Original Article

Prophylactic Use of Trihexyphenidyl (Artane) in Schizophrenia and Psychosis: A Critical Review of Literature to Guide for Evidence Based Practice in Zambia

W. A. Sheikh

Department of Psychiatry, Livingstone Central Hospital, Livingstone

ABSTRACT

Background: Anticholinergic drugs are particularly used in psychiatric practice to counteract the EPS secondary to antipsychotic drugs. Trihexyphenidyl (Benzhexol), commonly known as 'Artane' is most widely used anticholinergic drug in Zambia. It is routinely prescribed as prophylaxis to counteract the side-effects in patients taking FGA. In anecdotal experience the abuse of artane is very common among mental patients as well as in the general public in Zambia. This article reviews the literature about psychiatric use, mechanism of action and abuse potential of trihexyphenidyl.

Objective: This review aim to critically review the literature about use of trihexyphenidyl to guide whether it is justified to use this drug for prophylaxis to counteract the side-effects of antipsychotics in Zambia.

Methodology: Literature search was conducted using MEDLINE via PubMed (from 1970-2018).Initially broad search was undertaken to find controlled studies, case reports and review articles and later some relevant bibliographic articles were reviewed to find some more studies.

Conclusion: There is generally no need to start an anticholinergic drugs when a patient is prescribed antipsychotics. For patients who are already on anticholinergic drugs, discontinuation of these drugs should be considered in patients with stable EPS. Anticholinergic drugs can be considered only in individuals with significant EPS when dose reduction and switching strategies have proven ineffective, or when the side effects are acute or severe.

INTRODUCTION

Schizophrenia is one of the most serious and debilitating psychiatric illness with life time prevalence of about 1% round the globe.[1,2] It is characterized by positive, negative, cognitive and affective symptoms. Since the introduction of chlorpromazine in 1952, antipsychotic drugs represent the mainstay of the pharmacological treatment for psychosis and schizophrenia.[2,3,4] Exact pathophysiological mechanisms underlying schizophrenia are unknown but consistent evidence points to an increased subcortical presynaptic dopamine neurotransmission.[2,5] On this neurochemical basis, all antipsychotics are dopamine D_2 receptor antagonists. By blocking dopaminergic neurotransmission in subcortical areas, they are capable of producing extra-pyramidal side-effects (EPS), such as Parkinsonism

Corresponding author:
Waqas Ahmed Sheikh
Department of Psychiatry, Livingstone Central Hospital,
P.O. Box 60091
Livingstone-Zambia
Phone number: +260977796947,
E. mail: sheikhdr@live.com

Key Words: *Antipsychotics, Schizophrenia, Trihexyphenidyl, Zambia*

(tremor, akinesia and rigidity), akathesia, dystonia and tardive dyskinesia (TD), occurring acutely or during chronic treatment.[2,4] In general, this propensity is more pronounced with the first-generation antipsychotics (FGA) than with the second generation antipsychotics (SGA).[2,6] In the past 2 decades, SGA replaced FGA as the standard treatment for schizophrenia in many parts of the world although there is recent evidence indicating no differences in their effectiveness.[2,6] In Zambia FGA like haloperidol, chlorpromazine, trifluoperazine, and fluphenazine decanoate are still used as first line treatments for psychosis and schizophrenia at all public clinics and hospitals. SGA like risperidone, clozapine etc. are available in public sector at teaching hospitals as 2nd line treatments but most of the SGA are available in private sector.

Anticholinergic drugs are particularly used in psychiatric practice to counteract the EPS secondary to antipsychotic drugs.[7,8] Trihexyphenidyl (Benzhexol), commonly known as 'Artane' is most widely used anticholinergic drug in Zambia. Trihexyphenidyl is routinely prescribed as prophylaxis to counteract the side-effects in patients taking FGA. In anecdotal experience the abuse of artane is very common among mental patients as well as in the general public in Zambia. Anticholinergic abuse has been reported in many clinical settings particularly in patients with severe mental illness, where the prevalence of misuse could reach 34%.[7, 11] In a 2008 news report, "trihexyphenidyl was seen to be used for recreational purposes among Iraqi soldiers and police, among other prescription drugs. The report states that the drugs were taken to relieve combat stress."[12] Different studies revealed that the purpose of abuse is to achieve a euphoric state and to enhance social skills.[13] This article reviews the literature about psychiatric use, mechanism of action and abuse potential of trihexyphenidyl.

