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EDITORIALS

Non-steroidal anti-inflammatory drugs and covid-19

Extra risk is plausible on current balance of evidence

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Emerging evidence suggests that the most serious complications of covid-19 are sepsis and cardiovascular or respiratory complications. They occur predominantly in elderly people and those with underlying health conditions.[1] Does use of non-steroidal anti-inflammatory drugs (NSAIDs) increase these risks? We don't know for certain, but additional risks are plausible on the current balance of evidence.

Evidence of harm

In observational studies, long term use of NSAIDs such as ibuprofen, naproxen, and diclofenac has been associated with higher rates of cardiovascular outcomes such as myocardial infarction, heart failure, and stroke[2]—albeit with ongoing debate about residual confounding.[3] Acute respiratory tract infections are already associated with increased risk of stroke and myocardial infarction, and short term use of NSAIDs during the illness is associated with further increases in risk.[4,5] NSAIDs cause nephrotoxicity,[6,7] which is more likely among the patient groups most likely to be seriously affected by covid-19 and is exacerbated by fever and dehydration.

A recent review of case-control studies suggests that NSAIDs are associated with higher rates of complications after respiratory tract infections, including complicated pneumonia, pleural effusions, prolonged illness, peritonsillar abscess, dissemination of infection to more than one site, or suppuration.[8] NSAIDs were also associated with delays in the prescription of effective antibiotic treatment for patients requiring hospital admission.[8]

The review's authors say the findings are plausibly explained by the inhibiting effect of NSAIDs on cyclo-oxygenases, which reduces polymorphonuclear recruitment and also inhibits the synthesis of lipoxins and resolvins, delaying the resolution of inflammation.[8] Case-control evidence is limited by confounding by indication, whereby NSAIDs are prescribed to treat the early symptoms of complications and are not causally related to those complications. But these associations persist even in studies that control for this kind of confounding.[8,9] Furthermore, one large case-control study found an association between NSAIDs and respiratory complications, whether the NSAIDs were taken long term or just to treat a short acute illness. This suggests that the association is not simply a result of increased prescription in response to acute illness.[10]

What about trial evidence in primary care settings? A large trial (n=889) randomised patients presenting with respiratory tract infections to advice to take paracetamol, ibuprofen, or both.[11] Re-consultations with new or unresolved symptoms or complications were documented in 12% of the paracetamol group and 20% of the ibuprofen group (adjusted risk ratio 1.67, 95% confidence interval 1.12 to 2.38). The 11 complications recorded in the ibuprofen group were quinsy, sinusitis (n=3), meningitis, pneumonia, otitis media (n=3), and progression or non-resolution of otitis media (n=2).

A second randomised trial in 3044 primary care patients gave half access to a website advising on self-management of respiratory tract infections, including advice to use NSAIDs.[12] Multivariate analyses suggested that among participants who developed respiratory tract infections, those with access to the website had more prolonged illness than controls without access—that is, more days of illness rated moderately bad or worse (difference 0.52 days; 95% CI 0.06 to 0.97, P=0.026). The effect could not be explained by reporting bias or confounding by indication and was attenuated after the authors controlled for use of the ibuprofen web pages.

This pragmatic trial evidence supports observational data suggesting that NSAIDs may cause more prolonged illness or complications when taken during respiratory tract infections.

What about covid-19?

Clearly, the big unknown is whether any of this evidence applies in the covid-19 epidemic. The evidence to date is not strong enough to support advising against all use of NSAIDs: the primary care trials above tested more regular dosing during respiratory infections, so we have little evidence about intermittent use, and it seems likely that that intermittent or occasional use could help patients with covid-19—for example, to relieve night time symptoms and aid sleep if paracetamol is inadequate, given the importance of sleep in immune defence.[13] Furthermore, patients with covid-19 may need NSAIDs for other symptoms such as musculoskeletal pain.

People taking low dose aspirin for secondary prevention of cardiovascular disease should continue their treatment. Aspirin

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has anti-inflammatory effects only at much higher doses (eg, 1-4 g per day).

In summary, reasonable evidence exists of a link between NSAIDs and both respiratory and cardiovascular adverse effects in several settings, but so far we have no evidence relating specifically to people with covid-19. Pending further research, a pragmatic and cautionary approach would be for the public to avoid these plausible harms: regular NSAID use should probably not be recommended as the first line option for managing the symptoms of covid-19.

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