Paracetamol use in COVID-19: friend or enemy?

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Abstract

COVID-19 pandemic represents an unprecedented sanitary threat: antiviral and host-directed medications to treat the disease are still urgently needed.

A great effort has been paid to find drugs and treatments for hospitalized, severely ill patients. However, medications used for the domiciliary management of initial symptoms, notwithstanding their importance, have not been and are not presently regarded with the same attention.

In analogy with other respiratory viral infections, COVID-19 patients in the early phase require specific antivirals (still lacking) and non-etiotropic drugs to lower pain, fever and control inflammation. Non-steroidal antinflammatory drugs (NSAIDs) and paracetamol (PAC) are widely used as non-etiotropic agents in these conditions and hence are both theoretically repurposable for COVID-19. However, a warning from some research reports and National Authorities raised NSAIDs safety concerns because of the supposed induction of ACE2 protein levels (the receptor used by SARS-CoV2 to enter host airways cells), the risk of bacterial superinfections and masking of disease symptoms. As a consequence, the use of NSAIDs was, and is, strongly discouraged while the alternative adoption of paracetamol is still preferred.

On the basis of novel data and hypothesis on the possible role of scarce glutathione (GSH) levels in the exacerbation of COVID-19 and of the GSH depleting activity of PAC, this commentary raises the question of whether PAC may produce an oxidative imbalance which could be detrimental in COVID-19 clinical outcomes.

Introduction

COVID-19 pandemic is posing an enormous sanitary threat. In the absence of specific vaccines and anti-SARS-CoV-2 drugs, medicines that may hamper COVID-19 virulence and reduce the high number of fatalities are urgently needed. To this end, many drugs have been repurposed, including tocilizumab, heparin, remdesivir, chloroquine, ivermectin, sarilumab, chromones[1].

Most of the effort has been so far devoted to the identification of medications to treat the life-threatening complications of COVID-19, namely cytokine storm and hypercoagulation [2,3] Surprisingly, however, poor attention has been paid by health authorities to the development of common guidelines to treat COVID-19 in the early phases, i.e. stage 1 to stage 2A [4].

This critical phase, similarly to other viral infections and according to a widely accepted pharmacological praxis, should be timely treated either with etiotropic drugs (which in COVID-19 case are still lacking) as well as with host-directed agents to attenuate the symptoms [5]. In particular. since the pivotal role of inflammation in COVID-19 life threatening complications had been identified shortly after the outbreak in Wuhan, particular attention should have been paid to identify the most active and appropriate antinflammatory drugs, and recommend their prescription at the presentation of the early symptoms to prevent their progression [1]. Despite this simple reasoning Health Authorities rather posed a number of warnings on the early use of a wide number of antinflammatory medications [1] including non-steroidal anti-inflammatory drugs (NSAIDs) [6]. According to these Authors, with the emergence of SARS-CoV-2 pandemic, the recommendation of precaution on NSAIDs was referred as to"*more topical than ever*" because of the reported worsening of bacterial and viral pulmonary infections, the supposed NSAIDs-associated overexpression of ACE2 [6] and the masking of symptoms which renders difficult grading the disease. As a result, the French Ministry of Health Olivier Veran and the Royal College of Obstetricians and Gynaecologists in the UK issued a safety concern regarding the use of NSAIDs [7]: this precautionary principle was then widely and transnationally accepted by the medical community

However, a closer view to NSAIDs pharmacodynamics might have led to opposite conclusions on their therapeutic value in SARS-CoV-2 infection. Indeed NSAIDs, by virtue of their renown antinflammatory and antiplatelet (especially aspirin) activities could be beneficial for both the early control of inflammation and the prevention of thromboembolism, thus theoretically limiting COVID-19 progression in a bimodal pattern. Moreover, as recently pointed by Martins-Filho et al. [8] "*To date, there is more speculation than robust scientific evidence that points to the true effect of NSAIDs, especially Ibuprofen, on COVID-19*", and "*there is no evidence supporting the association between Ibuprofen and increased risk of severity of COVID-19*". In parallel, accumulating evidence is drastically scaling back the supposed role of ACE2 upregulation by renin-angiotensin inhibitors in COVID-19 severity [9] which, according to some Authors' view, might even be beneficial [10].

