

Betydningen af gener og miljø for interindividuelle forskelle i farmakokinetiske og -dynamiske egenskaber af de orale antidiabetika rosiglitazon og metformin

Metformin is an oral antidiabetic drug that has been known for more than 90 years. Despite metformin being an old drug, very little is known about how metformin works and which factors may influence the effect of metformin. Because the patent on metformin has expired many years ago, there are no financial reasons to investigate these properties and thus the industry has no interest in this. This leaves publicly financed research to fill the gap of knowledge regarding this research. Rosiglitazone is an oral antidiabetic drug that was withdrawn from the European market in 2010 due to cardiac side effects. The knowledge about rosiglitazone can be drawn onto other drugs that are metabolized like rosiglitazone.

The main objective of the Ph.D. project is to help understand the environmental and heritable aspects of metformin and rosiglitazone to improve the treatment of type 2 diabetics with oral antidiabetics. This is a subject that has received much attention over the last few years. A high variation in both the pharmacokinetics and the response to the oral antidiabetics has been shown, which is quite possibly due to genetic variation.

The project is performed at Clinical Pharmacology – Institute of Public Health at University of Southern Denmark. The main supervisor is professor Kim Brøsen. Professor Kaare Christensen (the twin registry, University of Southern Denmark) and chief physician, PhD Kurt Højlund (department of endocrinology, Odense University Hospital) are co-supervisors.

The first study will look into the genetic aspects of rosiglitazone and give an understanding of the interindividual differences in the response to this drug.

It was recently shown that there is a huge interindividual difference in the pharmacokinetic and pharmacodynamic effect of metformin. This can be caused by two factors; environmental and heritable. It is not possible to determine the importance of these two factors and the metformin studies in this Ph.D. project will help uncover this.

The second study will investigate the possible drug-drug interaction of metformin and St. John's wort, which will give an insight into the environmental factors that influence the response to metformin.

The third study will examine the heritable aspects of metformin. We will study the minimum concentrations of metformin in twins who are in steady state with metformin. We will include 50 monozygotic and 50 dizygotic pairs, and this will give an insight into the extent of the heritable factors in the pharmacokinetics of metformin.

The fourth and final study is aimed at developing a pharmacokinetic/pharmacodynamic model based on a study, which is currently ongoing. This study's main objective is to be able to predict the pharmacokinetics of metformin using only a few blood samples, and thus be able to easier implement pharmacogenetics in the clinic.