Multiple drugs

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Various toxicities, off-label use and lack of efficacy: case report

A 73-year-old man developed hypotension following sedation with fentanyl, midazolam and propofol, and neuromuscular blockade with cisatracurium besilate. Additionally, he also experienced prolongation of QT interval (QTc) following off-label therapy with hydroxychloroquine for acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and treatment with amiodarone for paroxysmal atrial fibrillation. He also received oseltamivir and immune globulin as off-label therapy for SARS-CoV-2. Further, he did not respond to escalating pressor support with norepinephrine, and he exhibited increasing inflammatory parameters (LOE) in spite of broad-spectrum antibiotic therapy with cefepime, doxycycline and vancomycin for ventilator-assisted pneumonia [*not all routes stated; dosages not stated*].

The man was admitted to an ICU in Boston in March 2020, due to acute hypoxaemic respiratory failure during the coronavirus pandemic. He had been well until 6 days earlier, when he developed dry cough and fever, accompanied by worsening fatigue. Multiple investigations were performed following admission; meanwhile, he started receiving off-label therapy with oseltamivir for suspected SARS-CoV-2 infection. He was eventually discharged and was advised to self-quarantine at home. However, over the subsequent 4 days, his symptoms persisted and his condition worsened. Hence, he was readmitted. He was thus intubated, and mechanical ventilation was initiated. He was sedated with IV propofol. He also received IV cisatracurium besilate [cisatracurium] as a muscle relaxation, IV cefepime for antibiotic coverage and IV norepinephrine as a pressor support. A review of his medical records revealed that he had been receiving multiple medications, including apixaban, and his history was notable for hypertension and atrial fibrillation. He later received IV fentanyl and IV midazolam for sedation, and empirical therapy comprising IV vancomycin and IV doxycycline. Apixaban (which he had been receiving prior to admission) was discontinued and was replaced with heparin. He received enteral hydroxychloroquine as an off-label therapy for the suspected SARS-CoV-2. Thereafter, hypotension was noted, which was thought to be due to fentanyl, midazolam, propofol and cisatracurium besilate. Additionally, the hypoxaemic respiratory failure was thought to have resulted from multifocal pneumonia or acute respiratory distress syndrome (ARDS). However, his symptoms rapidly progressed while he was receiving oseltamivir, and since he presented during the initial increase in SARS-CoV-2 infections in Massachusetts, Covid-19 was thought to be the leading diagnosis. Of note, he exhibited elevated levels of troponin-T, suggesting myocardial injury, a common finding in patients with SARSCoV-2 infection. However, his low central venous pressure and normal central venous oxygen saturation suggested that the hypotension was probably secondary to the use of sedative and paralytic medications, we well as distributive shock in the context of infection, rather than a cardiogenic cause. Subsequent analyses raised suspicions for myopericarditis secondary to infection with SARS-CoV-2. Therefore, IV immune globulin (off-label for SARS-CoV-2) was added to his ongoing hydroxychloroquine. Serial ECGs were performed to monitor the QTc interval during treatment with hydroxychloroquine. On day 3, he developed paroxysmal atrial fibrillation with a rapid ventricular response. During this time, the QTc was approximately 475 msec; hence, he started receiving IV amiodarone. The prolonged QTc was attributed to hydroxychloroquine, whereas the paroxysmal atrial fibrillation was thought to have resulted from stress due to the critical illness. His QTc interval was monitored every 8 hours while he was receiving both, hydroxychloroquine and amiodarone. His prolonged QTc interval prompted the discontinuation of hydroxychloroquine (since both, hydroxychloroquine and amiodarone are known to prolong the QTc ineterval), while amiodarone was continued in an effort to maintain sinus rhythm. His clinical course was complicated by metabolic encephalopathy and progressive renal failure, which was managed with intermittent haemodialysis. He subsequently developed high-grade fever and leucocytosis, which raised concerns for a secondary bacterial infection. He had been receiving escalating pressor support and broad-spectrum antibiotic coverage for ventilator-assisted pneumonia, in spite of which, he exhibited rising lactate levels. His condition continued to deteriorate, and his family opted for comfort care. He died on hospital day 18 [*immediate cause of death not stated*]. Autopsy was not performed. The final diagnosis was SARS-CoV-2 infection with acute respiratory distress syndrome and suspected myopericarditis []*durations of treatments to reactions onsets and outcomes of the reactions not stated*].

Kazi DS, et al. Case 18-2020: A 73-year-old man with hypoxemic respiratory failure and cardiac dysfunction. New England Journal of Medicine 382: 2354-2364, No. 24, 11 Jun 2020. Available from: URL: http://doi.org/10.1056/NEJMcpc2002417