”Managementul pacienților cu tuberculoză și diabet zaharat”

Probleme farmacologice în co-gestionarea diabetului zaharat și a tuberculozei

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dr.șt.med., IMSP SCR ”Timofei Moșneaga”

26 mai 2021; 27 mai 2021; 2 iunie 2021

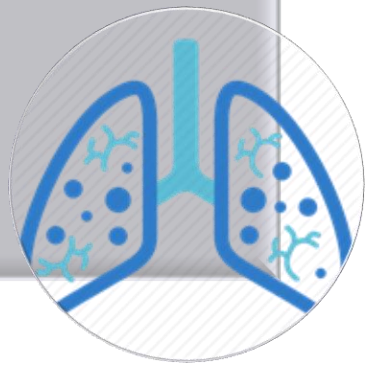
Tratamentul

- **CERTITUDINE**
- ↑ riscul de eșec al tratamentului TBC,
- ↑ riscul deces și recidivă,
-
- **INCERTITUDINE**
- ??? controlul optim glicemic - poate atenua parțial sau pe deplin aceste efecte negative
- ??? tratamentul anti- tuberculos trebuie ajustat la pacienții cu diabet zaharat

Diabet zaharat

- Tuberculoza – scade pofta de mîncare, greutatea, activitatea fizică – afectând homeostazia glucozei,
- Tuberculoza activă asociată cu inflamația și insulinorezistență
- Interacțiunea între medicamente
- Sugererează – ideea controlului glicemic optim al diabetului

Tuberculoza



CELEBRATING 100 YEARS OF INSULIN

Almost a hundred years ago, some clinicians observed and **reported an association between diabetes mellitus and tuberculosis.**
Insulin was introduced in 1922, and of those type 1 diabetes patients **who did not die from diabetic coma, many were thought to die from tuberculosis.**
In 1934, Howard Root, a physician from Boston, used autopsy studies to conclude that **juvenile diabetes was associated with a 10-fold increased risk of tuberculosis**, mostly occurring within years following recovery from diabetic coma.
Tuberculosis was also more common in adults with diabetes, following **the onset of diabetes in 85% of cases.**

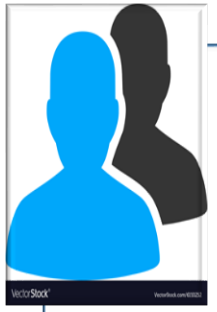
Trop. Med. Infect. Dis. 2021, 6, 8.
https://doi.org/10.3390/tropicalmed6010008

Barierele în tratamentul pacienților cu DZ și TBC

Inflamația cronică, IR, scăderea poftei de mâncare

Interacțiunea între medicamente

Risk de toxicitate înalt



Aderența slaba la tratament

Educația, monitorizarea intensivă, intervenții în modul de viață

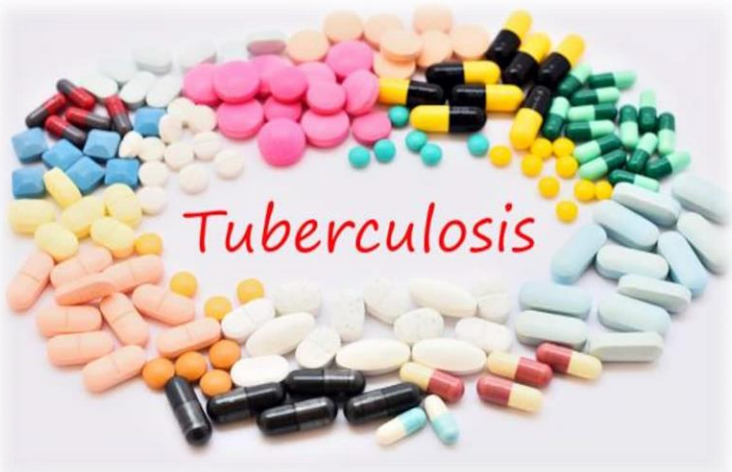
Inerția clinică,

Cunoștințe insuficiente

Accesibilitatea la servicii de diagnostic și medicamente, colaborarea intersectorială, instrumente de monitorizare

- Proprietăți farmacocinetice
- Complicații cronice
- Deprinderi dăunătoare
- Patologie cardiovasculară
- Risc de hipoglicemie

