

Bewertung relevanter pharmakokinetischer Interaktionen von Antidiabetika

EADV- Symposium

„Arzneimittelinteraktionen im Rahmen der Diabetestherapie“

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Eine pharmakokinetische Interaktion ist umso relevanter,

- ... je größer ihre Auswirkung auf Plasmakonzentration des betroffenen Wirkstoffs ist,
- ... je kleiner das therapeutische Fenster des betroffenen Wirkstoffs ist,
- ... je geringer die Toleranz des/der Patienten/in ist,
- ... je weniger die Interaktion bekannt (und damit antizipierbar) ist.

Metformin

hat einen etablierten prognostischen Nutzen bei Patienten mit DM Typ 2,

hat wenige (umschriebene) gravierende Risiken, Laktatazidose (?),

wird nicht metabolisch eliminiert und ist damit nicht anfällig für metabolische Interaktionen mit anderen Arzneimitteln,

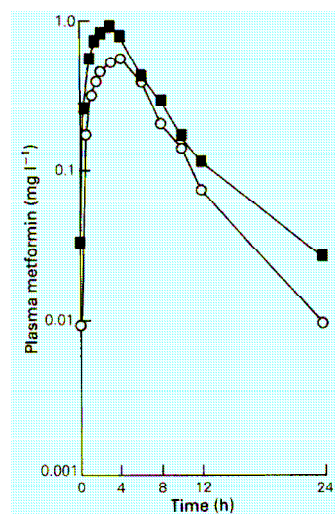
wird renal eliminiert; seine $CL_r \gg GFR$, also tubuläre Sekretion.

Metformin: Interaktion mit Cimetidin

7 gesunde Probanden nahmen
Metformin 250 mg/d (10 Tage)
± Cimetidin 2 x 400 mg/d (Tage 6 – 10)

Metformin-Plasmakonzentrationen

Mean plasma concentration-time profile for metformin when given alone as 0.25 g daily (○) and when co-administered with cimetidine 0.4 g twice daily (■) in seven subjects.



Somogyi A, Stockley C, Keal J, Rolan P, Bochner F: Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; 23: 545-551

Cimetidin reduziert die renale Clearance von Metformin

7 gesunde Probanden nahmen Metformin 250 mg/d (10 Tage) ± Cimetidin 2 x 400 mg/d (Tage 6 – 10)

Table 1 Comparison of pharmacokinetic data for metformin when given alone (250 mg day⁻¹) and when combined with cimetidine in seven subjects

| Parameter | Metformin | Metformin + cimetidine | Significance (P) |
|--|------------------|------------------------|------------------|
| C_{max} (mg l ⁻¹) | 0.59 ± 0.24 | 1.02 ± 0.39 | 0.008 |
| t_{max} (h) | 3.3 ± 0.8 | 2.5 ± 0.6 | 0.078 |
| AUC ₀₋₂₄ (mg l ⁻¹ h) | 4.26 ± 1.64 | 6.23 ± 2.09 | 0.008 |
| fe_0^{24} | 0.50 ± 0.13 | 0.52 ± 0.11 | NS |
| CL_R (0-24) (ml min⁻¹) | 527 ± 165 | 378 ± 122 | 0.008 |

NS— $P > 0.05$.

$$CL_R = \frac{Ae}{AUC}$$

Somogyi A, Stockley C, Keal J, Rolan P, Bochner F: Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; 23: 545-551

Metformin:

Interaktion mit Cimetidin

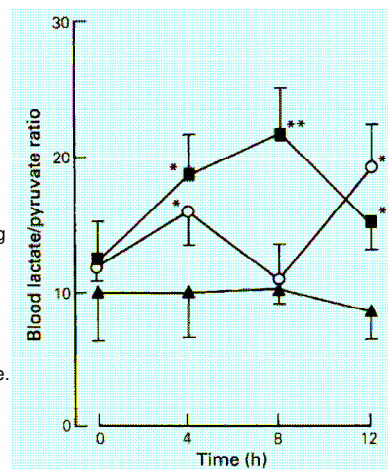
7 gesunde Probanden nahmen Metformin 250 mg/d ± Cimetidin 2 x 400 mg/d

Laktat:Pyruvat-Quotient im Blut

Mean blood lactate to pyruvate ratios in seven subjects following

- cimetidine (▲)
- metformin (○)
- metformin + cimetidine (■)

