EpiCare web session, 9 April, 2020

ANTISEIZURE MEDICATIONS AND CHALLENGES IN THE COVID-19 PANDEMIC

Focus on drug interactions and special treatment issues

Cecilie Johannessen Landmark, PhD
The National Center for Epilepsy and Oslo University Hospital, Norway

Emilio Perucca, MD
C. Mondino National Neurological Hospital, EpiCARE, Pavia and University of Pavia, Italy

Simon Shorvon, MD
The National Hospital for Neurology and Neurosurgery, London, UK

Eugen Trinka, MD
University Hospital Paracelsus Medical University, Salzburg, Austria

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

Italy and Spain have turned the corner, with numbers of new cases now in decline, following in China's footsteps


Age Distribution of Covid-19 Casualties in Italy

<table>
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<tr>
<th>Age range</th>
<th># casualties</th>
<th>% casualties</th>
<th>death rate (% of infected)</th>
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<td>Total</td>
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Does COVID-19 Affect the CNS?
Tissues Expressing ACE2 Receptors - Possible Targets of Covid-19 Infection

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)

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**

EpiCARE Steering Committee, 2020 (and other sources)
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


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-dysrhythmic potential

EKG check before /after treatment may be indicated
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

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


- 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

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Text Legend:
- ↑ Potential increased exposure of the concomitant drug
- ↓ Potential decreased exposure of the concomitant drug
- Potential increased exposure of COVID drug
- Potential decreased exposure of COVID drug
- No significant effect

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 safety monitoring or dosage adjustment unlikely to be required
- No clinically significant interaction expected

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

- 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

<table>
<thead>
<tr>
<th>Enzyme inducers (CYP3A, CYP2B, CYP2C, UGT, and possibly other enzymes)</th>
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<tbody>
<tr>
<td>Enzyme inhibitors (specific enzymes inhibited vary across ASMs)</td>
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<tr>
<td>Mixed inducer/inhibitor (enzyme affected vary across ASMs)</td>
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<tr>
<td>Little or no propensity to induce or inhibit drug metabolizing enzymes</td>
</tr>
<tr>
<td>Most ASMs are affected by interactions</td>
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<tr>
<td>Exceptions are those ASMs that are excreted renally as their main pathway of elimination</td>
</tr>
</tbody>
</table>

**Older**
- Ethosuximide
- Phenobarbital
- Phenytoin
- Carbamazepine
- Clonazepam
- Clobazam
- Primidone
- Sulthiame
- Valproic acid
- Other BZ

**Newer**
- Felbamate
- Gabapentin
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Pregabalin
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

**Newest**
- Cannabidiol
- Brivaracetam
- Cenobamate
- Eslicarbazepine
- Everolimus
- Lacosamide
- Perampanel
- Rufinamide
- Stiripentol

**Bold characters** indicate stronger interaction potential

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)

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
- Emapalumab
- Sarilumab

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

### Antimicrobial 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

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

Chloroquine
Hydroxychloroquine

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

https://www.covid19-druginteractions.org

April 7, 2020
Antiviral Drugs & ASMs

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

**Enzyme inducing ASMs** (especially carbamazepine, phenobarbital, 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.

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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.

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Cao B et al., New Eng J Med, March 2020
https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8N7Y86-7swfF3KmkUF2fIIP306F_o66a0MgxK1uZtI1c8
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 35% of people taking ARVs. Patients receiving phenytoin may require a levetiracetam dosage increase of approximately 50% to maintain unchanged lamotrigine serum concentrations (Level C). Patients receiving valproate may require a fenytoin/diphenytoin dosage increase of approximately 50% to maintain unchanged lamotrigine serum concentrations (Level C). Patients receiving valproate may require a zidovudine dosage reduction to maintain unchanged lamotrigine serum concentrations (Level C). Coadministration of valproate and lamotrigine 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 ritonavir/atazanavir and lamotrigine may not require lamotrigine dosage adjustment (Level C). Coadministration of ritonavir 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.

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 Cmin 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.
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.

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

**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**