafter.[9] If neutropenia develops during treatment, clozapine would either need to be monitored more frequently, stopped temporarily, or discontinued, based on the severity of neutropenia. The process of regular monitoring CBC and ANC appears to be successful in allowing safe use of clozapine while avoiding deaths due to clozapine-induced agranulocytosis[10]

It is worth mentioning, that clozapine-induced agranulocytosis can be transient.[11]

CARDIAC TOXICITY

Clozapine is uncommonly but importantly related to myocarditis, often fatal or near fatal and sometimes in relatively young patients with early onset after treatment initiation, since it usually develops within the first month after initiation of therapy. The most striking feature about this condition is the wide diversity of nonspecific symptoms that occur in afflicted patients. Fever is one of the first manifestations, accompanied with C-reactive protein (CRP) increase. Up to 5 days later there is cardiac enzyme (troponin) increase. According to guidelines, CRP and troponin monitoring (before therapy, weekly later), and observation for symptoms should be performed. Troponin is marker of heart failure, but this complication is less common. Recent study confirmed that clozapine related myocarditis risk

is higher in elderly patients, during dose tritration process or in simultaneous sodium valproate therapy.[12,13] Three proposed potential risk factors for myocarditis are:
Genetic factors influencing metabolism; clinical management involving rapid dose titration and environmental factors leading to high ozone in the breathed atmosphere and consequential cholinergic dysfunction.[14] Since all clozapine manufacturers maintain registries of treated patients as part of their monitoring for agranulocytosis, it would seem prudent and extremely worthwhile for symptoms of myocarditis to be monitored concurrently as part of the registry process.[13]

CONCLUSION

Clozapine is probably the most effective antipsychotic. Undoubtedly speaking treatment with clozapine may be very beneficial for patient. Therefore we need to consider, whether side effects of clozapine should hinder physicians from prescribing clozapine to broader group of patients. Since there are some proved methods of monitoring patients and therefore preventing fatal symptoms progress to death, maybe use of clozapine should be recommended to patients in earlier stages of the disease. Another argument for earlier use of clozapine is that effectiveness of clozapine dramatically decreases after 2-3 years of inefficient treatment with other antipsychotics.

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