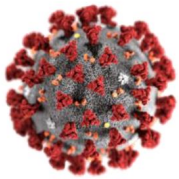
EpiCare web session, 9 April, 2020



ANTISEIZURE MEDICATIONS AND CHALLENGES IN THE COVID-19 PANDEMIC

Focus on drug interactions and special treatment issues

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Co-founded by the EU

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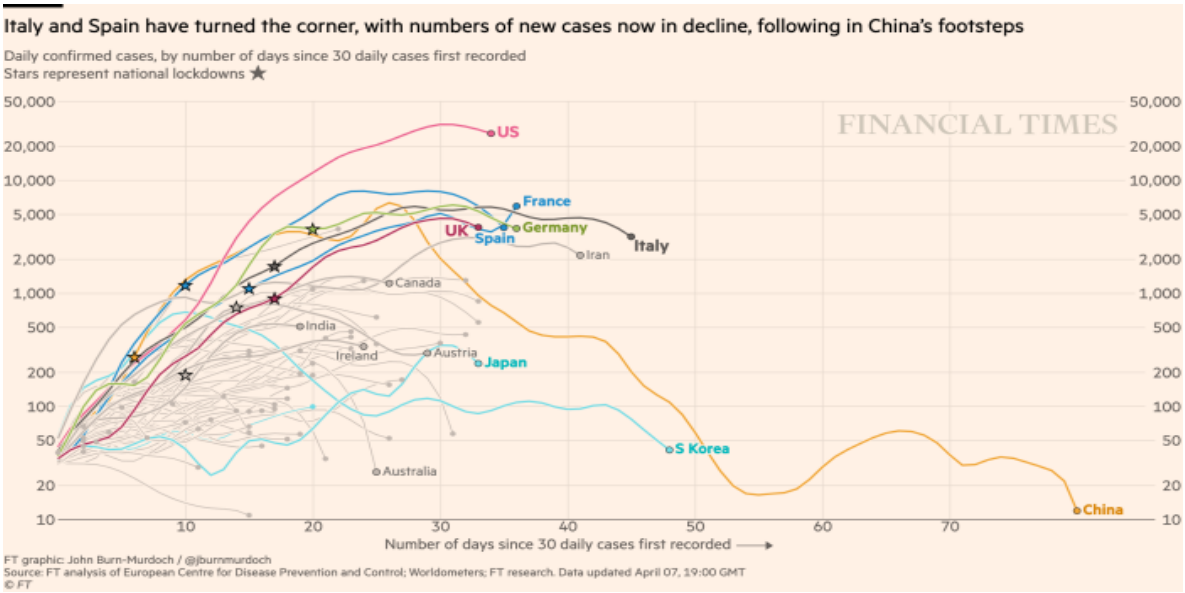
Outline

- General introduction to Covid-19 and epilepsy
- Special treatment issues in PWE, interactions and risks
- Classification of drug interactions and predictions
- Interactions between Covid-19 treatments and antiseizure medications (ASMs)
- Special clinical management issues (separate slide file)

The Evolution of the Covid-19 Pandemic Across the World



https://www.ft.com/coronavirus-latest (April 8, 2020)

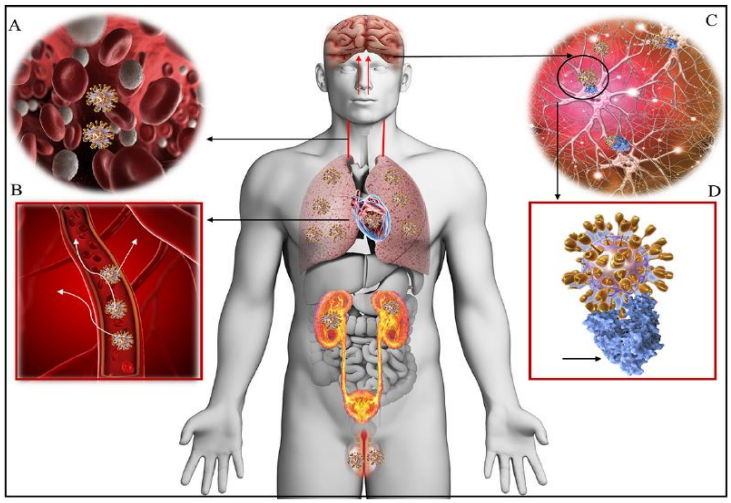
Age Distribution of Covid-19 Casualties in Italy