- Aderență terapeutică
- Toxicitate
- Reacții adverse
- Multidrogrezistență
- Interacțiuni medicamentoase



Interacțiuni medicamentoase

- **Metformina**
- **Sulfanilureicele**

  (Gliclazid, Glimepirid)
- **Repaglinida**
- **Sitagliptina**
- **Insulina**

- **Rifampicina**
- **Izoniazida**
- **Pirozinamid**
- **Florchinolone**
- **Linezolid**
- **Cicloserina**

Workneh M., Bjune G. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity A systematic review. PLoSOne, 12, 2017, Pizzol D., Gonnaro F tuberculosis and diabetes: current state and future perspectives. Trop Med Int Health 2016, 21, 694-702

Rifampicina

Rifampicin may **affect blood glucose concentrations** and induce hyperglycemia by **augmenting intestinal absorption** of glucose or **reducing insulin sensitivity**.

Rifampicin increases the clearance of most oral antidiabetic drugs that are commonly used in sulphonylureas are metabolized in the liver by **cytochrome P450 enzymes**, of which rifampicin is a very potent inducer.

RMP **increases the metabolism of many drugs** commonly used by DM patients, **including statins**, all oral DM drugs except metformin, **calcium channel blockers, angiotensin-converting-enzyme inhibitors, digoxin, warfarin, and some antihypertensive drugs**.

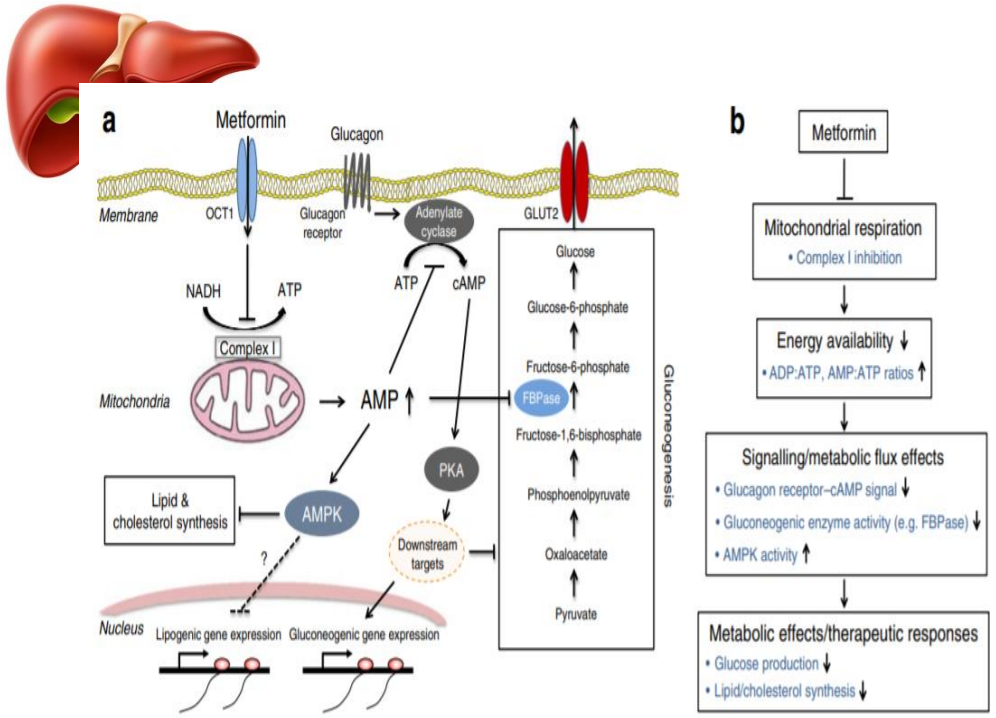
Riza AL, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol 2014;2:740–53

