The effect of CYP2C19 polymorphism on the pharmacokinetics and acid-inhibitory effects of oral lansoprazole and omeprazole

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Lansoprazole (LPZ) and omeprazole (OPZ) are metabolized by CYP2C19 and CYP3A4. The major metabolic pathway for OPZ is hydroylation by CYP2C19.

The aim of the study was to compare the effect of CYP2C19 genotype status on pharmacokinetics and acid-inhibitory effects of LPZ with that of OPZ.

A randomized three-way crossover study was performed in 12 H. pylori-negative healthy Caucasian subjects. Subjects received OPZ 10 mg o.d. and LPZ 15 mg o.d. for 7 days with a 2-week washout period. Plasma concentrations of LPZ and OPZ were measured at day 1, and gastric pH was monitored at day 1 and 6 of drug administration. CYP2C19 genotype was determined by a PCR-RFLP method.

CYP2C19 status was determined in 11 subjects; six were homozygous extensive metabolizers (homEMs) and five were heterozygous extensive metabolizers (hetEMs). There were no significant differences between hetEMs and homEMs in median 24 h gastric pH and % of time pH>4 during the baseline period. At day 1 of OPZ administration area under the concentration time curve (AUC) and acid-inhibitory effect (median 24 h pH) were significantly greater in hetEMs than in homEMs (Table 1). At day 1 of LPZ administration AUC and acid-inhibitory effect were not significantly different between hetEMs and homEMs, although there was a trend towards an increased AUC and acid-inhibitory effect in hetEMs. Therefore we compared the acid-inhibitory effect of LPZ and OPZ to baseline.

Compared with baseline median 24 h pH and % of time pH>4 at day 1 were significantly increased in hetEMs, but not in homEMs for both LPZ and OPZ. At day 6 the differences in acid-inhibitory effect between hetEMs and homEMs were not significant.

At day 1 of administration acid inhibitory effect of LPZ 15 mg and OPZ 10 mg is affected by CYP2C19 polymorphism. Compared with baseline, there was at day 1 a significant acid-inhibitory effect in hetEMs, but not in homEMs.

The International Quality of Life Study of patients with angina pectoris on nitrate therapy

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In the Dutch Mononitrate Quality of Life Study Group (DUMQOL) 50 mg once daily isosorbide mononitrate 30% immediate 70% sustained release formulation significantly improved health related quality of life (QOL) indices in a Dutch population of patients with stable angina pectoris [1].

The objective was to study whether the Dutch results can be generalized across nations and populations as well as across times.
An ongoing self-controlled open label study evaluates the effects of 3-month once daily treatment regimen vs 3-month multiple dose immediate release isosorbide mononitrate (10–20 mg three times daily) on self-reported aspects of QOL in patients with stable angina pectoris. The patients are assessed similarly to those in the Dutch Study. Translated versions of the DUMQOL questionnaire are used for assessing QOL. Five aspects of QOL are measured using a self-report questionnaire: functional dependence (eight items), side effects (seven items), anginal pain (five items), psychological distress (four items), and dissatisfaction with current disease status (two items). All items are scored on five-point ordinal scales, and the sum of the item scores is used for further evaluation. Higher scores thus indicate worse QOL.

At present data are available from the Czech Republic (n = 60), Portugal (n = 379), and Germany (n = 606). Of the 1045 patients included, 1010 (97%) completed the study. Intention to treat data are summarized in Table 1.

The results of the current study underscore the beneficial effects as established in the earlier Dutch study. The long term benefit of once daily isosorbide mononitrate is generalizable across nations and time.


### Table 1

<table>
<thead>
<tr>
<th>Multiple dose (i.e. mean)</th>
<th>Once daily (i.e. mean)</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td>Side effects</td>
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<tr>
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<td>4.8 (3.8)</td>
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<tr>
<td>Psychological distress</td>
<td>8.6 (3.7)</td>
<td>6.8 (3.6)</td>
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<td>Dissatisfaction</td>
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<table>
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<tr>
<th>Class I</th>
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<th>Class IV</th>
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<td>Once daily (%)</td>
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</table>

<0.0001

### Randomized phase I and pharmacological study of weekly or 2-weekly gemcitabine and cisplatin in advanced non-small cell lung cancer

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Cisplatin (cis) and gemcitabine (gem) are cytotoxic drugs that have shown synergism in non-small cell lung cancer (NSCLC). The standard schedule doses gem weekly and cis once every 4 weeks. We believe that increasing the dose-intensity of cis could further optimize the efficacy of this combination in NSCLC. Therefore, we are performing a phase I/II trial with weekly or 2-weekly gem+cis to determine a schedule with the highest dose-intensity of both agents with manageable toxicity. A secondary objective is to study the pharmacokinetics of this combination.