Age range	# casualties	% casualties	death rate (% of infected)
0 - 9	1	0,0%	0,1%
10 - 19	0	0,0%	0,0%
20 - 29	7	0,0%	0,1%
30-39	35	0,2%	0,4%
40-49	141	0,9%	0,8%
50-59	591	3,8%	2,4%
60-69	1.821	11,7%	8,8%
70-79	5.103	32,8%	23,2%
80-89	6.254	40,2%	31,2%
>90	1.616	10,4%	27,0%
Not recorded	2	0,0%	1,2%
Total	15.571	100,0%	12,2%

https://lab24.ilsole24ore.com/coronavirus/ (April 8, 2020)

Does COVID-19 Affect the CNS?

Tissues Expressing ACE2 Receptors - Possible Targets of Covid-19 Infection



Baig AM, et al. ACS Chem Neurosci. 2020 Apr 1;11(7):995-998.

Neurological Manifestations of COVID-19

- **Neurological signs / symptoms usually not prominent**
  - Exceptions: headache, ageusia, anosmia
- **Reports of individual cases with 'encephalitis-like' presentation**
- **Seizures not commonly seen**
  - Rarely as initial presentation
  - May occur in severely ill patients as part of hypoxic / encephalopathic complications
  - May occur as part of underlying co-morbidity (epilepsy)

Managing People with Seizures and Epilepsy in the Current COVID-19 Scenario

- **Focus on safety**
  - Prevention of infection (minimization of hospital visits, special protection for people at high risk, e.g. elderly people, and those on immunosuppressant therapies)
  - Prevention of epilepsy-related complications (deferral of non-urgent treatment changes, lower threshold for use of rescue medication, emphasize importance of adherence, minimize risk of running out of medication)
  - Deferral of non-urgent investigations (EEG, MRIs, as appropriate)
  - Ensure easy access to phone/online consultations - including whenever feasible psychological support services)

- **Clear communication, planning and reassurance**
  - PWE are not generally at greater risk of being infected, or being liable to complications
  - PWE and/or caregivers should receive clear instructions on how to deal with specific situations (e.g. breakthrough seizures, fever, upper respiratory tract symptoms
  - A management plan should be in place whenever possible (e.g. should caregiver require quarantine, or hospital admission)

EpiCARE Steering Committee, 2020 (and other sources)

Managing Covid-19 Infection in People with Seizures and Epilepsy: Special Concerns

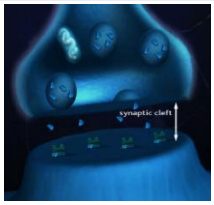
- **Influence of COVID-19 treatments on seizure susceptibility (e.g. seizure precipitation by drugs used to treat COVID-19 and its symptoms)**

- **Influence of antiseizure medications (ASMs) on COVID-19 and its symptoms (e.g., immunosuppression by everolimus or steroids, respiratory depression by benzodiazepines)**

- **Interactions between COVID-19 treatments and ASMs**

Mechanisms of Drug-Drug Interactions

- **Pharmacodynamic interactions**
  - Occur at the site of action
  - Do not involve changes in plasma drug levels
  - Example: additive QT prolongation by chloroquine and azithromycin
- **Pharmacokinetic interactions**
  - Absorption
  - Distribution
  - **Metabolism (enzyme induction or inhibition)**
  - Excretion
- **Clinical impact**
  - May have no, moderate or serious consequences
  - Individual variability is common
  - *Ask, measure, act*



Patsalos and Perucca, Lancet Neurol, 2003, Patsalos et al., Epilepsia 2008; Patsalos Clin Pharmacokin 2013a,b, Johannessen Landmark et al., Adv Drug Deliv Rev, 2012, Epileptic Disord 2016, Exp Opin Metab Tox, 2020

Pharmacodynamic interactions : Risk of Serious Cardiac Dysrhythmias as an Example

- **Caution when co-prescribing drugs that alter cardiac rhythm or conductions (EKG check advisable)**

Examples: Lopinavir/ritonavir, lacosamide and eslicarbazepine all prolong PR interval

Atazanavir, chloroquine, hydroxychloroquine, azithromycin all prolong QT interval

