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Blood Pressure and Heart Rate Changes During Clozapine Treatment

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Abstract

People with schizophrenia are 3–4 times more likely to die from cardiovascular disease than the general population. Clozapine (CLZ) is the gold standard of treatment for refractory schizophrenia. It has been associated with tachycardia and recent evidence shows individuals prescribed CLZ may develop blood pressure (BP) elevation and hypertension. The purpose of this study was to examine the effects of CLZ on BP and heart rate (HR). This was a retrospective chart review of patients 18–75 years old with a DSM IV diagnosis of Schizophrenia or Schizoaffective disorder. Primary outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR measured 12 weeks before and 24 weeks during CLZ treatment. Eighteen patient records were included in this study. The mean stabilized CLZ dose was 441.7 ± 171.8 mg/day. DBP (t = 1.02, df = 79.5, = 2.00, 0.049) and HR (t = 1.32, df = 355 = −4.61, < 0.0001) were significantly higher after CLZ initiation. A trend was noted for increase in SBP (p = 0.071). 22 % of patients met criteria for hypertension before CLZ and 67 % during CLZ treatment (Chi Square = 6.25, df = 1, p = 0.0124). No significant changes in weight or renal function occured during CLZ treatment. No patients had evidence of cardiomyopathy. The data suggest CLZ may be associated with a rise in BP and HR. The results of this study support previous literature that found an increase in SBP/DBP regardless of CLZ dose, occurring early in treatment. Due to high risk of cardiovascular morbidity and mortality, more work is needed to determine risk factors and understand the mechanism of action that may cause this side effect.

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Compliance with Ethical Standards

Conflict of Interest Deanna L. Kelly is on the Advisory Board for Stigma Project funded by Otsuka.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Keywords

Clozapine; Blood pressure; Schizophrenia; Hypertension; Tachycardia; Heart rate

Introduction

Schizophrenia is a chronic, often disabling illness that affects approximately 24 million worldwide [1]. People with schizophrenia have a shorter life span, between 10 and 25 years less, and are 3–4 times as likely to die from cardiovascular disease than the general population [2]. Many risk factors for cardiovascular disease exist including increased lipid levels, cigarette smoking, sedentary lifestyle, hypertension, and obesity [3].

Clozapine (CLZ) is considered the gold standard of treatment for people who remain symptomatic despite two adequate trials of other antipsychotic agents [3]. CLZ is the most effective antipsychotic for patients who do not respond to treatment with first or second generation antipsychotics [3, 4]. There are multiple studies which provide evidence of the superiority of CLZ [5–11]. CLZ has also been associated with longer treatment duration, greater improvement in symptoms, and higher patient and clinician subjective ratings [12, 13]. However, CLZ is often underutilized, in part, due to its side effect profile [14].

CLZ has a host of side effects associated with its use including some serious cardiovascular effects such as cardiomyopathy, myocarditis, and metabolic syndrome [15, 16] Tachycardia is also known to occur, and recent evidence has shown that individuals prescribed CLZ may develop blood pressure (BP) elevation and hypertension [17–24]. In this study, we examined BP and heart rate (HR) changes during CLZ treatment.

Methods

Sample and Procedure

Medical records of adult patients between the ages of 18 and 75 years old admitted to an inpatient research unit with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) diagnosis of Schizophrenia or Schizoaffective disorder and initiated on CLZ were reviewed [25]. Forty-eight charts were identified for inclusion. 15 patients were excluded due to missing medical records, 13 because they did not have 24 weeks of follow up after the initiation of CLZ treatment, and two due to unknown CLZ treatment initiation date. Demographic information was collected for all patients. Systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, blood urea nitrogen (BUN), serum creatinine (SCr), glomerular filtration rate (GFR), CLZ dose and blood level, and weight were collected for 12 weeks before and 24 weeks during CLZ treatment. The University of Maryland and State of Maryland Department of Health and Mental Hygiene Institutional Review Boards approved this study.

Statistical Methods

All values for SBP, DBP, HR, weight, BUN, SCr, and GFR were collected and means were analyzed before and after starting CLZ using t tests. Dichotomous variables were compared

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using Chi Square. Mean values for maximum stabilized CLZ dose, CLZ level, norcloza-pine level, and total CLZ level were also calculated. The following definitions were used to evaluate BP and HR: Eighth Joint National Committee (JNC8) Guideline for the Management of Hypertension defines hypertension as a SBP reading≥140 mm Hg and/or DBP reading of≥90 mm Hg on a minimum of two separate occasions [26]. The American Heart Association (AHA) defines tachycardia as a HR >100 beats per minute [27].

Results

There were 18 patient records included in this study. The mean age of the group was 36.4 ± 12.5 years with the majority, male, Caucasian and cigarette smoking (Table 1). Two patients were diagnosed with hypertension.

