Danish Society for Pharmacology

8th Annual Meeting

Molecular Pharmacology on the Move:
From Basic to Translational Science

Program

20. januar 2016, kl. 10.00 – 21.00

Syddansk Universitet, Hovedindgangen
Auditorium 0100, Campusvej 55, Odense

Sponsors:

BCPT

Basic & Clinical Pharmacology & Toxicology

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Information

Mødet er arrangeret af

Dansk Selskab for Farmakologi, en paraplyorganisation for:

- Dansk Selskab for Farmakologi og Toksikologi
- Dansk Selskab for Klinisk Farmakologi
- Dansk Selskab for Klinisk Kemisk Farmakologi
- Danmarks Farmaceutiske Selskab
- Dansk Selskab for FarmakoEpidemiologi

Praktiske Informationer:

- Frokost og kaffepauser er inkluderet i mødet

- Middagsbilletter kan købes på AU webshop

- Posters skal være sat op før symposiet starter

- Foredragsholderne bedes sørge for, at præsentationerne er klar i auditoriet senest 30 min før foredraget skal afholdes

Sekretariat:

- Institut for Biomedicin – Farmakologi, Att.: Jytte Kragelund, Aarhus Universitet, Bartholins Allé 6, 8000 Aarhus C.
  Tlf.: 8716 7604; e-mail: jk@biomed.au.dk

Program

09.30 Registration and coffee

10.00 Introduction to meeting: Ulf Simonsen, Aarhus University

Session 1

10.05 *Receptor signal transduction – from molecular binding to in vivo efficacy in man*
Professor Thue Walter Schwartz, The NNF Center for Basic Metabolic Research, Copenhagen University

Session 2 10.35 - 12.05 Parallel session

Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) – concept and applications
Chairman: Claus Løland

10:35 *G protein-coupled designer receptors (DREADDs) - concept, signaling and prospect"*
Professor Gerald Thiel, Universität des Saarlandes, DE

11:15 *Chemogenetic and optogenetic approaches to investigate central control of feeding and systemic insulin sensitivity*
Dr. Sophie Steculorum, Max Planck Institute for Metabolism Research, DE

11:40 *Advanced opto- and chemogenetic approaches to study neurological diseases*
Professor Merab Kokaia, Lund University, SE

10.35 - 12.05 Parallel session

Which medicine should have priority?
Chairmen: Eva Aggerholm Sædder, AUH, Birgitte Klindt Poulsen, AUH

10:35 *Prioritizing according to NICE*
Dr. Amanda Adler, FRCP, NICE, United Kingdom

11:10 *The pharmacoeconomic perspective*
Kjeld Møller Pedersen, Professor of Public and Health Economics, SDU

11:25 *A perspective on prioritizing in oncology*
Lars Henrik Jensen, Consultant, Vejle Hospital

11:40 *A Danish model*
Professor Hanne Rolighed Christensen, Bispebjerg Hospital

11:55 *Discussion*

Session 3 **Free oral communications**

Chairmen: Helle Holst, Jo DeMey

12:15 O1. A *model based approach for joint analysis of pain intensity and opioid consumption in postoperative pain*
Katrine R. Knøsgaard and colleagues, University of Copenhagen

12:25 O2. *Modelling of endpoint postponement for all-cause mortality in statin trials*
Morten Rix Hansen and colleagues, University of Southern Denmark

12:35 O3. *Inhibition of micro-fibrillar associated protein 4 as a potential therapy targeting choroidal neovascularisation in age related macular degeneration*
Bartosz Pilecki and colleagues, Universities of Nottingham and Southern Denmark

12:45 **Lunch**

Session 4 **Posters and Coffee**

13:45-14:30 **Posters – Guided Tours**

Chairmen: Ole Bjerrum, Charlotte Uggerhøj Andersen

Session 5 **Hot topics in Danish Pharmacology – based on suggestions from the 5 member societies**
Chairmen: Jesper Hallas, Harrie Boonen

14:30 (DSFE) *Pharmacolepidemiological aspects of the Diabetes Impact Study*
Professor Anders Green, Institute of Applied Economics and Health Research (ApEHR), Copenhagen

14:45 (DFS) *Multifaceted intervention to improve medication adherence in patients with hypertension: a randomised, controlled trial*
Dr. Ulla Hedegaard, University of Southern Denmark

15:00 (DSK2F) *Morphine revisited – a pharmacokinetic metamodel of morphine and its active metabolite*
Dr. Eva Sverrisdóttir, Dept. of Drug Design and Pharmacology, University of Copenhagen

15:15 (DSFTM) *SorCS1, encoded by the type 2 diabetes susceptibility gene SORCS1, is a potent regulator of peripheral insulin sensitivity*
Mads Kjolbye, Dept of Biomedicine, Aarhus University

15:30 (DSKF) *Somatic sequencing to target treatment of cancer*
Britt Elmedal Laursen, Aarhus University Hospital

15:45 **Break**

Session 6 16:00-17:30 Workshops - Parallel sessions

1) Therapeutic Drug Monitoring and Management in psychiatric patients
Chairmen: Helle Angelo, Trine Meldgaard, Charlotte Vermehren

16:00 *TDM in Psychiatry*
Gesche Jürgens, Senior Consultant, Unit of Clinical Pharmacology
Roskilde University Hospital

16:30 *Medication Reviews for psychiatric patients in the Region of Southern Denmark.*
Tina Hoff Duedahl, Clinical Pharmacist and Merete Willemoes Nielsen, Pharmacist,
Region of Southern Denmark

17:00 ***T**herapeutic **D**rug **M**anagement in Denmark; status and perspectives.*
Helle Angelo

2) Pharmacology teaching in Denmark
Chairman: Kim Brøsen

16:00 *Basic Pharmacology at SDU*
Ulrike Muscha Steckelings

16:10 *Clinical Pharmacology at SDU*
Per Damkier

16:20 *Basic Pharmacology at AU*
Ulf Simonsen

16:30 *Clinical Pharmacology at AU*
Britt Elmedal Laursen

16:40 *Basic Pharmacology at KU*
Thue Walter Schwartz

16:50 *Clinical Pharmacology at KU*
Henrik Enghusen Poulsen

17:00 *Discussion*

3) Challenges in modern toxicology
Chairmen: Philippe Grandjean, Jesper Bo Nielsen

