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Therapeutic and recreational methadone cardiotoxicity

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ABSTRACT

Several classes of drugs have been associated with an increased risk of cardiovascular disease and occurrence of arrhythmias potentially involved in sudden deaths in chronic users even at therapeutic doses. The study presented herein focuses on pathological changes involving the heart possibly due to methadone use. 60 cases were included in the study in total and were divided into three groups (therapeutic methadone users: 20 cases, recreational methadone users: 20 cases, and sudden death group in subjects who had never taken methadone: 20 cases). Autopsies, histology, biochemistry and toxicology were performed in all cases. Macroscopic and microscopic investigation results in therapeutic methadone users were similar to those observed in sudden, unexpected deaths in non-methadone users. In recreational methadone consumers, macroscopic and microscopic examination of the heart failed to provide results consistent with acute or chronic myocardial or coronary damage, thereby corroborating the hypothesis of death most likely following respiratory depression.

1. Introduction

Several classes of recreational and therapeutic drugs acting primarily on the central nervous system have additional effects on the heart and vessels, which may contribute to morbidity and mortality. Use or abuse of illicit drugs such as cocaine and amphetamines are traditionally associated with an increased risk of cardiovascular complications including arrhythmias, myocardial infarction and cerebrovascular accident.[1]

Therapeutic doses of methadone may trigger ventricular arrhythmias such as torsade de pointes tachycardia, which appears to be responsible for cases of sudden cardiac death in opioid dependent patients receiving substitution therapy.[2]

Exhaustive microscopic investigations of the myocardium, along with in-depth toxicology and biochemistry, are therefore mandatory in the evaluation of sudden unexpected deaths due to potential methadone cardiotoxicity.

The study presented herein focuses on pathological changes involving the heart that may be due to methadone use and their possible role in the occurrence of sudden cardiac death.

2. Materials and methods

2.1. Study design and study populations

The present study was performed during 2010–2015 and was designed as a retrospective study. Three study groups were retrospectively formed. The first group consisted of 20 therapeutic methadone users (all males, mean age 34 years). All these cases were former heroin abusers on methadone maintenance and were admitted to the mortuary due to sudden, unwitnessed deaths. Personal data and medical records, when available, were collected from families, clinical patient databases, general practitioners and local health services. Electrocardiograms and/or echocardiograms registered during regular or occasional medical check-ups were not systematically available. Death and medico-legal autopsy intervals ranged between 24 and 48 h. The causes of death were not identified based on macroscopic or microscopic findings. Moreover, toxicology and biochemical investigations failed to provide unequivocal evidence suggesting death following drug intoxication or metabolic disturbances. The cause of death was considered cardiac

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arrhythmia based on the results of all postmortem investigations and the exclusion of other obvious causes of death.

The second group (recreational methadone users) consisted of 20 age-, race- and gender-matched forensic autopsy cases (all males, mean age 37 years). All cases included in this group originated from forensic practice and were admitted to the mortuary following witnessed, recreational methadone consumption. Death and medico-legal autopsy intervals ranged between 19 and 45 h. None of these cases benefitted from methadone substitution therapy. Histology, toxicology and biochemistry results were consistent with the hypothesis of death following methadone intoxication and ruled out other obvious causes of death.

The third group (sudden death group) consisted of 20 age-, race- and gender-matched forensic autopsy cases (all males, mean age 38 years). All cases included in this group originated from forensic practice and were admitted to the mortuary following sudden, unexpected death. All these cases were void of any drug treatment at the time of death and had never consumed therapeutic or recreational methadone. Death and medico-legal autopsy intervals ranged between 20 and 46 h. A cardiac cause of death could be identified in 6 out of 20 cases based on macroscopic and microscopic findings as well as negative toxicology and biochemical investigations. In the remaining 14 cases, the cause of death was not identified based on autopsy and histology results. Toxicological and biochemical investigation did not provide evidence suggesting drug intoxication or death due to metabolic disturbances. Cardiac arrhythmia was therefore judged the most likely cause of death based on all postmortem investigation findings.