Patients with advanced disease are randomized to receive weekly or 2-weekly gem on day 1 plus cis on day 2. In the weekly scheme such a course is given in week 1, 2, 3, 5, 6 and 7, and in the 2-weekly scheme in week 1, 3, 5 and 7. The total dose-intensity of the two schedules is equal, which means that the doses per administration in the 2-weekly scheme are 50% higher than in the weekly scheme. Per cohort of six patients the dose is increased until the maximum-tolerated dose (MTD) is reached. Pharmacokinetics (PK) of gem, its deaminated metabolite dFdU, and its phosphorylated active metabolite dFdCTP are studied during course 1, and cis (total and free) PK in plasma as well as intranuclear Pt-GG and Pt-AG DNA-adducts in WBC are determined in weeks 1 and 3.

As yet, 73 patients have been entered into the study (35/38 M/F; median age 53, range 34–76 years; median PS WHO 1, range 0–2) with stage IIIB (42%) and IV (58%) NSCLC. Doses were increased stepwise from 25 mg m\(^{-2}\) to 60 mg m\(^{-2}\) cis and 600 mg m\(^{-2}\) to 1000 mg m\(^{-2}\) gem in the weekly schedule. Further dose escalation in this scheme was hampered by the occurrence of dose-delays, caused by haematological toxicity (mainly neutropenia). On the 2-weekly schedule the starting...
dose was 37.5 mg m\(^{-2}\) cis and 900 mg m\(^{-2}\) gem and has been increased to 90 mg m\(^{-2}\) cis in combination with 1500 mg m\(^{-2}\) gem, which is most likely the MTD. On this schedule, dose-limiting toxicity consists of nausea, vomiting and ototoxicity. Other commonly observed side-effects are fatigue, constipation and neutropenia. Haematological toxicity has not exceeded CTC grade 3 in any patient. An interim response evaluation demonstrated partial remissions in 31% of patients. However, the response rate is strongly dependent on disease stage and clinical condition at study entry, and difficult to interpret in the mixed patient population in our trial. PK parameters for gem and cis in plasma were not different from literature data. An interaction was found between gem and the platinum-DNA adducts in WBC: when increasing the dose of gem, both types of adducts formed, Pt-GG– and Pt-AG, decreased.

We have demonstrated that chemotherapy with gemcitabine in combination with cisplatin at an almost double dose-intensity than in the standard schedule, is feasible. The PK interaction of this combination is subject of further studies. Furthermore, we have recently continued this clinical trial investigating the reversed administration sequence.

Pharmacokinetics of vancomycin in (pre)term neonates and influence of covariates

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In order to optimize the dosage regimen of vancomycin in neonates, we investigated the population pharmacokinetics and the influence of covariates on the individual pharmacokinetic parameters.

Data from 105 preterm and term neonates were analyzed retrospectively. Their Post Conceptional Age (PCA) ranged from 26.5 to 44.1 weeks. Post Natal Age (PNA) was 13.7 (8.2) (mean (s.d.)), range: 4–54 days. Plasma vancomycin trough and peak concentration pairs were routinely obtained around the second dose and on several days thereafter (mean 5.8 concentrations/infant). Routine gentamicin drug monitoring, immediately preceding the vancomycin course, was available in 65 infants (mean 4 concentrations/infant). Both population and individual pharmacokinetic parameters of vancomycin were calculated according to a one-compartment open model with a non-parametric expectation maximization algorithm (NPЕM2, USCPACK 10.7; University SC, USA). Calculations were also performed with an iterative Bayesian fitting procedure and maximum \(a \ posteriori\) Bayesian fitting (MW\/~PHARM 3.50, Mediware, The Netherlands). The influence of several demographic and clinical covariates was calculated using stepwise multiple regression analysis with SPSS 10.0 software (Chicago, IL, USA). Recent literature indicates that serum creatinine in the first 2 weeks of life does not reflect glomerular filtration rate [1]. Therefore we also calculated the correlation between \(K_d\) gentamicin and \(K_d\) vancomycin.