16:00 *Dealing with mixed exposures*
Marta Axelstad Petersen, DTU-FOOD, DK

16:20 *Transgenerational toxicology*
Karin Broberg, Lund University, Sweden

16:40 *The prospect of in silico toxicology*
Karine Audouze, Université Paris Diderot, France

17:05 *Toxicological evidence in prevention*
Pál Weihe, Thorshavn, Faroe Islands

Session 7 **Lecture by the BCPT Nordic Prize Winner 2015**

Chairman: Kim Brøsen

17:30 *Paracelsus revisited: The dose concept in a complex world*
Philippe Grandjean, University of Southern Denmark

18:15 **Awards to best oral communication and best poster**

18:25 **Closure of meeting: Ulf Simonsen, Aarhus University**

18:30 Drinks at the poster area

19:00 Dinner at the Campus Restaurant

Organizing Committee:
Helle Angelo, Trine Meldgaard Lund, Dorte Glintborg, Christian Fynbo Christiansen, Helle Holst, Claus Juul Løland, Harrie Boonen and Ulf Simonsen.

Posters

P1: PROTOCOL FOR THE CYTONOX STUDY

C. Gade[1], G. Mikus[3], H.R. Christensen[1], K.P. Dalhoff[1], J.C. Holm[2], H. Holst[1]
[1]Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, Denmark. [2]Children´s Obesity Clinic, Department of Paediatrics, Holbæk Hospital, Denmark.
[3]Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Germany

P2: HYDROGEN SULFIDE RELAXATION INVOLVES MITOCHONDRIAL COMPLEX I AND III IN RAT SMALL ARTERIES

E.R. Hedegaard, A. Gouliaev, A.K. Winther, D.D.R. Arcanjo, M. Aalling, N.S. Renaltan, M.E. Wood, M. Whiteman, N. Skovgaard, U. Simonsen
Department of Biomedicine, Pulmonary and Cardiovascular Pharmacology, Aarhus University, Aarhus C, Denmark and University of Exeter Medical School, United Kingdom.

P3: GENERIC SWITCHING AND NON-PERSISTENCE AMONG MEDICINE USERS: A COMBINED POPULATION-BASED QUESTIONNAIRE AND REGISTER STUDY

J. Rathe, M. Andersen, D.E. Jarbøl, R. dePont Christensen, J. Hallas, J. Søndergaard.
Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense, Denmark

P4: ALTERED STIFFNESS IN CORONARY ARTERIES AND EFFECT OF PIRFENIDONE ON ENDOTHELIUM-DEPENDENT VASO-DILATATION IN TYPE 2 DIABETIC (DB/DB) MICE

L. Beck, R. Carlsson, R. Hernanz, M. Sheykhzade, and U. Simonsen
Aarhus University, Department of Biomedicine, and University of Copenhagen

P5: CARDIOVASCULAR DRUGS AND ERECTILE DYSFUNCTION – A SYMMETRY ANALYSIS

L. Rasmussen, J. Hallas, K.G. Madsen, A. Pottegård.
Clinical Pharmacology, Department of Public Health, University of Southern Denmark, DK-5000 Odense C, Denmark

P6: RNA OXIDATION IN TYPE 2 DIABETES: A NOVEL MECHANISM AND BIOMARKER?

Laura K. Kjaer[1], Vanja Cejvanovic[1], Trine Henriksen[1], Cramer Christensen[2], Ivan Brandslund[2], Henrik E. Poulsen[1]
[1] Q7642, Laboratory of Clinical Pharmacology, Bispebjerg Hospital.
[2] Dept. of Clinical Biochemistry, Vejle County Hospital

P7: GLUCAGON-LIKE PEPTIDE-1 IMPROVES ENDOTHELIUM-DEPENDENT VASODILATATION IN SMALL ARTERIES EXPOSED TO HIGH GLUCOSE

Maj Bangshaab, Michael Gejl Jensen, Ulf Simonsen
Department of Biomedicine, University of Aarhus, Wilhelm Meyers Alle 4, 8000 Aarhus C, Denmark

P8: THE IMPACT OF OPIOID TREATMENT ON REGIONAL GASTROINTESTINAL TRANSIT

J.L. Poulsen[1], D. Jørgensen[1], A.E.Olesen[1,2], C. Brock[1,2], T.H. Sandberg[1], K. Krogh[3], & A.M. Drewes[1,4]
1 Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark; 2 Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark; 3 Neurogastroenterology Unit, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark: 4 Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

P9: CALCIUM CHANNEL BLOCKER POISONINGS IN DENMARK

S. Al-Gibouri, J.T. Andersen, E. Jimenez-Solem, K.M, T.S Petersen, S. Bøgevig, K.P. Dalhoff, M.B Christensen
Department of Clinical Pharmacology, Bispebjerg and Frederiksberg, Copenhagen, Denmark

P10: POPULATION MODELLING OF THE SYNERGISTIC EFFECTS OF MORPHINE AND GABAPENTIN IN THE RAT: A RESPONSE SURFACE APPROACH

T Papathanasiou, RV Juul, C Gabel-Jensen, AM Heegaard, M Kreilgaard and TM Lund
Dep of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen

P11: PROPERTIES OF NAPI-IIB AND ITS INFLUENCE ON DEVELOPING HEART VALVE DISEASE

T.V. Luong, Å.L. Jönsson, V.G. Rasmussen, J.H. Christensen, H.H. Kimose, E.R. Hedegaard, S. Mogensen, C. Wagner, U. Simonsen.
Department of Biomedicine, Aarhus University, Bartholins Allé 6, 8000 Aarhus C, Denmark.

