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Persistent tachycardia in clozapine treated patients: A 24-hour ambulatory electrocardiogram study

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ABSTRACT

Tachycardia is associated with cardiovascular mortality. Tachycardia is also a known clozapine adverse effect. However, whether clozapine-associated tachycardia is persistent is not known. Thirty clozapine-treated patients with clinical tachycardia were investigated with 24-hour ambulatory electrocardiography (ECG). Baseline peripheral heart rate (HR) was 106.7 ± 7.8 . The ambulatory ECG 24-hour-HR was 98.7 ± 9.7 . Baseline HR and 24-hour-HR correlated strongly ($r = 0.74$, $p = 0.000003$). Daytime HR was 106.4 ± 9.9 and nighttime HR 89.2 ± 12.0 . Low dose bisoprolol reduced HR significantly. The high 24-hour-HR indicates a persistent tachycardia. Tachycardia should not discourage from clozapine use but the findings indicate a need of guidelines for detection and treatment of clozapine-associated tachycardia.

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1. Introduction

About one third of individuals with schizophrenia are considered to be treatment resistant or minimally responsive to conventional antipsychotics. In these cases, clozapine is the preferred treatment option (Leucht et al., 2013; McEvoy et al., 2006). Clozapine has superior efficacy for psychotic symptoms but several typical side effects, among them anticholinergic and positive chronotropic properties (Cohen et al., 2001; Merrill et al., 2005). Clozapine associated tachycardia is accordingly a well-known but often over-looked problem in daily clinical work. We previously reported a tachycardia prevalence of 33% based on all clozapine-treated patients ($n = 174$) in a defined catchment area (Nilsson et al., 2017). The tachycardia was in most cases not detected or treated. Hitherto there is a lack of knowledge whether this clozapine associated tachycardia is persistent or transient. There is also a paucity of studies on the pharmacological treatment of clozapine associated tachycardia (Lally et al., 2016). In the general population, tachycardia is reported as an independent risk factor for both cardiovascular and all-cause mortality (Greenland et al., 1999; Palatini et al., 2006). Total mortality has also been shown to increase with a higher sleeping heart rate (Ben-Dov et al., 2007; Hansen et al., 2008; Johansen et al., 2013). Tachycardia is thus a potentially serious long-term side effect in clozapine treatment.

Clozapine may be the only efficient pharmacotherapy in treatment resistant schizophrenia. Therefore, clozapine implies a treatment that often is unchangeable, the patient must stay on clozapine and the side effects have to be managed (Nielsen et al., 2013). Tachycardia may infrequently be a reason for treatment discontinuation (Legge et al., 2016) but clozapine associated tachycardia is often covert, i.e. neither the patient nor the caregivers are aware of the problem. Consequently, a significant tachycardia might persist during years without adequate treatment implying a considerable cardiac health risk in the long run.

The aims of the present study were: 1) to assess the chronotropic properties of clozapine during day and night with ambulatory 24-hour electrocardiogram (ECG) in patients with a clinical routine measurement of peripheral heart rate (HR) indicative of tachycardia, 2) to compare single peripheral HR measurement with the heart rate during 24-h ECG monitoring, 3) to assess variables that may influence 24-h HR like hemoglobin concentration, Body Mass Index (BMI) or clozapine serum concentration, and 4) to test the hypothesis that low-dose beta-blocking pharmacotherapy will lower the HR in clozapine associated tachycardia without a clinical relevant reduction in blood pressure.

2. Methods

The study was approved by the regional ethics review board in Uppsala, Sweden. Tachycardia was defined as a resting HR of >100 beats per minute (bpm). According to clinical routines, clozapine-treated patients were examined with resting peripheral pulse measurements by the means of an automatic blood pressure and pulse monitor (Omron

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M6W, Omron Health Care, Kyoto, Japan). Thirty patients with HR > 100 were then referred for an ambulatory 24-hour ECG monitoring. There was an interval between the baseline peripheral pulse measurement and 24-hour ECG of about 1–2 months.

Ambulatory 24-h Holter ECG was recorded in a 2-channel, 5-electrode paradigm with a GE SEER Light Ambulatory Recorder and analyzed with the GE Marquette MARS Holter system (GE Medical systems, Milwaukee, WI 53223 USA). Electrode placements were below right and left clavicle, over I5 sin, I4 dx on the right sternal edge and on the lower right chest wall (ground). When persistent tachycardia was present, the clinical routine was to initiate beta-blocking pharmacotherapy (Stryjer et al., 2009). In 11 patients, beta-adrenergic antagonists were not introduced due to relatively lower 24-h HR, non-adherence for add-on beta-block or comorbid low blood-pressure/orthostatism. Most patients were treated with bisoprolol ($n = 15$) while atenolol and metoprolol were used in two patients respectively. Doses of 25 mg atenolol and 50 mg metoprolol were considered equipotent with 2.5 mg bisoprolol (Lithell et al., 1987). Follow-up peripheral HR and blood pressure was measured in patients with add-on beta-blocking therapy. Means and standard deviations are expressed for normally distributed data, medians and inter quartile ranges otherwise. Student's *t*-tests were used for comparisons of means. Correlation analyses for variables that might influence HR like hemoglobin concentration, BMI or clozapine concentration, were performed with Pearson product-moment correlation and Spearman's rank correlation.