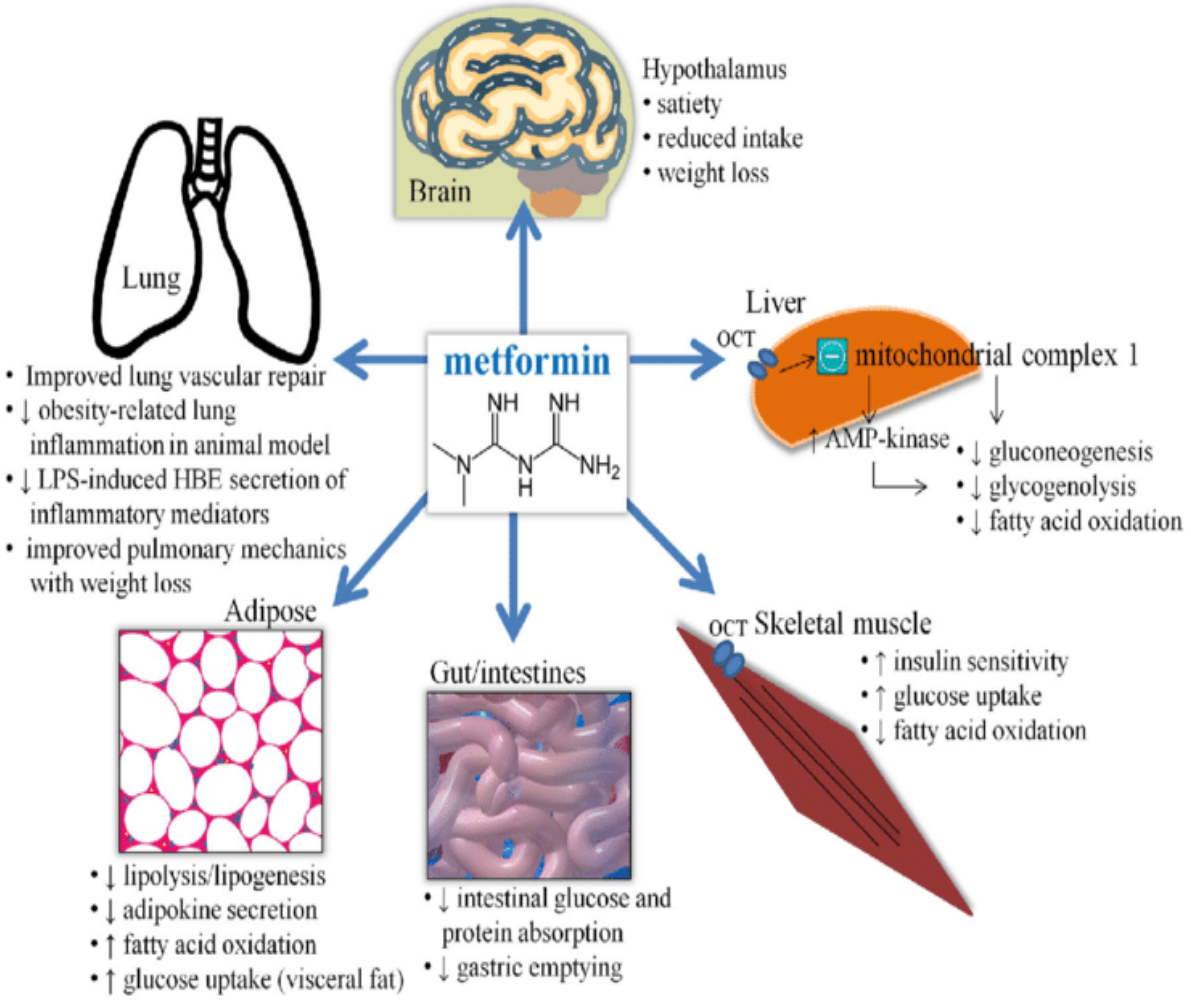
Rifamycins Drug interactions

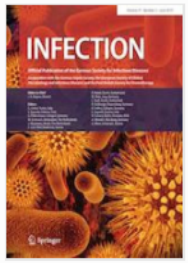
Drug Category	Drug / Drug Class	Nature of Interaction	Recommendations
Acid Blocking Agents	Antacids	↓ absorption of rifamycins	Give 1 hour prior to Antacid use
	Proton Pump Inhibitors (omeprazole, esomeprazole)	↓ blood levels of PPI's	Avoid Use
Antibiotics	Macrolides (erythromycin, e.g.)	May ↓ rifamycin levels in blood and ↑ levels of Clarithromycin and Erythromycin in blood	Use Azithromycin if possible
	Tetracyclines (doxycycline)	May ↓ levels of these antibiotic classes	Monitor infection closely, consider increasing dose, or use alternative antibiotic
	Fluoroquinolones		
	Linezolid		
Anticoagulants/ Antiplatelet agents	Warfarin, Dabigatran, Rivaroxaban, Clopidogrel	Antithrombotic activity ↓, greater risk of clotting	Monitor response closely and adjust dose as needed. Avoid use with rivaroxaban, dabigatran.
Anticonvulsants	Phenytoin, Lamotrigine, autoinducing agents	Metabolism of these agents may be harder to predict, subtherapeutic blood levels possible	Therapeutic Drug Monitoring encouraged, consider choosing alternative agent
Antidiabetic Medications	Sulfonylureas (glyburide, glimepiride)	May ↓ levels in blood, lessening the glycemic lowering effect	Monitor glycemic control closely, increase agents as needed
	Thiazolidinediones (pioglitazone)		
	Metformin		

Metformina

- Clasa biguanidelor – **I linie** în tratamentul DZ 2
- Activează AMP proteinkinaza (AMPK)
- Organul țintă principal – **ficatul**
- **Reduce gluconeozgeneza hepatică**