Three subgroups were defined: \(<30, \geq30\) and \(<37, \geq37\) weeks’ PCA. Their population parameters (median + mean DF50+DF95) are reported in the same order:

\[K_d (h^{-1}) = 0.0889 (0.0229), 0.1090 (0.0249), 0.1634 (0.0458)\] and \(V/W \ (l/kg^{-1}) = 0.5487 (0.1362), 0.4950 (0.1368), 0.4229 (0.0914)\). Results obtained with NPЕM2 and MW\/~PHARM were almost identical. A significant \((P < 0.001)\) correlation was found between \(K_d\) of gentamicin and vancomycin \((r = 0.579)\) and between serum creatinine and \(K_d\) of vancomycin \((r = -0.563)\). Stepwise multiple linear regression analysis yielded the following statistically significant equations:

\[K_d (h^{-1}) = -0.0123 - 0.00042 \text{ serum creatinine} \] (\(\mu\text{mol l}^{-1}\) + 0.00406 PCA + 0.00096 PNA \(r^2 = 0.545; n = 102\))

\[K_d (h^{-1}) = -0.03956 - 0.242000 K_d \text{ gentamicin} (\text{mg l}^{-1}) \] + 0.00337 PCA + 0.00093 PNA \(r^2 = 0.513; n = 65\)

\[V(l) = 0.105 + 0.449 \text{ weight} \ (kg) \] \(r^2 = 0.650; n = 105\)

\[V(l) = -0.209 + 0.475 \text{ weight} \ (kg) + 0.434 (V/W \text{ gentamicin}) \] \(r^2 = 0.700; n = 65\)

A significant correlation was demonstrated between vancomycin elimination rate and serum creatinine concentrations. The correlation with gentamicin kinetics could be used in practice if plasma creatinine concentrations are not available or biased. The predictive value of the observed correlations has to be validated prospectively in clinical practice.

Reference

Biomarkers for the effects of benzodiazepines in healthy volunteers

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Studies of novel drugs in healthy volunteers are traditionally concerned with kinetics and tolerability, but useful information may also be obtained from biomarkers of clinical endpoints. A useful biomarker should meet the following requirements: a consistent response across studies and drugs; a clear response of the biomarker to a therapeutic dose; a dose–response relationship; a plausible relationship between biomarker, pharmacology and pathogenesis. In the current review, all individual tests found in studies of benzodiazepine agonists registered for anxiety in healthy volunteers since 1966 were progressively evaluated for compliance with these requirements. A MedLine search yielded 56 different studies, investigating the effects of 16 different benzodiazepines on 73 different (variants of) neuropsychological tests, which could be clustered into seven neuropsychological domains. Subjective and objective measures of alertness were most sensitive to benzodiazepines. The most consistent effects were observed on saccadic peak velocity (SPV) and visual analogue scores (VAS) of alertness, where 100% and 79% of all studies respectively showed statistically significant effects. A dose–response relationship could be constructed for temazepam and SPV, which was used to determine dose equivalencies for seven different benzodiazepines relative to temazepam. These dose equivalencies correlated with the lowest recommended daily maintenance dose ($r^2 = 0.737$, $P < 0.05$, Figure 1).

The relationship between SPV-reduction and clinical efficacy could reflect the aiming for maximum tolerated concentrations in drug development, or it could represent a common basis behind SPV reduction and anxiolytic activity for benzodiazepines (probably sedation). Similar to previous findings, the number of tests used in human psychopharmacology appears to be excessive and their sensitivity and reproducibility low.