Combining drugs that prolong PR and/or QT interval may increase risk of dysrhythmias

Propofol also has relatively high pro-dysrhytmic potential

EKG check before /after treatment may be indicated

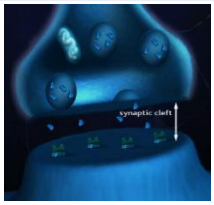
Treating patients diagnosed with epilepsy with investigational anti COVID-19 drugs
Document produced by the Israeli ILAE Chapter (courtesy Dr. Sara Eyal

https://www.covid19-druginteractions.org

https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8Nr7Y86-Thswhf3KmkUFZlftIP3OLF_oe6a0MguxKM1UzTi_tC8

Predicting Metabolic Drug-Drug Interactions

- The enzymes responsible for the metabolism of individual drugs are mostly known
- Effect of individual drugs on those enzymes are also mostly known
- This set of information permits to predict with reasonable accuracy whether a drug affects the metabolism of another drug, or viceversa



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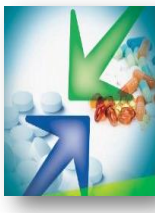
Predicting Metabolic Drug-Drug Interactions: Lopinavir, Ritonavir and ASMs as an Example

- Phenytoin is a potent inducer of cytochrome CYP3A4 - lopinavir and ritonavir are CYP3A4 substrates
- Predictably phenytoin increases lopinavir and ritonavir clearance

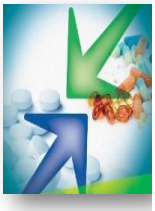
- Ritonavir inhibits CYP3A4, which metabolizes carbamazepine (CBZ), and induces UGT1A4, which metabolizes lamotrigine (LTG)
- Predictably, ritonavir may increase the serum levels of CBZ, and reduce those of LTG



Birbeck et al, Epilepsia, 2012; 53(1):207-14; Berbel Garcia et al, Clin Neuropharmacol 2000;23(4):216-8; Kato et al Pharmacotherapy. 2000;20(7):851-4

Minimizing Risk of Adverse Drug Interactions in Covid-19: Patients who Require Initiation of an ASM

- Consider medications being taken by the individual (whether Covid-19 related or not) , and other medications likely to be started during the course of Covid-19
- Select an ASM unlikely to be involved in adverse interactions with those medications
- Other factors need to be considered, e.g. seizure type and context, comorbidities, any need for rapid titration, availability of monitoring services, etc.
- In the light of current uncertainty about the evolution of the pandemic, these considerations may apply to any patient started on ASMs in the coming months



Potential Interactions between ASMs and Drugs Used in the Management of Covid-19

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITAZ	RBV	TCZ
Carbamazepine	↑⇓	↑⇓	⇓	↔	⇓	⇓	↔	↔	↓
Clonazepam	↑	↑	↔	↔	↔	↔	↔	↔	↔
Eslicarbazepine	⇓ ♥	⇓ ♥	⇓	↔	⇓	⇓	↔	↔	↔
Ethosuximide	↑	↑	↔	↔	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lacosamide	↔ ♥	↔ ♥	↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↓ 50%	↔	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Oxcarbazepine	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔
Perampanel	↑	↑	↔	↔	↔	↔	↔	↔	↔
Phenobarbital (Phenobarbitone)	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↓
Phenytoin	⇓	⇓	⇓	↔	⇓	⇓	↑	↔	↓
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	⇓	↓⇓	⇓	↔	⇓	⇓	↔	↔	↓
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔
Sultiame	↑	↑	↔	↔	↔	↔	↔	↔	↔
Tiagabine	↑	↑	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproate (Divalproex)	↔	⇑ 38%	↔	↔	↔	↔	↔	↔	↔
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↔	↔	↔	↔	↔	↔	↔	↔

Text Legend

↑ Potential increased exposure of the comedication
↓ Potential decreased exposure of the comedication
⇑ Potential increased exposure of COVID drug
⇓ Potential decreased exposure of COVID drug
↔ No significant effect

♥ One or both drugs may cause QT and/or PR prolongation. ECG monitoring is advised if coadministered.

Numbers refer to increase or decrease in AUC as observed in drug-drug interaction studies.

