

A HISTOLOGICAL STUDY OF THE HEPATIC AND RENAL EFFECTS OF ORAL BROMOCRIPTINE MESYLATE IN SWISS ALBINO MICE

1.0 INTRODUCTION

Bromocriptine, an [ergoline](#) derivative, is a [dopamine agonist](#) that is used in the treatment of [pituitary tumors](#), [Parkinson's disease](#) (PD), [hyperprolactinaemia](#), [neuroleptic malignant syndrome](#), and [type 2 diabetes](#). a dopamine D2 receptor agonist, was newly formulated as bromocriptine-QR, a high-absorbing tablet, which upon oral administration produces a short duration pulse of bromocriptine within the circulation. When given in the morning, bromocriptine-QR increases dopaminergic activity at the time of day that CNS dopaminergic activities normally peak in nondiabetic humans [21]. Preclinical studies indicate that this circadian 'resetting' dopamine signal replicates neurochemistry characteristic of the insulin-sensitive condition [22]. In clinical studies of patients with T2DM, such treatment improves an array of metabolic derangements present in the diabetic state [23,24].

Bromocriptine is a potent agonist at [dopamine](#) D2 receptors^[2] and various [serotonin](#) receptors. It also inhibits the release of [glutamate](#), by reversing the glutamate [GLT1](#) transporter. Bromocriptine is (5 α)-2-Brom-12 ϕ -hydroxy-2 ϕ -(1-methylethyl)-

5 α -(2-methylpropyl) ergotaman-3 α , 6 α , 18-trione. The molecular formula is C₃₂H₄₀BrN₅O₅ and the molecular weight is 654.62. Bromocriptine, an ergot alkaloid, is a hygroscopic white powder that is freely soluble in 40% C₂H₅OH, 60% H₂O solutions. For use as an antidiabetic agent, solid-tablet preparations of bromocriptine mesylate with excipients are used. Exposure of bromocriptine to water or high humidity causes breakdown of bromocriptine to bromocriptinine; therefore, tablets should be kept with desiccant in cool, dry areas.

Bromocriptine is extensively metabolized in the gastrointestinal tract and liver with the formation of at least 20 – 30 metabolites [32]. Bromocriptine has high affinity for the cytochrome P450 CYP3A4 and hydroxylations at the proline ring of the cyclopeptide moiety are a main metabolic pathway. On the basis of the structure of the metabolites, four major pathways for bromocriptine metabolism have been identified. They are: oxidation at position 8 α in the proline fragment of the peptide molecule, resulting in various hydroxylated compounds; oxidative ring opening of the primary 8 α -hydroxylated intermediate to generate the glutamic acid derivative; hydrolytic cleavage of the molecule, leading to the formulation of 2-bromolysergic acid, its amide and their epimers at position 8; and epimerization at position 8 of the bromolysergic acid moiety, leading to the formation of the isoderivatives. Bromocriptine is almost exclusively metabolized by the liver, with approximately 6% being cleared by the kidneys.]