Reference

Interventions to obtain an early switch from intravenous to oral antibiotic therapy in a Dutch teaching hospital: translating studies into clinical practice

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Several studies [1, 2] have shown that a similar therapeutic outcome is obtained in patients who made an early switch from intravenous (i.v.) to oral antibiotic therapy, and those who did not make this switch. Benefits of an early switch are patient comfort and mobility, reduced length of hospital stay and cost savings. The purpose of this study is to reduce the number of days with unnecessary intravenous antibiotic therapy in hospitalized patients. We defined intravenous to oral switch criteria based upon a publication of Sevinc et al. [3]. We also set up a multidisciplinary team (medical microbiologist, hospital pharmacists, physicians, nurses and quality assurance manager) that guided interventions. Adherence to these criteria was measured on internal medicine wards before (‘control’ group) and after interventions (‘intervention’ group). The primary parameter was the number of days with unnecessary intravenous antibiotic therapy. Interventions consisted of: 1) Oral presentations of switch criteria guidelines to physicians and nurses, 2) handing out pocket size switch guideline cards to prescribing physicians and 3) actively suggesting switch therapy to physicians on a daily basis when patients were identified who fulfilled switch criteria, yet were not switched. In the
control group, only 26% (9/35) of patients eligible to be switched were actually switched within the predefined timeframe, resulting for the whole group to a total amount of 96 unnecessary i.v. days (median 2). In the intervention group 84% (37/44) of patients switched within time, leading to a total number of only 9 unnecessary i.v. days (median 0) (Figure 1). Material cost savings (antibiotics and medical supplies) obtained in the intervention group were €3250 in 2 months. The study is now being extended to surgical wards. Preliminary results on these wards are similar to those obtained on the internal medicine wards. After successful implementation is reached on all wards, an annual cost reduction for the hospital (777 beds) of €87,000 is expected. In conclusion, simple interventions can lead to a significant reduction of unnecessary intravenous antibiotic therapy and substantial cost savings.

References

Motilin kinetics and effects on proximal stomach in patients with functional dyspepsia (FD) and healthy volunteers

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Motilin is involved in the regulation of upper gastrointestinal (GI) motility and it has been suggested that motilin may play a role in the pathogenesis of poorly understood clinical entities such as FD. The present study was performed in order to further investigate the effects of exogenous motilin on the proximal stomach of healthy volunteers and patients with FD.

Eight healthy volunteers and 12 FD patients (Rome II, early satiety) were infused with synthetic motilin (4 pmol kg\(^{-1}\) min\(^{-1}\)) or placebo over 90 min in a double-blind, randomized, cross-over study. Proximal gastric volume was measured with a barostat device at a predefined pressure and during isobaric distensions. Abdominal symptoms such as fullness, nausea and abdominal pain were scored by Visual Analogue Scales (VAS). Gallbladder volume was measured by ultrasonography and plasma motilin concentrations were measured with a radioimmuno-assay.

Treatment effect within a patient group was estimated with paired Student’s t-test, and differences between the two groups were investigated using unpaired Student’s t-test. Data are given as mean (± s.d.) and differences are expressed with the corresponding 95% confidence intervals (95% CI).

The plasma concentration–time curves for motilin were similar between healthy volunteers and patients.
Baseline gastric volumes were similar for both groups; 269 ± 147 ml (healthy volunteers) and 265 ± 98 ml (FD patients).

Compared with placebo, motilin reduced proximal gastric volume by 112 ml (95% CI: 29, 195 ml) in FD patients and by 96 ml (95% CI: −7.3, 200) in healthy volunteers (Figure 1).

In the FD-patients, motilin decreased maximal compliance by 76.1 ml mm Hg⁻¹ (95% CI: 8.8, 143.4) compared with placebo, and was similar to that observed in healthy volunteers. Patients were significantly more nauseous (p=0.04) during motilin compared with placebo, whereas healthy volunteers did not experience nausea. Motilin reduced gall bladder volume by 33% (95% CI: 20, 45) in the FD patients and by 6% (95% CI: −13, 25) in the healthy volunteers. The difference in gall bladder volume was significant between the groups.

Motilin significantly reduced proximal gastric volume and compliance in dyspeptic patients and healthy volunteers by a similar magnitude. In dyspeptic patients, motilin induced nausea, and evoked a greater gall bladder volume reduction.

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**A recirculatory model for tissue plasminogen activator with saturable endothelial binding**

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Tissue plasminogen activator (t-PA) binds to the endothelium *in vitro* [1]. This binding may be crucial in the prevention of thrombus formation. The aim of the present study was to develop a mathematical model to quantify the binding of t-PA to the endothelium *in vivo*.

Nine healthy male volunteers received a continuous low dose infusion with recombinant t-PA (3.75 µg min⁻¹) and, as control, an infusion with indocyanine green (ICG; 0.5 mg min⁻¹), both for 40 min. A circulatory model was developed using non-linear mixed effect modelling.