From pre to post BP and HR data collected associated with CLZ treatment, there was a significant increase in DBP (t = 1.45, df = 79.5 = −2.00, 0.049) and HR (t = 1.32, df = 355 = −4.61, <0.0001). There was also a trend noted to an increase in SBP (Table 2). In the 12 weeks prior to CLZ treatment, 4/18 (22 %) patients met criteria for JNC-8 diagnosis of hypertension. During CLZ treatment 12/18 (67 %) met criteria for hypertension (Chi Square = 6.25, df = 1, p = 0.0124). There were 6/18 (33 %) patients prior to initiation of CLZ and 15/18 (83 %) patients during CLZ therapy who met AHA diagnosis of tachycardia (HR > 100 bpm) (Chi Square = 8.028, df = 1, p = 0.0046). In the two patients who had documented history of an ICD9 code diagnosis of hypertension, neither met hypertension criteria in the evaluation prior to treatment. However, one became hypertensive during treatment with CLZ, despite receiving antihypertensive medications.

Table 3 characterizes renal function and weight before and during CLZ treatment. No significant differences were noted in these variables. None of the patients had evidence of cardiomyopathy.

Discussion

Overall the data suggest CLZ may be associated with an increase in DBP, SBP, and HR. The number of patients meeting the definition of hypertension tripled and the number of patients who met the definition of tachycardia more than doubled during CLZ treatment. The results are consistent with previous studies that found an increase in SBP/DBP regardless of CLZ dose and occurred early in treatment. For example, Henderson et al. noted elevations in BP developed relatively soon after initiation and increased to the hypertensive range after 6 months [28]. Additionally, a significant positive correlation between weight gain and the increase in SBP was described [28]. Woo et al. compared CLZ with olanzapine and up to 16.7 % of CLZ patients met criteria for hypertension over that time period, compared with 5.4 % on olanzapine [29]. In a small study by Oyewumi et al., autonomic dysfunction during CLZ dose titration was demonstrated [30]. Of note, a weak correlation between clozapine:norclozapine ratio and BP elevation was found [30]. We did not find an association between increased BP and HR and renal function or weight in the study, suggesting there may a mechanism of BP elevation independent of obesity.

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It has been suggested that the mechanism of hypertension may partly involve an autonomic dysfunction due to adrenergic hyperactivity of CLZ [17, 31] The response of the hypertension to α2 adrenoceptor blockers further supports the latter [17, 32]. CLZ has an affinity for α2 adrenoreceptors that is 18 times higher than olanzapine [33]. The antagonistic effect of CLZ on α2 receptors resulting in prolonged release of noradrenaline from synaptic reuptake has been surmised to cause this elevation in BP [29, 33–35]. It is noteworthy that the presentation of CLZ induced hypertension has been very similar to pheochromocytoma, with elevated BP and urinary catecholamines [32]. We did not examine urinary catecholamines in this study. Our group is conducting a pilot study to examine the impact of CLZ on renal dopamine receptors which also may contribute. We have reported that the germline deletion of the dopamine D4 receptor in mice causes hypertension [36]. CLZ has higher affinity for the D4 receptor than for the other dopamine receptors, including the D2 receptor [37]. Nevertheless, germline deletion of the dopamine D2 receptor in mice also causes hypertension [38].

Our small pilot study is limited in that it is a retrospective chart review and, therefore, limited to the information documented in the patient's medical record. Also, some variables collected were not present in all patients, such as GFR. Factors like caffeine use, intensity of cigarette smoking, exercise habits, and sodium intake may have contributed to the increases in BP and HR that we were unable to measure. Due to the high risk of cardiovascular morbidity and mortality in this population, more work is needed to determine risk factors and understand the mechanism of action that may cause this side effect.

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Biographies

Sarah M. Norman, PharmD, BCPS completed her post-graduate year two Psychiatric Pharmacy Residency at University of Maryland School of Pharmacy. She completed her post-graduate year one Pharmacy Practice Residency at University of Montana Skaggs School of Pharmacy. She received her Doctor of Pharmacy degree from The University of Arizona College of Pharmacy. Dr. Norman is a Clinical Assistant Professor at University of Texas at El Paso School of Pharmacy. Dr. Norman's research interests include patient medication education, psychiatric pharmacy, and medication induced adverse effects.

Kelli M. Sullivan, MPH earned her Bachelor of Science in Biology and Psychology from the University of Maryland. Sullivan earned her Master's in Public Health from the George Washington University. She supported clinical trials and outcomes studies organized by the Treatment Research Program at the Maryland Psychiatric Research Center for over 5 years. Sullivan currently supports the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC), a network of nine North American Centers that are collaborating in diagnostic testing, genetic studies, and clinical trials in patients with impairments in mucociliary clearance. Sullivan is located at the University of North Carolina at Chapel Hill.

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Fang Liu, MS joined the Treatment Research Program (TRP) at the Maryland Psychiatric Research Center (MPRC) in July 2007. She graduated from the University of Maryland, Baltimore with her master's degree in Epidemiology. Before joining TRP, she worked at the University of Maryland Schools of Medicine and Nursing and engaged in the data analysis of several NIH-sponsored clinical trials. Currently, she serves as a statistician at MPRC and is interested in statistical analysis for clinical studies in psychiatry.

