

PHASE I CLINICAL TRIAL TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF ONE INTRAMUSCULAR INJECTION OF RISPERIDONE ISM® AT DIFFERENT DOSE STRENGTHS IN SUBJECTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (PRISMA-1)

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Introduction: Risperidone ISM is a new long acting intramuscular injection of risperidone, intended for a 4-weekly administration, without oral supplementation. A clinical trial was conducted to characterize the pharmacokinetics and to evaluate the safety of Risperidone ISM® in subjects with schizophrenia or schizoaffective disorder (ClinicalTrials.gov identifier: NCT01788774).

Material and Method: A total of 36 subjects were randomized (1:1:1) to receive a single IM injection of Risperidone ISM®: 13 (50 mg), 12 (75 mg) and 11 (100 mg). Blood samples were collected through 75 days post-dose to measure the plasma concentrations of risperidone and 9-OH-risperidone.

Results: A total of 36 subjects received a single IM injection of Risperidone ISM®. The mean plasma concentration of the active moiety (risperidone + 9-OH-risperidone) in the 50 mg, 75 mg, and 100 mg group, respectively, was 21.4 ng/mL, 24.6 ng/mL, and 29.6 ng/mL (24 hours after injection); 22.8 ng/mL, 24.5 ng/mL, and 31.4 ng/mL (48 hours after injection); and 12.2 ng/mL, 17.3 ng/mL, and 20.0 ng/mL (Day 30 after injection).

Overall, 34 subjects (94.4%) experienced at least 1 Treatment Emergent Adverse Event (TEAE) during the study. The percentage of subjects reporting at least 1 TEAE was similar across the 3 dose groups (92.3%, 100%, and 90.9% in the 50, 75 and 100 mg group, respectively). Two subjects experienced an SAE and no deaths occurred during the study. There were no EPS-related SAEs and no subjects experienced significant change of any C-SSRS parameter.

Conclusions: Risperidone ISM® provided a sustained release of risperidone that achieved monthly therapeutic plasma levels within the first day without oral supplementation. Risperidone ISM® was found to be safe and well tolerated.

METABOLIC ACIDOSIS WITH A HIGH ANION: A DRUG-DRUG INTERACTION BETWEEN PARACETAMOL AND FLUCLOXACILLIN

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Background: Five-oxoprolinase is a product of disordered glutathione metabolism in the gamma glutamyl cycle: glutathione deficiency removes the feedback inhibition resulting in the formation of γ -glutamylcysteine and elevated concentrations of γ -glutamylcysteine leading to the formation of 5-oxoprolinase, which is degraded by 5-oxoprolinase. Both paracetamol and flucloxacillin interact with the gamma glutamyl cyclase. Paracetamol depletes glutathione which leads to the accumulation of γ -glutamylcysteine that is a precursor for 5-oxoprolinase and flucloxacillin inhibits 5-oxoprolinase which also leads to accumulation of 5-oxoprolinase. The accumulation of 5-oxoprolinase, an acid residue, may lead to a high anion gap and a metabolic acidosis. Although a few cases of this drug-drug interaction are published, it is still not included in the summary of product characteristics of paracetamol and flucloxacillin or included in medication safety monitoring systems in hospitals and pharmacies.

Material and Methods: We analyzed all submitted reports to the Netherlands' Pharmacovigilance Centre Lareb till 31 December 2014 on this drug-drug interaction.

Results: Lareb received 3 reports of metabolic acidosis where both paracetamol and flucloxacillin, used in therapeutic doses, were marked as suspected and interacting drugs. The cases concern 3 females of older age (67, 72 and 78 years). The aberrant mechanism of the 72 year old female was treated with acetyl cysteine; she died. The other 2 women were treated with sodium bicarbonate and recovered. We could not confirm a relationship between the treatment and the outcome of the interaction.

Conclusions: Our reported cases contribute to the suspicion of a relationship between metabolic acidosis and concomitantly used paracetamol and flucloxacillin. This drug interaction should be included in the summary of drug characteristics and included in medication monitoring systems in health institutions.

EVALUATION OF ACUTE CARDIOVASCULAR EFFECTS OF IMMEDIATE-RELEASE METHYLPHENIDATE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Introduction: Attention-Deficit Hyperactivity Disorder (ADHD) is a frequent condition in children and often extends into adulthood. Immediate release methylphenidate (IR-MPH) has raised concerns about potential cardiovascular adverse effects within a few hours after administration. This study was carried out to investigate acute effects of IR-MPH on ECG in a pediatric population.

Methods: A total of 54 consecutive patients with ADHD (51 males and 3 females; mean age = 12.14±2.6 years, range 6-19 years), receiving a new prescription of methylphenidate (MPH), underwent a standard ECG 2 hours before and after the administration of IR-MPH 10 mg per os. Basal and post-treatment ECG parameters, including mean QT (QTc), QT dispersion (QTd) interval duration, T peak – T end (TpTe) intervals and TpTe/QT ratio were compared. **Results:** Significant modifications of both QTc and QTd values were not found after drug administration. QTd fluctuated slightly from 25.7 ± 9.3 ms to 25.1 ± 8.4 ms; QTc moved from 407.6 ± 12.4 ms to 409.8 ± 12.7 ms. A significant variation in blood pressure (BP) (Systolic BP 105.4 ± 10.3 vs 109.6 ± 11.5; $P < 0.05$. Diastolic BP 59.2 ± 7.1 vs 63.1 ± 7.9; $P < 0.05$) was observed, but all the data were within normal range. Heart rate (HR) moved from 80.5 ± 15.5 bpm to 87.7 ± 18.8 bpm. No change in TpTe values was found but a statistically significant increase in TpTe/QTc intervals was found with respect to basal values (0.207 ± 0.02 ms vs 0.214 ± 0.02 ms; $P < 0.01$).

Conclusions: The findings of this study show no significant changes in ECG parameters. Our data suggest a relative cardiovascular safety of IR-MPH in childhood, even if stimulants may exert a cardiovascular effect on BP and HR. TpTe values can be an additional parameter to evaluate borderline cases.

THE EFFECT OF DEXMEDETOMIDINE AND DEXKETOPROFEN ON RAT SIATIC NERVOUS

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