COVID-19 treatment in patients with comorbidities: Awareness of drug-drug interactions.

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Abstract

In a recent issue of Br J Clin Pharmacol Smith et al1 published an outstanding commentary titled 'Dosing will be a key success factor in repurposing antivirals for Covid-19'. They highlighted that the success in our repurposing efforts will be dependent on 'getting the dose right' for drugs which have been developed for different indications and stressed some of the unique challenges of treating this particular disease. They pointed the reader to lopinavir/ritonavir (LPV/r) as an example of a repurposed antiviral and the limited experience of this drug regimen (and other treatments) in the elderly population with comorbidities – ie those most at risk from Covid-19. It is on the issue of comorbidities, polypharmacy and drug-drug interactions (DDIs) that we wish to comment.

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In a recent issue of Br J Clin Pharmacol Smith et al[1]published an outstanding commentary titled 'Dosing will be a key success factor in repurposing antivirals for Covid-19'. They highlighted that the success in our repurposing efforts will be dependent on 'getting the dose right' for drugs which have been developed for different indications and stressed some of the unique challenges of treating this particular disease. They pointed the reader to lopinavir/ritonavir (LPV/r) as an example of a repurposed antiviral and the limited

experience of this drug regimen (and other treatments) in the elderly population with comorbidities – ie those most at risk from Covid-19. It is on the issue of comorbidities, polypharmacy and drug-drug interactions (DDIs) that we wish to comment.

Age-related comorbidities result in complex polypharmacy and an increased risk of DDIs[2]. Furthermore, physiological changes related to ageing may affect both pharmacokinetics (PK) and pharmacodynamics (PD) thereby putting elderly patients at risk of inappropriate prescribing and adverse drug reactions. In the case of LPV/r, particular attention needs to be focussed on PK interactions involving inhibition of CYP3A4 and some transporters[2]. To aid health care professionals managing LPV/r (and other antiretroviral) DDIs in HIV patients we developed the online resource www.hiv-druginteractions.org[3]which is extensively cited in national and international treatment guidelines. However, in addition to PK interactions, LPV/r is known to cause QT prolongation and is on the CredibleMeds listing[4] for drugs with a possible risk of torsades de pointes (TdP). Indeed the drug label for LPV/r includes the warning to 'avoid use with QT-prolonging drugs' because of DDIs and effects on PR and QTc[5].

Possibly of greater topicality at present is the risk of QT prolongation and TdP in Covid-19 patients given the repurposed drugs chloroquine and hydroxychloroquine. This has been highlighted in recent cohort studies[6,7] and in warnings from the EMEA[8] and FDA[9].

Patients given experimental COVID-19 therapies will often be clinically unstable with organ dysfunction, and the development of toxicities from DDIs must be carefully considered. These very ill patients may not only be receiving an experimental COVID drug with a known or possible risk of TdP as single agents or combined (LPV/r, chloroquine, hydroxychloroquine, azithromycin)[4] but can have other risk factors for TdP such as hypokalemia, female gender, age > 70 years as well as concomitant (eg some anaesthetics, muscle relaxants, analgesics, antiarrhythmics, antibacterials, antipsychotics, gastrointestinal agents) thereby potentially increasing the risk of TdP[10]. The CredibleMeds website classifies drugs into those with a known risk, a possible risk and a conditional risk of TdP. However, there is still the challenge of giving appropriate clinical advice to guide the safe use of a COVID therapy and one or more co-medications in individual patients. Having established prescribing resources for managing DDIs in other viral infections (with a database of commentaries on >30,000 DDIs, with data systematically collected from medical and scientific literature, information from drug regulatory authorities or expert opinion), to meet the challenge of the COVID pandemic a similar resource is now available at www.covid19-druginteractions.org[11]. DDIs are graded into four levels and colour coded: i) no clinically significant interaction expected (green); ii) potential interaction likely of weak relevance (yellow); iii) potential interaction that may require close monitoring, alteration of drug dosage or timing of administration (amber); and iv) drugs should not be co-administered (red). It is made clear that the decision to give or not give drugs is always the responsibility of the prescriber with many other factors having to be considered such as age and electrolyte imbalance. In addition since chloroquine and hydroxychloroquine have very long half-lives (30-60 days) DDIs may occur even after discontinuing treatment[9]. Systematic medication review should aim at discontinuing unnecessary QT prolonging drugs or finding alternatives devoid of QT risk. The use of decision support systems is important in effective management of drug therapies in COVID patients.

Author Contributions

DBa, CM, CH, FM, AB, SG, DBu, SK, have all been involved in the development of the web resource www.covid19-druginteractions.org. Dba, CM and DBu wrote this manuscript.

Competing Interests.

DBa, SK received educational grant funding for www.covid19-druginteractions.org from Novartis and Abbvie.

References

1. Smith PF, Dodds M, Bentley D, Yeo K. Dosing will be a key success factor in repurposing antivirals for COVID-19. Br J Clin Pharmacol 2020; Apr 17. doi: 10.1111/bcp.14314.

2. Back DJ & Marzolini C. The challenge of HIV treatment in an era of polypharmacy. J Int AIDS Soc. 2020; 23, e25449.

3. http://www.hiv-druginteractions.org (2020). Accessed April 28th 2020

4. http://www.CredibleMeds.org (2020). Accessed April 28th 2020.

5. Kaletra® prescribing information (April 2020). Accessed April 28th 2020

6. Borba MGS, Val FFA, Sampaio VS et al. Effect of high vs low dose chloroquine diphosphate as adjunctive therapy for patients hospitalised with severe respiratory syndrome coronavirus 2 (Sars-Cov-2) infection: A randomised clinical trial. JAMA Netw Open 2020; April 1: 3 (4) e208857.

7. Chorin E, Dai M, Shulman E et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020; https://doi.org/10.1038/s41591-020-0888-2.

8. EMEA news release April 23rd 2020. http://www.ema.europa.eu.

9. FDA drug safety communication. April 24th 2020. http://www.fda.gov/safety

10. http://www.medsafetyscan.org. Accessed April 28th 2020.

11. http://www.covid19-druginteractions.org. Accessed April 28th 2020.