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A Case of QT-interval Prolongation in the Context of High-dose, Intravenous Midazolam in a Methadone Maintained Patient

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Authors' contributions

This work was carried out in collaboration between all authors. Author LJ wrote the draft of the manuscript. Author SB managed the literature searches. Author LS contributed to the correction of the draft and provided the case. Authors SB and author JJ supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The following case illustrates a case of significant prolonged QT-interval (QTc) prolongation following intravenous administration of high-dose midazolam in a patient with severe hyperactive delirium. A prolonged QTc represents a potentially life-threatening condition associated with Torsades de Pointes (TdP) and sudden cardiac death (SCD). Although the predictive value of a prolonged QTc and the occurrence of TdP and SCD has not yet been fully established, heightened awareness in medicine and psychiatry has arisen with respect to the administration of psychotropics. Benzodiazepines, although known to prolong the QTc, have been considered as rather safe medications with this respect. For example, low-dose midazolam has not been shown to cause QTc prolongation. In the following case, however, high-dose midazolam caused a significant prolongation of the QTc, which has to date, not yet been reported.

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1. INTRODUCTION

By definition, the QT-interval is the measure between the Q- and T-wave in the cardiac electrical cycle representing its de- and repolarization. Prolongation of QTc is a risk factor for ventricular tachyarrhythmia such as TdP with the potential of subsequent SCD. Electrocardiographically, TdP represents as a characteristic polymorphic, ventricular tachycardia, which is hemodynamically unstable, causes a sudden drop in blood pressure, subsequent dizziness and syncope. Although most episodes of TdP rapidly revert back to sinus rhythm, persistence or even progression into ventricular fibrillation occurs, which in turn, in the absence of prompt medical intervention, causes SCD [1,2].

Within recent years, QTc-prolonging agents have received special attention due to this potentially fatal outcome. Foremost, antipsychotics, typical and atypical, have been studied extensively with respect to their QTc-prolonging properties [3]. The human Ether-a-go-go Related Gene (hERG) has been identified as one confounder of prolonged QTc and codes for a potassium ion channel - often simply referred to as hERG - which is known to contribute to cardiac electrical activity and coordination. When this channel's ability to conduct electrical current is inhibited or compromised such in certain families with rare mutations or by the administration of various medications, the risk for TdP and subsequent SCD is increased [1,2]. Beyond antipsychotics, selective serotonin reuptake inhibitors, various antimicrobials, methadone, to a lesser degree benzodiazepines, as well as hypokalemia and hypomagnesemia have been identified as confounders for QTc-prolongation [2,3].

Midazolam, a short-acting benzodiazepine regularly used for sedation, has at low doses not yet been shown to cause QTc-prolongation [4,5], however, high-dose midazolam might cause significant QTc-prolongation.

2. CASE PRESENTATION

Mrs. G. is a 34-year-old patient with an extensive debilitating, psychiatric history including opiate dependence, currently on methadone maintenance (180 mg), cocaine, alcohol, benzodiazepine, and cannabis dependence in remission. In her adolescence a severe substance use career started including heroin and cocaine by inhalation and insufflation, as well as excessive use of alcohol and benzodiazepines. Due to an attention-deficit/ hyperactivity disorder she was prescribed a regimen of methylphenidate (180 mg immediate-release formulation, 20 mg sustained-release formulation). Her cognitive and functional abilities - she was wheelchair-bound after an incident of overdosing with coma and ischemic myelenic trauma - as well as behavior deteriorated severely as a result of a DSM 5 major neurocognitive disorder secondary to severe prolonged substance use [6]. She was hospitalized psychiatrically multiple times and attempts were made to stabilize her, control her behavior with various psychotropics including olanzapine (5 mg), quetiapine (200 mg), diazepam (50 mg), trazodone (150 mg), venlafaxine (75 mg).