P12: NUCLEIC ACID OXIDATION RELATION TO IRON STATUS IN A GENERAL POPULATION

Vanja Cejvanovic[1], Christina Ellervik[2], Laura K Kjaer[1], Allan Weimann[1], Henrik E. Poulsen[1]
[1]Q7642, Department of Clinical Pharmacology, Bispebjerg Hospital; [2]Department of Laboratory Medicine, Boston Children's Hospital

Abstracts

Free communications

Abstract O1

A MODEL BASED APPROACH FOR JOINT ANALYSIS OF PAIN INTENSITY AND OPIOID CONSUMPTION IN POSTOPERATIVE PAIN

Katrine R. Knøsgaard, R.V. Juul, A.E. Olesen, K.V. Pedersen, M. Kreilgaard, L.L. Christrup, P.J. Osther, A.M. Drewes, T.M. Lund.
Department of Drug Design and Pharmacology, University of Copenhagen, Denmark

Joint analysis of pain intensity scores and opioid consumption is encouraged in trials of postoperative pain, but no approach has previously been introduced that takes into account the complexity of their interrelation in time. In this study we applied a model-based approach (using NONMEM 7.3) to simultaneously study pain intensity based on 748 observed numerical rating scores (NRS) and the probability of requesting opioid when allowed (NRS≥3) based on 51 observed morphine and oxycodone dosing events in a 4 hours postoperative period for 44 patients undergoing percutaneous kidney stone surgery. Pain scores followed truncated Poisson distribution with zero-inflation at baseline and time-dependent mean score ranging from 0.93 to 2.45. Serial correlation was greatly present in NRS scores with up to 70.1% inflated probability that a patient would score the same NRS as at the preceding time-point. The probability of requesting opioid at NRS≥3 was strongly correlated with the number of previous doses given to the subject ranging from 89.8% for requesting the first dose to 26.1% after three previous doses. Significant reduction in pain scores after both 1.0mg/kg morphine and 1.0mg/kg oxycodone was found ($p<0.001$). The reduction of pain intensity was significantly related to the pain intensity at time of opioid request ($p<0.001$), but no difference between the two opioids were found ($p = 0.224$). As illustrated with clinical trial simulations, the joint model-based analysis of pain intensity and opioid consumption data allows detailed causal analysis of interventions in the postoperative pain period, potentially separating analgesic effects from confounding effects

Abstract O2

MODELLING OF ENDPOINT POSTPONEMENT FOR ALL-CAUSE MORTALITY IN STATIN TRIALS

Morten Rix Hansen [1,2] Anton Pottegård [1] Asbjørn Hróbjartsson Per Damkier [1,2] René dePont Christensen Kasper Søltoft Larsen [1] Malene Elisa Lopez Kristensen [1] Palle Mark Christensen [1] Jesper Hallas [1,2]
[1)] Clinical Pharmacology, University of Southern Denmark, Odense, Denmark
[2)] Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Denmark

The ‘average postponement of the outcome event’ has been proposed as a way of presenting the magnitude of effect for preventive medications. The aim of this study was to present a novel method for modeling endpoint postponement (EP) from trial data and compare it with the usual approach of measuring the area between survival curves. We also present a formalized meta-analysis of modeled EP for all-cause mortality in statin trials.

We identified 15 controlled statin trials that fulfilled our inclusion criteria. With the original method, average EP was calculated as the area between Kaplan-Meier curves by counting pixels on magnified prints. Our novel method EP modeling can compute EP without Kaplan-Meier

curves. The modeled EP was computed for all 15 trials on the basis of (1) hazard ratio or relative risk (2) the cumulative event rate in the untreated group and (3) the trial's running time. The modeled EP was subjected to a meta-analysis.

The overall results of the meta-analyses was an EP of all-cause mortality of 11.2 days.

Modeled EP estimates agreed reasonably with EPs based on pixel-counting. The modeled EP is amenable to meta-analyses and may be a useful approach to presenting the benefit of preventive treatment. Based on modeled EP estimates, statin treatment results in a surprisingly small gain in average survival

Abstract O3

INHIBITION OF MICRO-FIBRILLAR ASSOCIATED PROTEIN 4 AS A POTENTIAL THERAPY TARGETING CHOROIDAL NEOVASCULARISATION IN AGE RELATED MACULAR DEGENERATION

Zoe Blackley[1], **Bartosz Pilecki**[2], Nikita Ved[1], Anders Schlosser[2], Uffe Holmskov[2], David Bates[1] and Grith Lykke Sorensen[2]

[1]Cancer Biology- Division of Cancer and Stem Cells- School of Medicine, University of Nottingham, Nottingham, United Kingdom; [2]Department of Cancer and Inflammation- Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark

Purpose

To evaluate inhibition of Micro-Fibrillar Associated Protein 4 (MFAP4) on choroidal neovascularization (CNV) in a mouse model of age-related macular degeneration (AMD).

Methods

All experiments complied with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Female C57BL/6J mice were subjected to laser-induced CNV, and intravitreally injected with either 1 µg ±MFAP4, 5 µg ±MFAP4, 1 µg mouse IgG or 1 µg ±VEGF-A on day 0 and day 7. Fluorescein angiography (FA) was undertaken at day 7 and day 14, and choroids stained for inflammation (CD45) and vasculature (isolectin B4, IB4).

Results

FA showed that injection of αMFAP4 reduced average lesion size and density on day 7 compared to IgG ($p < 0.01$) and αVEGF-A positive controls ($p < 0.05$) and both αMFAP4 and αVEGF-A reduced average lesion size and density by day 14 compared to IgG ($p < 0.001$ and $p < 0.05$ respectively). IB4 staining indicated that both αMFAP4 and αVEGF-A reduced lesion fluorescence intensity ($p < 0.05$). Both αMFAP4 and αVEGF-A treatments also reduced infiltration of macrophages into the lesion site ($p < 0.01$ and $p < 0.05$).

Conclusions

These results show that inhibition of MFAP4 results in a significant decrease in neovascular lesions in an animal model of AMD. The reduction in macrophage infiltration suggests a potential mechanism of action for anti-MFAP4 treatment. Together, this suggests that inhibition of MFAP4 could be a potential novel AMD therapeutic.