OBJECTIVE

This review aim to critically review the literature about use of trihexyphenidyl to guide whether it is justified to use this drug for prophylaxis to counteract the side-effects of antipsychotics in Zambia.

METHODOLOGY

Literature search was conducted using MEDLINE via PubMed (from 1970-2018) and using the key words:

Trihexyphenidyl, benzhexol, artane, anticholinergic drugs, first and second generation antipsychotics, schizophrenia, antiparkinsonian drugs, use, and misuse.

Initially broad search was undertaken to find controlled studies, case reports and review articles and later some relevant bibliographic articles were reviewed to find some more studies.

PHARMACOLOGY OF TRIHEXYPHENIDYL

Acetylcholine (Ach) is an excitatory neurotransmitter in the brain and has multiple physiological functions in the nervous system.[8] Ach exerts its effects by binding two major subtypes of receptors: the metabotropic muscarinic receptors[14] and inotropic nicotinic receptors.[15]

Dopamine and Ach have reciprocal relationship with each other in the nigrostriatal pathway. Dopamine normally inhibit Ach release from postsynaptic nigrostriatal cholinergic neurons, thus suppressing Ach activity there (Figure 1).[8]

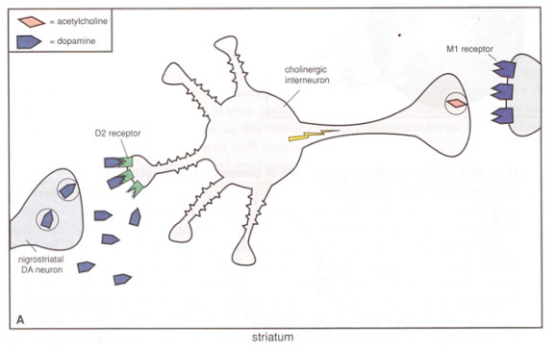

FIGURE 1, Reciprocal Relationship of Dopamine and Acetylcholine.[8]

If dopamine receptors are blocked by FGA, then dopamine can no longer suppress Ach release, so Ach becomes overly active, and produce EPS[8](Figure 2).[9]

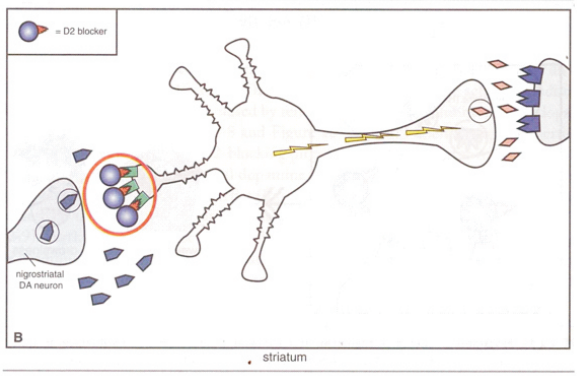

FIGURE 2, Dopamine, Acetylcholine and D2 Antagonism.[9]

One compensation for this over activity of Ach is to block it with anticholinergic agent like trihexyphenidyl. Thus trihexyphenidyl will diminish the excess Ach activity caused by removal of dopamine inhibition when dopamine receptors are blocked by FGA[8](Figure 3).[10]

This relieves EPS like Parkinsonism and acute dystonia. This has led to the common strategy of giving trihexyphenidyl along with FGA in order to reduce EPS. Unfortunately this concomitant use of trihexyphenidyl doesn't lessen the ability of FGA to cause TD. It also causes the well- known side effects associated with anticholinergic agents, such as dry mouth, blurred vision, constipation, urinary retention and cognitive dysfunction.[8]

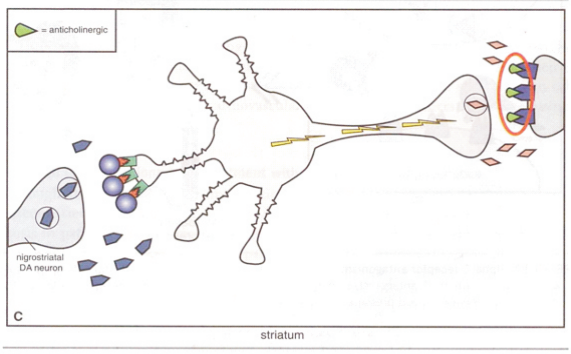

FIGURE 3, D2 Antagonism and Anticholinergic Agents.[10]

On the other hand, trihexyphenidyl also act as a potent indirect dopamine agonist.[7,16] in the limbic system, which is a set of interconnected brain structures including the nucleus accumbens and the ventral tegmental area, involved in motivation, learning, memory and reward. This can in part explain the abuse potential of trihexyphenidyl in both psychiatric and non-psychiatric patients.[7]

