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Norclozapine

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Abstract: **Clozapine (CLZ) is one of the most frequently prescribed antipsychotic for schizophrenia (SCH), especially for treatment resistant SCH. CLZ is known to have a positive effect on negative symptoms of SCH, suicide risk, cognition and antipsychotic-induced movement disorder. It is debated that many beneficial properties of CLZ might be due to its active metabolite, N-Desmethylclozapine (NDMC). On the contrary, CLZ is also thought to antagonize some of the beneficial properties of NDMC. In this paper, we will discuss the action of NDMC on various receptors in brain and peripheral system – muscarinic (M), serotonergic (5-HT), dopaminergic (DA) opioid, adrenergic, N-methyl-D-aspartate (NMDA), gamma-Aminobutyric acid (GABA), Calcium ion channel and histaminergic receptors, giving emphasis on its action on muscarinic receptor in light of recent evidence that suggests that NDMC may have pro-cognitive property by improving working memory through its action on muscarinic receptor. Lastly, we will also try to answer if NDMC has the potential to use as a solo antipsychotic.**

Keywords: **Norclozapine, symptoms of SCH, gamma-Aminobutyric acid (GABA).**

1. INTRODUCTION

CLZ, an atypical antipsychotic is known to improve negative symptoms of SCH (1, 2) and cognition (6). It is effective in treatment resistant SCZ (3, 4), reduces suicide risk (5) besides having a low incidence and less severe extrapyramidal side effects (2, 7). Clozapine is metabolized in the body into: N- Desmethyclozapine (norclozapine) and clozapine N-oxide (8, 9). Both these compounds are active metabolites and their concentration is found to be lower than their parent compound by 20-30% and 10-50% respectively (9). While clozapine N-oxide rapidly converts back to CLZ, NDMC does not and hence its concentration ranges from 49 - 140% in SCH patients (10). Other metabolic pathways are also involved in CLZ metabolism via which hydroxylated and protein-reactive metabolites are formed (11, 12). The protein reactive metabolic pathway and clozapine N-oxide pathways are reversible pathways that may lead to extended pharmacological effects of CLZ (13). CYP1A2, CYP3A4, CYP2D6 and CYP2C19 have been implicated in formation of these metabolites including NDMC (14, 15).

Numerous studies have pointed that many beneficial effects of NDMC may play an important role in the beneficial effects of CLZ i.e. negative and positive symptoms, cognition and quality of life (10, 16-18). A study found that 350 ng/ml dose of CLZ and NDMC 350 ng/ml is required to achieve therapeutic benefit (19) while Weiner et al., (2004) found that it is the ratio of NDMC/CLZ that best predicts the positive clinical outcome. In contrast, it is argued that desirable qualities of NDMC might be antagonized by its parent compound, CLZ (20). Weigmann et al., (1999) in their study done on rats found that the concentration of CLZ in brain is higher than NDMC which may indicate a less prominent effect of NDMC on brain (21).

2. DISCUSSION

Dopaminergic receptor:

NDMC interacts with DA D1-D4 receptors like CLZ. But unlike CLZ, NDMC has potent partial agonist activity on D2 and D3 receptor subtypes. CLZ has inverse agonist/antagonist action on D2 and D3 receptors (22, 23). Further, CLZ is

shown to block the agonist actions of NDMC (24). This difference on dopaminergic receptor subtypes in NDMC may confer a more efficacious and stable effect. Many DA agonists have a more potent effect on pre-synaptic receptors as compared to post-synaptic (25). Lameh et al., (2009) suggest that better efficacy seen in NDMC might be due to an agonist effect of NDMC on pre-synaptic DA receptors where receptor reserve is high and antagonist effect at post-synaptic DA receptors which have a low DA receptor reserve (20, 25). The partial agonist activity of NDMC may also be advantageous in terms of negative symptoms and a low propensity for extra-pyramidal side effects (EPS). It is not known whether the antagonist effects of CLZ and NDMC on D4 receptor (24) adds to any significant antipsychotic effects because in clinical trials selective D4 receptor antagonists have not been able to produce antipsychotic advantage (27).