Poster Session

Poster P1

PROTOCOL FOR THE CYTONOX STUDY

C. Gade[1], G. Mikus[3], H.R. Christensen[1], K.P. Dalhoff[1], J.C. Holm[2], H. Holst[1]
[1]Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, Denmark. [2]Children´s Obesity Clinic, Department of Paediatrics, Holbæk Hospital, Denmark. [3]Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Germany

In Denmark, 3-5% of the children are considered obese. Obesity is associated with pathophysiological alterations, which may lead to alterations in the pharmacokinetics of drugs. In adults, obesity is found to influence important drug metabolizing enzyme pathways. The impact of obesity related alterations on drug metabolism, and its consequences for drug dosing remains largely unknown in children and adults. An altered drug metabolism may contribute significantly to therapeutic failure or toxicity. The aim of this trial is to investigate the in vivo clearance of CYP3A4, CYP2E1 and CYP1A2 substrates in obese vs. non-obese children.

The CYTONOX study is an open label explorative pharmacokinetic trial. We intend to include 50 obese and 50 non-obese children. The primary endpoints: in vivo clearance of CYP3A4, CYP2E1 and CYP1A2 substrates, will be defined by using well-tested probes; midazolam, chlorzoxazone and caffeine. Each of the probes will be administered as single doses. Subsequently, blood- and urine samples will be collected at pre-specified times.

The aim of the CYTONOX trial is to investigate the in vivo clearance of CYP3A4, CYP2E1 and CYP1A2 in obese versus non-obese children. The results are expected to be used as basis for drug dosing recommendations of obese children in the future.

Poster P2

HYDROGEN SULFIDE RELAXATION INVOLVES MITOCHONDRIAL COMPLEX I AND III IN RAT SMALL ARTERIES

E.R. Hedegaard, A. Gouliaev, A.K. Winther, D.D.R. Arcanjo, M. Aalling, N.S. Renaltan, M.E. Wood, M. Whiteman, N. Skovgaard, U. Simonsen
Department of Biomedicine, Pulmonary and Cardiovascular Pharmacology, Aarhus University, Aarhus C, Denmark and University of Exeter Medical School, United Kingdom.

Endogenous hydrogen sulfide (H2S) is involved in the regulation of vascular tone. We hypothesized that lowering of calcium and opening of K channels as well as calcium-independent mechanisms are involved in H2S-induced relaxation in rat mesenteric small arteries.

Amperometric recordings revealed that free [H2S] after addition to closed tubes of NaHS, Na2S, and GYY4137 were, respectively, 14%, 17%, and 1% of added amount. Simultaneous measurements of [H2S] and tension showed that 15 µM of free H2S caused 61% relaxation in superior mesenteric arteries. Simultaneous measurements of smooth muscle calcium and tension revealed that NaHS lowered calcium and caused relaxation of norepinephrine-contracted arteries, while high extracellular potassium reduced NaHS relaxation without corresponding calcium changes. In norepinephrine-contracted arteries, NaHS (1 mM) lowered phosphorylation of myosin light chain, while phosphorylation of myosin phosphatase target subunit 1 (MYPT-1) remained unchanged. Blockers of voltage-gated KV7 channels inhibited NaHS relaxation, and blockers of mitochondrial complex I and III abolished NaHS relaxation.

Conclusion: the present findings suggest that low micromolar concentrations of free H2S by a dual mechanism opens K channels followed by lowering of smooth muscle calcium and by a mechanism involving mitochondrial complex I and III leads to uncoupling of force, and hence vasodilation.

Poster P3

GENERIC SWITCHING AND NON-PERSISTENCE AMONG MEDICINE USERS: A COMBINED POPULATION-BASED QUESTIONNAIRE AND REGISTER STUDY

J. Rathe, M. Andersen, D.E. Jarbøl, R. dePont Christensen, J. Hallas, J. Søndergaard.
Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense, Denmark

Generic substitution means that one medicinal product is replaced by another containing the same active substance. It is strictly regulated with respect to its bioequivalence. Although generic substitution is widely implemented, it still remains to be answered how generic switch influences persistence to long-term treatment, and if it is modified by patients' concerns about medicine and views on generic medicine. This study focuses on users of antidepressants and antiepileptics, and their experience of generic switching.

The study was an observational cohort study. By use of a prescription database, we identified patients who had redeemed prescriptions on generically substitutable drugs, and a questionnaire was mailed to them. We analyzed predictors of discontinuation in relation to generic switch and patients' attitudes towards generic medicines and concerns about their medicine.

Patients who experienced their first-time switch of a specific drug were at higher risk of non-persistence, Hazard Ratio 2.98, 95% CI (1.81;4.89) versus those who had never switched, and 35.7% became non-persistent during the first year of follow-up. Generic switching did not influence persistence considerably in those having previous experience with generic switching of the specific drug. Stratified analyses on users of antidepressants and antiepileptics underpin the results, showing higher risk of non-persistence for first-time switchers for both drug categories.

In conclusion, patients who were first-time switchers of a specific drug were at higher risk of non-persistence compared to never switchers and those having experienced previous generic switching.

Poster P4

ALTERED STIFFNESS IN CORONARY ARTERIES AND EFFECT OF PIRFENIDONE ON ENDOTHELIUM-DEPENDENT VASO-DILATATION IN TYPE 2 DIABETIC (DB/DB) MICE

L. Beck, R. Carlsson, R. Hernanz, M. Sheykhzade, and U. Simonsen
Aarhus University, Department of Biomedicine, and University of Copenhagen

Background: For improving the diagnosis and treatment of cardiovascular disease, there is a need for a better understanding of cellular mechanisms of heart disease. Both endothelial cell dysfunction and vessel stiffness is associated with worsening of the prognosis in patients with cardiovascular diseases. This project investigated the relationship between development of dysfunction in endothelial cell layer and the development of vessel stiffness and the vascular effects of an antifibrotic drug, pirfenidone. **Methods:** We investigated the structural and mechanical changes in the left anterior descending coronary artery (LAD) arteries and aorta from type 2 diabetic db/db mice and normoglycaemic (db+/db) mice. Results: The mechanical parameters indicated an increased vascular elasticity in the arteries from the 15-week old male db/db mice and the structural parameters suggest that the arteries undergo compensated hypotrophy. The structural and mechanical parameters of the arteries from 13-week old, female mice show quite an opposite tendency. In the LAD, we found that pirfenidone induced endothelium-dependent nitric oxide mediated relaxations which involved also K channel activation. In aorta acetylcholine relaxation was impaired in segments from male db/db mice and restored in the presence of pirfenidone. **Conclusion:** The present findings suggest that there is not a general relation of the presence of endothelial dysfunction to altered stiffness in diabetic mice, although further testing is required to address whether there is a local relation. The antifibrotic drug pirfenidone restored endothelium-dependent vasodilatation probably by a mechanism lowering smooth muscle membrane potential in aorta from diabetic animals.