However, the warning still prevails and paracetamol (PAC) was proposed as a safer and recommendable alternative for the early and domiciliary management of pain and fever in COVID-19 patients. Unfortunately PAC has no or negligible anti-inflammatory and antiplatelet activity [11] but, despite lacking these potentially valuable activities, represents the only drug that has been continuously used for the timely and domiciliary management of COVID-19.

Is this choice pharmacologically and toxicologically correct? Although generally considered safe, PAC adverse effects may theoretically vary depending on specific conditions, namely those occurring in COVID-19, which are sensitive to patients' oxidative state [12].

Glutathione levels and COVID-19

An interesting breakthrough in the relationships between the disease and oxidative stress may derive from four independent articles published between April and May 2020 pointing to the importance of reduced glutathione (GSH, the most important soluble antioxidant) cellular levels and integrity of the related antioxidant routes in COVID-19 pathogenesis [13–16].

The first article is a commentary which proposes glucose-6 phosphate dehydrogenase (G6PD) deficiency as a factor contributing to COVID-19 morbidity and mortality [13]. According to the Authors' view, G6PD deficiency leads to a fall in GSH-dependent antioxidant activity, which in turn causes a lower capacity to overcome SARS-CoV-2 infection. The second article reports the cases of two COVID-19 pneumonia patients successfully treated with high doses of supplemental intravenous GSH and oral N-acetyl-cysteine [14]. The third one, a human ecologic study, hypothesizes on the correlation between the glutathione S-transferase T1 (GSTT1) polymorphism and the outcome of COVID-19 [15]. Using univariate and multivariate analyses, the GSTT1 and GSTM1 null genotypes, known to be associated to an increased risk of several oxidative stress-related multifactorial diseases [17], were also found more prone to COVID-19. The last article is a thoughtful viewpoint/case report where the Author comments on the importance of antioxidant defense integrity in viral infections and suggests that low GSH levels may have a pathogenic role of in COVID-19, especially in the progression toward the more aggressive presentation of the disease [15].

A wide panel of converging reasons lends support to this hypothesis.

GSH, an abundant tripeptidyl molecule, plays pivotal roles in protecting cells against oxidative stress-induced cellular damage, in detoxifying xenobiotics and in drug metabolism [18].

Decreased GSH levels are associated with the common features of aging as well as of a wide range of pathological conditions, comorbidities, smoking habit [19] which, intriguingly, represent the major risk factors for COVID-19.

On the contrary, resistance to viral diseases positively correlates with the extent of GSH stores, whose abundance has been associated with better individual's responsiveness to viral infections [20,21]: in particular, GSH is known to protect host immune cells operating in oxidatively stressing environments and contributes to their optimal functioning. GSH has been shown to inhibit replication of various viruses at different phases of their reproductive cycle [22,23]: this antiviral property of GSH seems to prevent increased viral loads and the subsequent massive recruitment of inflammatory cells, release of cytokines and reactive oxygen species (ROS) into the lung that incidentally characterize also the last COVID-19 stages. Of note, preventive supplementation of the GSH precursor N-acetylcysteine (NAC) significantly reduced the incidence of clinically apparent influenza, especially in higher risk elderly population [20].

Importantly, the deficiency of GSH in the alveolar fluid in Acute Respiratory Distress Syndrome patients was found to correlate with the increased ROS-mediated lung cell injury and inflammation [23]: again, supplemental NAC resulted in the prevention of this aggravating condition.

In addition GSH levels positively correlate with those of active vitamin D [24], whose deficiency seems to play a detrimental role in COVID-19 [25]. GSH deficiency results in the activation of von Willebrand Factor [26] and in the accumulation of ROS, which affect clotting and platelet activation, impair endothelial function and predispose to the risk of thrombotic events [27]: notably, hypercoagulation is a prominent life-threatening complication in COVID-19 patients [28].

Polonikov also reports his clinical observations on four moderate-severe COVID-19 cases: while the three patients with normal/high plasma levels of GSH have rapidly recovered, the one with the lower GSH levels, higher plasma ROS and ROS/GSH ratio experienced the most severe illness and, at the date of publication, was still sick [16]. Notably, the independent reports by Horowitz et al. and Polonikov [14,16] - although referring to a scarce number of cases - reciprocally strengthen each other in highlighting the relevance of poor GSH levels in COVID-19 clinical progression as well as the importance of maintaining/repleting GSH pools as a countermeasure against SARS-CoV2 virulence. To this end, it is important noting that the major risk factors for severe COVID-19 illness are ageing, comorbidities, smoking habit, all characterized by intrinsically low antioxidant capacity and high ROS/GSH ratios [16] (see Fig.1). Hence, according to precautionary principle any condition potentially leading to further depletion of GSH stores should be carefully avoided.

