EDITORIAL

COVID-19 and the quality use of medicines: evidence, risks and fads

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Principles of ethical prescribing for self and others: hydroxychloroquine in the COVID-19 pandemic

The COVID-19 pandemic is rapidly evolving and determining the appropriate response is complex. The severity of COVID-19 and the limited evidence for any treatment have added to the complexity of clinical decision making and prescribing. A vaccine is not yet available, but decisions about treatment are needed now.

Fear in the community has resulted in people trying unproven remedies. These fads include consuming bleach,[1] and gargling warm salt water or vinegar.[2] Each fad has varying toxicity and none is of likely benefit. Consuming chloroquine from an aquarium product[3] and drinking methanol have been fatal.[4] High-dose vitamin C has been discouraged as a treatment for COVID-19,[5] but reports that it is being prescribed to,[6] and studied in,[7] patients with COVID-19 could confuse the public about its place in therapy. These examples highlight the need for balanced discussions of the harms and benefits of each proposed treatment.

Australian healthcare workers have the opportunity to learn from colleagues overseas with advice being received daily. There are many anecdotes about treatment, usually conveying a brief and narrow perspective. Each can consciously and subconsciously influence our clinical decisions.

Information about the purported effects of drugs in COVID-19 is rapidly changing. Most reports focus on what is new, rather than summarising what has been learnt to date. It is easy to miss when a treatment claim becomes discredited or raises new safety concerns.

Currently, supportive care is the mainstay of treatment for COVID-19. Suggested drug treatments have been based mostly on in vitro studies or biomarkers from observational studies. At best, preliminary data from these studies should be considered hypothesis generating and prompt more research, rather than guiding clinical management. Many clinicians are not experts in research methods, so we may not appreciate the limitations of the results based on the shortcomings of the methods used in some of these studies.

Over 300 trials including more than 50 drug or biological treatments for COVID-19 have been registered.[8] These will generate both hope and uncertainty. Currently the main approaches include inhibiting viral replication with chloroquine, hydroxychloroquine or antiviral drugs,[9] immune modulation by corticosteroids, tocilizumab or stem cells, and administration of convalescent sera.

Some studies that have been popularised by the media have been uploaded to online preprint servers without the rigour of peer review. This may not be apparent from an abstract or media report so a high level of scepticism is required.

A global survey of physicians in early April 2020 found that hydroxychloroquine and azithromycin were prescribed or seen to be prescribed by nearly 50% of respondents. However, only 38% perceived efficacy in COVID-19.[10] Some healthcare workers have prescribed hydroxychloroquine for themselves and their families. This represents extrapolation of the very low-quality evidence for treatment[11] to experimental use for prophylaxis.[12] The decision may have been their own, but it has been rumoured that some doctors were advised by their employer to self-prescribe hydroxychloroquine due to their increased risk of being infected by patients with COVID-19. This highlights the ethical questions about prescribing experimental treatments.[13] It is important to distinguish off-label from experimental prescribing.

Given the rate that the pandemic is evolving, the processes required to start a clinical trial may appear prolonged. However, these processes are necessary to develop a protocol, allocate resources and ensure patients are monitored to avoid treatment-related deaths. An experimental treatment should only be prescribed after informed consent is obtained.

The doses of some drugs being prescribed for COVID-19 are high compared to those used for their approved indications. Clearly, the greater the dose the greater risk of harm, and this is likely to be compounded in older patients with multiple comorbidities or those with viral myocarditis.

Some studies have used combinations of drugs which makes it difficult to assess their individual efficacy and toxicity. The combination of hydroxychloroquine and azithromycin is associated with cardiotoxicity, including a newly prolonged QTc interval of over 500 ms in 10–20% of participants.[14,15] A preprint publication of a retrospective study reported higher mortality in patients receiving hydroxychloroquine than those who did not.[16] Cardiotoxicity including ventricular tachycardia and death with higher doses of chloroquine prompted the early cessation of a Brazilian study.[17] Preventable drug-induced toxicity due to overdosage may have occurred in other

pandemics, including aspirin for influenza in 1918–19[18] and ribavirin for severe acute respiratory syndrome in 2003.[19]

In March 2020 there was much discussion that renin–angiotensin system inhibitors may increase the severity of COVID-19.[20-22] Much of this concern then subsided and it was recommended for patients taking these drugs to continue them.[20,22] The harm from stopping these drugs in patients with heart failure or other high-risk cardiovascular conditions is probably far greater than the unproven risk of severe COVID-19.[23,24] Subsequent studies confirmed that there was no increased risk from COVID-19 with renin–angiotensin system inhibitors,[25-28] confirming the earlier advice. There have also been concerns about non-steroidal anti-inflammatory drugs (NSAIDs) notably ibuprofen.[21] The current position is that NSAIDs can be used when indicated, but paracetamol is likely to be an acceptable alternative.[29-32]

Another risk from the increased prescribing of unproven drugs is that it creates a shortage of these drugs for patients who rely on them. For example, there has been a shortage of hydroxychloroquine for systemic lupus erythematosus, and reports of possible ivermectin efficacy in COVID-19 led to shortages within days. The shortages also impact on the supply of medicines for clinical trials. Regulators, funders and policymakers have needed to enforce or introduce regulations to prevent inappropriate prescribing and stockpiling. The Therapeutic Goods Administration and Pharmaceutical Benefits Scheme have now restricted who can prescribe hydroxychloroquine.[33,34]

COVID-19 is presenting a number of challenges. We should not compound the crisis by inappropriate prescribing based on inadequate evidence, which increases the risk of harm and causes drug shortages. At present all prescribing for COVID-19 is experimental. Healthcare professionals must constantly analyse the literature and stay up to date using trusted resources. We need to explain clearly the challenge of balancing harm and benefit to our patients, friends and family. The COVID-19 pandemic is an opportunity to improve the health literacy of the public and to emphasise the principles of the quality use of medicines to ensure drugs are used safely and effectively. <

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