PROPHYLACTIC USE OF TRIHEXYPHENIDYL

Anticholinergic agents like trihexyphenidyl have long been considered the treatment and prophylaxis of choice for antipsychotic-induced EPS. The EPS treated with trihexyphenidyl include Parkinsonism (tremors, rigidity& bradykinesia) and acute dystonia.[17] Trihexyphenidyl however is known to worsen TD.[18] Xerostomia, blurred vision, xerophthalmia, constipation and flushed skin are the common side effects of trihexyphenidyl.[19,20] Delayed micturition, urinary retention and sexual dysfunction are occasionally seen.[19,20] A more worrisome effect often seen in aging patients is cognitive impairment.[20,21]Abuse of anticholinergic drugs like trihexyphenidyl can lead to euphoria and psychosis.[19,22]

In the patients treated with anticholinergic drugs, the need for anticholinergic drugs is frequently not reassessed and many patients may remain on them for several years or even decades. WHO Heads of Centers Collaborating in WHO coordinated Studies on Biological Aspects of Mental Illness (1990) issued a consensus statement against the prophylactic use of anticholinergic drugs in patients receiving antipsychotics. [23] They recommended that "anticholinergic use be limited to when Parkinsonism arose and when other measures such as dose reduction or antipsychotic switching have failed.[23]Switching to lesser EPS-producing antipsychotics such as quetiapine or clozapine is an option that may limit or avoid the use of anticholinergic drugs like trihexyphenidyl in some patients".[23] "The 2009 Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations[24] stated that the prophylactic use of anticholinergic drugs to reduce the incidence of

EPS was not warranted in patients treated with SGA, but should be evaluated on an individual basis for patients treated with FGA".[24]

DISCUSSION

Trihexyphenidyl and other anticholinergic drugs have been used for the prophylaxis and the treatment of antipsychotic-induced EPS for decades. Studies have shown the evidence for the effectiveness of trihexyphenidyl in treatment of EPS like Parkinsonism and acute dystonia[17]but it worsens TD.[18] Naja & Halaby in a critical review of anticholinergic use and misuse in psychiatry in 2017 found out that anticholinergic drugs more particularly trihexyphenidyl can be more abused than other antiparkinsonian agents.[7] However it is still poorly understood if this class of difference is attributable to stimulatory properties of trihexyphenidyl as compared with the other compounds, or simply because trihexyphenidyl is most commonly prescribed of all anticholinergic drugs.[7,25]The abusers of trihexyphenidyl were predominantly single, males, unemployed, of poor socio-economic status and suffering from a more severe mental illness.[7] The aim of the abuse is to achieve a high state, reducing the depressive and negative symptoms secondary to the cholinergic system hyperactivity.[7,26]Buhrich et al in 2000[11] in their study assessed misuse of anticholinergic drugs in a population of 50 patients with serious mental illness, who were assertively managed by a community-based outreach team in Sydney, Australia. One third of the patients reported having misused anticholinergic drugs in the previous month. All anticholinergic drugs were misused and the trihexyphenidyl was misused most frequently. On direct questioning, the reason given was "to get high".[11] In Zambia, anecdotal experience has been in line with the findings of these studies as trihexyphenidyl has been the most commonly prescribed anticholinergic drug by the mental health professionals in Zambia.

Trihexyphenidyl and other anticholinergic drugs are associated with cognitive impairment in aging patients,[20,21] however the cognitive impairments usually improve after the discontinuation of the drugs. Desmarais et al in a literature review about anticholinergic drugs in 2012[19], quoted a study by Drimer et al in 2004, who discontinued biperiden in 27 elderly in-patients, taking antipsychotics for schizophrenia.Patients were administered ADAS-Cog before and 10 days after discontinuation of biperiden. In total, 21 patients completed the study. Significant improvements on ADAS-Cog total score and ideational praxis and orientation subscales were observed after the discontinuation of anticholinergic drugs.[19,27]

Stopping of anticholinergic drugs may influence compliance to antipsychotic drugs. Desmarais et al in a literature review about anticholinergic drugs in 2012[19], quoted a study by Saran (1986), who observed that 9 out of 59 patients (18.3%) from a health center who agreed to reduce or discontinue their anticholinergic drugs stopped taking their antipsychotics. These patients didn't have clinical EPS before reduction or cessation of anticholinergic drugs.[28] Saran warned about the decreased compliance with antipsychotic medicationsas a result of adverse effects following the reduction or discontinuation of anticholinergic drugs.[28]

