Multiple drugs

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Various toxicities: 3 case reports

A case report of 3 men aged 73-76 years with COVID-19 undergoing haemodialysis (HD) were described, who developed retroperitoneal haemorrhage and/or upper gastrointestinal bleeding during anticoagulant/antiplatelet treatment with heparin, aspirin, clopidogrel, prasugrel or nafamostat. Out of these 3 men, 2 men exhibited lack of efficacy during off-label treatment with dexamethasone, methylprednisolone and/or favipiravir for COVID-19 or COVID-19 pneumonia [*not all routes, dosages and outcomes stated; durations of treatments to reactions onsets not stated*].

Case 1: The 73-year-old man had a history of diabetes, hypertension, aortic stenosis, heart failure, peripheral arterial disease and angina. He had been undergoing HD for diabetic nephropathy. He underwent coronary stenting for angina, 7 years before. He had been receiving anticoagulant therapy with clopidogrel 75mg and aspirin 100mg. He was admitted to the hospital following a diagnosis of COVID-19 based on a positive finding for SARS-CoV-2 PCR, performed to detect COVID-19. Before admission, he had a sore throat, wet cough and malaise. Thorough investigations were conducted and the severity of COVID-19 was considered as mild. His risk of thrombotic complications was considered high due to slightly elevated D-dimer concentration and HD. On day 1 of hospitalisation, he received SC heparin [heparin calcium] injection of 5 000U, twice daily. During HD, he was administered heparin [heparin sodium] infusion with an initial bolus of 1 000U and continuous infusion of 1 000U/h and a total of 4 000U/session. On day 2 of hospitalisation, he developed a fever. On day 4 of hospitalisation, he started receiving off-label dexamethasone 6mg for COVID-19. His BP remained within the range of 120 to 140 mm Hg. On day 6 of hospitalisation, he developed low back pain that changed to abdominal pain the following day. Thereafter, he developed circulatory shock during HD. Before HD, blood tests showed decrease in Hb concentration and increase in creatine kinase concentration which suggested retroperitoneal hemorrhage. At this time, his activated partial thromboplastin time (APTT) was prolonged slightly. Contrast-enhanced CT was performed which showed a giant left iliopsoas haematoma and the extravasation of contrast medium confirming retroperitoneal haemorrhage. Angiography showed multiple sites of contrast medium leakage, pseudoaneurysms and coil embolization to the proximal part of the left fourth lumbar artery with no leakage. He underwent blood transfusions, appropriate infection prevention measures and urgent interventional radiology (IVR) was performed. He had a HAS-BLED score of 4. The IVR was successful and complete haemostasis was achieved. A total of 8U of RBCs was transfused. His antithrombotic therapy with low-dose aspirin and heparin were discontinued. His anticoagulant therapy was changed to nafamostat and clopidogrel was continued. Following the bleeding event, he required a small amount of oxygen as he recovered from COVID-19 pneumonia. The administration of dexamethasone for 10 days improved his clinical condition. After 3 weeks, his anticoagulant during HD was changed to dalteparin and no rebleeding was observed. On day 60, he was transferred to another institution for rehabilitation. Retroperitoneal haemorrhage was attributed to aspirin, clopidogrel and heparin.

Case 2: The 76-year-old man had a history of diabetes, hypertension and ischemic heart disease. He had been undergoing HD for diabetic nephropathy. He had been receiving prasugrel for the ischemic heart disease. He was diagnosed with COVID-19, however he was asymptomatic. Subsequently, he was admitted to the hospital. On day 4 of hospitalisation, he had fever, fatigue and an elevated D-dimer concentration. He received prophylactic SC heparin [heparin calcium] injection 5000U, twice daily. During HD, he was administered heparin [heparin sodium] infusion with an initial bolus of 1000U and continuous infusion of 1000U/h and a total of 4000U/session. On day 6 of hospitalisation, he started receiving off-label dexamethasone and oxygen due to worsening of the COVID-19 pneumonia symptoms. On day 9 of hospitalisation, left thigh pain appeared and plain CT showed a left iliacus hematoma, which confirmed retroperitoneal hemorrhage. He had a HAS-BLED score of 3. He discontinued heparin. He was treated unspecified opioid analgesics for pain control. During HD, the dose of heparin was reduced. On day 12 of hospitalisation, his respiratory condition worsened (lack of efficacy to dexamethasone) and his D-dimer concentration further increased. He started receiving off-label methylprednisolone 500mg for 3 days. He restarted heparin 5000U/day. However, his respiratory failure progressed (lack of efficacy to methylprednisolone), which led to acute respiratory distress syndrome and multiple organ failure. Eventually, on day 21 of hospitalisation, he died. Retroperitoneal haemorrhage was attributed to prasugrel and heparin.

Case 3: The 74-year-old man had a history of hypertension, resection of gastric cancer and vertebroplasty for spinal canal stenosis. He had been undergoing HD for hypertensive nephrosclerosis. Before 15 days of current admission, he underwent surgery for a strangulated ileus. He had been discharged 6 days before current admission. He developed fatigue, 2 days before admission. On the day of admission, his fatigue worsened with the development of respiratory failure after HD. Therefore, he visited an emergency hospital and he had positive finding for the SARS-CoV-2 antigen test. Thereafter, he was admitted to the hospital. After thorough investigations, he was diagnosed with COVID-19. He was administered oxygen, however, his oxygen saturation remained at 90% and he started receiving off-label dexamethasone and favipiravir. On day 2 of hospitalisation, he transferred to a hospital with an intensive care unit (ICU) due to further progression of his respiratory failure (lack of efficacy). Immediately after the transfer, he underwent invasive mechanical ventilation. He started receiving remdesivir and off-label methylprednisolone 1g for 3 days. He started receiving IV infusion of heparin [heparin sodium] 10 000U/day. On day 3 of hospitalisation, continuous haemodiafiltration (CHDF) with nafamostat 20 mg/h was started. On day 4 of hospitalisation, he developed tar-like stool and he was diagnosed with upper gastrointestinal bleeding. Thereafter, his treatment with heparin was discontinued. However, as the CHDF circuit life was shortened and frequent circuit replacement was required, the dose of nafamostat gradually increased to 60 mg/hour on day 9 of hospitalisation. On day 12 of hospitalisation, his anaemia progressed. Contrast-enhanced CT revealed a right iliopsoas hematoma and the leakage of contrast medium which confirmed retroperitoneal haemorrhage. He had a HAS-BLED score of 3. IVR was performed and hemostasis was achieved. However, on day 54 of hospitalisation, he died as a result of complications of delayed anastomotic leakage following strangulated ileus surgery, cytomegalovirus antigenemia and an iliopsoas abscess. Upper gastrointestinal bleeding was attributed to heparin and nafamostat, while retroperitoneal hemorrhage was attributed to nafamostat.

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