Incidence of Adverse Reaction of Drugs used in COVID-19 Management: A Retrospective, Observational Study

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Introduction

• A study by Sun et al. in China on COVID-19 patients with treatment (N = 217) recorded an adverse drug reaction (ADR) rate of 37.8%.¹
• Safety surveillance activity is important due to unestablished safety profile of off-label medications used in COVID-19.

Objectives

• Primary outcome: To establish the incidence of ADR due to off-label drugs used in COVID-19 management
• Secondary outcomes: To establish the type of ADRs occurred, to identify potential risk factors for ADR and to evaluate the reporting rate of ADR by healthcare professionals

Methods

Eligibility criteria
Patients > 12 years with suspected or confirmed COVID-19 diagnosis who were initiated on medications for COVID-19 from 1 March 2020 to 31 May 2020 in Sungai Buloh Hospital

Instrument
• Case report form to record patient’s demographics, COVID-19 drugs, lab parameters & details of suspected ADR
• Suspected ADRs were evaluated with a trigger tool of pre-defined laboratory values or documented undesirable effects listed in the product inserts

Data analysis
• Patient demographic, incidence & types of ADR, as well as ADR reporting rate were tabulated using descriptive analysis
• The association of risk factors for ADRs was evaluated using Chi-square test, as well as simple & multiple logistic regression

Discussion

• The most observed ADRs were diarrhea & hyperbilirubinaemia, which are known side effects for lopinavir/ritonavir and atazanavir, respectively.²
• Female gender is a potential risk factor due to differences in circulating hormonal levels, having more prescription drugs, & the higher dose used in relation to their body weight.³
• Patients who developed ADR were mostly diagnosed with COVID-19 stage 3 (39.3%) or stage 4 (36.1%), which could have been contributed by the use of protease inhibitors in this group of patients.
• Every addition of a COVID-19 drug to the treatment regime increases the risk of ADR by 3.38 times, possibly due to drug-drug interactions.⁴
• The underreporting rate was 80.1%, due to inexperience, insensitivity, & lack of training in pharmacovigilance among HCWs.⁵
• The study was limited by convenience sampling. Favipiravir & tocilizumab were not widely used during the study period, resulting in poor representation.

Results

Incidence & classification of ADR

217/1,080 patients (20.1%) experienced suspected ADR

Table 1: Classification of ADRs (n = 246 ADR events)

| ADR according to system organ class | Incidence of ADR |
|-----------------------------------|-----------------|
| Blood & lymphatic system disorders | Anaemia 2 (0.8%) |
|                                    | Cardiac disorders 34 (13.8%) |
|                                    | QT prolongation 4 (1.6%) |
|                                    | Bradycardia 1 (0.4%) |
|                                    | ST elevation 1 (0.4%) |
| Gastrointestinal disorders         | Diarrhea 76 (30.9%) |
|                                    | Nausea & vomiting 27 (11.0%) |
|                                    | Abdominal pain 4 (1.6%) |
| Hepatobiliary disorders            | Hyperbilirubinemia (without jaundice) 77 (31.3%) |
|                                    | Elevated liver transaminases 6 (2.4%) |
|                                    | Hyperbilirubinemia (with jaundice) 5 (2.0%) |
|                                    | Elevated alkaline phosphatase 1 (0.4%) |
| Nervous system disorders           | Giddiness 3 (1.2%) |
|                                    | Headache 1 (0.4%) |
| Renal & urinary disorders          | Acute kidney injury 2 (0.8%) |
|                                    | Skin & subcutaneous tissue disorders 1 (0.4%) |
|                                    | Rash 2 (0.8%) |

Incidence of ADR is reported as n (%), where % is calculated by incidence of ADR/n.

Risk factors of ADR

Table 2: Independent risk factors of ADR

| Variable | Multivariate analysis | Adjusted OR (95% CI)* | P value |
|----------|-----------------------|-----------------------|---------|
| Female | 1.53 (1.06, 2.20) | 0.024 |
| COVID-19 category |                      |                       |         |
| Stage 3 | 2.58 (1.20, 5.55) | 0.015 |
| Stage 4 | 4.17 (1.79, 9.73) | 0.001 |
| No. of COVID-19 drug(s) | 3.34 (2.51, 4.44) | <0.001 |

*Forward & Backward LR applied. Hosmer & Lemeshow = 0.121. Classification table = 83.2. No multicollinearity was detected. ROC = 0.83 (0.79, 0.86; P value < 0.001). Only variables with P value < 0.05 were included in the adjusted OR.

Reporting rate of ADR by healthcare professionals

• Only 49 events (19.9%) were reported
• Most commonly reported ADRs were: - Hyperbilirubinemia (65.3%) - QT prolongation (28.6%)

Conclusion

20.1% of the patients experienced ADR from drugs used in COVID-19 management. Female, diagnosis of COVID-19 stage 3 and stage 4 (highest category during hospitalisation), and the number of COVID-19 drugs were identified as independent risk factors of ADR. More research is warranted in ADR surveillance to maximise patient safety.

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