REVIEW ARTICLE

Psychopharmacological treatment of Delirium in patients who are COVID-19+

Fabrizio Pavone M.D.[1], Andrea Fagiolini M.D.[2], Stefano Gelati M.D.[3], David K Ho M.D.[3*]

Pavone F, Fagiolini A, Ho DK, et al. Psychopharmacological treatment of Delirium in patients who are COVID-19+. JCPN 2020;3(1):1-5.

The scale and speed of the COVID-19 pandemic has been devastating both to patients and healthcare systems globally. This article provides concise and accessible information regarding well known pharmacological treatments for delirium in patients who are COVID+. It draws from the experience from clinicians in Italy, which was the initial epicentre of the outbreak in Europe. The agents reviewed here provide effects, side effects and interactions with other medications which are commonly used to treat patients, including antiviral agents. In conclusion, clinicians should recognise and treat delirium promptly in COVID+ patients given its potential to alleviate distress in patients, and allow for healthcare systems not to be unduly distracted by patients who present with delirium and agitation.

Key Words: *Delirium; Hypokinetic delirium; Agitation*

INTRODUCTION

The World Health Organization declared COVID-19 as a pandemic on 11th March 2019 [1]. At the time of writing, there are 4,836,329 confirmed cases, and 319,213 deaths in 213 countries or territories worldwide [2]. The speed and scale of the Sars-Cov-2 virus transmission and infection has not been seen since the pandemic of 1918. This novel coronavirus is known to cause acute respiratory symptoms including pneumonia, respiratory distress, and death. A significant proportion of patients who are severely ill with this infection consist of the elderly, and a considerable number of patients will require treatment in Intensive Care Units [3]. Both these scenarios lend to an increased probability of delirium occurring [4]. Delirium can be extremely distressing for patients, many of whom are already experiencing significant anxiety as a result of respiratory difficulties. For clinicians, delirium can inadvertently place undue burden on healthcare staff who are already experiencing difficulties with managing an unprecedented surge of patients. Prompt treatment of delirium however, is therefore of substantial utility during the acute phase of illness. In the longer term, delirium is known to be a strong predictor of mortality, certainly in mechanically ventilated patients [5]. This article provides clinical information and experience from Italy, which became the epicentre of COVID-19 in Europe. It aims to provide immediate psychopharmacological options for clinicians managing a large number of severely unwell patients with SARS-CoV-2 infection, and who present with delirium/ and or psychosis.

TREATMENT OPTIONS

Dexmedetomidine (For patients in Intensive Care Units)

This is an alpha 2 agonist, sedative-anxiolytic-analgesic that does not cause respiratory depression. Most common side effects: hypotension, hypertension and bradycardia (be mindful of interactions with beta blockers), occurring in 25%, 15% and 13% of cases respectively. It can be used in cases of kidney failure. It is metabolised by oxidation by CYP450 2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19. It inhibits CYP2B6. There is possible induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4 (although mainly *in vitro* studies). Please consider that many antiviral drugs are eliminated by oxidation, especially by CYP3A4 and 2D6. Therefore, Dexmedetomidine potentially reduces the concentrations of antiviral drugs. If it is used for a short period of time, the effect should not be too pronounced [6,7].

Clonidine

Risk/benefit assessment should be carried out by the ICU consultant.

Tiapride (Not in the BNF)

This is useful in patients who experience agitation (hyperkinetic delirium) and receiving treatment with Lopinavir/Ritonavir (Lo/Ri). The dose range is 50 mg - 300 mg in 24 hours. Tiapride is metabolised renally, therefore it does not interfere with the CYP involved in the metabolism of Lo/Ri or the most commonly used antibiotics. Tiapride can be administered orally, intramuscularly (if coagulation is not a problem) and also IV (useful in cases of malabsorption). In case of hyperkinetic delirium, start on Tiapride 100 mg intramuscularly, this can be repeated up to three times in 24 hours. As soon as possible, switch to oral, with a higher dose at night to improve sleep/wake cycle (50 mg 8 A.M., 50 mg 4 P.M., 100 mg 10 P.M). It is necessary to assess the possibility of QTc prolongation against the benefit in the short term of the sedative effect of the drug. The risk of arrhythmias, especially if associated with Lopinavir, is present but relatively low. More caution is required for patients with hypokalaemia and hypomagnesaemia (e.g. vomiting and diarrhoea). Always monitor oxygen saturation due to the risk of respiratory depression.

Sulpiride

Tiapride is not available in the UK, however Sulpiride is known to have very similar pharmacokinetic properties. Sulpiride has an excellent interaction profile and it can be used quite safely with antiretrovirals (including Remdesivir) and Chloroquine/Hydroxychloroquine. Sulpiride in the UK is only available as an oral treatment so its application is going to be limited. The dose will need to be individualized but doses above 400 mg a day are likely to be required.