Serotonin receptor:

Serotonin receptors 5-HT1A, 5-HT1B, 5-HT2A, 5-HT3 and 5-HT4, facilitates DA release whereas 5-HT2C receptor has an inhibitory effect of 5-HT on DA release (28). Clozapine and NDMC have high affinity and act as inverse agonist (17) at 5HT2A receptors (22, 23). Clozapine and NDMC have also been shown to have the highest 5HT2A/D2 potency (approx. 10/1) as compared to other atypical antipsychotics (24, 29). Hence, the modulatory effect of 5HT2A on DA plays a significant role in the antipsychotic effect of CLZ and NDMC (20).

Both CLZ and NDMC are 5HT2C receptor inverse agonists (29). However, no correlation has been found between the 5HT2C receptor and antipsychotic effect (30). CLZ and NDMC are 5HT1C receptor antagonist as seen in rat studies. NDMC has more affinity to 5HT1C as compared to CLZ (31).

NDMC and its parent compound, CLZ are weak partial agonist on 5HT1A receptor (32). Although 5HT1A receptor inverse agonist increase DA in frontal cortex and have anti-cataleptic activity; how significant is the role of 5HT1A receptor on the antipsychotic profile of CLZ and NDMC is not known (20). Both CLZ and NDMC are inverse agonist at 5HT6 and 5HT7 receptors (17) but no correlation has been found between these receptors and antipsychotic effect (33).

A postmortem study was done to examine the effect of CLZ and NDMC on forskolin stimulated adenylyl cyclase (AC) activity and on 5HT1A receptors (34). The study found that AC activity is still present in autopsy tissues of human brains. Forskolin was shown to stimulate basal enzymatic activity of AC which was more pronounced in prefrontal cortex (PFC). Forskolin induced increase in enzymatic activity was inhibited by CLZ in hippocampus but not in PFC or raphe nuclei. Both CLZ and NDMC showed a high affinity for 5HT1A receptors in hippocampus and cortex respectively. They also displaced (3H) 8-OH-DPAT specific binding to PFC, hippocampus and raphe nuclei although NDMC displaced in all three brain regions with low affinity as compared to CLZ.

Muscarinic receptor:

There are 5 muscarinic receptors, M1 to M5 present in humans (35, 36). Out of these 5 receptors, M1 receptor has been shown to have a predominant role in SCH (37). M1 receptors are abundantly found in cortex and hippocampus (38, 39). Lower muscarinic M1 receptor activity is found in prefrontal cortex (40) (Brodman area 9 and 46) and in caudate-putamen and anterior cingulate cortex (41) in SCH patients. Acetylcholine (Ach) impacts various domains of cognition such as attention, learning and memory (42, 43). In SCH, various domains of cognition are disturbed (44) and trials to use Donepezil, an Acetylcholinesterase inhibitor have not been shown to have any positive effects (45).

A study done was done on rats to examine the role of NDMC on DA and Ach. They found that NDMC has a propensity to increase DA levels in medial prefrontal cortex (mPFC) and hippocampus. Such an effect was not observed in nucleus accumbens (NAC). This effect of NDMC was dose dependent i.e. low doses of NDMC (5mg/kg) failed to show any effect on DA release but high dose of NDMC (10 mg/kg and 20 mg/kg) significantly decreased DA and Ach release in mPFC and hippocampus but not NAC. Telenzepine, M1 antagonist was shown to block the DA release effect of NDMC. This may signifies that the effect of NDMC on DA release is dependent on M1-receptor. CLZ was shown to inhibit the effect of NDMC on ACH in mPFC but did not suppress the release of DA in MPFC. The effect of CLZ was in contrast to that of 5HT 1A receptor antagonist, WAY 100635 which blocked NDMC induced release of DA but not ACH. The study showed that NDMC is M1 agonist. Thus it can increase the level of DA and ACH in cortex which may have potential benefit in improving cognition in SCH patients. The study also showed that CLZ can inhibit M1 agonist effect of NDMC (46).

A study done was done to examine if NDMC has discriminative stimulus effect like its parent compound CLZ. The study found that like CLZ, NDMC also has discriminative stimulus effect but unlike CLZ, the discriminative effects are different. This difference may be due to M1 agonist property of NDMC (47). Another study also deduced the presence of discriminative stimulus property of NDMC (48).

