TOXICOLOGICAL INVESTIGATION ON A NEW TOPICAL HYDROXYPROPIL-BETA-CYCLODEXTRIN GEL BASED FORMULATION IN MALE RAT

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Introduction: The treatment of the androgenetic alopecia (AGA) is based on only two medications: minoxidil MXD (topical) and finasteride (oral). The therapeutic effects of MXD in AGA are mediated by multiple mechanisms involving potassium channel-related cell proliferation, nitric oxide-mediated enhancement of blood flow to the hair follicles and inhibition of the androgen pathway. MXD is available as alcoholic/propylene-glycol (MXD/ethanolic/propyl-glycol) solutions from 1% to 5% w/v and as a 5% w/v foam formulation. Adverse reactions including pruritus, dryness, irritation, dermatitis, headache and hypotension have been reported in patients treated with MXD/ethanolic/propyl-glycol solution. The long-term efficacy of MXD is limited. In this work we evaluated the toxicology of a novel based hydroxypropil-b-cyclodextrin MXD (MXD/HP-b-CD) GEL formulation in male rat.

Material and method: The effects of 3weeks repeated dosing of MXD formulations at concentration 0.035%-3.5% or 3.5% w/v one/twice per day applied to the dorsal area of the rat (N rats per group=3) were investigated. The cardiovascular effects were evaluated by telemetry monitoring the heart rate (HR), QT intervals and arterial pressure in freely moving laboratory animals. At the end of treatment, parasternal long-axis assessment (B-mode) and short-axis measures (M-mode) of left ventricular diastolic and systolic volumes, stroke volume, cardiac output, wall thickness, ejection fraction and fractional shortening using the echocardiography were performed. Histopathological analysis of the tissues and hematochemistry evaluation were performed in the treated rats.

Results: MXD/ethanolic/propyl-glycol solution and MXD/HP-β-CD GEL (3.5% w/v) enhanced the hair growth of the rats by 80.1±2% and 84.3±4%, respectively. The topical administration of single daily dose of MXD/ethanolic/propyl-glycol solution at 3.5% w/v concentration (SF=136rat vs human) caused a percentage reduction in systolic, diastolic and mean blood pressure with respect to the baseline respectively of -22.52±1%, -22.89±2%, and -23.04±3% in the rats as evaluated by student t test ($p<0.05$MXD vs baseline). The application of twice daily doses of the same formulation to the rat (SF=272) caused a further reduction of these parameters. These effects were not reversible following washout. In contrast, no significant effects were observed on these parameters with the MXD/HP-β-CD GEL formulation. A not significant enhancement of HR was observed with either formulation. A decrease of the QTc interval and of the ST segment was observed following the treatment with once and twice daily dose of MXD 3.5% (w/v-w) in the rats treated with either formulation vs baseline ($p<0.05$MXD vs baseline). In addition, the MXD/ethanolic/propyl-glycol solution caused an enhancement of the T amplitude. An enhancement of systolic (+30.23%) and diastolic (+18.24%) left ventricle diameter, systolic (+89.91%) and diastolic (+45.8%) left ventricle volume, stroke volume (+30.9%), left ventricle mass (+33.71%), systolic (+36.32%) and diastolic (+20.89%) left ventricle diameter was observed in the rats treated with MXD/ethanolic/propyl-glycol solution (3.5% w/v). The MXD/HP-β-CD GEL rats were moderately affected. The MXD formulations caused marked histological lesions in the kidney, liver, skeletal and cardiac muscle with no effects in dermal tissues; the histological sections of MXD/ethanolic/propyl-glycol solution treated rats were severely affected. The MXD ethanol/glycol propylene solution caused an enhancement of blood GOT, ALK and K^+ levels vs other groups ($p<0.05$). The NTProANP-NTProBNP levels were elevated in either MXD group vs vehicles; the hematochemistry parameters of the MXD/ethanol/glycol propylene treated rats were severely affected ($p<0.05$).

Discussion and conclusion: The MXD/HP-β-CD GEL formulation at doses effective in enhancing hair growth shows a favorable toxicological profile for a topical long-term use.