Delays were observed in the ICG concentration profile that were not captured by a one- or two-compartment model. The ICG concentration profile was best described by a three-compartment recirculatory model with a total distribution volume of 3.0 l (s.e. mean 0.3, inter-individual coefficient of variation (CV) 17%) and plasma flow through the ring of 0.771 min⁻¹ (s.e. mean 0.20, CV 0%; fixed). t-PA antigen, activity and t-PA/PAI-1 complex profile showed a marked delay in increase at the beginning of the infusion, that was not captured by the circulatory model. Incorporating a reversible and concentration-dependent binding component in the model resulted in an accurate description of the t-PA concentration profile. In the resulting model (Figure 1), binding of t-PA was characterized by an affinity constant of 0.29 ml ng⁻¹ (s.e. mean 0.14, CV 114%) and a concentration of binding sites of 99 ng ml⁻¹ (s.e. mean 12, CV 0%).

Clearance was estimated at 0.411 min⁻¹ (s.e. mean 0.02, CV 18%), and endogenous production at 2.06 µg min⁻¹ (s.e. mean 0.07, CV 6%).

The *in vivo* characteristics of the t-PA binding site (Kd ~ 51 pM) correspond with a high affinity t-PA endothelial binding site described *in vitro* (Kd 28 pM). The current model provides a means of quantification of t-PA binding and may provide a tool to study the t-PA binding *in vivo*. Assessing the capacity of the endothelium to bind t-PA and possibly other endogenous substances may serve as a novel tool to assess endothelial function.

**Reference**

Adherence to and dosing of statins differs according to apolipoprotein E-genotypes

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Discontinuation and poor compliance is a major problem in long-term therapy, and in particular with cholesterol lowering drugs.

Several studies have indicated that the cholesterol lowering efficacy of statins differs according to apoE genotypes. In effect LDL-cholesterol lowering capacity appears to be smaller in subjects with the ε4 allele. This reduced response in ε4 carriers may influence dosing regimens and discontinuation in daily practice.

Our objective was to assess whether the use of statins in daily practice differs according to apoE genotypes.

We used data from The Rotterdam Study, a population based prospective cohort study in the Netherlands, which started in 1990 and included 7,983 subjects of 55 years and older. Pharmacy records were available for approximately 99% of the cohort as of January 1, 1991. These records include the name of the drug, day of dispensing, dosage form, number of units dispensed, prescribed daily dose (PDD) and the Anatomical Therapeutic Chemical (ATC) code of the drug. During follow-up (until 31-05-2000) 1037 subjects started to use statins. We excluded 239 subjects because of missing data. We used the PDD to compare dosages of different statins. The PDD was calculated as: daily prescribed dose / standard dosage of the drug when prescribed for the main indication. The first PDD was the dose of the first statin prescription the patient received and the final PDD was the last dose that was prescribed for the patient. We used the Cox proportional hazard model to determine the rate of discontinuation in the first 3 years of statin use. We excluded subjects with the ε2ε2 genotype (n = 4) from this analysis.

Subjects with the ε4ε4 genotype had a relative risk (RR) of 2.28 (95% CI 1.02, 5.12) to discontinue their statin-therapy within 3 years compared with subjects with the ε2ε3 genotype. In women this RR was 1.70 (CI 0.53, 5.42), vs 3.18 (CI 1.01, 10.03) in men. The dosage of the last prescription was significantly higher (P < 0.05) for subjects with ε3ε4 and ε4ε4 (1.16 PDD) compared with subjects with the ε3ε3 genotype (1.03 PDD).

ApoE genotype is a determinant of both dosage regimens and discontinuation of statin therapy. This entails that those subjects who are genetically prone to develop hypercholesterolaemia show the highest risk of discontinuation of treatment precisely for that condition. This warrants further investigation.

Patterns of lipid lowering drug use after the withdrawal of cerivastatin

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In August 2001, the lipid lowering drug cerivastatin was withdrawn from the market after its use was associated with the deaths of 52 patients due to rhabdomyolysis.

Our aim was to assess the patterns of lipid lowering drug use after the withdrawal of cerivastatin.