An experiment was done on rats to find the effect of NDMC on sensorimotor gating. It showed that CLZ (3-10 mg/kg) and NDMC (10-30 mg/kg) antagonized the pre-pulse inhibition (PPI) induced by methamphetamine (3mg/kg), ketamine (5mg/kg) and scopolamine (0.3 mg/kg). It also showed that CLZ, NDMC and Raclopride (selective D2 antagonist) failed to inhibit disruption in PPI by M100907 (5HT2A antagonist). The investigators pointed that this may reflect a possible role of M1 muscarinic receptor on antipsychotic effect of CLZ and NDMC (49). The study also examined the relation between NDMC and prolactin level and found that NDMC (30 mg/kg) did not show any significant change in plasma prolactin level.

Most recently**,** Rajji et al., (2015) (50) proposed a hypothesis that the ratio of CLZ/NDMC strongly correlates with cognition than CLZ or NDMC alone and that this ratio would also predict working memory performance in SCH patients irrespective of age, gender, education and symptom severity. This study was done on 30 (SCH = 25; SAD = 5) participants with stable dose of CLZ and showed a negative correlation between working memory and CLZ/ NDMC ratio. No significant correlation was found between other measures of cognition based on measurement and treatment research to improve cognition in SCH (MATRICS) consensus cognitive battery (MCCB) used in the study i.e. processing speed, (trail making test), attention/vigilance, verbal learning, visual learning, reasoning and problem solving and social cognition. Serum anticholinergic concentration and clozapine concentration were found to have a strong association. No significant relation was seen between working memory and salivary alpha-amylase. The investigators proposed monitoring CLZ/NDMC ratio routinely. Any cognitive decline can thus be managed by detecting the reasons behind any increase in the ratio (50). Alternatively, NDMC level can be increased by avoiding higher dosages of CLZ i.e. saturation of N-desmethylation may cause increase in NDMC levels (51). A CLZ/ NDMC ratio of >2 is suggestive of saturation in CLZ metabolism (51)**.**

NMDA receptor:

In an experiment done by Sur C et al., (2003) showed that NDMC modulates NMDA receptor mediated current through its action on M1 receptor (52).

Similar study was done to examine the effect of CLZ as compared to typical antipsychotic, haloperidol on PFC using ensemble unit recording and recording behavior stereotypy. The study resulted in showing that CLZ and NDMC differently modulate the activity of PFC as compared to Haldol. They had inhibitory effect on neurons showing high baseline activity and excitatory effect on neurons with low baseline activity. MK801 was used in this study that resulted in behavioral stereotypy which closely resembles SCH (53). Disruptions on PFC neurons due to NMDA receptor produced by MK801 were decreased by CLZ and NDMC (54).

Maehara S et al., (2011) (55) ,conducted an experiment on rats to find if NDMC can improve social and cognitive deficits found in SCH. NMDA antagonist, MK-801 was given to the rats to reduce social interaction without any effect on locomotion. NDMC at a dose of 1-3 mg/kg was shown to improve social deficit caused by MK-801. It also improved object recognition performance after 24 hrs. of training trial. However, such an effect of NMDC was seen on a higher dose (10mg/kg). Thus, NDMC may have potential positive effects on learning and memory consolidation but at a higher dose.

GABA receptors:

NDMC has been shown to antagonize GABA-A receptor with a potency matching to that of CLZ. Micromolar concentration of CLZ and NDMC is sufficient to affect cerebrocortical and hippocampal GABAA receptors (56, 57). Micheal and Trudeau (2000) (57) conducted an experiment on rat ventral tegmental area (VTA) neurons and found that CLZ dose-dependent inhibits GABAnergic inhibitory post synaptic currents. This effect of CLZ was similar to SR-95531 which is a specific receptor antagonist. Another study also showed that CLZ and NDMC play a role at hippocampus inhibitory and excitatory synapses (49). Cultures of rat hippocampus neurons that contained GABAnergic and glutamatergic neurotransmitters and almost negligible monoamines were used to examine the effect on synaptic

transmission. NDMC like CLZ was shown to depress inhibitory neurotransmission at 1-30 micromolar and excitatory inhibition at 30 micromolar concentration. CLZ and NDMC suppressed inhibitory neurotransmission more efficiently. These results were akin to the results of the Micheal and Trudeau study (2000). The investigators suggest that CLZ and NDMC exerted these effects through their action on postsynaptic GABAnergic receptors though the role of presynaptic neurons cannot be ruled out.