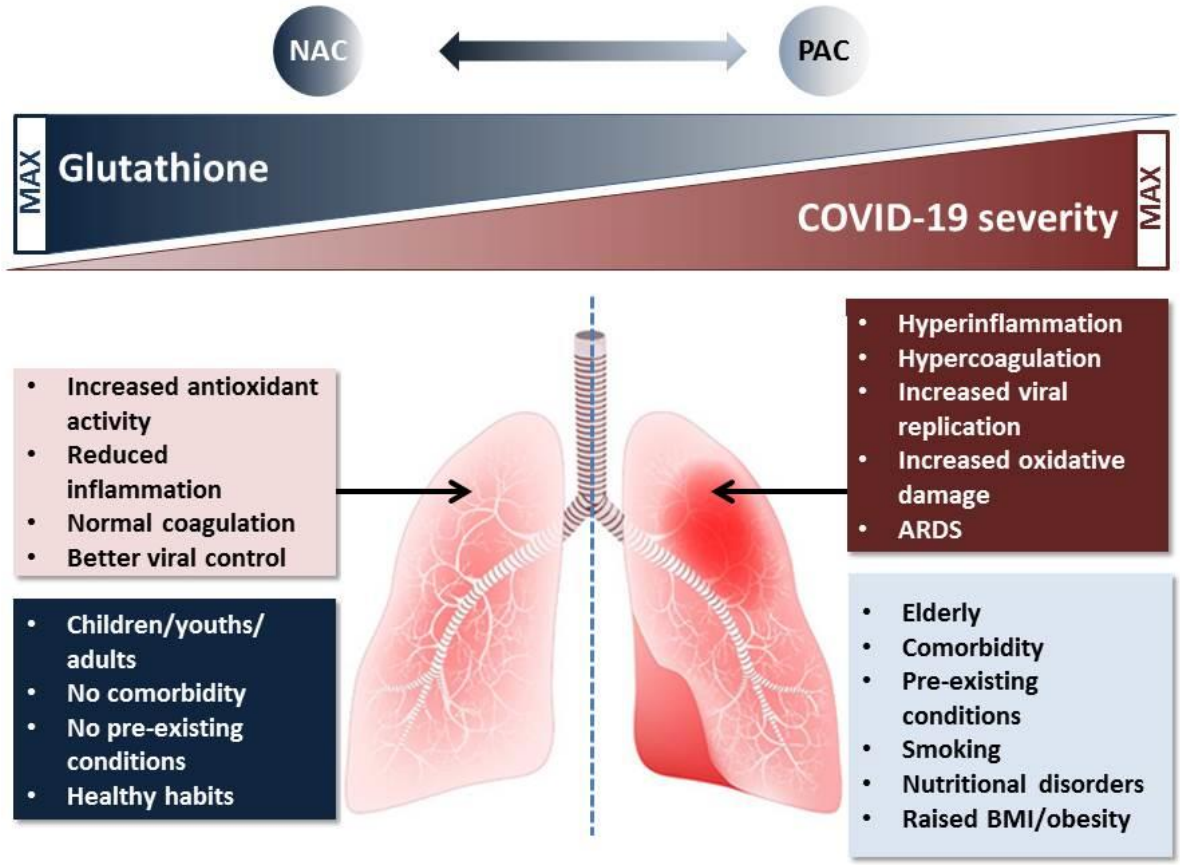

Figure 1. Proposed mechanism of the glutathione-paracetamol-COVID-19 interactions. Low risk population groups (blue box) have normal/high GSH levels which contribute to reduce the severity of COVID-19 (pink box). On the contrary, high risk population groups (pale blue box) are characterized by low GSH levels which cannot help modulating the deleterious events causing (brick-red box) severe COVID-19. N-acetylcysteine supplementation increases, while paracetamol may reduce GSH availability, especially in per se low-GSH subjects. ARDS, acute respiratory distress syndrome; BMI, body mass index; NAC, N-acetylcysteine; PAC, paracetamol.