A total of 36 Dutch community pharmacies were invited to extract medication histories from all patients who were prevalent users of cerivastatin (index group) on August 10, 2001 (index date), and from two age and gender matched controls. The controls had to be a prevalent user of any other statin at the index date. Medication histories were complete for a follow up period of 3.5 months (November 26, 2001: last day of the study). Logistic regression models were used to assess the association between patient and medication characteristics and discontinuation of lipid lowering drug use, defined as no prescription refilled for any lipid lowering drug after the index date and before end of the study.

Of the 36 community pharmacies, 31 participated in the study (response rate 86.1%). Medication histories were available for 234 index patients and 431 matched controls. On the last day of the study, 37 patients in the index group (15.8%) and 41 controls (9.5%) had not refilled a prescription for any lipid lowering drug, and were therefore assumed to have discontinued lipid lowering drug use (OR = 1.8; 95% CI 1.1, 3.0). In men, the risk of discontinuation was similar for both users of cerivastatin and users of any other statin (OR = 0.9; 95% CI 0.5, 1.9), whereas in women the risk of discontinuation was higher for those using cerivastatin (OR = 3.4; 95% CI 1.7, 6.8). Stratification by age showed that dis-
continuation was more pronounced in those younger than 50 years of age (OR = 3.8; 95% CI 0.7, 22.4) than in older age categories (ORs ranging from 1.6 to 1.8, none statistically significant). Stratification by prescribed daily dose at the index date (expressed as defined daily doses (DDD)) showed that discontinuation was also more prevalent in those with the lowest doses of statins, <1.00 DDDs day\(^{-1}\) (OR = 5.5; 95% CI 1.8, 15.6), compared with 1.00–1.99 DDDs day\(^{-1}\) (OR = 1.1; 95% CI 0.5, 2.5) and 2.00 DDDs day\(^{-1}\) (OR = 1.8; 95% CI 0.8, 3.7). In the cerivastatin group, 130 patients (66.0%) filled a new prescription for a lipid lowering drug before the theoretical end date of the prevalent prescription at the index date compared with 139 (35.6%) controls (OR = 3.5; 95% CI 2.5, 5.1).

Most of the patients who were on cerivastatin therapy switched to other lipid lowering drugs before they ran out of tablets. However, discontinuation of lipid lowering drug use was more prevalent in these patients than in users of other statins, especially in women, younger patients and those with low doses of statin therapy.

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Nasal drug delivery to the cerebrospinal fluid: transport of a lipophilic compound

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The aim of this study was to investigate the possibility of direct transport of drugs from the olfactory area to the cerebrospinal fluid (CSF) by intranasal administration (i.n.) of a lipophilic drug in human volunteers. In a large number of animal studies evidence has been found for drug transport via the nose to the brain [1]. Human studies are suggesting such a transport, for instance for i.n. midazolam [2], on pharmacodynamic grounds, but pharmacokinetic evidence is as yet missing.

This study evaluates drug CSF concentrations in patients at the neurosurgery department after i.n. and intravenous (i.v.) administration of melatonin, used in this study as a lipophilic model compound. It has been chosen because it is an endogenous relatively safe compound, for which a very good nasal absorption has been reported [3].

In a pharmacokinetic study, patients at the neurosurgery department with an external cerebrospinal drain were recruited. Three patients were included. Each patient received on one day melatonin i.n. as a dose of 400µg (200µg in each nostril) and on another day 200µg melatonin i.v. Blood samples and CSF samples were collected just before and at 5, 10, 20, 0, 40, 60, 120 and 180 min after drug administration. Melatonin concentrations were measured with h.p.l.c. Concentration–time curves of the plasma and CSF concentrations of melatonin were compared after i.n. and i.v. administration.

The nasal absorption of melatonin in blood is fast and efficient. Peak plasma concentrations after i.n. are reached within 20 min and are comparable with those reached after i.v. administration. The AUC\(_{\text{CSF}}\)/AUC\(_{\text{plasma}}\) after i.n. administration was in all three patients not larger than after i.v. administration. In the three investigated patients the increase in CSF melatonin concentration after i.n. administration appeared to be comparable with that after i.v. administration (Table 1).

The increase of the melatonin concentrations in the CSF does not differ largely in the period 0–180 min, whether the drug is administered i.n. or i.v., indicating that the drug enters the CSF via the systemic circulation and the blood–brain barrier.