Opioid receptor:

In a study done by Kabayashi et al., (1999) (58) to examine the effect of CLZ on opioid receptors and G protein activated inwardly rectifying K channel (GIRK) found that CLZ has delta and kappa agonistic properties and acts as a GIRK channel blocker.

NDMC is a full agonist on delta opioid receptor. In a study done to examine the effect of NDMC on cloned as well as native opioid receptors, found that NDMC is 82% as efficacious as delta receptor agonist – DPDPE which is in contrast to CLZ (affinity as compared to NDMC is 10-fold lower). NDMC was found to have no activity on nociceptin receptor (NOP) receptors and was shown to have low affinity to kappa opioid receptor. Thus, NDMC may have beneficial effects due to its strong delta agonist property which may be relevant in the light of the fact that even small levels of NDMC is capable of exerting its effect due to the high affinity (59).

Delta opioid receptors are thought to play an important role in cell death and survival by coupling delta opioid receptor to intracellular signaling cascades such as mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinase (PI3K/Akt) signaling pathways (60). Phosphorylated Akt (activated form) phosphorylates glycogen synthase kinase -3B (GSK-3B) thereby inactivating it. It is to be noted that selective inhibition of GSK-3B may be a suitable target of intervention in antidepressants, mood stabilizers and antipsychotics (61-63). NDMC has been shown to modulate Akt and GSK-3B phosphorylation state by its delta opioid agonist property (64). Thus NDMC might even have a neuro-protective role (64).

Since in animal studies, delta - receptors have shown to be involved in emotional and cognitive function (65, 66), it is suggested that the mood stabilizing effect seen on patients with CLZ may be due to NDMC's activity on delta receptor (20)**.** Collu F. et al., (2012) (67) conducted a study to see ligand receptor interaction using CLZ and NDMC based on their difference of only one methyl group in their structures. They found that lack of an extra methyl group in NDMC bestows more flexibility and expands the possibility of rearrangements and greater interaction within the delta opioid receptor. The authors concluded that this small difference in the structure of CLZ and NDMC may be responsible for subtle changes in their actions.

Effect on Calcium channel:

Hippocampal neurons are known to express various types of Ca^{+} channel: P/Q-, N-, R-, L-, and T- (49). At high concentrations, CLZ and NDMC have been shown to have an inhibitory effect on voltage gated Ca^{+} and Na^{+} channels. This may have an inhibitory effect on both excitatory and inhibitory presynaptic neurotransmission (49). CLZ has also been shown have an inhibitory effect on voltage gated Ca^{+} channels in adrenal chromaffin cells (68) and native T-type Ca^{+} channels in human thyroid C cells (69, 71)**.** Ohno-Shosaku T. et al., (2011) (49) proposes the imbalance of excitatory and inhibitory neurotransmission may be the reason behind desirable and undesirable profile of NDMC and its parent compound.

Alpha adrenoceptors:

NDMC and CLZ are alpha-1 adrenoceptors antagonist (17, 70). Out of CLZ and NDMC, NDMC has 5-fold lower affinity for binding to alpha-1 adrenoceptors as compared to CLZ (20).

Histamine receptors:

NDMC and CLZ have an antagonistic action on H1 receptors. CLZ and NDMC bind with almost similar affinity to H1 receptor but CLZ has more potency as compared to NDMC on H1 receptor (17, 70). This may be advantageous as it means less sedative or increase in weight for the patients (20).

Can NDMC be used as an antipsychotic?