Paracetamol for the early, routine management of COVID-19: toxicological implications

As discussed above, a precautionary principle regarding ACE2 overexpression was the main reason for the decision to discourage the use of NSAIDs in favor of PAC, generally reputed as a safe drug [6].

However, contrary to this opinion, we believe that in the specific case of COVID-19 it is of paramount importance taking due account of the fact that PAC and its metabolites are known to decrease GSH levels [29]. Although the drop in hepatic or renal GSH is the most toxicologically relevant interaction, plasma GSH and free cysteine are significantly reduced over 3 h after 2g PAC administration [30] in human volunteers; furthermore, clinically attainable concentrations of PAC have been shown to decrease in vitro intracellular GSH in human pulmonary macrophages, type II pneumocytes and lymphocytes [31,32]. Notably, the depletion of GSH in airway mucosa is considered as the most biologically plausible mechanism of the well-established epidemiologic association between PAC use and asthma prevalence/severity in children and adults [33,34].

Oxidized metabolites of PAC have also been shown to form GSH-conjugates which inhibit glutathione reductase (GR): the decreased activity of GR hampers the detoxification and antioxidant capacity of the GSH-GSSG cycle, further aggravating the pro-oxidative status in the cell [35].

From a different but relevant toxicological perspective, a study by Klopčič et al. indicates that PAC, in the absence of adequate, physiological levels of GSH, may give rise to genotoxic quinone imine metabolites [36]. As a consequence, although clinical application of PAC is generally safe, in the case of severely depleted GSH levels PAC should be administered with caution, especially in subjects with severe GSH depletion which, again, are those at higher risk of developing severe COVID-19 disease.

Conclusion

On the whole, PAC may lead to GSH depletion, especially in those population groups at higher COVID-19 risk [37] where this phenomenon may increase the risk of developing severe COVID-19 disease. The following considerations further strengthen the criticism toward the use of PAC as a safer alternative to NSAID:

1) PAC has been preferred to NSAIDs for the symptomatic and domiciliary management of the early stages of COVID-19, a choice grounded on a precautionary and theoretical principle.

2) Counterintuitively, however, the same precautionary principle has not been applied to PAC itself, and the risks of developing severe COVID-19 associated to the reduction of GSH might be far higher than the benefits derived from discouraging the use of NSAIDs.

3) In addition, PAC has the capacity to reduce fever and pain as well as NSAIDs [38] and may equally mask the symptoms and delay the objective grading of the disease but, importantly, it lacks the NSAIDs antinflammatory and antiplatelet activities that might be fundamental in containing COVID-19 exacerbation [28]. Although merely anecdotal, there is wide and transnational evidence of patients left at home with mild symptoms for more than a week receiving only PAC until their worsening conditions required hospitalization and, not rarely, admission to intensive care units.

4) The routinary use of PAC in at risk categories, along with their intrinsically frail conditions, may have further worsen the scarcity of GSH, especially in western countries where PAC consumption is particularly high. Such a situation may have rendered this group of population even more susceptible to SARS-CoV2 at the time of its spreading. To this end a merely speculative but intriguing hypothesis is that PAC adoption might even have contributed to the high virulence of

COVID-19 observed in many EU countries and USA. Notably, in most countries PAC is freely sold as an OTC drug, raising the risk of unintentional abuse and increased adverse effects [39].

5) No answer can be given to the above open questions because PAC efficacy/adverse effects, unlike most of the drugs repositioned for COVID-19 therapy, have not yet been evaluated in controlled clinical trials or analyzed through retrospective analyses. These trials, as well as studies aimed at determining the levels of GSH in the plasma of PAC-treated *vs* –untreated COVID-19 patients should be encouraged. As a corollary, it would be equally important to further investigate whether GSH or NAC supplementation should be adopted in the course of the prolonged use of fairly high doses of paracetamol, not limited to COVID-19.

Hence, the preferential use of PAC in COVID-19 as a safer alternative to NSAIDs should be carefully reconsidered and NSAIDs use eventually reappraised. Finally, Countries entering unlock phase should promote the development of more rational treatment guidelines for COVID-19, taking due account of the above facts and considerations to avoid that the same mistake - if concerns on PAC are ascertained - may be repeated by those ones still facing the worst scenarios.

Conflict of interest statement: the Authors declare that there is no conflict of interest.

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