Modelling of tolerance and rebound in normal and diseased rats

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. **Isaksson C**., Wallenius K., Peletier LA., Toreson H., and Gabrielsson J.
Turnover modeling of non-esterified fatty acids in rats after multiple intravenous infusions of nicotinic acid
Dose-Response **2009**, 7: 247-269

II. **Ahlström C**., Peletier LA., Jansson-Löfmark R., and Gabrielsson J.
Feedback modeling of non-esterified fatty acids in rats after nicotinic acid infusions
Journal of Pharmacokinetics and Pharmacodynamics **2011**, 38: 1-24

III. **Ahlström C**., Peletier LA., and Gabrielsson J.
Quantitative analysis of rate and extent of tolerance of biomarkers: Application to nicotinic acid-induced changes in non-esterified fatty acids in rats
Submitted to European Journal of Pharmaceutical Sciences, **2011**

IV. **Ahlström C**., Peletier LA., and Gabrielsson J.
Challenges of a mechanistic feedback model describing nicotinic acid-induced changes in non-esterified fatty acids in rats
In manuscript

V. **Ahlström C**., Peletier LA., and Gabrielsson J.
Feedback modeling of non-esterified fatty acids in obese Zucker rats after nicotinic acid infusions
In manuscript

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Modelling of tolerance and rebound in normal and diseased rats

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Abstract

The development of rebound and tolerance is an important consideration when optimizing medical therapy, both with respect to drug dosing and adverse effects. By using quantitative approaches to study these processes, potential risks can be minimized. In this thesis nicotinic acid (NiAc)-induced changes in non-esterified fatty acids (NEFA) were used as a tool to investigate key determinants of tolerance and rebound in normal Sprague Dawley and in obese Zucker rats, a disease model of dyslipidaemia. The aim of the studies was to develop and challenge a model that described tolerance and rebound following different durations, rates and routes of NiAc administration.

In normal rats, administration of NiAc resulted in a rapid decrease in NEFA plasma concentration, followed by rebound, the extent of which depended on both the level and duration of drug exposure. Rebound oscillations followed long duration of NiAc exposure. During constant drug exposure, increasing NEFA concentrations indicated tolerance development. The pharmacodynamic characteristics of NiAc-induced changes in NEFA differed in normal and diseased rats, with NEFA baseline concentrations being increased, rebound diminished, and tolerance development more pronounced in the diseased animals.

The non-intuitive pattern of NiAc-induced changes in NEFA was captured by a feedback model with a moderator distributed over a series of transit compartments, where the first compartment inhibited the formation of response and the last stimulated the loss of response. The model was based on mechanistic principles, mimicking the dual actions of insulin in inhibiting the hydrolysis of triglycerides to NEFA and glycerol, and stimulating the re-esterification of NEFA. In both the normal and diseased rats, the model described the pharmacodynamic characteristics adequately.

The concentration-response relationship at steady state was shifted upwards and to the right, and was shallower, in diseased rats compared to normal rats. The extent of such shifts demonstrates the impact of disease at equilibrium in the system.

These studies have shown that by eliciting different exposure patterns and taking into account both the washout dynamics of the administered drug and the pharmacodynamic characteristics of normal and diseased animals, a mechanistically-based feedback model was able to tease out important information about tolerance and rebound.

Keywords: feedback modelling, tolerance, rebound, pharmacokinetics, pharmacodynamics, dyslipidaemia, nicotinic acid, non-esterified fatty acids

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