The concentration of NDMC can be 20-150% of clozapine concentration (9). Positron emission tomography (PET) scan has not been able to predict receptor occupancy of D2 and 5HT2A in atypical antipsychotics (71). Therefore, to

understand the pharmacokinetics and pharmacodynamics of CLZ and NDMC in a better way, a pharmacokinetic model has been proposed (72, 73). The investigators used rat brains using quantitative micro dialysis to measure the levels of CLZ and NDMC in plasma and brain extracellular fluid. The results were then applied to human models. Plasma and CSF levels of risperidone and escitalopram were also measured as these antipsychotics are known to cross blood brain barrier by P-glycoprotein mediated efflux (74) and predominant passive transport (75), respectively. They found that there is a net efflux of CLZ and NDMC across blood brain barrier which uses a similar mechanism as Risperidone (73). A similar study using rat brains and micro dialysis was able to predict the median percentage of receptor occupied by CLZ and NDMC. The study found that for D2, the median receptor occupancy (MRO) was from 6-42%, 9-52% and 11-59% for 200, 300 and 400 mg dosages of CLZ, respectively i.e. an increase in dose resulted in greater receptor occupancy. This was in contrast to the MRO of 5HT2A that decreased with higher doses i.e. the MRO decreased from 93-52%, 95% to 62% and 96% to 69% with 200, 300 and 400 mg dose respectively in time interval from 6 to 24 hours. The MRO for M1, A1, and H1 was 74% to 99% respectively and for A2 receptors was 3-40%. The only MRO found for NDMC was for D2 receptors which were 1.1 % - 17.3% (72).

CLZ has been shown to increase the expression of immediate-early gene c-fos and its protein, Fos in PFC (76, 77) and shell nucleus of NAC (76, 77) and thalamic paraventricular nucleus (77). Unlike typical antipsychotic, CLZ however does not enhance Fos expression in dorsolateral striatum (78). Deutch et al. (1998) (77) were first to find in vivo effect of NDMC by measuring Fos expression in rats. NDMC, like CLZ was shown to induce Fos expression in the same brain regions as its parent compound, thus verifying it has an in vivo role is used as an antipsychotic.

A landmark study was done to examine the efficacy and safety of NDMC as compared to that of haloperidol (typical), clozapine (atypical) and aripiprazole (partial agonist atypical) using preclinical models. The various domains compared were: brain D2 and 5HT2 receptor occupancy, animal models depicting antipsychotic effect (amphetamine induced locomotion and conditioned avoidance response), striatal Fos induction, catalepsy and prolactin levels. NDMC exerted dose dependent occupancy on 5HT2 receptors comparable to that of CLZ and higher than haloperidol and aripiprazole. This dose dependent effect of NDMC was not seen for D2 receptors. As compared to haloperidol, clozapine and aripiprazole, NDMC showed a very low D2 receptor occupancy that too at a very high dose. Except from haloperidol, no other antipsychotic medication showed catalepsy. NDMC was not as effective as the other antipsychotics in inhibiting amphetamine-induced locomotion although it inhibited it partially. Similarly, NDMC inhibited conditioned avoidance response but at a very high dose (100mg/kg) and after a long period (240 mins) as compared to other drugs used. NDMC like CLZ failed to induce Fos in dorsolateral striatum unlike haloperidol and aripiprazole. The expression of Fos in NAC was significant for haloperidol and clozapine. Aripiprazole and NDMC induced Fos in NAC at a higher dose. Apart from haloperidol, none of the drugs showed increase in prolactin levels. The investigators concluded that NDMC has the potential to be used an effective antipsychotic only at higher dosage and endorsed the use of NDMC as adjunct to other antipsychotics (79).

Given the possibility of many beneficial effects associated by giving NDMC as a solo medication for the treatment of SCH, a clinical trial was done to evaluate its efficacy and safety by Acadia pharmaceuticals. NDMC failed to show a superior effect than placebo in its phase IIb trial (80). Sur et al., 2003 (52) advocate using NDMC as add on therapy to existing antipsychotics. In any case, NDMC seems to have an advantage over CLZ as it has shown to have less adverse effects than its parent compound, CLZ.