Poster P5

CARDIOVASCULAR DRUGS AND ERECTILE DYSFUNCTION – A SYMMETRY ANALYSIS

L. Rasmussen, J. Hallas, K.G. Madsen, A. Pottegård.
Clinical Pharmacology, Department of Public Health, University of Southern Denmark, DK-5000 Odense C, Denmark

Erectile dysfunction is a common problem among patients with cardiovascular diseases and the influence of cardiovascular drugs is much debated. The aim of this study was to evaluate the short-term potential for different cardiovascular drugs to affect the risk of being prescribed a drug against erectile dysfunction.

We employed a symmetry analysis design and included all Danish male subjects born before 1950 who redeemed their first ever prescription for a cardiovascular drug and a 5-phospodiesterase inhibitor within a six month interval during 2002-2012. If the cardiovascular drug induces erectile dysfunction, this would manifest as a non-symmetrical distribution of subjects being prescribed the cardiovascular drug first vs persons following the opposite pattern. Furthermore, we calculated the number of patients needed to treat for one additional patient to be treated for erectile dysfunction (NNTH).

We identified 27,551 male subjects who initiated a cardiovascular drug and a 5-phosphodiesterase inhibitor within a six-month interval. Sequence ratios showed minor asymmetry in prescription orders after adjustment for trends in prescribing. This asymmetry was most profound for thiazides (1.28; 95% CI 1.20-1.38), calcium channel blockers (1.29; 1.21-1.38) and ACE inhibitors (1.29; 95% CI 1.21-1.37), suggesting a small liability of these drugs to provoke erectile dysfunction. NNTH values were generally large, corresponding to a generally small absolute effect.

Our study does not suggest that cardiovascular drugs strongly affect the risk of being prescribed a drug against erectile dysfunction on a short-term basis.

Poster P6

RNA OXIDATION IN TYPE 2 DIABETES: A NOVEL MECHANISM AND BIOMARKER?

Laura K. Kjaer[1], Vanja Cejvanovic[1], Trine Henriksen[1], Cramer Christensen[2], Ivan Brandslund[2], Henrik E. Poulsen[1]
[1]Q7642, Laboratory of Clinical Pharmacology, Bispebjerg Hospital; [2]Dept. of Clinical Biochemistry, Vejle County Hospital

Objective: In type 2 diabetes we have suggested that high urinary excretion of 8-oxo-2´-guanosine (8-oxoGuo), as a measure of global RNA oxidation, is associated with poor survival independent of classical risk factors (Diabetes Care 2011;34:2594). As a proof-of-concept we investigated 8-oxoGuo in a new larger cohort of type 2 diabetes patients.

Research design and methods: We obtained a urine sample from a cohort of 2778 type 2 diabetics and followed them for a median of 6.3 years and the association with long-term mortality was assessed by Cox proportional hazards regression.

Results: Cox regression survival analysis showed a 2.95 significant hazard ratio for death in respect of 8-oxoGuo excretion after multivariate adjustment. Like our previous finding, DNA oxidation urinary marker 8-oxodG did not show any prognostic value.

Conclusions: We conclude that it is now established that RNA oxidation marker 8-oxoGuo is an independent risk factor for death in type 2 diabetes.

Perspectives: RNA oxidation represents oxidative stress intracellularly, hypothesized to result from mitochondrial dysfunction with increased production of hydrogen peroxide in diabetes due to the diabetic state. We suggest that the intracellular RNA oxidation is compartmentalized from

the traditional biomarkers from the extracellular compartment, and therefore provides independent prognostic value. RNA modification can result in formation of truncated and/or modified proteins, thus RNA oxidation could be a novel disease mechanism.

Poster P7

GLUCAGON-LIKE PEPTIDE-1 IMPROVES ENDOTHELIUM-DEPENDENT VASODILATATION IN SMALL ARTERIES EXPOSED TO HIGH GLUCOSE

Maj Bangshaab, Michael Gejl Jensen, Ulf Simonsen
Department of Biomedicine, University of Aarhus, Wilhelm Meyers Alle 4, 8000 Aarhus C, Denmark

Glucagon-like peptide-1 (GLP-1) is an incretin hormone. The major known physiological function of GLP-1 is that it regulates glucose-dependent insulin biosynthesis and hence is involved in glycemic control. Moreover, GLP-1 has been suggested to have a cardioprotective effect.

The aim of the present study is to examine whether there is a possible vasorelaxant effects of GLP-1, and the mechanisms underlying such effect in small rat mesenteric arteries and human subcutaneous arteries.

Arterial segments (internal diameter ≈ 200-300 µm) were mounted in microvascular myographs for isometric tension recordings.

In rat mesenteric arteries and human subcutaneous small arteries contracted with phenylephrine, GLP-1 failed to cause relaxation. However, GLP-1 (1 nM, 10 nM) improved acetylcholine induced relaxation in rat mesenteric arteries after incubating the vessels with a high glucose concentration for 2 hours (40 mM). Acetylcholine relaxation obtained at a low glucose concentration (5 mM), was unchanged in the absence versus the presence of GLP-1.

Our findings suggest that at physiological concentrations of GLP-1, the peptide has no direct vasodilating effects, but an indirect effect by improving endothelium-dependent relaxation in the presence of high glucose. This may contribute to the blood pressure lowering effect of GLP-1 analogue treatment found in type 2 diabetic patients. Other possible indirect effects of GLP-1 need to be examined further.