It is evident that i.n. administration of a lipophilic compound could be an interesting alternative route of administration, giving high blood and also high CSF concentrations, but the results of this study provide no indication for an additional transport mechanism of the lipophilic compound directly from the nose to the CSF.

Table 1 AUC (0, 180 min) of melatonin in CSF after i.n. and i.v. administration.

<table>
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<th>AUC (CSF) after i.n.</th>
<th>AUC (CSF) after i.v.</th>
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<td>Patient Z</td>
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References

REM sleep reduction as a biomarker for the effects of antidepressants in healthy volunteers

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The potential use of REM sleep as a predictive biomarker for therapeutic effects of antidepressants in healthy volunteers was investigated.

A literature search was performed to select studies investigating the effects of different antidepressants on REM sleep in healthy volunteers after single or multiple dose administration. To assess the specificity of REM sleep as a biomarker for the effects of antidepressants, the effects of other CNS drugs on REM sleep were also investigated.

A significant REM sleep reduction (mean 29.9%) was shown for 16 of the 21 investigated antidepressants after single dose and (mean 28.9%) for 11 of the 13 investigated antidepressants after multiple dose administration. Significant effects were observed at therapeutic doses of various antidepressants and generally increased with rising doses. REM sleep effects for each antidepressant were linearly normalized to therapeutic doses, by dividing the REM-effect by the investigated dose and multiplying by the therapeutic dose. These normalized REM sleep reductions were highly variable and showed no relationship with relevant pharmacological properties of the used drugs. No quantifiable dose–response relationship could be constructed after single dose administration. A dose–response relationship with a REM sleep response after multiple dose administration could not be evaluated without the confounding factor of time. REM sleep reduction was not specific for antidepressants. Benzodiazepines for instance caused a dose normalized REM sleep reduction of 10.4% on average.

The limited value of REM sleep as a biomarker in healthy volunteers could be explained by the different sleep pattern in healthy volunteers compared with depressive patients. It is known that REM sleep duration is induced in depressive patients and that antidepressants mostly reduce these higher REM sleep durations. However, it is still not known if the therapeutic effect of antidepressants is due to these REM sleep reductions. The limited value of REM sleep as a biomarker could also partly be explained by the complex relationship between the pharmacokinetics of the individual drugs and the variable time course of REM-sleep and other sleep stages throughout the night. Models that take these complex relationships into account may provide more comprehensive and quantifiable results, which could allow dose–REM sleep effect relationship and/or correlations with the pharmacology of the antidepressants.

Although REM sleep reduction occurs with most of the antidepressants, it is of limited value as a biomarker for antidepressant action in healthy volunteers. Its specificity for antidepressants is limited, and it does not show a quantitative dose–response relationship to antidepressant agents.

Bosentan, a dual endothelin receptor antagonist, activates the pregnane X nuclear receptor

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Recent clinical studies have shown that bosentan, a dual endothelin receptor antagonist, decreases the exposure to various substrates of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. When bosentan and glibenclamide were given concomitantly to healthy subjects, the plasma concentrations of both compounds decreased suggesting that glibenclamide also has enzyme-inducing properties [1]. The aim of the study was to investigate if bosentan, its metabolites and glibenclamide can activate the pregnane X receptor (PXR), a nuclear receptor that regulates the transcription of CYP3A4 [2].

CV-1 monkey kidney cells were transiently transfected with a luciferase reporter plasmid containing three copies of the ER6 response element (PXRE) of CYP3A4, and an expression plasmid for human PXR (hPXR). The cells were then incubated with the test compounds at varying concentrations and the activity of luciferase determined.

At a concentration of 25 µM, bosentan, Ro 47-8634 and glibenclamide but not the other two metabolites of bosentan, Ro 48-5033 and Ro 64-1056 activated PXR (Figure 1).

An EC50 of 19.9 µM was determined for bosentan whereas rifampicin had an EC50 value of 1.9 µM. Co-incubation of sub-maximal but clinically relevant concentrations of bosentan (1 µM) and glibenclamide (0.5 to 5 µM) resulted in a more pronounced activation of PXR than with each compound alone. The effects of both compounds were additive, however, no synergism was detected.

The findings are consistent with the observation that in man rifampicin is a more potent inducer than bosentan. Furthermore, they provide a molecular mechanism for the interactions observed between bosentan and several drugs.

