Presented at North American Congress of Clinical Toxicology 2021– Virtual

Published in Clin Toxicol 2021;59(11):1052

31. Remdesivir associated bradycardia identified through the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project

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Background: The American College of Medical Toxicology's (ACMT) Toxicology Investigators Consortium (ToxIC) developed a multi-center active surveillance and reporting system to identify adverse events related to COVID-19 therapies. This project, the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project, has identified a signal of remdesivir associated bradycardia. A more detailed investigation into this effect was then undertaken.

Methods: This is an active surveillance project with 15 participating medical centers focusing on identifying possible ADEs, medication errors, toxicity and/or overdose related to any medication or substance administered with intent to treat or prevent COVID19 infection. Cases are actively identified by direct contact with treating providers, pharmacists, and chart review. Cases were submitted between 11/23/20 and 4/30/21 by site principal investigators and trained research assistants. Utilizing a standardized data collection tool, we gathered specific data including patient demographics, case narrative, exposure details, clinical signs and symptoms, and treatment and outcomes surrounding the ADE. We identified a signal of remdesivir associated bradycardia in FACT's first month. ToxIC alerted the sites and instituted a specific remdesivir bradycardia data collection instrument that includes vital signs, specific signs and symptoms, medication administration records, laboratories before, during and after each remdesivir dose, (potassium, troponin, TSH, creatinine), and relevant cardiac diagnostic studies (e.g. EKG, echocardiogram). Bradycardia was defined as any recorded heart rate 60 bpm sustained for 8 hours or longer. Cases were evaluated for seriousness based on the FDA regulatory definition of serious (21 CFR 314.80). Non-parametric and descriptive statistics were performed in SPSS (v.23, IBM, Armonk, NY).

Results: Between November 2020 and April 2021, 118 cases of remdesivir-related bradycardia were identified. Cases with detailed heart rate information were analyzed (N = 70). Serious effects were identified in 32 cases (45.7%), with 29 being potentially life-threatening. The most common reason for a potentially life-threatening event was a heart rate < 45 bpm in 28 cases (87.5%) with 1 case of QRS prolongation (3.1%). There were no deaths in the cases evaluated during the submission period. In most cases (80%, N = 56) 4 or more doses of remdesivir were administered. The median hospital stay was 9 days (IQR 6-14). Lowest heart rate prior to remdesivir was significantly different than lowest heart rate following remdesivir by pairwise chisquare analysis. Bradycardia following remdesivir infusion was more likely to occur after doses 3, 4, and 5 than doses 1 and 2. Eight cases had a total of 10 specific interventions for the bradycardic event.

Conclusions: Bradycardia during remdesivir treatment outside the immediate infusion period has been identified by this study and is a potentially serious unlabeled event. The FACT Project, in collaboration with the FDA, is continuing to collect detailed information on these cases for the evaluation and further characterization of this safety signal.