Title: Population pharmacokinetics of repaglinide in Type 2 diabetes mellitus patients and genetic polymorphisms of *CYP3A4* and *CYP2C8.*

Introduction

Repaglinide is a novel prandial glucose regulator for the treatment of type 2 diabetes mellitus. Repaglinide is mainly metabolized in the liver by CYP3A4 (Dornhorst, 2001) and CYP2C8 (Bidstrup *et al*., 2003). In this study, serum levels of repaglinide after single dose administration to Type 2 patients diabetes mellitus is determined using High Performance Liquid Chromatography (HPLC). The data is plugged into a Nonparametric Expectation Maximisation (NPEM) programme to determine the population pharmacokinetic parameter values of repaglinide such as AUC, $t_{1/2}$, C_{max}, k_{el} & Vd. The distribution of alleles *CYP3A4*4, CYP3A4*5, CYP3A4*18, CYP2C8*2, CYP2C8*3 and CYP2C8*4* is also investigated. Finally, the clinical relevance of these variants in determining repaglinide pharmacokinetics will be investigated.

Objectives

General Objective

To establish the influence of *CYP3A4* and *CYP2C8* genetic polymorphisms on the pharmacokinetics' of repaglinide in Type 2 diabetes mellitus patients.

Specific Objectives

1) To develop and validate an HPLC method for the determination of repaglinide serum concentrations.
2) To determine pharmacokinetics profile ($t_{1/2}$, AUC, C_{max}, $t_{max,}$ k_{el} and Vd) of repaglinide in Type 2 diabetes mellitus patients.
3) To optimize polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and multiplex polymerase chain reaction techniques and use these methods to study *CYP3A4* and *CYP2C8* genetic polymorphisms among Type 2 diabetes mellitus patients.
4) To establish population pharmacokinetic models for repaglinide in order to determine the influence of the *CYP3A4* and *CYP2C8* polymorphisms on repaglinide's pharmacokinetics.

Expected outcomes

An HPLC method using a simple liquid-liquid extraction and HPLC with UV detection for repaglinide will be developed and validated in human serum. PCR-RFLP and multiplex PCR will be optimized for the determination of *CYP3A4* and *CYP2C8* genetic polymorphisms among Type 2 diabetes mellitus patients. Population pharmacokinetic models using NPEM will be established to determine the final influence of the *CYP3A4* and *CYP2C8* polymorphisms on repaglinide's pharmacokinetics.