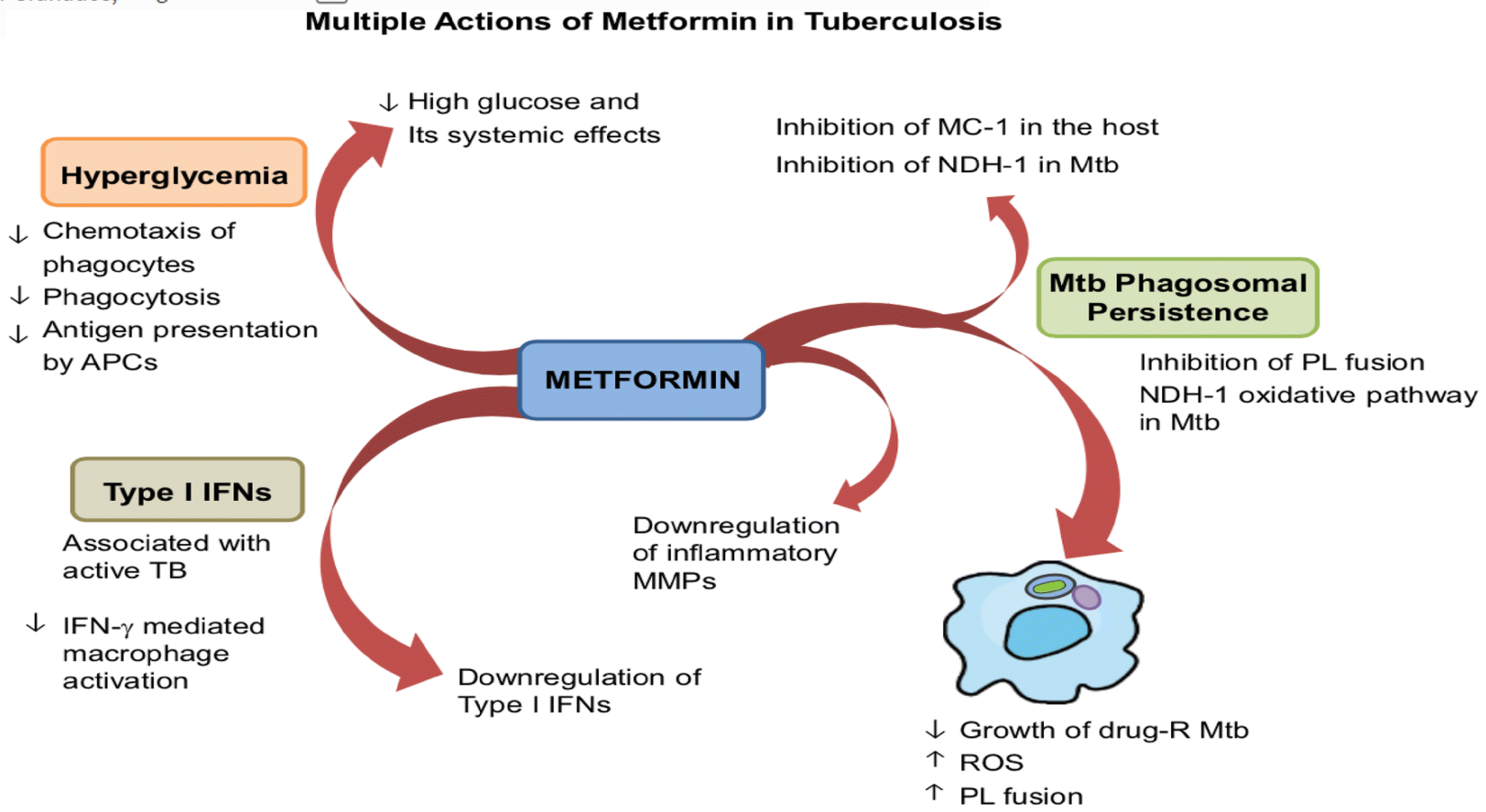
Infection
pp 1–6 | Cite as

Metformin in tuberculosis: beyond control of hyperglycemia

Authors | Authors and affiliations

William Oglesby, Ali M. Kara, Hector Granados, Jorge L. Cervantes

The multiple actions of metformin in tuberculosis. Diagram showing the effects of metformin on hyperglycemia, type I interferon (IFN) downregulation, Mtb phagosomal persistence, oxidative chains, inflammatory matrix metalloproteinases (MMPs), in phago-lysosome (PL) fusion



frontiers in Microbiology

REVIEW
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Metformin as Host-Directed Therapy for TB Treatment: Scoping Review

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[1] Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, [2] Africa Health Research Institute, Durban, South Africa, [3] School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa, [4] Max Planck Institute for Infection Biology, Berlin, Germany, [5] MRC-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit, Doris Duke Medical Research Institute, University of KwaZulu-Natal, Durban, South Africa

Host-directed therapy (HDT) provides a largely unexploited approach as adjunctive anti-TB therapy. Firstly, HDT may impair Mtb replication and survival by disrupting Mtb manipulation of macrophage pathways, thus rendering the bacteria more sensitive to host defenses (Hawn et al., 2015).

Tuberculosis (TB) disease is an international health concern caused by the bacteria *Mycobacterium tuberculosis (Mtb)*. Evolution of multi-drug-resistant strains may cause bacterial persistence, rendering existing antibiotics ineffective. Hence, development of new or repurposing of currently approved drugs to fight *Mtb* in combination with existing antibiotics is urgently needed to cure TB which is refractory to current