Key to abbreviations

ATV	Atazanavir	CLQ	Chloroquine
LPV/r	Lopinavir/ritonavir	HCLQ	Hydroxychloroquine
RDV	Remdesivir	RBV	Ribavirin
FAVI	Favipiravir	TCZ	Tocilizumab
		IFN-β	Interferon beta

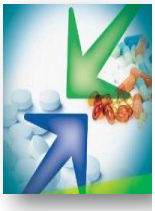
Colour Legend

These drugs should not be coadministered
Potential interaction which may require a dose adjustment or close monitoring.
Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.
No clinically significant interaction expected

https://www.covid19-druginteractions.org (accessed April 8, 2020)

Minimizing Risk of Adverse Drug Interactions in Covid-19: Patients on ASMs who Require Initiation of Covid-19 Therapies

- In a real world setting, the most vulnerable patients will receive not only ASMs, but other medicines which may also interact with Covid-19 treatments – in critically ill patients, PK changes unrelated to drug interactions also occur
- Drug-drug interactions may not be easily avoided, particularly in patients taking enzyme inducing ASMs
- Reliable information on magnitude of expected interactions is often missing – even when available, individual variability can be substantial
- Risk to benefit ratio is difficult to assess – focus especially on risk, as benefit from Covid-19 treatments is unclear at present (this will change in the future, as Covid-19 trials are completed)
- Adverse consequences can be minimized by dose adjustments, aided by monitoring tools as appropriate (e.g., EKG for cardiac affects, plasma drug level monitoring, etc) - close clinical observation is essential



ASMs and Metabolic Drug Interactions

Susceptibility to *cause* interactions

- **Enzyme inducers (CYP3A, CYP2B, CYP2C, UGT, and possibly other enzymes)**
- **Enzyme inhibitors (specific enzymes inhibited vary across ASMs)**
- **Mixed inducer/inhibitor (enzyme affected vary across ASMs)**
- Little or no propensity to induce or inhibit drug metabolizing enzymes

Most ASMs are *affected* by interactions

- Exceptions are those ASMs that are excreted renally as their main pathway of elimination

Bold characters indicate stronger interaction potential

Older	*Newer*	*Newest*
Ethosuximide	**Felbamate**	**Cannabidiol**
Phenobarbital	Gabapentin	Brivaracetam
Phenytoin	Lamotrigine	Cenobamate
Carbamazepine	Levetiracetam	Eslicarbazepine
Clonazepam	Oxcarbazepine	Everolimus
Clobazam	Pregabalin	Lacosamide
Primidone	Tiagabine	Perampanel
Sulthiame	Topiramate	**Rufinamide**
Valproic acid	Vigabatrin	**Stiripentol**
Other BZ	Zonisamide	

Some drugs shown in green might occasionally affect the metabolism of some substrates, usually at high doses (e.g., perampanel 12 mg/day increases the clearance of contraceptive steroids)

Patsalos and Perucca, Lancet Neurol, 2003, Patsalos et al., Epilepsia 2008; Patsalos Clin Pharmacokin 2013a,b, Zaccara and Perucca. Epileptic Disord. 2014 ; Johannessen Landmark et al., Adv Drug Deliv Rev, 2012, Epileptic Disord 2016, Exp Opin Metab Tox, 2020

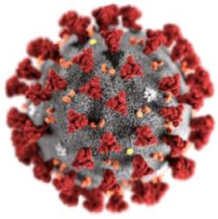
Drugs Used in Covid-19 Treatment

Antimalaria drugs:
- Chloroquine
- Hydroxychloroquine

Antiviral drugs:
- Remdesivir (experimental)
- Lopinavir/Ritonavir
- Darunavir/cobicistat
- Oseltamivir
- Favipiravir
- Atazanavir
- Ribavirin
- Nitazoxanide

Immunomodulating drugs:
- Interferon-beta
- Tocilizumab
- Anakinra
- Emapamulab
- Sarilumab

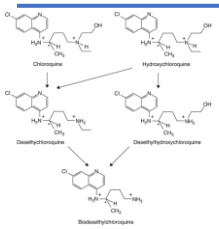
Antibacterial drugs:
- Azithromycin
- Ceftriazone
- Piperacillin/tazobactam