Poster P8

THE IMPACT OF OPIOID TREATMENT ON REGIONAL GASTROINTESTINAL TRANSIT

J.L. Poulsen[1], D. Jørgensen[1], A.E.Olesen[1,2], C. Brock[1,2], T.H. Sandberg[1], K. Krogh[3], & A.M. Drewes[1,4]
[1]Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark: [2]Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark; [3]Neurogastroenterology Unit, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [4]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Aims: To employ an experimental model of opioid-induced bowel dysfunction (OIBD) in healthy human volunteers, and evaluate the impact of opioid treatment compared to placebo on gastrointestinal (GI) symptoms and motility, assessed by questionnaires and regional GI transit times using the 3D-Transit system.

Methods: Twenty-five healthy males were randomly assigned to oxycodone or placebo for five days in a double blind, cross-over design. Adverse GI effects were measured with the bowel function index, gastrointestinal symptom rating scale, patient assessment of constipation symptom questionnaire, and bristol stool form scale. Regional GI transit times were determined

using the 3D-Transit system and segmental transit times in the colon were determined using a custom Matlab® graphical user interface.
Results: GI symptom scores increased significantly across all applied GI questionnaires during opioid treatment. Oxycodone increased median total GI transit time from 22.2 to 43.9 hours (P=0.0003), segmental transit times in the cecum and ascending colon from 5.7 to 9.9 hours (P=0.01), rectosigmoid colon transit from 2.7 to 9.0 hours (P=0.04), and colorectal transit time from 18.6 to 38.6 hours (P=0.001). No association between questionnaire scores and segmental transit times were detected.
Conclusions: Self-assessed GI adverse effects and increased GI transit times in different segments were induced during oxycodone treatment. This detailed information about segmental changes in motility has great potential for future interventional head-to-head trials of different laxative regimes for prevention and treatment of constipation.

Poster P9

CALCIUM CHANNEL BLOCKER POISONINGS IN DENMARK

S. Al-Gibouri, J.T. Andersen, E. Jimenez-Solem, K.M, T.S Petersen, S. Bøgevig, K.P. Dalhoff, M.B Christensen
Department of Clinical Pharmacology, Bispebjerg and Frederiksberg, Copenhagen, Denmark

Objective: Poisoning with a calcium channel blocker (CCB) is a potentially fatal event that often requires treatment in a hospital. The objective of this study was to describe the CCBs poisoned population in Denmark during the past 5 years.
Methods: All enquiries concerning CCBs reported to the Danish Poison Information Center (DPIC) from 2009 to 2015 were paired with outcome data from the Danish National Patient Register and analysed.
Results: Of 126,987 enquiries to the DPIC, 350 (0.3%) concerned CCBs. Age distribution was bimodal peaking at 0-5 years and 40-50 years, and children (0-16 years) accounted for 24% of all poisonings. Amlodipine was involved in 58% of all cases. Enquiries were more frequent concerning females (56%) ($p<0.02$), with no gender differences in the proportion of accidental/unintended poisonings (43% of cases). Most patients required hospitalisation (79%) including all children. Unintentional poisonings were often mono-exposures (78%), whereas intentional poisonings often were caused multiple drugs exposures (84%). In total, 7 patients (2% of the exposures) died, all from intentional poisoning. All but one of the fatal poisonings died within the first two days of hospital admission. The CCBs involved in multidrug fatal poisoning were amlodipine (n=3), verapamil (n=1), and felodipine (n=1). Verapamil was the only cause of fatal CCB mono poisonings (n=2).
Conclusion: From 2009 to 2015, enquiries to the DPIC concerning CCBs were infrequent, but one fourth concerned children and most cases resulted in hospitalisation. Mortality occurred only in adults with intentional exposures, and only verapamil led to death in mono poisoning.

Poster P10

POPULATION MODELLING OF THE SYNERGISTIC EFFECTS OF MORPHINE AND GABAPENTIN IN THE RAT: A RESPONSE SURFACE APPROACH

T Papathanasiou, RV Juul, C Gabel-Jensen, AM Heegaard, M Kreilgaard and TM Lund
Dep of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen (trine.lund@sund.ku.dk)

Combination of morphine and gabapentin has shown to be promising for managing postoperative pain. Finding the right combination however has proven to be a challenge. PKPD modelling can be used to identify the optimal concentration effect relationship of combinations.

In a blinded, randomized, 16 arms study, the pharmacokinetic (PK) and pharmacodynamic (PD) interactions of morphine and gabapentin were evaluated. In the plantar incision model in the rat, a series of blood samples and hindpaw withdrawal thresholds, after subcutaneous administration of morphine (1, 3 and 7 mg/kg), gabapentin (10, 30 and 100 mg/kg) or their combination (9 combinations of the above doses) were obtained. Population PKPD modelling was performed in NONMEM 7.3

Morphine and gabapentin distribution were best described with a three- and a one-compartment model respectively. No significant PK interactions were identified. Synergistic effects in the PD level were characterized using a response surface approach. Up to 21.9% less morphine concentration was needed to return to pre-surgery withdrawal threshold in presence of gabapentin in concentrations up to ~40 ug/ml.

The synergistic effects of morphine and gabapentin were well described using a response surface approach. This study highlights the importance of finding the right combination in multimodal analgesia and the developed model might help in guiding clinical studies for the selection of appropriate doses.

Poster P11

PROPERTIES OF NAPI-IIB AND ITS INFLUENCE ON DEVELOPING HEART VALVE DISEASE

T.V. Luong, Å.L. Jönsson, V.G. Rasmussen, J.H. Christensen, H.H. Kimose, E.R. Hedegaard, S. Mogensen, C. Wagner, U. Simonsen.
Department of Biomedicine, Aarhus University, Bartholins Allé 6, 8000 Aarhus C, Denmark.