therapy. The shortening of TB therapy and reduction in lung injury can be achieved using adjunctive host-directed therapies. There is a wide range of probable candidates which include numerous agents permitted for the treatment of other diseases. One potential candidate is metformin, a Food and Drug Administration (FDA)-approved drug used to treat type 2 diabetes mellitus (DM). However, there is a scarcity of evidence supporting the biological basis for the effect of metformin as a host-directed therapy for TB. This scoping review

Yu *et al. BMC Infectious Diseases* (2019) 19:859
https://doi.org/10.1186/s12879-019-4548-4

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review

Xinyu Yu[1†], Ling Li[2†], Liangtao Xia[1], Xin Feng[1], Fan Chen[3], Shiyi Cao[3*] and Xiang Wei[1,4,5,6*]

Results: This systematic review included 6980 cases from 12 observational studies. The meta-analysis suggested that metformin prescription could decrease the risk of TB among diabetics (pooled odds ratio [OR], 0.38; 95%CI, 0.21 to 0.66). Metformin prescription was not related to a lower risk of LTBI (OR, 0.73; 95%CI, 0.30 to 1.79) in patients with diabetes. Metformin medication during the anti-tuberculosis treatment is significantly associated with a smaller TB mortality (OR, 0.47; 95%CI, 0.27 to 0.83), and a higher probability of sputum culture conversion at 2 months of TB disease (OR, 2.72; 95%CI, 1.11 to 6.69) among patients with diabetes. The relapse of TB was not statistically reduced by metformin prescription (OR, 0.55; 95%CI, 0.04 to 8.25) in diabetics.

Conclusions: According to current observational evidence, metformin prescription significantly reduced the risk of TB in patients with diabetes mellitus. Treatment outcomes of TB disease could also be improved by the metformin medication among diabetics.