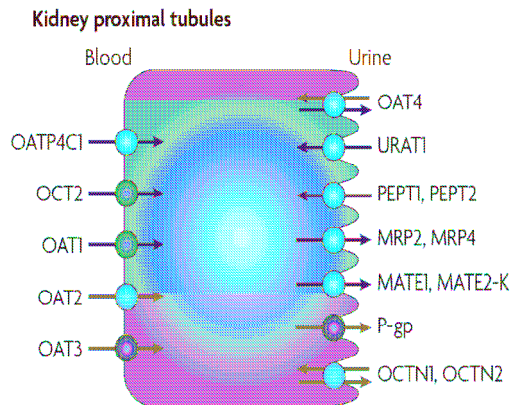
* significantly different ($P < 0.05$) compared with cimetidine,
 ** significantly different ($P < 0.05$) compared with metformin alone.
 The bars indicate 1 s.d.



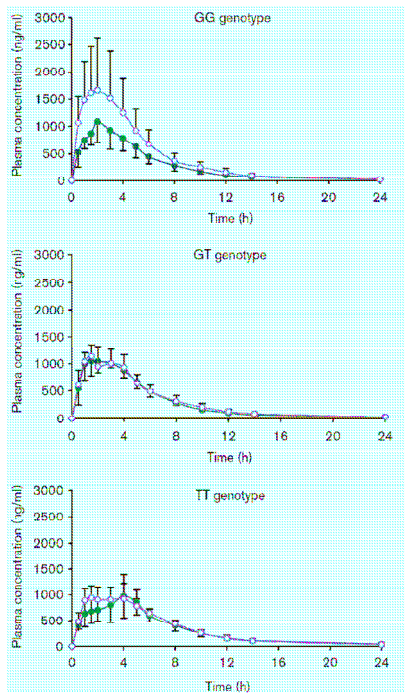
Somogyi A, Stockley C, Keal J, Rolan P, Bochner F: Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 1987; 23: 545-551

Transportproteine an Biomembranen: Metformin ist im proximalen Tubulus ein Substrat von ...

- multidrug and toxin extrusion 1 (MATE1)
- multidrug and toxin extrusion 2-K (MATE2-K)
- organic cation transporter 2 (OCT2)



Giacomini KM et al. for The International Transporter Consortium: Membrane transporters in drug development. *Nat Rev Drug Discov* 2010; 9: 215-236



OCT2 808G>T-Polymorphism und Metformin-Cimetidin-Interaktion

Plasma concentration–time profiles of metformin when given alone (●) or in combination with cimetidine (○) in healthy volunteers with different genotypes.

Metformin was given as a single oral dose of 500 mg on two separate sessions and cimetidine was administered at 400 mg twice daily for 6 days.

Data represent mean+SD.

Wang ZJ, Yin OQP, Tomlinson B, Chow MSS:
OCT2 polymorphisms and in-vivo renal functional consequence:
studies with metformin and cimetidine. *Clin Pharmacol Ther* 2008; 18: 637-645

Metformin und Rifampicin

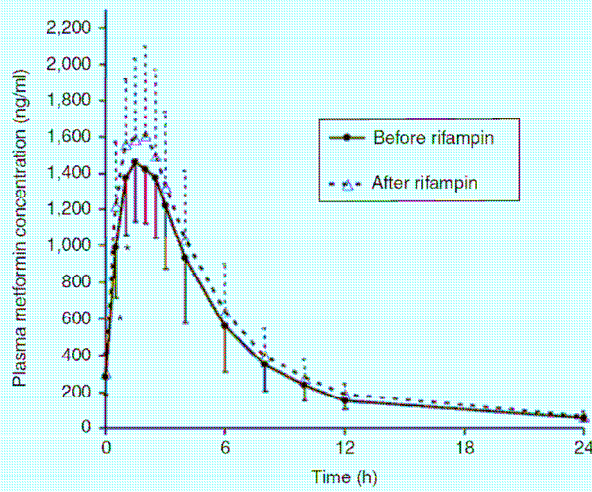


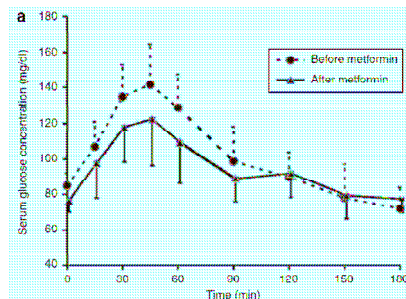
Figure 2 The plasma concentration–time curve of metformin on day 2 (before rifampin treatment) and on day 14 (after rifampin treatment). Metformin concentrations were measured after the second dose of metformin. Data are expressed as mean \pm SD ($n = 16$). * $P < 0.05$ (before rifampin treatment vs. after rifampin treatment).