Calcific aortic valve disease (CAVD) is characterized by thickening and calcification of the aortic valve leaflets, leading to insufficient function of the heart valves. CAVD is associated with a high mortality and the only effective treatment is surgical valve substitution. CAVD is mainly seen in the elderly and the cause is often unknown. Pulmonary alveolar microlithiasis (PAM) is a rare lung disorder, which is characterized by accumulation of calcium phosphate concretions in the lungs. PAM is associated with mutations in the SLC34A2 gene, which encodes NaPi-IIb. The transporter is expressed in several tissues and we have earlier identified SLC34A2 mRNA in human aortic valve. The aim of the present study is to investigate the expression and the localization of the sodium-phosphate co-transporter NaPi-IIb in human calcified aortic valves. Furthermore, to characterize a newly developed antibody with affinity for NaPi-IIb in cells that highly express NaPi-IIb.

Molecular characterization of NaPi-IIb will be conducted by determining the levels of mRNA and protein with RT-PCR, and Western Blot, respectively. The localization of the transporter within the cell will be investigated with immunostaining and confocal laser scanning microscopy. Characterization of the antibody will be performed with Western Blot.

Perspectives: This project will contribute with new knowledge about the possible role of NaPi-IIb in the development of CAVD. An improved knowledge about the mechanisms will hopefully lead to better treatment possibilities.

Poster P12

NUCLEIC ACID OXIDATION RELATION TO IRON STATUS IN A GENERAL POPULATION

Vanja Cejvanovic[1], Christina Ellervik[2], Laura K Kjaer[1], Allan Weimann[1], Henrik E. Poulsen[1]
[1]Q7642, Department of Clinical Pharmacology, Bispebjerg Hospital: [2]Department of Laboratory Medicine, Boston Children's Hospital

Oxidation of nucleic acids has been linked to development of major human diseases. DNA oxidation can be measured as urinary excretion of 8-oxo-2´-deoxyGuanosine (8oxodG) and RNA oxidation as 8-oxo-2´-guanosine (8oxoGuo). In epidemiological studies high excretion of 8oxodG is linked to development of lung and breast cancer, and high urinary excretion of 8oxoGuo is linked to poor survival in type 2 diabetes patients. It has been shown that 8-oxoGuo is increased in patients with the iron accumulating disease hereditary hemochromatosis, and that individuals in general populations with iron overload have increased risk of mortality. Iron is a metal with redox properties and can via the Fenton reaction produce reactive oxygen species (ROS). ROS can via secondary reactions cause oxidative damage to cellular macromolecules such as DNA and/or RNA.

We investigated a mixed suburban cohort population sample of 3567 individuals (males=1456) for urinary excretion of 8oxodG and 8oxoGuo. We found a significant increased urinary excretion of 8oxodG and 8oxoGuo with increased levels of se-ferritin.

To investigate the role of mitochondrial H2O2 production in formation of 8-oxoGuo, we incubated mouse muscle biopsies in a high-resolution respirometer. Addition of iron salt did not change the mitochondrial respiration or H2O2 production, but nearly doubled the levels of 8-oxoGuo.

We conclude that body iron stores, as indicated by se-ferritin, is a determinant of oxidation of nucleic acids, by a mechanism where nucleic acids is oxidized by a Fenton reaction.

Session 5.
Hot topics in Danish Pharmacology – based on suggestions from the 5 member societies

ABSTRACT

MULTIFACETED INTERVENTION TO IMPROVE MEDICATION ADHERENCE IN PATIENTS WITH HYPERTENSION: A RANDOMISED, CONTROLLED TRIAL

Ulla Hedegaard[1], Lene Juel Kjeldsen[3], Anton Pottegård[1]; Jan Erik Henriksen [4], Jess Lambrectsen[5], Jørgen Hangaard[5]; Jesper Hallas [1].
[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark. [3]The Danish Research Unit for Hospital Pharmacy, Amgros I/S, Copenhagen. [4]Department of Endocrinology, Odense University Hospital, Denmark. [5]Department of Internal Medicine, Odense University Hospital - Svendborg, Denmark.

Introduction
In patients with hypertension, medication adherence is often suboptimal, thereby increasing the risk of ischemic heart disease and stroke. In a randomized trial, we investigated the effectiveness of a multifaceted pharmacist intervention in a hospital setting to improve medication adherence in hypertensive patients.
Methods
Patients (N=532) were recruited from 3 hospital outpatient clinics and randomized to usual care or a 6-month pharmacist intervention comprising collaborative care, medication review, tailored adherence counselling including motivational interviewing and telephone follow-ups.
The primary outcome was composite medication possession ratio (MPR) to antihypertensive and lipid-lowering agents, at one-year follow-up, assessed by analyzing pharmacy records.
Secondary outcomes at 12 months included persistence to medications, blood pressure, hospitals admission and a combined clinical endpoint of cardiovascular death, stroke or acute myocardial infarction.
Results
At 12 months, 20.3% of the patients in the intervention group (N=231) were non-adherent (MPR < 0.80) compared with 30.2% in the control group (N=285) (RD -9.8 (95% CI -17,3;-2.4) and median MPR (IQR) was 0.93 (0.82-0.99) and 0.91 (0.76-0.98), p=0.02. The combined clinical endpoint was reached by 1.3% in the intervention group and 3.1% in the control group (RR 0.41 [95% CI, 0.11-1.50]. No significant differences were found for persistence, blood pressure or hospital admission.
Conclusion
A multifaceted pharmacist intervention in a hospital setting led to a sustained improvement in medication adherence for patients with hypertension. The intervention had no significant impact on blood pressure and secondary clinical outcomes.