Based on recommendations and reports from:
WHO, China, South-Korea, US, EMA

Cao-B et al., New Eng J Med, March 2020
https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected . March 13th 2020
https://www.eahp.eu/sites/default/files/covid-19-clinical-information-and-treatment-guidelines_0.pdf
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19
https://www.covid19-druginteractions.org
https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html April 7, 2020
https://sph.nus.edu.sg/wp-content/uploads/2020/03/COVID-19-Science-Report-Therapeutics-30-Mar.pdf
https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

Antimalaria drugs & ASMs



Enzyme inducing ASMs are expected to reduce serum levels of chloroquine and hydroxychloroquine – not necessarily a contraindication to combined use

Chloroquine
Hydroxychloroquine

ASMs

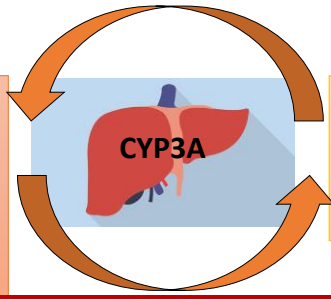
Evaluation:
- Widely used in malaria
- Immune modulating effects (RA)
- Available in many countries
- Some evidence of efficacy
- May prolong QT-interval
- Ongoing studies, Hydroxy- less toxic

No evidence of changes in levels of most commonly used ASMs. Chloroquine and hydroxychloroquine may lower seizure threshold, but risk is probably negligible

Cartegiani et al., J Crit Care, 2020, Liu-J et al., Nature, March 18, 2020
https://www.covid19-druginteractions.org
https://www.ema.europa.eu/en/news/covid-19-chloroquine-hydroxychloroquine-only-be-used-clinical-trials-emergency-use-programmes
https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8Nr7Y86-ThswhF3KmkUFZlftIP30LF_oe6a0MguxKM1UzTi_tC8

Antiviral Drugs & ASMs

Antiviral drugs
Ritonavir, lopinavir
(strong inhibitors of CYP3A4)
Cobicistat, Atazanavir
(CYP3A4 inducers)
Ritonavir
(UGT inducer)



Enzyme inducing ASMs
(especially carbamazepine, phenobarbiytal, phenytoin): Increase clearance of antiviral drugs

Risk of altered ASM response, and risk of lack of efficacy of antiviral drugs
Dosage adjustments may be necessary

- Ritonavir/lopinavir antiretroviral drugs used in HIV
- Available in many countries
- Some evidence of interactions with ASMs
- Ongoing studies in Covid-19, negative study by Cao et al.

Cao-B et al., New Eng J Med, March 2020
Asconape, Curr Neurol Neurosci rep, 2018, Burger et al., Clin Pharm Ther, 2008
https://www.covid19-druginteractions.org, Birbeck et al., Epilepsia, 2012, Okulicz et al., Epi Res, 2013
https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8Nr7Y86-Thswhf3KmkUFZlftIP30LF_oe6a0MguxKM1UzTi_tC8

Examples: Antiviral Drugs & ASMs

ASMs affecting antiretroviral drugs

Phenytoin: Reduces serum concentration of lopinavir/ritonavir by 30-50%, requires up to 50% dosage increase of antiviral drugs to maintain a stable serum concentration. Use TDM if possible.

Antiretroviral drugs affecting ASMs

Ritonavir/lopinavir: May increase the serum concentrations of carbamazepine and other CYP3A substrates e.g. everolimus due to potent CYP3A4 inhibition and P-glycoprotein inhibition. Dosage adjustments may be required to maintain stable serum ASM concentrations. Use TDM if possible.

Ritonavir (combined with lopinavir or atazanavir): Reduces serum concentrations of lamotrigine (LTG) by 30-50%, requires up to 50% increase of LTG dosage to maintain a stable serum LTG concentration, due to induction of UGT1A4. Use TDM if possible.