Cho SK et al.: Rifampin enhances the glucose-lowering effect of metformin and increases OCT1 mRNA levels in healthy participants. *Clin Pharmacol Ther* 2011; 89 (3): 416-421

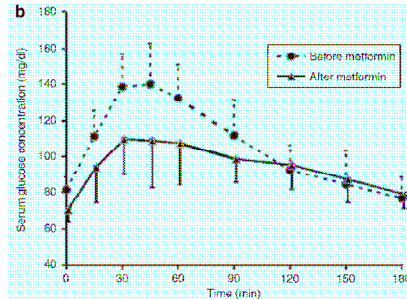
Metformin und Rifampicin

Serum glucose levels were determined by means of oral glucose tolerance tests before and after metformin administration. Data are expressed as mean \pm SD ($n = 16$).

(a) before the 10-day course of rifampin



(b) after the 10-day course of rifampin



Cho SK et al.: Rifampin enhances the glucose-lowering effect of metformin and increases OCT1 mRNA levels in healthy participants. *Clin Pharmacol Ther* 2011; 89 (3): 416-421

Metformin und Rifampicin

Table 1 The glucose-lowering effect parameters of metformin before and after rifampin treatment in healthy participants (n = 16)

| Parameter | Before rifampin | After rifampin | P |
|--|-----------------|----------------|-------|
| ΔG_{\max} (mg/dl) | 31 ± 14 | 44 ± 14 | 0.024 |
| $\Delta AUC_{\text{gluc}60}$ (mg/dl-min) | 914 ± 510 | 1,412 ± 555 | 0.020 |
| ΔAUC_{gluc} (mg/dl-min) | 1,679 ± 1,155 | 2,378 ± 1,316 | 0.121 |

Data were evaluated by Wilcoxon signed-rank test and are expressed as mean ± SD.

ΔAUC_{gluc} , difference in total area under the plasma concentration–time curve for glucose before and after metformin treatment; $\Delta AUC_{\text{gluc}60}$, difference in partial area under the plasma concentration–time curve for glucose (0–60 min after ingestion, during which glucose concentration increases) before and after metformin treatment; ΔG_{\max} , difference in maximum glucose level before and after metformin treatment.

Cho SK et al.: Rifampin enhances the glucose-lowering effect of metformin and increases OCT1 mRNA levels in healthy participants. *Clin Pharmacol Ther* 2011; 89 (3): 416-421

Metformin und Rifampicin

Pharmacokinetic parameters of metformin in healthy participants (n = 16) before and after a 10-day course of rifampin

| | Before rifampin | After rifampin | P |
|------------------------------------|-----------------|----------------|-------|
| $AUC_{\text{met}(0-1)}$ (ng/ml-h) | 909 ± 209 | 1,077 ± 258 | 0.003 |
| $AUC_{\text{met}(0-2)}$ (ng/ml-h) | 2,340 ± 484 | 2,664 ± 634 | 0.015 |
| $AUC_{\text{met}(0-6)}$ (ng/ml-h) | 625 ± 1,531 | 6,997 ± 2,012 | 0.049 |
| $AUC_{\text{met}(6-24)}$ (ng/ml-h) | 3,149 ± 1,048 | 3,675 ± 1,275 | 0.121 |
| $AUC_{\text{met}(0-24)}$ (ng/ml-h) | 9,408 ± 2,410 | 10,672 ± 3,149 | 0.049 |
| $t_{1/2}$ (h) | 7.38 ± 3.09 | 6.81 ± 1.86 | 0.501 |
| C_{\max} (ng/ml) | 1,536 ± 350 | 1,692 ± 114 | 0.070 |
| T_{\max} (h) | 1.63 ± 0.53 | 1.59 ± 0.64 | 0.881 |
| CL_R (ml/min) | 501 ± 97 | 580 ± 101 | 0.008 |
| $SrCL_R$ (ml/min) | 398 ± 92 | 475 ± 98 | 0.005 |
| CL_{Cr} (ml/min) | 109 ± 15 | 105 ± 15 | 0.173 |

Data were evaluated by Wilcoxon signed-rank test and are expressed as mean ± SD.