Deltagerliste (pr. 17. januar 2016)

Amanda Adler	NICE, United Kingdom
Åsa Lina Alle Madsen	Aarhus Universitetshospital
Charlotte Andersen	Aarhus Universitetshospital
Helle Raun Andersen	University of Southern Denmark
Jon Trærup Andersen	Bispebjerg Hospital
Stig Ejdrup Andersen	Roskilde Sygehus
Helle Riis Angelo	DSK2F
Helle Byg Armandi	Region Hovedstadens Apotek
Karine Audouze	Université Paris Diderot - Sorbonne Paris Cité
Maj Bangshaab	Aarhus University
Lilliana Beck	Aarhus University
Helle Kirstine Mørup Bergholdt	Rigshospitalet
Jan Beyer	University of Southern Denmark
Kaya Bittkau	Aarhus University
Ranja Bjerring	University of Southern Denmark
Ole Bjerrum	University of Copenhagen
Harrie Boonen	University of Copenhagen
Lars Brandt	University of Southern Denmark
Sara Bøgh Breinholt	Bispebjerg Hospital
Julie Broe	Amgen
Kim Brøsen	Syddansk Universitet
Jesper Bælum	University of Southern Denmark
Søren Bøgevig	Bispebjerg Hospital
Karin Cederberg	University of Southern Denmark
Vanja Cejvanovic	Bispebjerg Hospital
Catrine Christensen	Bispebjerg Hospital
Hanne Rolighed Christensen	Bispebjerg Hospital
Mikkel Bring Christensen	Bispebjerg Hospital
Marie Louise Christiansen	Bispebjerg Hospital
Christine Dalgård	University of Southern Denmark
Kim Dalhoff	Bispebjerg Hospital
Per Damkier	University of Southern Denmark
Niels Damsbo	University of Southern Denmark
Jo De Mey	University of Southern Denmark
Dorthe Dideriksen	Odense Universitetshospital
Jindong Ding	University of Southern Denmark
Asbjørn Drewes	Aalborg University Hospital
Tina Hoff Duedahl	Sygehusapoteket Sygehus Lillebælt
Astrid Eliasen	Bispebjerg Hospital
Zandra Ennis	Odense University Hospital
Christina Gade	Bispebjerg Hospital
Dorte Glintborg	Amgros
Ida Hasselbalch Grandjean	University of Southern Denmark

Philippe Grandjean	University of Southern Denmark
Anders Green	University of Copenhagen
Ellen Grodum	Fredericia Sygehus
Anne Karmisholt Grosen	Aarhus Universitetshospital
Jesper Hallas	University of Southern Denmark
Morten Rix Hansen	Odense Universitetshospital
Kirstine Harboe	Lægemiddelstyrelsen
Morten Hedegaard	Novartis Healthcare
Elise Hedegaard	Aarhus University
Louise Størling Hedegaard	Bispebjerg Hospital
Ulla Hedegaard	Odense Universtity Hospital
Jakob Henriksen	Aarhus Universitetshospital
Jo Hermann	University of Southern Denmark
Helle Holst	Bispebjerg Hospital
Henrik Horneberg	University of Southern Denmark
Lene Høimark	Aarhus Universitetshospital
Kurt Højlund	University of Southern Denmark
Maija Haastrup	Aarhus Universitetshospital
Guðný Ingadóttir	Bispebjerg Hospital
Lars Henrik Jensen	Vejle Hospital
Tina Kold Jensen	University of Southern Denmark
Majbritt Jepsen	AstraZeneca
Helle Johannesen	University of Southern Denmark
Gesche Jürgens	Roskilde University Hospital
Debbie Jørgensen	Aalborg University Hospital
Mads Kjolbye	Aarhus University
Laura Kofoed Kjær	Rigshospitalet
Lisbeth E. Knudsen	University of Copenhagen
Katrine Knøsgaard	Københavns Universitet
Merab Kokaia	Lund University, SE
Hans Jørn Kolmos	University of Southern Denmark
Jytte Kragelund	Aarhus University
Emil List Larsen	Rigshospitalet
Marianne Larsen	Roskilde Sygehus
Britt Elmedal Laursen	Aarhus Universitetshospital
Peter Mygind Leth	University of Southern Denmark
Trine Meldgaard Lund	University of Copenhagen
Thien Vinh Luong	Aarhus University
Claus Løland	University of Copenhagen
Terese Matthesen	Bispebjerg Hospital
Camilla Mikkelsen	Region Hovedstadens Apotek
Edon Morina	Rigshospitalet
Flemming Nielsen	University of Southern Denmark

Jesper Bo Nielsen	University of Southern Denmark
Merete Willemoes Nielsen	Telepsykiatrisk Center, Region Syd
Kirsten Nielsen	Region of North Jutland
Anne Estrup Olesen	Aalborg Universitetshospital
Karin Broberg Palmgren	Lund University, SE
Theodoros Papathanasiou	University of Copenhagen
Andreas J. T. Pedersen	Syddansk Universitet
Kjeld Møller Pedersen	University of Southern Denmark
Marta Axelstad Petersen	DTU - Food
Kasper Meidahl Petersen	Bispebjerg Hospital
Tonny Studsgaard Petersen	Bispebjerg Hospital
Henrik Poulsen	Bispebjerg Hospital
Birgitte Klindt Poulsen	Aarhus University Hospital
Lotte Rasmussen	University of Southern Denmark
Jette Østergaard Rathe	Odense Universitetshospital
Mette Mørch Klemmensen Reilev	The Research Unit for General Practice, Odense
Lene Ørskov Reuther	Bispebjerg Hospital
Thue Walter Schwartz	Copenhagen University
Maja Simonsen	Syddansk Universitet
Ulf Simonsen	Aarhus University
Kenneth Skov	Region Sjælland
Espen Jimenez Solem	Bispebjerg Hospital
Tore Bjerregaard Stage	University of Southern Denmark
Ulrike Muscha Steckelings	University of Southern Denmark
Sophie Steculorum	Max Planck Institut for Metabolism Research, DE
Eva Sverrisdottir	University of Copenhagen
Eva Sædder	Aarhus Universitetshospital
Freja Sørup	Klinisk Farmakologisk Enhed, Roskilde
Gerald Thiel	Universität des Saarlandes, DE
Peter Thiis	University of Southern Denmark
Amalie Timmermann	University of Southern Denmark
Charlotte Vermehren	Copenhagen University
Hans Villendrup	Novartis
Siri Vinther	Bispebjerg Hospital
Pál Weihe	Færøernes Sygehusvæsen
Erik Worsøe	Self employed
Annette Zeberg	University of Southern Denmark
Thomas Øhlenschlæger	Odense Universitetshospital
Signe Harring Østoft	Bispebjerg Hospital
Lise Aagaard	University of Southern Denmark

Noter

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