From the WHO Heads of Centers consensus statementagainst the prophylactic use of anticholinergic drugs in patients receiving antipsychotics(1990)[23] and PORT Treatment Recommendations about the prophylactic use of anticholinergic drugs to reduce the incidence of EPS,[24] it is obvious that the prophylactic use of anticholinergic drugs in patients receiving antipsychotics is not justified. The department of psychiatry at Livingstone Central Hospital in collaboration with the hospital management and pharmacy department made a decision in February 2018 to restrict the prescription of trihexyphenidyl to the consultant psychiatrist only in order to reduce the prophylactic use of trihexyphenidyl. It was decided that each patient presenting with EPS will be examined by the psychiatrist who will decide about use of trihexyphenidyl from case to case basis. It was noted that majority of patients who were using trihexyphenidyl didn't need it. Many patients demanded for trihexyphenidyl without even having

any EPS. They were given awareness about abuse potential and harmful effects of trihexyphenidyl by the health staff. This has been successful in drastically reducing the average monthly consumption of trihexyphenidyl from 1350(5mg) tablets in 2017 to about less than 100(5mg) tablets in 2018.

CONCLUSION

Trihexyphenidyl and other anticholinergic drugs have been used for prophylaxis and treatment of antipsychotic-induced EPS for decades, [19] they are, however, associated with adverse effects, notably on cognition, and can worsen TD. There is also strong potential for abuse associated with trihexyphenidyl. There is generally no need to start an anticholinergic drugs when a patient is prescribed antipsychotics. For patients who are already on anticholinergic drugs, discontinuation of these drugs should be considered in patients with stable EPS. Discontinuing anticholinergic drugs may improve TD, cognition, and perhaps psychiatric symptoms.[19] Anticholinergic drugs can be considered only in individuals with significant EPS when dose reduction and switching strategies have proven ineffective, or when the side effects are acute or severe. Three months of anticholinergic drugs treatment has been considered as adequate time period after which an attempt for discontinuation should take place.[19]

RECOMMENDATIONS

1. For patients taking FGA the prophylactic use of anticholinergic drugs like trihexyphenidyl is not recommended. Trihexyphenidyl can only be used if patient manifests EPS. So the decision to use trihexyphenidyl should be determined on case-by case basis.
2. For patients taking SGA, prophylactic use of trihexyphenidyl is not recommended.
3. Continued use of trihexyphenidyl should be re-evaluated in patients with controlled symptoms every 3 months.
4. Older patients or patients with high risk of cognitive disorder who use trihexyphenidyl should consider discontinuation due to high risk of cognitive decline and dementia

ABBREVIATIONS

EPS: Extrapyramidal symptoms, FGA: First generation antipsychotics, SGA: Second generation antipsychotics, TD: Tardive dyskinesia,PORT: Patient outcomes research team, ADAS-cog: Alzheimer's disease assessment scale-cognitive subscale, WHO: World Health Organization

DECLARATIONS

Ethical Approval

Not applicable in case of review article.

Competing Interest

The author declare that he has no competing interests.

Funding

No funding was received for publication of this article.

ACKNOWLEDGEMENTS

I am very grateful to my wife Ayesha Khalid for her continuous assistance and support in the write up of this article. Special thanks to the management of Livingstone Central Hospital for their support.

REFERENCES

1. Insel TR. Rethinking schizophrenia. *Nature* 2010; 468: 187-193.
2. Ogino S, Miyamoto S, Miyake N, Yamaguchi N. Benefits and limits of anticholinergic use in schizophrenia: focusing on its effect on cognitive function; *Psychiatry & Clinical Neurosciences* 2014; 68: 37-49.
3. Miyake N, Miyamoto S, Jarskog LF. New serotonin/ dopamine antagonists for the treatment of schizophrenia. *Clin. Schizophr. Relat. Psychoses* 2012; 6: 122-133.
4. Sadock BJ, Virginia AS. *Synopsis of Psychiatry, Behavioral Sciences/ Clinical Psychiatry*. 10th ed. Philadelphia, USA. LippincottWilliams & Wilkins 2007; 467-498.