$AUC_{\text{met}(a-b)}$, area under the plasma concentration–time curve from time point a to time point b; CL_{Cr} , creatinine clearance; CL_R , renal clearance; C_{\max} , maximum plasma concentration; $SrCL_R$, renal clearance by tubular secretion; $t_{1/2}$, elimination half-life; T_{\max} , time of maximum plasma concentration.

Cho SK et al.: Rifampin enhances the glucose-lowering effect of metformin and increases OCT1 mRNA levels in healthy participants. *Clin Pharmacol Ther* 2011; 89 (3): 416-421

Metformin und iodhaltige Kontrastmittel: Risiko für Laktatazidose (LA)?

Nierenfunktionseinschränkung durch KM wird als Verbindungsglied angesehen.

Existierende Leitlinien sind inkonsistent in Bezug auf ihre Empfehlungen

- zur Notwendigkeit, Metformin zu unterbrechen,
- zum Zeitpunkt der Unterbrechung,
- zur Notwendigkeit, die Nierenfunktion vor Metformin-Wiederbeginn zu prüfen.

Es gibt keine Evidenz für die Annahme eines erhöhten LA-Risikos bei Metformin-Patienten mit normaler Nierenfunktion, wenn sie eine übliche Einzeldosis eines KM für ein CT oder eine andere nichtangiografische Untersuchung erhalten.

Goergen SK, Rumbold G, Compton G, Harris C: Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology* 2010; 254 (1): 261-9

Metformin und Kontrastmittel

Table 1 Summary of guideline statements on metformin use in procedures requiring intravenous contrast administration

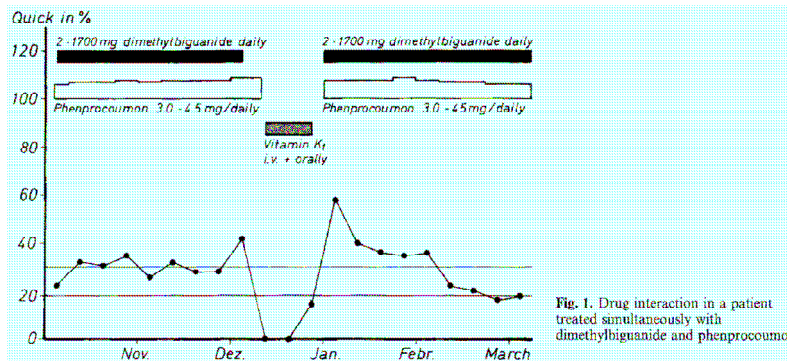
| Professional body | Metformin advice |
|---|---|
| NICE ²⁵ | Should be withdrawn if serum creatinine is $\geq 150 \mu\text{mol/l}$, if the hepatic function is deranged or if any cause of tissue hypoxia is likely |
| ACC/AHA/SCAI ²⁶ | Whenever possible, metformin (especially in those with pre-existing renal dysfunction) should be withheld for 24 h before performing PCI and for 48 h afterwards ²⁶ |
| American Diabetes Association ²⁷ | Discontinue for 48 h after contrast dye procedures. Contraindicated if serum creatinine is $> 1.5 \text{ mg/dl}$ in men or $> 1.4 \text{ mg/dl}$ women |
| Royal College of Radiologists ²⁸ | <ul style="list-style-type: none"> ▶ If serum creatinine is normal, and a low volume of contrast agent ($\leq 100 \text{ ml}$) is to be administered intravenously, no special precaution is required ▶ If serum creatinine is normal, but $\geq 100 \text{ ml}$ of contrast agent or the intra-arterial route is to be used, metformin should be withheld for 48 h after the procedure ▶ If the serum creatinine is raised, the need for the contrast agent should be reassessed. If contrast injection is deemed necessary, metformin should be withheld for 48 h before and 48 h after the contrast is given and the renal function reassessed before restarting the metformin treatment |
| <i>Suggested recommendation</i> | <p><i>For use of Contrast:</i></p> <ul style="list-style-type: none"> ▶ If the serum creatinine is normal, no need to withdraw ▶ If the serum creatinine is raised $> 150 \mu\text{mol/l}$ (or 1.5 mg/dl): <ul style="list-style-type: none"> – Contrast $\leq 100 \text{ ml}$—no need to withdraw – Contrast $> 100 \text{ ml}$—withdraw for 48 h before and 48 h after the contrast is given and reassess the renal function before restarting metformin <p><i>When contrast is not used:</i></p> <ul style="list-style-type: none"> ▶ Withdraw if creatinine $> 150 \mu\text{mol/l}$ (or 1.5 mg/dl) ▶ No need to withdraw in patients with heart failure |

No guideline has been published from the Joint British Societies (JBS) or British Cardiovascular Intervention Society (BCIS) on metformin use in cardiac catheterisation procedures.