Effect of Smoking:

Smoking promotes the metabolism of CLZ by inducing CYP1A2 (81). CYP1A2 gets induced by polycyclic aromatic hydrocarbons and not nicotine (82). In a retrospective study in real-world clinical setting (population PK study) to measure the effect of smoking on 197 patients on CLZ found that oral clearance increased by 6.0L/h and 4.5L/h in smokers and males respectively. The oral clearance for NDMC increased 11.3 and 7.6L/h in smokers and male gender, respectively. Therefore like CLZ, the oral clearance of NDMC is also susceptible to smoking (83). In another retrospective study CLZ and NDMC levels were measured after a ban on smoking was placed in hospital. The study showed that both CLZ and NDMC levels statistically increased by 46% ($p = 0.004$) and 23% ($p = 0.02$) respectively after 14-68 days of ban on smoking. The increase in NDMC levels may be because of the effect of smoking on UDP-glucuronosyltransferase enzymes which are involved in the metabolism of NDMC. No statistically significant change was

seen in CLZ/NDMC ratio (p = 0.2) before the ban (2.4) and after the ban ratio (2.6). This suggests the CLZ is more vulnerable to the effects on smoking in comparison to NDMC (84).

Sialorrhea:

A prominent side effect of CLZ is sialorrhea (85). CLZ exerts a mixed effect on salivary secretion. Intravenous administration of CLZ was shown to result in large increase in salivary secretion from submandibular gland and parotid glands (more in submandibular as compared to parotid) which was further increased by chronic denervation (86). This effect of CLZ is due to its action on M1 muscarinic receptor on acinar cells of the glands and is independent of central nervous regulation, pre-synaptic intraglandular circumstances and circulating catecholamine (86). The same investigators conducted a similar study on rats to see the effect of NDMC on salivary secretion. They found a similar response by NDMC as was seen in rats on CLZ i.e. direct action on M1 muscarinic receptor of submandibular glands leading to hyper salivation which was enhanced by chronic denervation. NDMC decreased the salivary secretion induced by methacholine and parasympathetic stimulation by M3 receptors, and reduced sympathetic evoked response by alpha-1 adrenergic receptor. NDMC was superior to CLZ in its excitatory effect on salivary glands. The authors concluded that increase in NDMC/CLZ ratio would increase the secretion during night and at rest. This they say would be beneficial for the patient's dry mouth is a common side effect of many antipsychotics (87) and NDMC by its action to increase saliva will help the complications that arose with dry mouth (88).

Memory:

An experiment done to examine the effect of CLZ on BDGF found that the levels of BDGF in brain are significantly higher on patients (p = 0.028) with daily CLZ therapy (89). This is in contrast to another study, which failed to find correlation between CLZ and NDMC and hippocampal expression of Brain-derived neurotrophic factor levels (90)[90]. However, the investigators also found that in rats on NDMC short and long term memory was not impaired, unlike CLZ. It was thus speculated that acute treatment of rats with NDMC does not deteriorate memory.

Hematopoietic system:

NDMC is a hematopoietic suppressant (91). Gershon et al., (1994) (91) measured the levels of CLZ and its active metabolites for their toxicity to hematopoietic precursors. They found that NDMC is more toxicity to hematopoietic precursors (CFU-GM, BFU-E and CFU-GEMM) than CLZ or any of its metabolites. This was in contrast to Hasegawa et al., study (1994) (92) where no such relation was found between NDMC and hematopoietic factor and potential role of a vulnerability factor was proposed for agranulocytosis although NDMC (like CLZ) has been shown to reduce thromboxane B2 production in healthy individuals (93).

Sedation:

There are concerns on the potential sedative effect of NDMC (94) but in a study, that showed NDMC to reduce hyperactive locomotion behavior in phospholipase C knockout mice did not produce sedation at a dose of 5mg/kg. Similar dose of CLZ i.e. 5 mg/kg is known to produce significant sedation in mice. This also puts NDMC at an advantage over CLZ (95).

3. CONCLUSION

NDMC has similar as well as contrasting pharmacological properties as compared to its parent compound clozapine. This difference can explain beneficial properties of NDMC such as improvement in working memory. By manipulating CLZ/NDMC ratio, it may be possible to take advantage of the beneficial properties. NDMC has been shown to have in vivo action and given its low tendency to cause sialorrhea, increase prolactin levels, hematopoietic disturbances, sedation, memory and cognition and less vulnerability to smoking as compared to its parent compound, it may be useful to use as an adjunct to antipsychotics.

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