References

Dipyridamole increases interstitial adenosine during intermittent isometric exercise but does not augment the pressor reflex

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Interstitial adenosine is increased during intermittent isometric exercise (handgrip) and may be an afferent signal for the pressor reflex. The effect of the nucleoside transporter inhibitor dipyridamole on interstitial adenosine concentration has never been studied in humans.

The aim of the study was to determine whether dipyridamole increases interstitial adenosine during handgrip and potentiates the exercise-induced pressor reflex.

In nine healthy volunteers, isometric hand-constrictions (50% of maximal force) were performed with and without dipyridamole (12 mg 100 ml⁻¹ min⁻¹, infused into the brachial artery). Interstitial adenosine was measured in the flexor digitorum superficialis muscle using microdialysis with h.p.l.c. detection. Blood pressure was measured at 2 min intervals (Dinamap). Peroneal nerve muscle sympathetic nerve activity (MSNA) was successfully recorded in four volunteers.

Intermittent handgrip increased dialysate adenosine by 0.3±0.1 and 0.5±0.1 nmol ml⁻¹ in the absence and presence of dipyridamole respectively (mean±s.e. mean; *P*<0.05 for effect of dipyridamole). Dipyridamole did not augment the handgrip-induced rise in MSNA in any of the volunteers. Handgrip increased blood pressure (SBP/DBP) by 9.6±2.4/4.5±2.0 and 10.4±2.2/7.0±1.3 mmHg in the absence and presence of dipyridamole respectively (*P* NS for dipyridamole effect). In none of the volunteers, dipyridamole augmented the exercise-induced rise in MSNA.

Dipyridamole increases interstitial adenosine during handgrip but does not potentiate the pressor reflex. Our data do not support a role for adenosine as a trigger of the exercise-induced pressor reflex in healthy volunteers.

Figure 1 Effect of bosentan, its metabolites and glibenclamide on PXR activity. Data represent mean ± s.d. of 3 experiments.
Desirudin: effect on blood coagulation tests \textit{in vitro} and following a subcutaneous administration in healthy volunteers

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Desirudin (Revasc®), a recombinant hirudin, is a highly specific direct thrombin inhibitor indicated for the prevention and treatment of thromboembolic disorders. To assess the efficacy and predict the haemorrhagic risk of direct thrombin inhibitors, the ecarin clotting time (ECT) has gained attention relative to the more commonly used activated partial thromboplastin time (aPTT).

The objective was to link \textit{ex vivo} and \textit{in vitro} therapeutic plasma concentrations of desirudin to various coagulation tests, in particular ECT.

Six healthy subjects were administered a therapeutic dose (15 mg) of desirudin subcutaneously (s.c.). Plasma was collected at specified time points for 24 h to assess the effect of desirudin on aPTT, ECT, thrombin time (TT) and prothrombin time (PT) and to determine its pharmacokinetic profile. For the \textit{in vitro} evaluation, human plasma spiked with concentrations of desirudin up to 725 nM was analysed for the above mentioned coagulation tests.

A mean ($\pm$ s.d.) peak desirudin concentration of $27.1 \pm 5.2$ nM was reached at $2.2 \pm 0.5$ h. Maximum fold increase vs baseline in aPTT and ECT was $1.79 \pm 0.16$ and $1.34 \pm 0.08$ at $2.5 \pm 1.0$ and $1.8 \pm 0.5$ h, respectively. TT was immeasurably prolonged ($>33$ fold increase) up to 8 h post dose, while PT was hardly affected ($1.05 \pm 0.01$). Based on the \textit{ex vivo} data (Figure 1a), aPTT was more responsive than ECT and both parameters displayed a linear correlation with desirudin within the observed concentration range. \textit{In vitro} data (Figure 1b) confirm the \textit{ex vivo} results over the clinical concentration range, but show that for ECT, linearity extends up to much higher concentrations, while for aPTT the curve is markedly less than linear, starting at concentrations only slightly higher than those observed in the \textit{ex vivo} study.

Both aPTT and ECT are linearly correlated with desirudin concentrations observed following a 15 mg s.c. dose in healthy volunteers. Although aPTT is more responsive than ECT, \textit{in vitro} data suggest that at higher doses of desirudin, ECT would be a more reliable parameter to monitor desirudin plasma concentrations, as it remains linear over a much wider concentration range compared with aPTT.