²⁸No accompanying level of evidence category.

Khurana R, Malik IS: Metformin: safety in cardiac patients. *Heart* 2010; 96: 99-102

Metformin und Phenprocoumon



Concomitant metformin and phenprocoumon therapy resulted in increased phenprocoumon elimination. Seven diabetic patients who were controlled with daily metformin doses of 1.1 g to 3 g required mean daily doses of 2.57 mg phenprocoumon to maintain adequate anticoagulation. An additional six patients who received 0.4 g to 1 g doses of metformin daily required only 2.27 mg of phenprocoumon. The half-life of phenprocoumon was also decreased approximately 33% (from 123 hours to 85 hours) while taking metformin 1700 mg daily.

An increase in liver blood flow has been observed in dogs secondary to metformin therapy. This may explain, in part, the enhanced elimination of phenprocoumon during combined therapy with these drugs.

Ohnhaus EE, Berger W, Duckert F, Oesch F: The influence of dimethylbiguanide on phenprocoumon elimination and its mode of action. *Klin Wochenschr* 1983; 61: 851-8

Metabolische Interaktionen mit Sulfonylharnstoffen bzw. Repaglinid

Table 4

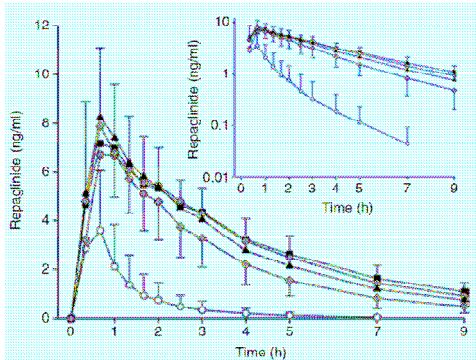
Potential interactions between sulfonylureas or repaglinide and drugs which alter hepatic enzymes

| <i>Inducers of metabolism (reduce concentration of hypoglycaemic drug)</i> | <i>Inhibitors of metabolism (increase concentration of hypoglycaemic drug)</i> |
|--|--|
| Phenytoin | Allopurinol* |
| Phenobarbitone | Chloramphenicol |
| Rifabutin | Cimetidine* |
| Rifampicin | Erythromycin 'Azole' antifungals |

* Repaglinide concentrations not increased

Shenfield GM: Drug interactions with oral hypoglycaemic drugs. *Aust Prescr* 2001; 24: 83-5

Repaglinid-Gemfibrozil-Interaktion



Mean \pm SD plasma concentrations of repaglinid in 10 healthy volunteers after a single oral dose of 0.25 mg repaglinid after pretreatment with 600 mg gemfibrozil twice daily, with varying dose intervals between the last gemfibrozil dose and repaglinid.

open circles, control phase (no pretreatment);
 solid squares, repaglinid simultaneously with gemfibrozil;
 solid circles, repaglinid 3 h after gemfibrozil;
 solid triangles, repaglinid 6 h after gemfibrozil;
 solid diamonds, repaglinid 12 h after gemfibrozil.

In summary, gemfibrozil greatly raises the plasma concentrations and enhances the effects of repaglinid even if repaglinid is administered 12 h after the last gemfibrozil dose.

The findings strongly suggest that this interaction is caused by mechanism-based inhibition of CYP2C8 by gemfibrozil glucuronide.