5. Fusor- Poli P, Meyer- Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part 1, Meta-analysis of Dopamine Active Transporter (DAT) density. *Schizophr Bull* 2013; 39: 22-32.
6. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis J M. Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis. *Lancet* 2009: 373: 31-41.
7. Naja WJ, Halaby A. Anticholinergic use and misuse in psychiatry: A Comprehensive and Critical Review. *Journal of Alcoholism and Drug Dependence* 2017; 5: 263. Doi: 10.4172/2329-6488.1000263.
8. Stahl SM. *Stahl's Essential Psychopharmacology, Neuroscientific Basis and Practical Application*. 3rdEd. New Delhi, India. Cambridge University Press 2008; 338-341. Figure 10.11A, Reciprocal relationship of dopamine and acetylcholine; p 338.
9. Stahl SM. *Stahl's Essential Psychopharmacology, Neuroscientific Basis and Practical Application*. 3rd Ed. New Delhi, India. Cambridge University Press 2008; 338-341. Figure 10.11B, Dopamine, acetylcholine, and D2 antagonism; p 339.
10. Stahl SM. *Stahl's Essential Psychopharmacology, Neuroscientific Basis and Practical Application*. 3rd Ed. New Delhi, India. Cambridge University Press 2008; 338-341. Figure 10.11 C, D2 antagonism and anticholinergic agents; p 339.
11. Buhrich N, Weller A, Kevans P. Misuse of anticholinergic drugs by people with serious mental illness. *Psychiatr Serv* 2000; 51: 928-929.
12. Mudhafer Al-Husaini, Erica Goode. Abuse of prescription drugs rises among stressed Iraqi soldiers. *The New York Times*. 20th December, 2008.
13. Dugas JE. Mood elevation and medications. *Dis Nerv Syst* 1977; 88: 958.
14. Conn PJ, Jones CK, Lindsley CW. Subtype-selective allosteric modulators of muscarinic receptors for the treatment of CNS disorders. *Trends Pharmacol Sci* 2009; 30: 148-155.
15. Kruse AC, Kobilka BK, Gautam D, et al. Muscarinic acetylcholine receptors novel opportunities for drug development. *Nat Rev Drug Discov* 2014; 13: 549-560.
16. Sharif M, Quik M, Holgate J, et al. Neuronal Nicotine Acetylcholine Receptor Modulators Reduce Sugar Intake. *PLoS ONE.* 2016; 11(3), e 0150270.
17. Haddad PM & Dursun SM. Neurological complications of psychiatric drugs: clinical features and management. *Hum Psychopharmacol*2008; 23 Suppl 1: 15-26.
18. Kalawans HL & Rubovits R. Effects of cholinergic and anticholinergic agents on tardive dyskinesia. *J Neurol Neurosurg Psychiatry.* 1974; 37: 941-947.
19. Desmarais JE, Beauclair L, Margolese HC. Anticholinergics in the era of atypical antipsychotics: short-term or long-term treatment? J Psychpharm 2012; 26 (9): 1167-1174.
20. Bezchlibnyk- Butler KZ, Remington GJ, Antiparkinsonian drugs in the treatment of neuroleptic-induced extrapyramidal symptoms. *Can J Psychiatry* 1994; 39: 74-84.
21. Cancelli L, Beltrame M, Gigli GL, et al. Drugs with anticholinergic properties: cognitive and neuropsychiatric side-effects in elderly patients. *Neurol Sci* 2009; 30: 87-92.
22. Barsoum A, Kolivakis TT, Margolese HC, et al. Diphenhydramine a central anticholinergic and antihistaminic: abuse with massive ingestion in a patient with schizophrenia. *Can J Psychiatry* 2000; 45: 846-847.
23. WHO, World Health Organization Heads of Centers Collaborating in WHO coordinated studies in biological aspects of mental illness. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. A Consensus Statement. *Br J Psychiatry* 1990; 156: 412.
24. Buchanan RW, Kreyenbuhl J, Kelley DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull* 2010; 36: 71-93.

25. Marken PA, Stoner SV, Bunker MT. Anticholinergic drug abuse and misuse. *CNS Drugs* 1996; 5: 190-199.
26. Tandon R, Greeden JF, Cholinergic hyperactivity and negative schizophrenia symptoms: a model of cholinergic/ dopaminergic interactions in schizophrenia. *Arch Gen Psychiatry* 1989; 46: 745-753.
27. Drimer T, Shahal B & Barak Y. Effects of discontinuation of long-term anticholinergic treatment in elderly schizophrenia patients. *Int Clin Psychopharmacol* 2004; 19: 27-29.
28. Saran AS, Use or abuse of antiparkinsonian drugs by psychiatric patient. *J ClinPsychiatry* 1986; 47: 130-132.