Commentary

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Is Glucagon Effective for Overdosing on Beta Blockers?

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Description

One of the most frequently prescribed classes of drugs is still beta blockers. Because of this, beta blockers are frequently involved in potentially fatal ingestions of one or more drugs that result in overdose death. To treat suspected or confirmed overdoses of beta blockers, a number of treatment options have been proposed. As an effective early management strategy for beta blocker toxicity, toxicology and emergency medicine textbooks and well-liked online sources like Up To Date recommend glucagon. Senart and LeClair present a retrospective case series in this issue that demonstrates that glucagon has no significant effect on beta blocker toxicity. We believe that reading the study from beginning to end has value and can teach readers valuable lessons, despite the fact that readers may not make it past the abstract due to the subpar conclusion. We applaud them for attempting to address a contentious issue and providing an answer to a question that has been asked by many for decades.

Antidotal Therapy Studies

Overcoming the usual drawbacks of retrospective clinical toxicology case series analysis and, specifically, antidotal therapy studies, we believe this study sheds light on significant issues. Was the antidote being used to prevent or treat toxicity? Would these patients have been referred to an Emergency Department (ED) or left at home with a follow-up phone call if they had first called a poison center with a story of "unintentional" or "accidental" exposure where no BP or HR would have been known? Is it appropriate to use the 20-minute window, which the package insert defines as glucagon's onset of action, for all routes of administration? Is a specific clinical response or a fixed dose the objective of antidotal therapy? Are these results sufficient to discourage the unproven but convenient and effective use of bolus and continuous antidote infusion? Due to the high number of "suboptimal" doses (52% received only 1-2 mg of glucagon), the authors do a good job of self-identifying some of these issues and candidly discussing confounding factors in their dosing assessment. They also mention that doses of glucagon greater than 5 mg were only given four times, so they were not considered a subgroup. Before administering glucagon, did treating physicians order one or more therapies, such as intravenous fluids, whose peak may have occurred 20 minutes later? Only that cases in which atropine was used were excluded is known. Was the administration of glucagon supplementary to stocking practices at specific practice sites? Inadequate documentation is a common problem in retrospective chart review studies, and the medical decision-making that is crucial for evaluating antidotal effect may be absent or difficult to interpret for an investigator. The authors of this study acknowledge that five hospitals were included, but the academic medical center administered half of all glucagon, while the other four community sites administered relatively few doses. Although retrospective studies are appropriate for infrequent or uncommon poisonings, they are most effective when conducted with a population-based cohort or registry. However, these studies may also lack sufficient information across all sites and patients to provide truly illuminating information and typically draw broad, bland, conservative conclusions that may accidentally result in a recommendation for consultation.

Clinical Toxicity

Standardizing the terms and analyses used to evaluate antidotal or focused therapy in clinical toxicity may be in order. When studying antidotes like glucagon, methylene blue, or even ECMO for the treatment of poisonings, we should adhere to retrospective study guidelines and objective scoring instruments like the Naranjo scale to minimize bias and appropriately address confounders. Due to the small number of patients who present with a single, acute ingestion of a poison compared to the larger patient population, the relative lack of data on the safety and efficacy of antidotes in healthy animal populations, and the ethical considerations of prospective, randomized controlled studies, the study of antidotes is notoriously difficult. In addition, clinical practice varies, and even antidotes that are considered to be the "current standard of care" may be used incorrectly (or not at all) by physicians, as was the case in this study, where the majority of patients received "suboptimal" glucagon. Additionally, antidotes like methylene blue, physostigmine, and glucagon are not widely available in the United States. We rely on outdated recommendations based on anecdote or expert opinion because of these shortages, which not only affect bedside care as the majority of references have

discussed but also prevent us from carrying out the rigorous studies required to determine if some of these antidotes are appropriate and in what dosage. Many people believe that retrospective studies can benefit from the widespread use of Electronic Medical Records (EMR) because vital signs automatically populate the chart, medication administration is time-stamped, patient demographics are easily accessible for data abstraction, and, most importantly, all of the data in the EMR is legible. However, human error persists in EMR data: Because they are busy treating a sick patient, nurses may misrecord the time it takes to administer medication, patients may become disconnected from machines, and essential demographic information must still be entered correctly by registration staff or the bedside provider. In addition, in order to keep up with charting in the increasingly crowded and complicated healthcare setting, many providers copy and paste data from previous visits or from other providers, employ template charting language, and employ other imperfect workaround strategies.

In the end, some of the issues that are typically associated with retrospective antidote studies may be alleviated by more deliberate collaboration among multiple healthcare systems. With more poisoned patients and different patterns of clinical practice, it might be possible to draw more nuanced conclusions about antidotes and make them more generalizable. Obviously, a prospective study of glucagon safety and efficacy would be ideal, but it would be constrained by ethical and logistical issues in a small, sensitive patient population. There aren't many studies on the safety and efficacy of glucagon for beta blocker toxicity, so we applaud the authors for taking on a difficult task with thoughtfulness.