Tornio A et al.: The effect of gemfibrozil on repaglinid pharmacokinetics persists for at least 12 h after the dose: Evidence for mechanism-based inhibition of CYP2C8 *in vivo*. *Clin Pharmacol Ther* 2008; 84 (3): 403-411

Dipeptidylpeptidase-4-Inhibitoren: Pharmakokinetische Eigenschaften

Table 1. Main pharmacokinetics characteristics of sitagliptin, vildagliptin and saxagliptin

| Parameters | Sitagliptin MK-0431* | Vildagliptin LAF237* | Saxagliptin BMS-477118* |
|-----------------------------------|----------------------|----------------------|-------------------------|
| T_{max} (h) | 1-4 | 1.75 | 2 |
| Volume distribution (L) | 198 | 71 | 151 |
| Terminal $t_{1/2}$ (h) | 12.4 | 2-3 | 2.5 |
| | | | 3.1 (active metabolite) |
| Total plasma clearance (ml/min) | 416 | 683 | NA |
| Renal clearance (ml/min) | 350 | 217 | 230 |
| Renal clearance (%) | 70 | 31 | NA |
| Primary metabolites | 6 (inactive) | LAY 151 (inactive) | BMS-510849 (active) |
| Absolute bioavailability (%) | 87 | 85 | 67 [†] |
| Fraction bound to protein (%) | 38 | 9.3 | Very low |
| Excreted in faeces (%) | 13 | 4.5 | 22 |
| Excreted in urine (%) | 87 | 85 | 75 |
| Proportion excreted unchanged (%) | 79 | 23 | 24 |
| Active tubular secretion | Yes | Yes | Yes |
| Substrate for p-glycoprotein | Yes | Yes | Yes |
| Substrate for CYP3A4 | Low | No | Yes |
| CYP3A5 | No | No | Yes |
| CYP2C8 | Very low | No | No |
| Dose proportionality | Yes | Yes | Yes |
| Effect of food | No | No | No |

Data were obtained in separate studies allowing only indirect comparisons.

NA, information not available.

*Company names given for these compounds when in development.

[†]Predicted instead of measured [57].

Scheen AJ: Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* 2010; 12(8): 648-58

Dipeptidylpeptidase-4-Inhibitoren: Pharmakokinetische Eigenschaften

Table 2. Main clinically relevant pharmacokinetics differences between the five dipeptidylpeptidase-4 inhibitors described in the present paper

| Characteristics | Sitagliptin MK-0431 | Vildagliptin LAF237 | Saxagliptin BMS-477118 | Alogliptin SYR-322 | Linagliptin BI 1356 |
|---------------------------------------|------------------------|------------------------|-------------------------------|-----------------------|------------------------|
| Therapeutic dose (mg/day) | 100 | 2 x 50 | 5 | 12.5–25 | 5 |
| Half-life | Long | Short | Short (but active metabolite) | Long | Very long |
| Administration | Once daily | Twice daily | Once daily | Once daily | Once daily |
| Active metabolite | No | No | Yes (BMS-510849) | No | No |
| Fraction bound to protein (%) | Intermediate | Low | Very low | Rather low | High |
| Renal excretion | Predominant | Intermediate | Predominant | Predominant | Low |
| Dose reduction with renal impairment | Yes (25–50 mg) | No | Yes (2.5 mg) | Probably yes | Probably no |
| Drug–drug interactions | No | No | Yes | No | No |
| Dose reduction with CYP3A4 inhibitors | No | No | Yes (2.5 mg) | No | No |

Scheen AJ: Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* 2010; 12(8): 648-58

Dipeptidylpeptidase-4-Inhibitoren: Interaktionen mit Einfluss durch andere Arzneimittel

Table 1. Effects of pharmacokinetic interactions of other coadministered drugs on the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values of sitagliptin, vildagliptin and saxagliptin (based upon the literature and labelling)^a

| Coadministered drug | Sitagliptin (% change) | | Vildagliptin (% change) | | Saxagliptin (% change) | |
|---|------------------------|-------------------|-------------------------|-----|------------------------|--------------------|
| | C_{max} | AUC | C_{max} | AUC | C_{max} | AUC |
| Metformin | ↔ | ↔ | ↓ 18 | ↔ | ↓ 21 | ↔ |
| Glyburide (glibenclamide) | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Pioglitazone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Simvastatin | ↔ | ↔ | ↔ | ↔ | ↑ 21 | ↑ 12 |
| Ketoconazole | ↔ | ↔ | ↔ | ↔ | ↑ 62 ^b | ↑ 145 ^b |
| Diltiazem | ↔ | ↔ | ↔ | ↔ | ↑ 63 ^b | ↑ 109 ^b |
| Digoxin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Rifampicin (rifampin) | ↔ | ↔ | ↔ | ↔ | ↓ 53 ^c | ↓ 76 ^c |
| Omeprazole | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Famotidine | ↔ | ↔ | ↔ | ↔ | ↑ 14 | ↔ |
| Simethicone [+Al(OH) ₃ + Mg(OH) ₂] | ↔ | ↔ | ↔ | ↔ | ↓ 26 | ↔ |
| Ciclosporin | ↑ 68 ^d | ↑ 29 ^d | ↔ | ↔ | ↔ | ↔ |
| Warfarin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

a. Most of these modest pharmacokinetic differences seen in trials were not considered clinically relevant.

