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Cardiac lesions induced by neuroleptic drugs in the rabbit

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Abstract

Sudden death seems to be more frequent following treatment with neuroleptic drugs in patients with pre-existing cardiac lesions, especially dilated and hypertrophic myocardiopathy. The present study was undertaken to confirm the hypothesis that myocardial lesions can be induced by neuroleptic drugs. Eight groups of 6 New-Zealand White rabbits were treated for 3 months: group I: controls (saline); group II: 15 mg/kg/day amisulpride; group III: 0.20 mg/kg/day haloperidol; group IV: 3 mg/kg/day levomepromazine; group V: 0.30 mg/kg/day olanzapine; group VI: 1.0 mg/kg risperidone, every 15 days; group VII: levomepromazine + haloperidol, same dose levels as single treatments; group VIII: levomepromazine + risperidone, same dose levels as single treatments. The hearts were immediately weighted and fixed, and paraffin sections were prepared and examined. Ventricular hypertrophy was observed following treatment with olanzapine and was still more marked with the combinations levomepromazine + haloperidol and levomepromazine + risperidone. Amisulpride and haloperidol induced necrotic lesions and levomepromazine, endocardial fibrosis. There was a lack of severe cardiac lesions following treatment with risperidone. The observed cardiac lesions can be compared to those seen in toxic myocarditis. These findings confirm the hypothesis that some neuroleptic drugs induce myocardial lesions. Further studies are warranted to demonstrate the effects of treatments of longer duration and the influence of pre-existing cardiac lesions.

Keywords: Neuroleptic drugs; Cardiotoxicity; Ventricular hypertrophy; Myolysis; Fibrosis; Necrosis; Rabbit

Introduction

The use of many medicinal products to treat cardiovascular, infectious or neoplastic diseases can be associated with functional or organic cardiac adverse effects. Drugs used for the therapy of psychiatric disorders including lithium salts, antidepressants and neuroleptic drugs have been incriminated in such severe adverse events. Indeed, quite a few case reports of sudden death have been published involving psychotropic drugs, especially neuroleptic drugs (Kumar, 1997; Hauben, 1999; Snaith, 1999). Death linked to the cardiotoxic potential of these drugs tends to occur more frequently in patients with pre-existing cardiac lesions

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with or without clinical manifestations and in this situation this can result in medico-legal problems. Overall, mortality in psychiatric patients is 2–5 fold higher than in the general population (Davidson, 2002; Straus et al., 2004). Life expectancy is 20% less in patients with schizophrenia than in non-psychotic patients (Newman and Bland, 1991).

In addition to suicide attempts and overdose, one of the major causes of elevated mortality in psychotic patients is thought to be cardiovascular illnesses. Newman and Bland (1991) described 301 deaths among 3623 patients with schizophrenia over a period of 10 years following diagnosis of the disease and start of antipsychotic therapy. Approximately 20% of deaths were linked to cardiovascular causes corresponding to 61 deceased patients, of whom 15 with sudden death. In a previous retrospective study (Frassati et al., 2004), we described 14 cases of sudden death that occurred between 1980 and 1999 in several psychiatric hospitals from the south-east of France. Neuroleptic drugs were thought to be involved in 13 cases and toxicological analyses ruled out overdose as the cause of death. Importantly, 13 of these 14 deceased patients had preexisting cardiac lesions evidenced at necropsy, including dilated myocardiopathy, ventricular hypertrophy, arrhythmogenic cardiopathy of the right ventricle, pericarditis, mitral valvular prolapse or epicardial muscular bridge. Because ventricular hypertrophy and dilatation were evidenced in 8 of these 13 patients, the question arose whether these lesions leading to the patients' death were induced by neuroleptic drugs.

To test this hypothesis, rabbits were treated with human therapeutic doses of commonly used neuroleptic drugs in psychiatric patients (amisulpiride, haloperidol, levomepromazine, olanzapine, risperidone) and selected combinations (levomepromazine + haloperidol and levomepromazine + risperidone).

Material and methods

Animals

Male and female New-Zealand White rabbits weighting 2.5 kg at the start of the study were used. They were purchased from CEGAV (Saint-Mars-d'Egrenne, France). The experimental protocol was approved by Claude Bernard University animals' ethics committee.

Treatment

Animals were randomly assigned to groups of 3 males and 3 females. They were treated with one intramuscular injection for 3 months as follows: G-I: saline; G-II: amilsupride (15 mg/kg daily); G-III: haloperidol (0.20 mg/kg daily); G-IV: levomepromazine (3 mg/kg daily); G-V: olanzapine (0.3 mg/kg daily); G-VI: risperidone (1.0 mg/kg every 15 days); G-VII: levomepromazine (3 mg/kg daily) + haloperidol (0.2 mg/kg daily); G-VIII: levomepromazine (3 mg/kg daily) + risperidone (1 mg/kg every 15 days). At the end of the treatment period, the animals were anesthetized with 400 mg/kg of intramuscular ketamine (Imalgène°, Merial, Lyon, France) and 32 mg/kg of intramuscular xylazine (Rompun°, Bayer, Puteaux, France). Thereafter, they were euthanatized with 88 mg/kg of intravenous pentobarbital (Dolethal°, Vetoquinol, Lure, France).

Histological examination

The hearts were immediately weighted and fixed using a mixture of ethanol, formaldehyde and acetic acid. After paraffin embedding, 5-μm sections were prepared and stained with HPS to study the architecture of cardiac fibers, the aspect of nuclei, the presence of myolysis, necrosis and interstitial fibrosis (either perivascular systematized or reticular non-systematized fibrosis), leukocyte infiltrates and dysplastic lesions in the distal coronary arteries.

Statistical analysis

Comparison of mean heart weights was performed using univariate analysis of variance and when found significant, treatment-related differences were analyzed with Dunnett's test. The presence of nucleus anomalies, myofibril disorganization, myolysis, necrosis, interstitial and endocardial fibrosis, lymphocyte infiltrates was assessed as follows: no change, mild, moderate, marked and severe changes. Treatment-related differences were analyzed using χ^2 test.

Results

No changes whatsoever were noted in control animals.

Heart weight

An increase in heart weight was noted in animals treated with olanzapine, or with the combinations levomepromazine + haloperidol and levomepromazine + risperidone (Fig. 1). These changes are considered to indicate treatment-induced global ventricular hypertrophy.