3. Results

Baseline characteristics as well as 24-hour ECG data are shown in Table 1. The mean resting peripheral HR at baseline was 106.9 ± 7.9 bpm. Ambulatory ECG performed 47 ± 35 days after resting pulse measurement, showed a mean 24-h HR of 98.7 ± 9.7 during the hours of day and night. The fluctuations in mean HR over 24 h for all patients are depicted in Fig. 1. Baseline resting HR and 24-h ECG HR were highly correlated ($r = 0.74$, $p < 0.0001$). The tachycardia found was of sinus type in all patients. Very high mean HR's were recorded during both 12 h daytime and 6 h during nighttime (Table 1). The number of arrhythmias was low in the majority of patients. There was no significant correlation between any HR measure and clozapine dose, clozapine plasma concentration, BMI or hemoglobin concentration in this study. The initiation of low dose beta-blocking agents reduced HR significantly

to mean 88.8 bpm at follow-up and also reduced diastolic, but not systolic blood pressure (Table 2).

4. Discussion

The main finding of the study was a very high mean 24-hour HR in clozapine treated patients. To the best of our knowledge, HR measured with ambulatory ECG over 24 h has never been studied in this patient group before. All Holter ECG HR means; the 24-h HR, the daytime HR and the nighttime HR were remarkably elevated from expected values. The mean 24-h HR of 98.7 bpm in our study, should thus be compared with reported mean 24-h HR levels of 73–77 bpm in several large scale studies in the general population (Aeschbacher et al., 2016; Hansen et al., 2008; Johansen et al., 2013; Kotsis et al., 2005). The nighttime recordings were correspondingly elevated with 23–25 bpm compared with general population studies (Ben-Dov et al., 2007; Hansen et al., 2008; Johansen et al., 2013). The second finding was a solid correlation between single clinical measurements of peripheral HR and 24-hour HR performed 1–2 months later. An isolated high resting HR at a routine clinical visit may thus be sufficient to raise the suspicion that the clozapine treated patient is suffering from a persistent tachycardia.

The long-time health risks of clozapine associated sinus tachycardia are presently unknown. Yet, an elevated heart rate is strongly associated with mortality in the general population (Greenland et al., 1999; Jensen et al., 2013; Palatini et al., 2006). Particularly nighttime HR has been reported to show positive correlation with mortality (Ben-Dov et al., 2007; Johansen et al., 2013). Hansen et al. showed that ambulatory nighttime HR predicted cardiovascular mortality with a risk increase of 14% per 10 bpm (Hansen et al., 2008). These data are noteworthy considering that many patients treated with clozapine also suffer from increased cardiovascular risk related to smoking and metabolic side effects with weight gain, hyperlipidaemia and risk for diabetes (Mitchell et al., 2013). Further, a recent study reports subclinical left ventricular dysfunction in clozapine treated patients with schizophrenia (Chow et al., 2014).

24-h ECG measurement might not be a feasible method in everyday clinical practice. According to the present findings, peripheral HR measurements repeated over at least two visits would give a fairly good estimate of whether persistent tachycardia is present or not. It is important to rule out the possible influence on HR of smoking or concomitant treatment with other positive chronotropic agents like anticholinergics, thyroid hormones or central nervous system stimulants.

Table 1
Characteristics of patients and results from ambulatory 24-hour ECG measurement.

	All clozapine treated patients $n = 30$	Patients subsequently treated with bisoprolol $n = 19$
Gender, male/female	20/10	15/4
Age, years, Md (IQR)	33.5 (26–41)	34 (27–41)
Body Mass Index	29.1 ± 6.7	29.9 ± 7.2
Hemoglobin, g/L	145.5 ± 13.5	147.9 ± 10.0
Smokers/non-smokers	8/22	7/12
Duration of disease, years, Md (IQR)	11 (5–17)	10 (5–17)
Duration of clozapine treatment, years, Md (IQR)	7 (3–13)	6 (1–13)
Clozapine dose, mg	394.2 ± 196.3	422 ± 220.3
Clozapine concentration, ng/mL, Md (IQR)	451 (337–569) ^a	461 (369–549)
Systolic blood pressure, mm Hg	128.4 ± 12.5	130 ± 12.5
Diastolic blood pressure, mm Hg	80.8 ± 9.7	84.5 ± 9.4
Heart rate at baseline, bpm	106.9 ± 7.9	107.5 ± 6.8
Ambulatory 24-hour ECG monitoring		
Mean Heart rate during 24 h, bpm	98.7 ± 9.7	100.5 ± 7.5
Mean Daytime HR 09–21, bpm	106.4 ± 9.9 ^b	107.9 ± 7.8
Mean Nighttime HR 24–06, bpm	89.2 ± 12.0 ^c	90.0 ± 11.1
Supraventricular arrhythmias during 24 h, Md (IQR)	2 (0–14)	4 (1–8)
Ventricular arrhythmias during 24 h, Md (IQR)	4 (0–8)	2 (0–14)

Data are mean \pm (SD) unless otherwise noted. HR = Heart rate, Md = median, IQR = Inter quartile range, bpm = beats per minute.

^a $n = 29$. Serum clozapine concentration on the same treatment dose as during 24-h ECG was missing in one patient.

^b $n = 25$. Due to technical problems, data was not extracted separately during daytime in 5 patients.

^c $n = 26$. Due to technical problems, data was not extracted separately during nighttime in 4 patients. Mean 24-hour HR was registered and available for all patients.

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