Cao-B et al., New Eng J Med, March 2020, Israeli chapter of ILAE, April 2020
Asconape, Curr Neurol Neurosci rep, 2018, Burger et al., Clin Pharm Ther, 2008
https://www.covid19-druginteractions.org, Birbeck et al., Epilepsia, 2012, Okulicz et al., Epi Res, 2013
https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8Nr7Y86-Thswhf3KmkUFZlftIP30LF_oe6a0MguxKM1UzTi_tC8

Epilepsia, 53(1):207–214, 2012
doi: 10.1111/j.1528-1167.2011.03335.x

SPECIAL REPORT

Antiepileptic drug selection for people with HIV/AIDS: Evidence-based guidelines from the ILAE and AAN

*†Gretchen L. Birbeck, ‡Jacqueline A. French, §Emilio Perucca, ¶David M. Simpson, #Henry Fraimow, **Jomy M. George, ††Jason F. Okulicz, ‡‡David B. Clifford, §§Houda Hachad, and §§René H. Levy for the Quality Standards subcommittee of the American Academy of Neurology and the ad hoc task force of the Commission on Therapeutic Strategies of the International League Against Epilepsy

Summary

A joint panel of the American Academy of Neurology (AAN) and the International League Against Epilepsy (ILAE) convened to develop guidelines for selection of antiepileptic drugs (AEDs) among people with HIV/AIDS. The literature was systematically reviewed to assess the global burden of relevant comorbid entities, to determine the number of patients who potentially utilize AEDs and antiretroviral agents (ARVs), and to address AED–ARV interactions. Key findings from this literature search included the following: AED–ARV administration may be indicated in up to 55% of people taking ARVs. Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of approximately 50% to maintain unchanged serum concentrations (Level C). Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations (Level C). Coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment (Level C). Patients receiving ritonavir/atazanavir may require a lamotrigine dosage increase of approximately 50% to maintain unchanged lamotrigine serum concentrations (Level C). Coadministration of raltegravir/atazanavir and lamotrigine may not require lamotrigine dosage adjustment (Level C). Coadministration of raltegravir and midazolam may not require midazolam dosage adjustment (Level C). Patients may be counseled that it is unclear whether dosage adjustment is necessary when other AEDs and ARVs are combined (Level U). It may be important to avoid enzyme-inducing AEDs in people on ARV regimens that include protease inhibitors or nonnucleoside reverse transcriptase inhibitors because pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C).

KEY WORDS: Antiepileptic drugs, Antiretrovirals, HIV, Epilepsy, Interactions, ARV Resistance, Toxicity, Pharmacokinetics.

Epilepsy Research (2013) 103, 245–253

ELSEVIER

journal homepage: www.elsevier.com/locate/epilepsyres

The impact of enzyme-inducing antiepileptic drugs on antiretroviral drug levels: A case-control study☆

Jason F. Okulicz[a,b], Greg A. Grandits[c], Jacqueline A. French[d], Emilio Perucca[e], Jomy M. George[f], Michael L. Landrum[a,b], Edward P. Acosta[g], Gretchen L. Birbeck[h,*]

Conclusions: ARV levels below C_{min} were more common in participants receiving EI-AEDs, the difference being statistically significant for intervals associated with EI-AED levels within the reference range. These data suggest that, in agreement with current guidelines, EI-AEDs should be avoided in patients receiving ARV therapy.

Corticosteroids & ASM

Phenobarbital, phenytoin and carbamazepine induce CYP3A and decrease the serum concentrations of the steroids by 30-50%. Dosage increase of prednisone/prednisolone/methylprednisolone 1.5-2-fold suggested for patients taking phenobarbital, phenytoin and carbamazepine.

Prednisone/prednisolone/ methylprednisolone

ASM
Carbamazepine, phenytoin, phenobarbital
Others not studied

Corticosteroids cause enzyme induction in high doses, but clinical relevance in terms of potential interactions unclear. No effect on CYP3A metabolism (midazolam) at 10 mg prednisone for 28 days.

Evaluation:
- May be relevant as comedication in critically ill patients

Stjernholm, Katz, J Clin Endocrin metab, 1975, Olivesi A. Biomed Pharmacother, 1986
Marcantonio et al., J Clin Pharmacol, 2014, Matulkovà et al, 2014

Summary

- **Pharmacodynamic interactions: consider pharmacological properties of drugs being combined!**
- **Pharmacokinetic interactions: mostly affecting drug metabolism**
  - Can be bidirectional
  - May cause enhancement or loss of activity of the affected drug
  - Can be anticipated based on knowledge of affected enzymes affected
  - Magnitude of interaction in the individual poorly predictable
  - May be controlled by use of TDM and dose adjustment
- **Use or avoidance of potentially interacting drugs rests on careful assessment of risk to benefit ratio in the individual patient**
- **Always monitor clinical response carefully, and adjust treatment as appropriate**