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Letter to Editor

Management of critically Ill COVID-19 patients: Exploring the potential of morphine and assessing disadvantages of acetaminophen

Dear Editor

As the COVID-19 pandemic has become a significant challenge to healthcare systems worldwide, it is crucial to explore effective treatment approaches for critically ill patients. Acetaminophen has often been administered as the first-line medication for pain relief and fever reduction in COVID-19 patients, with little consideration given to its potential toxicities. However, high doses of acetaminophen in critically ill COVID-19 patients can pose certain disadvantages (1).

Firstly, acetaminophen has limited anti-inflammatory properties, which may be a concern considering the prominent role of inflammation in COVID-19 lung complications. While acetaminophen can alleviate pain and reduce fever, medications with stronger anti-inflammatory effects may be more beneficial in managing the inflammatory response associated with severe COVID-19. Secondly, acetaminophen can potentially cause liver toxicity, especially when taken in high doses or for an extended period. When absorbed from the intestine, acetaminophen is metabolized in the liver cells through two major pathways: glucuronidation and sulfation. The majority of acetaminophen is metabolized via glucuronidation, producing a non-toxic metabolite that is eliminated in the urine. However, in cases of high-dose or prolonged acetaminophen use, when the glucuronidation pathway becomes saturated, a smaller fraction is metabolized through sulfation and another pathway called cytochrome P450 (CYP) 2E1.

The CYP2E1 pathway produces a harmful protein called N-acetyl-p-benzoquinone imine (NAPQI) in the mitochondria. Under normal conditions, NAPQI is rapidly detoxified by glutathione, which neutralizes and eliminates toxic substances. However, excessive acetaminophen consumption overwhelms the available glutathione stores, resulting in the accumulation of NAPQI and subsequent hepatocyte necrosis (2). The severity of the disease is influenced not only by the acetaminophen dosage and initial liver damage but also by the inflammatory response triggered by acetaminophen-induced liver injury. During hepatocyte necrosis, damaged cells release danger-associated molecular patterns (DAMPs), which are recognized by neutrophils and resident hepatic macrophages (Kupffer cells), activating these immune cells. Activated hepatic macrophages release proinflammatory cytokines like IL-1β or TNF-α, as well as chemokines such as CCL2, further amplifying inflammation and promoting the recruitment of immune cells, including bone-marrow-derived monocytes and neutrophils, to the liver. Acetaminophen-induced liver toxicity can manifest as hepatocellular necrosis and liver failure (2, 3).On the other hand, morphine, a potent opioid analgesic, has several advantages when used in critically ill COVID-19 patients. Firstly, morphine effectively manages severe pain, which is a significant concern in critically ill patients, especially those experiencing respiratory distress or other complications. By alleviating pain, morphine improves patient comfort and enhances their ability to cooperate with necessary medical interventions.

Furthermore, morphine has the potential to improve oxygenation in severe COVID-19 cases and commonly prescribed to relieve dyspnea in these patients (4, 5). It reduces respiratory workload, oxygen consumption, and enhances oxygenation (6). Sirohiya et al. observed a significant decrease in DNRS (dyspnea numeric rating scale), respiratory rate and oxygen saturation in COVID-19 patients 24 h and 72 h after the start of morphine administration, while, blood pressure and heart rate were not significantly altered after treatment (7). By reducing anxiety, improving ventilation efficiency, and decreasing the ratio of dead space ventilation, morphine enhances breathing and oxygen exchange. This is particularly beneficial in critical care settings for maintaining adequate oxygenation for COVID-19 patients (8). Moreover, other observed effects of morphine may be translatable for similar manifestations associated with COVID-19. One study investigated the potential of using morphine to prevent damage caused by