Metformina

In a recent retrospective analysis **from Taiwan**, those with DM (30%) had a 1.9-fold higher mortality, but among this **group metformin** use was associated with **lower mortality** (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.39–0.82).22

The advantages of metformin include extensive experience with the drug, extremely low risk of hypoglycaemia, effectiveness, low cost, beneficial effects on cardiovascular disease, **lack of clinically relevant interaction with RMP** (TANDEM, unpublished) and a potential benefit on TB itself.

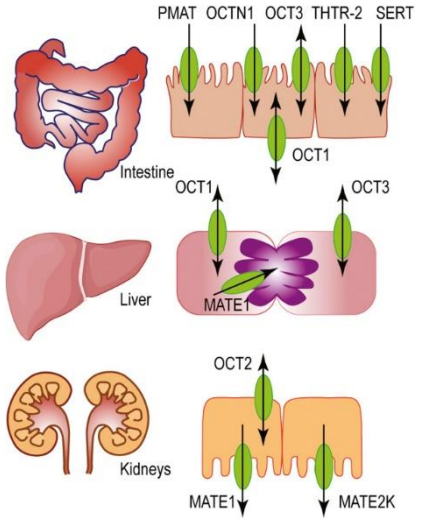
Metformina + Rifampicina

Rifampicin Alters Metformin Plasma Exposure but Not Blood Glucose Levels in Diabetic Tuberculosis Patients

Lindsey H.M. te Brake[1,2,†], Vycke Yunivita[3,†], Resvi Livia[4], Nanny Soetedjo[5], Eleonora van Ewijk-Beneken Kolmer[1], Jan B. Koenderink[2], David M. Burger[1], Prayudi Santoso[6], Reinout van Crevel[7], Bachti Alisjahbana[4], Rob E. Aarnoutse[1], Rovina Ruslami[3] on behalf of the TANDEM Consortium

This study was the first to evaluate the effect of rifampicin on metformin exposure and activity in patients with TB-DM. We observed an **increase in metformin exposure,** with an AUC0–τ GMR (exposure during vs. after TB treatment) of 1.28 (90% CI 1.13–1.44), **suggesting a PK interaction** (bio-inequivalence) when metformin is co-administered with rifampicin.23 This interaction did not result in a statistically significant change in the glucoselowering effect of metformin.

Metformina - absorbția intestinală, captarea hepatică și excreția renală a Met mediată de OCTs (organic cation transporters) și MATE1 and MATE2K (multidrug and toxin extrusion protein 1 and 2K), - membrii transportorilor solubili.



Rifampicina agonistul PXR (pregnane X receptor), factor de transcriție care reglează genele implicate în detoxificare, inclusiv a enzimelor de metabolizare a medicamentelor și a transportorilor acestora.
Induce upregularea transportorilor OCT.

Sulfaniureicele

The **two main disadvantages** are the risk of **hypoglycaemia and strong drug interactions with RMP** that show wide inter-individual variation but result in their efficacy being reduced by 30–80%.

Antidiabetic drug		Change in exposure (AUC[1])	Enzyme induction	Reference
Insulin		no effect anticipated		no studies published
Sulphonylureas	Tolbutamide	strong decrease		40, 41
	Glibenclamide (Glyburide)	-39%	CYP2C9	42
	Gliclazide	-70%	CYP2C9	43
	Glimepiride	-34%	CYP2C9	44
	Glipizide	-22%	CYP2C9	42

Rifampicina și Pioglitazona

British Journal of Clinical Pharmacology DOI:10.1111/j.1365-2125.2005.02515.x

Effect of rifampicin on the pharmacokinetics of pioglitazone

Tiina Jaakkola, Janne T. Backman, Mikko Neuvonen, Jouko Laitila & Pertti J. Neuvonen
Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