2.2. Postmortem investigations

Medico-legal autopsies, histology, toxicology and postmortem biochemical investigations were systematically performed. Immunohistochemistry (antibodies against fibronectin and c5b9 in the myocardium) was also performed in selected cases among therapeutic methadone users (8 out of 20 cases) and recreational methadone users (8 out of 20 cases). Immunohistochemistry was systematically performed in the sudden death group. The immunohistochemical markers whose expression was investigated in these cases were chosen because they are known to react should early myocardial ischemia occur. Medical records and clinical histories as well as police reports pertaining to each case were consistently reviewed before conclusions were made. Conventional autopsies were performed within 48 h after death and were carried out jointly by two forensic pathologists (at least one board-certified) as in accordance with both local standards and international guidelines for medico-legal autopsies. The guidelines for autopsy investigation developed by the Association for European Cardiovascular Pathology were also adopted.

Peripheral blood from the femoral veins, cardiac blood, vitreous humor, urine, cerebrospinal and pericardial fluids as well as gastric contents, hair and samples of certain tissues (liver, brain and skeletal muscle) were recovered for toxicological and biochemical analyses. Systematic toxicological analysis based on the use of chromatographic techniques and mass spectrometry was performed in all cases. Cocaine, heroin, codeine (3-methylmorhpine), morphine, buprenorphine, methadone and its metabolite EDDP were systematically analyzed in hair samples.

Biochemical investigations systematically included determination of troponin I, troponin T and NT-proBNP levels in postmortem serum from femoral blood.

Conventional histology was systematically performed and included haematoxylin-eosin (HE) stain of brain, heart, lung, liver and kidney samples. Full thickness areas involving the left anterior, lateral free wall and left posterior ventricle as well as interventricular septum, and the right anterior, lateral free wall and right posterior ventricle were sampled. Histology stains for the myocardium and coronary arteries systematically included the following colorations: HE, Mallory-Azan, Masson trichrome Goldner with light green and Verhoeff van Gieson. Immunohistochemical reactions using antibodies against fibronectin and C5b-9 of both cardiac ventricles were also performed in selected cases, as stated above.

3. Results

Table 1 summarizes toxicological investigation results (peripheral blood methadone concentration range and median) in all studied groups. Ethanol was detected in blood in 9 out of 20 cases in therapeutic methadone users, 12 out of 20 cases in recreational methadone users and 5 out of 20 cases in sudden death cases.

In therapeutic methadone users, toxicology performed in blood and urine failed to reveal other recreational or prescription drugs. Hair analysis confirmed methadone use during the months preceding death.

In recreational methadone users, toxicology performed in blood failed to reveal other recreational or prescription drugs, thus ruling out recent use of other drugs. Methadone was detected in hair in 2 out of 20 cases, thus excluding recent methadone use in 18 out of 20 cases.

In the group of therapeutic methadone users, circumstantial elements (medical records obtained from clinical patient databases, general practitioners and local health services, personal data collected from relatives and friends, house searches carried out by the authorities) confirmed methadone treatment (treatment duration: 1–4 years) and good patient compliance. In the group of recreational methadone users, circumstantial elements and postmortem investigations findings confirmed non-recent methadone consumption in 18 out of 20 cases.

In therapeutic methadone users, external examinations and autopsies were globally unremarkable and revealed no evidence of myocardial infarction, coronary artery thrombosis or pulmonary embolism. Hearts were normal in shape, with no cavity dilatations. Dimensions and wall thicknesses fell in normal ranges. Asymmetrical left ventricular hypertrophy was not observed. The coronary arteries arose from normally located patent ostia possessing normal anatomical disposition and did not show evidence of significant luminal narrowing.

The main myocardial and coronary artery histological findings (Table 2) consisted of interstitial and perivascular fibrosis, fibroadipous metaplasia within the left ventricle, contraction band necrosis, myocardial cell segmentation, intercalated disc widening and bundles of contracted myocytes alternating with bundles of distended myocardium. Most coronary arteries were normal or showed only slight intima thickening in their subepicardial portion. Occasionally, the coronaries were characterized by scattered fatty streaks as well as intima and media thickening. No statistically significant differences were observed among the tested groups.

Immunohistochemistry failed to reveal diffuse necrosis or group cell necrosis. Occasional single cell necrosis within the left ventricle was observed. Postmortem biochemical investigations did not show significant increased in troponin levels in any of these cases.

Similar macroscopic and microscopic findings, with no statistically significant differences, were observed in recreational methadone users and sudden death cases, thus suggesting that cardiac arrhythmia might be considered the most likely cause of death, with no relation to unspecific cardiac histological findings. As indicated above, a cardiac cause of death was identified in 6 out of 20 sudden death cases based on all postmortem investigation findings.