Due to unexplained swelling of the right lower extremity, soft tissue-infections, decubiti and fever, the patient was transferred to medicine at the University Hospital Zurich for work-up and management. After a soft-tissue infection was confirmed, oral ciprofloxacin (1 g) and intravenous amoxicillin/clavulanic acid (6.6 g) were administered daily starting on the day of admission. In the course of hospitalization, Mrs. G. developed a severe hyperactive delirium, management approaches with quetiapine 400 mg remained futile, symptoms of delirium aggravated rapidly, thus, symptomatic sedation with continuous, intravenous administration of 15 mg/h midazolam was initiated on day 5 and all psychotropics not deemed necessary such as trazodone, venlafaxine and olanzapine were discontinued. Subsequently, methadone was reduced to 180 mg. With continuing severe agitation on midazolam 40 mg/h, continuous, intravenous administration of clonidine 1200 mcg/h was added and maximized to 1800 mcg/h resulting in improvement of symptoms.

Despite methadone and various antipsychotic administrations at baseline and the initiation of ciprofloxacin, the QTc was before the onset of delirium within normal range (379ms). In the course of hospitalization, escalating doses of midazolam were required in an attempt to control the disruptive and self-injurious behavior, as well as harm to self and environment, reaching 60

mg/h with additional as needed administration of 10 mg - summing up to 1500 mg daily. Upon initiation of midazolam administration, the QTc increased substantially. In an attempt to reduce midazolam and clonidine, quetiapine was restarted at 300 mg daily. However, this attempt was not successful and the patient remained on midazolam which caused a QTc-prolongation reaching 605 ms on day 12. After the completed course of antibiotics, the QTc remained elevated at 544 ms. Upon discontinuation of midazolam two days later and ongoing clonidine management, the QTc decreased further to 510 ms within a day and the patient was transferred back to the general ward from where she was transferred back to psychiatry after sufficient management of her infectious disease.

3. DISCUSSION

In this case, high-dose midazolam caused an apparent dose-responding prolongation of QTc interval. Although the patient received several QTc-prolonging psychotropics such as methadone, olanzapine, quetiapine, trazodone, venlafaxine, the QTc was 379 ms on a stable regimen of these. Due to the soft- tissue infection antibiotic therapy with ciprofloxacin was initiated which did not prolong the QTc. As a result of this infection, the patient developed a severe hyperactive delirium which proved to be challenging in its management. Upon initiation of short-term sedation with midazolam, the QTc increased in a dose- dependent manner by approximately 220 ms reaching 605 ms on the seventh day of delirium. All attempts of discontinuing QTc-prolonging psychotropics were futile. With tapering and discontinuation of midazolam, the QTc reached 510 ms again and the patient was able to be transferred back to psychiatry. It has been reported that the QTc increased after the initiation of benzodiazepines in patients on methadone maintenance [7]. Generally, benzodiazepines have been thought to have a low propensity to increase the QTc interval [3]. In this patient, despite female sex and psychotropic drug administration, no further known QTc-prolonging risk factors were present. A transient initial hypokalemia was efficiently corrected with values in the normal range whilst QTc prolongation. In two studies, ciprofloxacin has not been associated with QTc prolongation despite previous reports [8,9]. Furthermore, the dose of methylphenidate, also known to increase the QTc [10], was not increased, rather slightly reduced in the course of hospitalization. In particular, the rapid decline of the QTc within a single day after discontinuation of midazolam pointed towards midazolam as the causing agent. Thus, in this patient the QTc prolongation was most likely aggravated by high-dose midazolam treatment on top of a stable regimen of methadone. There a two potential etiologies contributing to this QTc-prolongation. 1) midazolam has been shown to be a low-affinity inhibitor at the hERG-receptor which is one of the leading causes of QTc prolongation and 2) midazolam has known to have anticholinergic activity which can also cause QTc prolongation [11]. Both methadone [12] and midazolam [13] are inhibitors at the hERG-receptor, as well as have anticholinergic properties [11]. Since the methadone dose remained the same, the addition of midazolam was likely the reason for this QTc prolongation.

4. CONCLUSION

In summary, although midazolam to date has not yet been shown to cause QTc-prolongation at low doses, in this case, however, the administration of high-dose midazolam in the context of methadone maintenance caused a significant prolongation causing a potentially life-threatening situation to the patient. It remains to be shown, if this effect extends to patients in the absence of methadone administration. However, since midazolam sedation is quite common in various settings, the awareness of potential QTc-prolongation, in particular with respect to its low-affinity hERG inhibition and anticholinergic activity, ought to be on every physicians' mind.

CONSENT

All authors declare that informed consent was given by the patient for publication of this case report.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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