reperfusion injury, which occurs after percutaneous intervention following a myocardial infarction. By blocking the entry of reactive oxygen species into cells and subsequently preventing cell death, morphine may have a protective effect in mitigating damage when oxygen supply is restored to the affected cells (9). Lastly, morphine has long been known to have immunosuppressive effects, particularly in relation to cytokine production. It impacts both the innate and adaptive immune systems and has suppressive effects on the immune response at the molecular and cellular levels. Various studies have shown that morphine can inhibit the production of cytokines such as TNFα, IFNγ, MCP 1, IL-12, and IL-6. It has also been observed that morphine can reduce the production of TNFα, IL-1, and IL-6 (10). In animal studies, morphine was found to inhibit the release of TNFα but had no significant effect on MCP1 release in the intraperitoneal cavity. Morphine treatment resulted in a decrease in TNFα, IL-1, IL-2, and MIP2 levels in lung tissue. When administered *in vivo*, morphine has been demonstrated to reduce delayed-type hypersensitivity reactions, cytotoxic T-cell activity, T-cell antigen expression, natural killer (NK) cell activity, antibody production, and neutrophil activity (11). Morphine was found to bind directly to ACE2, a receptor implicated in COVID-19, suggesting its potential as immunosuppressant adjuvants for managing the cytokine storm associated with the disease (12, 13). In addition, based on the findings from in vitro and in vivo models in non-COVID-19 conditions (14), it is proposed that morphine may have a beneficial outcome by mitigating the cytokine storm during the early stages of severe COVID-19.

However, further research is needed, as the timing of morphine administration appears to affect its impact on cytokine production. Moreover, the use of morphine should be carefully considered and administered under the supervision of medical professionals due to the risks associated with opioids, including respiratory depression and the potential for addiction or dependency. Additionally, it could be potentially harmful in late stages of severe COVID-19, especially in the presence of septic shock. Close monitoring and dosage adjustments are necessary to ensure patient safety and optimal pain management.

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References

1. Mostafa EMA, Tawfik AM, Abd-Elrahman KM. Egyptian perspectives on potential risk of paracetamol/acetaminophen-induced toxicities: Lessons learnt during COVID-19 pandemic. Toxicol Rep 2022; 9: 541-8.
2. Mazaleuskaya LL, Sangkuhl K, Thorn CF, et al. PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses. Pharmacogenet Genomics 2015; 25: 416-26.

3. Krenkel O, Mossanen JC, Tacke F. Immune mechanisms in acetaminophen-induced acute liver failure. Hepatobiliary Surg Nutr 2014; 3: 331-43.
4. Wong AK, Demediuk L, Tay JY, et al. COVID-19 end-of-life care: symptoms and supportive therapy use in an Australian hospital. Intern Med J 2021; 51: 1420-5.
5. Hetherington L, Johnston B, Kotronoulas G, et al. COVID-19 and hospital palliative care - A service evaluation exploring the symptoms and outcomes of 186 patients and the impact of the pandemic on specialist Hospital Palliative Care. Palliat Med 2020; 34: 1256-62.
6. Natalini G, Di Maio A, Rosano A, et al. Remifentanil improves breathing pattern and reduces inspiratory workload in tachypneic patients. Respir Care 2011; 56: 827-33.
7. Sirohiya P, Pandey K, Sagiraju HKR, Bhatnagar S. Effectiveness of morphine in managing refractory dyspnoea in patients with coronavirus disease (COVID-19). Indian J Palliat Care 2022; 28: 443-6.
8. Tanaka-Yagi Y, Yamaguchi T, Matsuda Y, et al. Morphine may contribute to improving respiratory failure in severe COVID-19: A case report. Indian J Palliat Care 2022; 28: 221-3.
9. Rentoukas I, Giannopoulos G, Kaoukis A, et al. Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. JACC Cardiovasc Interv 2010; 3: 49-55.
10. Cruz FF, Rocco PR, Pelosi P. Anti-inflammatory properties of anesthetic agents. Crit Care 2017; 21: 67.
11. Hudzik B, Nowak J, Zubelewicz-Szkodzinska B. Consideration of immunomodulatory actions of morphine in COVID-19 - Short report. Eur Rev Med Pharmacol Sci 2020; 24: 13062-4.
12. Roshanravan N, Ghaffari S, Hedayati M. Angiotensin converting enzyme-2 as therapeutic target in COVID-19. Diabetes Metab Syndr 2020; 14: 637-9.
13. Peter AE, Sandeep BV, Rao BG, Kalpana VL. Calming the Storm: Natural Immunosuppressants as Adjuvants to Target the Cytokine Storm in COVID-19. Front Pharmacol 2021; 11: 583777.
14. Fukada T, Kato H, Ozaki M, Yagi J. Impact of the timing of morphine administration on lipopolysaccharide-mediated lethal endotoxic shock in mice. Shock 2016; 45: 564-9.