Results

Rifampicin decreased the mean total area under the plasma concentration-time curve ($AUC_{0-\infty}$) of pioglitazone by 54% (range 20–66%; $P = 0.0007$; 95% confidence interval −78 to −30%) and shortened its dominant elimination half-life ($t_{1/2}$) from 4.9 to 2.3 h ($P = 0.0002$). No significant effect on peak concentration (C_{max}) or time to peak (t_{max}) was observed. Rifampicin increased the apparent formation rate of M-IV and shortened its t_{max} ($P < 0.01$). It also decreased the $AUC_{0-\infty}$ of M-IV (by 34%; $P = 0.0055$) and M-III (by 39%; $P = 0.0026$), shortened their $t_{1/2}$ (M-IV by 50%; $P = 0.0008$, and M-III by 55%; $P = 0.0016$) and increased the $AUC_{0-\infty}$ ratios of M-IV and M-III to pioglitazone by 44% ($P = 0.0011$) and 32% ($P = 0.0027$), respectively. Rifampicin increased the M-IV/pioglitazone and M-III/pioglitazone ratios in urine by 98% ($P = 0.0015$) and 95% ($P = 0.0024$). A previously unrecognized metabolite M-XI, tentatively identified as a dihydroxy metabolite, was detected in urine during both phases, and rifampicin increased the ratio of M-XI to pioglitazone by 240% ($P = 0.0020$).

Conclusions

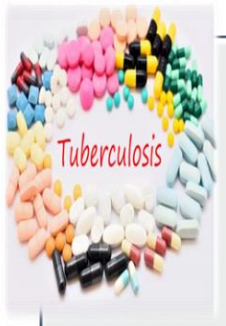
Rifampicin caused a substantial decrease in the plasma concentration of pioglitazone, probably by induction of CYP2C8. Concomitant use of rifampicin with pioglitazone may decrease the efficacy of the latter drug.

Interacțiunile medicamentoase

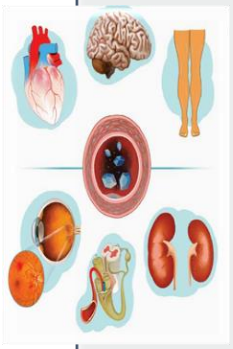
Grupa de preparate	Efecte clinice	Interacțiune - Rifampicina	Recomandări
Metformina	↓producerea G de către ficat ↓absorbția G in intestin ↑sensibilitatea la insulină	↔	abs
Sulfanilureice	↑secreția de insulină		• Glipizida de preferință • Monitorizare mai frecventă • Ajustarea dozelor
Glimepirid		↓ 30%	
Glipizid		↓ 22%	
Repaglinida	↑secreția de insulină	↓ 31-57%	• Monitorizare mai frecventă • Ajustarea dozelor
Sitagliptin	↑secreția de insulină glucozodependentă ↓apetitul ↓secreția de glucagon	↓concentrația	• Monitorizare mai frecventă • Ajustarea dozelor nu este necesară
Exenatida	↑secreția de insulină glucozodependentă ↓apetitul ↓secreția de glucagon	↔	abs

Interelația DZ + TBC

Preparatele antidiabetice influențează rezultatele tratamentului



Preparatele antituberculoase influențează nivelul glicemiei



Implicarea asupra farmacocineticii a DZ:

*absorbție (obezitate, circulația la nivelul mușchilor sau golirea grastrică),

*distribuirea (circulația medicamentelor) (glicozilarea proteinelor transportatoare),

*biotransformare (reglarea enzimolor);

*eliminarea medicamentelor (nefropatie).

Factorii de risc cardiovascular

Cardiovascular risk	Target	The intervention	Specific considerations in TB patients
Smoking	Stop smoking	Counselling	Relevant for TB treatment outcomes and reducing relapse rates of disease
Obesity	Body mass index > 23 (Asian) or > 25 (other)	Counselling (diet, physical activity)	Often ~10% weight gain as a result of anti-tuberculosis treatment
Excessive alcohol consumption	Avoid alcohol intake during anti-tuberculosis treatment	Counselling	Risk of liver dysfunction associated with anti-tuberculosis drugs
Hypertension	<130/80 mmHg	Antihypertensive treatment	RMP reduces the efficacy of some antihypertensive drugs (calcium channel blockers and ACE inhibitors) No interaction with thiazide diuretics ACE inhibitors cause cough in 10–15% of patients
Hyperlipidaemia	LDL < 2.6 mmol/l (100 mg/dl)	Statins: 1) for those aged >40 years; 2) for those with previous cardiovascular disease	Rifampicin reduces the efficacy of most statins
Established cardiovascular disease (previous myocardial infarct, stroke, peripheral arterial disease)	Secondary prophylaxis	Aspirin Statin	Risk of bleeding (e.g., haemoptysis in pulmonary TB)

Să fim o echipă !

pentru a realiza lucruri mari și frumoase