Promazine

This can be used acutely (24-48 hours) in cases where there has been a poor response to Tiapride. It is possible to use Promazine IM (if not contraindicated because of coagulation problems), with a dose of 50-300 mg in 24 h. Promazine has a strong antihistamine effect, and a weak alpha-adrenergic, and anticholinergic effect. Its cardiovascular risk is lower

[1]*Azienda Socio-Sanitaria Territoriale (ASST) di Pavia, Italy;* [2]*Dipartimento di Medicina Molecolare e Dello Sviloppo, Universita di Siena, Italy;* [3]*Essex Partnership University NHS Foundation Trust, Kemble Way, Wickford, UK*

[*]**Correspondence to:** *David K Ho, Essex Partnership University NHS Foundation Trust, Kemble Way, Wickford, Essex, SS11 7FE, UK, Telephone: 01268 568092 (Extn. 4092), e-mail* **David.ho@nhs.net**

Received date: *May 01, 2020;* **Accepted date:** *May 25, 2020;* **Published date:** *May 30, 2020*

compared to many other typical antipsychotics. It is slightly sedative: monitor risk of respiratory depression. Interactions with Promazine (hepatic metabolism: CYP 1A2, 2C19 and 3A4) can occur (Lo/Ri on CYP 3A) but they are minimal with short term use (3-4 days), in accordance with its very short half-life (6 hours). There are no significant interactions with the most commonly prescribed antibiotics due to a predominantly renal metabolism of Tazobactam, Piperacillin and Doxicillin (the latter with 50% hepatic metabolism). With hydroxychloroquine (hepatic metabolism CYP 2D6, 2C8, 3A4, 3A5), its interaction with Promazine does not indicate an absolute contraindication, in the short term. As for Tiapride, it is necessary to assess the possible QTc prolongation (for example in association with Lopinavir) and monitor O_2 saturations for the risk of respiratory depression (only moderate risk in case of short-term use). The risk of arrhythmias in association with Lopinavir is relatively low. More caution should be used in patients with hypokalaemia and hypomagnesaemia (e.g. vomiting and diarrhoea).

Aripiprazole

This is useful for hypokinetic delirium. In hyperkinetic delirium, it is used mainly in the immediate release IM formulation (9.75 mg per vial). Aripiprazole does not have anticholinergic activity, and has low antihistaminic effect. The risk of arrhythmias is very low and the risk of respiratory depression is low. Although the risk of interactions with other medication is low, (its concentration increases with CYP 2D6 and 3A4 inhibitors), it is advisable to use a relatively low dose. The maximum dose in the absence of CYP inhibitors is three vials a day, with a minimum interval of two hours.

Haloperidol

The use of haloperidol in delirium has been extensively studied. The first dose should be between 2 mg and 5 mg. There is a low risk of respiratory depression. It is not antihistaminic and not anticholinergic. There is however a high risk of arrhythmias, due to QTc prolongation. Other commonly known risks include dystonia, and oculogyric crisis, and seizures due to the lowering of the seizure threshold.

Paliperidone

This is useful in patients with delirium, especially characterized by persistent symptoms of delusions or hallucinations, providing there is a lack of severe agitation. The suggested dose is 3 mg - 6 mg a day. Paliperidone has a minimal if at all hepatic metabolism.

Benzodiazepines

Avoid benzodiazepines unless delirium tremens is suspected. There are possible adverse interactions with respiratory related conditions and is contraindicated in acute pulmonary insufficiency and marked neuromuscular respiratory weakness.

DISCUSSION

As with all management and prescribing practices, it is essential that the choice of treatment is made by the treating physician. This in turn, should be based on the clinical presentation, concomitant medical treatment, and the individual characteristics of the patient including their co-morbidities. Further considerations include; drug to drug interactions including recommendations by the Liverpool Drugs Interaction Group [8], no observed significant interaction involving the use of psychotropics with immunosuppressants (Tocilizumab, inhibitor of the IL-6 receptor) in clinical practice, caution advised with the use of intramuscular psychotropics and heparin, and the use of corticosteroids can potentially increase delirium. Particular note should be taken by clinicians with regards to the risk of QT interval prolongation.

CONCLUSION

The use of some of the medication described here is in the 'off-label' category and should be used in accordance with local prescribing formularies. The prescribing of pharmacological agents however, should be considered by clinicians when managing COVID + patients, in this global medical emergency whereby healthcare systems are being stretched to the limit. It is likely to provide significant benefit to patients and health care systems in the face of this pandemic.

AUTHORS CONTRIBUTIONS

Dr. Fabrizio Pavone – Researched and provided clinical information.

Prof. Andrea Fagiolini - Researched and provided clinical information.

Dr. Stefano Gelati – Researched and reviewed article.

Dr. David Ho – Researched and reviewed article.

FUNDING

No funding sources.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. World Health Organization.
2. https://coronavirus.jhu.edu/map.html
3. Coronavirus Disease 2019 (COVID-19) in the EU/EEA and the UK-8th update. European Centre for Disease Prevention and Control.
4. Qiu HB. The keypoints in treatment of the critical novel coronavirus pneumonia patient. Chinese Journal of Tuberculosis and Respiratory Diseases. 43 (2020): E022.
5. Wesley EE. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 291.14 (2004): 1753-1762.
6. Stahl's Essential psychopharmacology: Neuroscience basis and practical applications.
7. https://bnf.nice.org.uk British National Formulary.
8. https://www.covid19-druginteractions.org.