Bethany A. DiPaula, PharmD, BCPP is an Associate Professor at the University of Maryland Baltimore School of Pharmacy. She is the Director of Pharmacy at Springfield Hospital Center and Residency Director for the University of Maryland School of Pharmacy PGY2 Psychiatric Pharmacy Residency Program. She also provides clinical pharmacist services at the Howard County Health Department. Dr. DiPaula completed her Doctorate in Pharmacy and psychiatric pharmacy residency training at the University of Maryland, School of Pharmacy. She is Board Certified in Psychiatric Pharmacy Practice. Dr. DiPaula's research interests include substance use disorder, specifically opioid use disorder, and psychiatric pharmacy.

Pedro A. Jose, MD, PhD is Professor of Medicine and Pharmacology and Physiology, The George Washington School of Medicine & Health Sciences. Dr. Jose received his MD degree from the University of Santo Tomas, Philippines and PhD degree from Georgetown University, USA. The primary goal of Dr. Jose's research is to determine the genetic and pharmacogenetic bases of human essential hypertension and the metabolic syndrome, as related to dopamine, adrenergic, and angiotensin receptor subtypes, dopamine regulatory genes (e.g., G protein-coupled receptor kinase 4, sorting nexins, gastrin, ion channels), inflammation, oxidative stress, renal sodium transport, and vascular reactivity.

Christopher A. Kitchen, MA serves as a Clinical Research Assistant for the Maryland Psychiatric Research Center (MPRC) and provides study coordination and support for Dr. Kelly at the Treatment Research Program. Mr. Kitchen completed his Masters in Human Services Psychology and Bachelor of Science degree at the University of Maryland Baltimore County. Mr. Kitchen has prior research experience in games and simulations, learning theory, addiction treatment and most recently in the area of schizophrenia related diseases.

Stephanie M. Feldman, MSW, LCSW-C is Director of Research Operations for the Maryland Psychiatric Research Center's Treatment Research Program. She received her Master's in Social Work from the University of Maryland School of Social Work and has worked in the research and mental health field for many years. Her areas of research interest focus on improving quality of life for those individuals living with serious mental illnesses.

Deanna L. Kelly, PharmD, BCPP is Professor of Psychiatry at University of Maryland Baltimore School of Medicine and Affiliate Professor in the School of Pharmacy. She is Director and Chief of the Treatment Research Program at the Maryland Psychiatric Research Center (MPRC). Dr. Kelly received her Bachelor of Science and Doctorate in Pharmacy at Duquesne University in Pittsburgh, PA. She completed residency training in psychiatric pharmacy practice at the University of Maryland and is Board Certified in Psychiatric

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Pharmacy Practice. Dr. Kelly's research interests include clinical trials for novel pharmacologic treatments, women's mental health and championing the use of clozapine.

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Table 1

Demographic information and clinical characteristics (n = 18)

Age, yr mean (SD) [range yr]	36.4 (12.5) [20–56]
Male, n (%)	11 (61.1)
Caucasian, n (%)	10 (55.6)
Special diet, n (%)	8 (44.4)
Smoker, n (%)	12 (67.7)
Diabetes mellitus type 2, n (%)	2 (11.1)
Hyperlipidemia, n (%)	6 (33.3)
Hypertension, n (%)	2 (11.1)
Polydipsia, n (%)	2 (11.1)
Maximum stabilized CLZ dose, mg/day mean (SD) [range mg/day]	441.7 (171.8) [100–800]
CLZ level, mcg/L mean (SD) [range mcg/L]	386.9 (177.7) [91–835]
Norclozapine level, mcg/L mean (SD) [range mcg/L]	210.9 (97.7) [31–595]
Total CLZ level, mcg/L mean (SD) [range mcg/L]	603.9 (263.0) [122–1430]

Special diet includes the following: low salt, low cholesterol, high protein, gluten free or high calorie

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Table 2

Mean systolic and diastolic blood pressure and heart rate

Variable	Before CLZ treatment	During CLZ treatment	Statistics
SBP, mm Hg mean (SD)	124.8 (12.0)	127.9 (12.2)	t = 1.02, df = 356, p = 0.071
DBP, mm Hg mean (SD)	80.6 (9.9)	83.3 (8.2)	t = 1.45, df = 79.5, p = 0.049
HR, bpm mean (SD)	90.9 (13.0)	98.4 (11.3)	t = 1.32, df = 355, p <0.0001

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Table 3

Laboratory and clinical values

Variable	Before CLZ treatment	During CLZ treatment	Statistics
BUN, mg/dL mean (SD)	12.4 (5.1)	12.7 (4.1)	t = 1.52, df = 72, p = 0.7720
SCr, mg/dL mean (SD)	0.8 (0.2)	0.8 (0.2)	t = 1.01, df = 72, p = 0.3780
GFR, mL/min/1.73 m^2 (SD)	108.1 (12.9)	108 (8.9)	t = 2.11, df = 28, p = 0.9761
Weight, lb mean (SD) (N = 17)	164.7 (39.0)	179.5 (47.1)	t = 1.46, df = 113, p = 0.1124