b. According to the labelling, the dosage of saxagliptin should be 2.5 mg once daily when it is coadministered with strong CYP3A4/5 inhibitors.

c. Clinical consequence still unknown, although probably modest.

d. These modest changes in sitagliptin pharmacokinetics were not considered clinically meaningful.

CYP = cytochrome P450; ↑ indicates an increase; ↓ indicates a decrease; ↔ indicates no significant change.

Scheen AJ: Dipeptidylpeptidase-4 inhibitors (gliptins). Focus on drug-drug interactions. *Clin Pharmacokin* 2010; 49 (9): 573-588

Dipeptidylpeptidase-4-Inhibitoren: Interaktionen durch Einfluss auf andere Arzneimittel

Table II. Effects of pharmacokinetic interactions of sitagliptin, vildagliptin and saxagliptin on the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values of other coadministered drugs (based upon the literature and labelling)^a

| Coadministered drug | Sitagliptin (% change) | | Vildagliptin (% change) | | Saxagliptin (% change) | |
|--------------------------------|------------------------|-------------------|-------------------------|----------------|------------------------|----------------|
| | C_{max} | AUC | C_{max} | C_{max} | AUC | C_{max} |
| Metformin | ↔ | ↔ | ↔ | ↑ 15 | ↔ | ↔ |
| Glibenclamide (glyburide) | ↔ ^b | ↔ ^b | ↔ ^b | ↔ ^b | ↑ 16 ^b | ↔ ^b |
| Pioglitazone | ↔ | ↔ | ↔ | ↔ | ↑ 14 | ↔ |
| Rosiglitazone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Simvastatin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Ketoconazole | ↔ | ↔ | ↔ | ↔ | ↓ 16 | ↓ 13 |
| Diltiazem | ↔ | ↔ | ↔ | ↔ | ↑ 16 | ↔ |
| Digoxin | ↑ 18 ^c | ↑ 11 ^c | ↔ | ↔ | ↔ | ↔ |
| Warfarin | ↔ ^d | ↔ ^d | ↔ ^d | ↔ ^d | ↔ | ↔ |
| Amlodipine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Valsartan | ↔ | ↔ | ↑ 14 | ↑ 24 | ↔ | ↔ |
| Flamipril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Norethisterone (norethindrone) | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Ethinylestradiol | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

- a. Most of these modest pharmacokinetic differences seen in trials were not considered clinically relevant.
 b. Despite the absence of significant effects of gliptins on the pharmacokinetic parameters of glibenclamide, a reduction in the dosage of any sulfonylurea compound is recommended in order to minimize the risk of hypoglycaemia.
 c. The prescribing information for sitagliptin calls for monitoring of patients who are treated with digoxin.
 d. The prothrombin time (measured by the INR) was not altered either.
- INR**=international normalized ratio; ↑ indicates an increase; ↓ indicates a decrease; ↔ indicates no significant change.

Scheen AJ: Dipeptidylpeptidase-4 inhibitors (gliptins). Focus on drug-drug interactions. *Clin Pharmacokin* 2010; 49 (9): 573-588

Sitagliptin und Ciclosporin

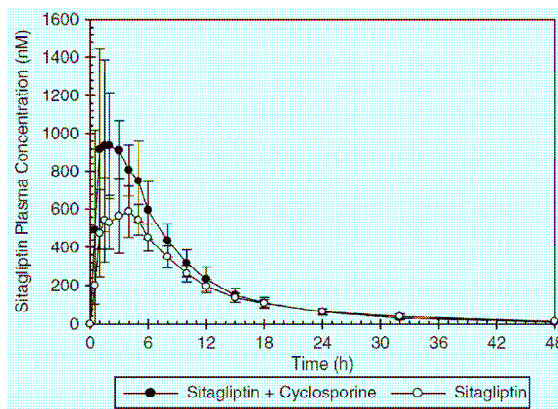


Figure 1. Mean (SD) sitagliptin plasma concentrations following a single oral 100-mg sitagliptin dose with or without a single oral 600-mg dose of cyclosporine (CSA) to young, healthy male subjects.

Krishna R et al.: Effect of a single cyclosporine dose on the single-dose pharmacokinetics of sitagliptin (MK-0431), a dipeptidyl peptidase-4 inhibitor, in healthy male subjects. *J Clin Pharmacol* 2007; 47: 165-174

Sitagliptin und Ciclosporin

Table I Summary Statistics for Sitagliptin Pharmacokinetic Parameters Following Administration of a Single Oral Dose of Sitagliptin (100 mg) With or Without a Single Oral Dose of CSA (600 mg) in Young, Healthy Male Subjects (N = 8)

| Sitagliptin Pharmacokinetic Parameter | Sitagliptin + CSA | Sitagliptin | Sitagliptin + CSA/Sitagliptin |
|---------------------------------------|--------------------------------|--------------------------------|-------------------------------|
| | Geometric LS Mean ^a | Geometric LS Mean ^a | GMR (90% CI) ^b |
| AUC _{0-∞} , μM·h | 9.17 | 7.13 | 1.29 (1.24, 1.34) |
| C _{max} , nM | 1185 | 706 | 1.68 (1.36, 2.08) |
| C _{24h} , nM | 61.1 | 63.5 | 0.96 (0.88, 1.05) |
| Cl _R , mL/min | 371 | 366 | 1.01 (0.87, 1.18) |
| t _{max} , h | 2.25 ^b | 4.00 ^b | 0.401 ^c |
| Apparent t _{1/2} , h | 10.6 ^d | 11.6 ^d | 0.011 ^c |
| f _{0,∞} | 0.838 | 0.658 | 0.016 ^c |
| CL _{CR} , mL/min | 121 | 92 | 1.31 (0.87, 1.99) |

CSA, cyclosporine; GMR, ratio of geometric least square means (sitagliptin + CSA/sitagliptin); CI, confidence interval; LS, least squares.

a. Back-transformed from log scale.

b. Median.

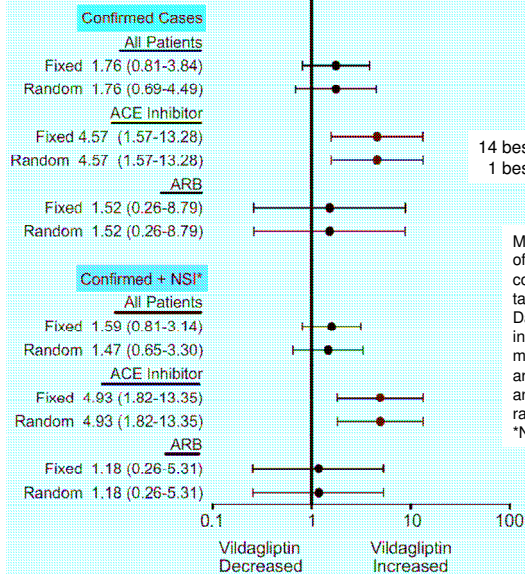
c. Between treatment P value.

d. Harmonic mean.

„The observed differences are not considered likely to be relevant.“

Krishna R et al.: Effect of a single cyclosporine dose on the single-dose pharmacokinetics of sitagliptin (MK-0431), a dipeptidyl peptidase-4 inhibitor, in healthy male subjects. *J Clin Pharmacol* 2007; 47: 165-174

Odds Ratio of Angioedema



DPP-4-Inhibitoren und ACE-Hemmer-assoziiertes Angioödem

14 bestätigte Fälle bei 2754 Vildagliptin+ACEI-Verwendern, 1 bestätigter Fall bei 1819 Patienten der Vergleichsgruppe.

Meta-analysis showing the effect of vildagliptin on the risk of angioedema, in all patients, those taking an angiotensin converting enzyme (ACE) inhibitor concurrently, and those taking an angiotensin-receptor blocker (ARB) concurrently. Data are presented as odds ratios and 95% confidence intervals. Odds ratios were estimated using the Peto method, in which all studies with a comparator treatment arm and an event in at least 1 arm were included. This analysis was conducted using both fixed effect (Fixed) and random effect (Random) models. *NSI indicates not sufficient information.

Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA: Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension* 2009; 54: 516-523