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EDITORIAL

Does Glucagon Really Work for Beta Blocker Overdose?

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Beta blockers remain one of the most commonly prescribed class of medications. As a result, beta blockers are frequently involved in potentially fatal single or multi-drug ingestions leading to death from an overdose [1, 2].

There are several proposed therapeutic options to treat suspected or confirmed beta blocker overdoses. Glucagon is recommended in toxicology and emergency medicine textbooks and popularly used online references such as UpToDate as an early management strategy for beta blocker toxicity [1].

In this issue, Senart and LeClair report a retrospective case series of the use of glucagon for beta blocker toxicity that essentially shows glucagon has no significant effect [3]. Readers might not get past the abstract because of the less than spectacular conclusion, but we think there is value and some useful lessons in reading the study from start to finish. We commend them for trying to answer a question many have asked for decades and addressing a controversial problem.

We believe that this study serves to illuminate important issues above and beyond the usual limitations of retrospective clinical toxicology case series analysis and, in this case with antidotal therapy studies specifically.

Was the antidote being used to treat toxicity or as prophylaxis? If any of these patients had called a Poison Center first with a story of "unintentional" or "accidental" exposure where no BP or HR would have been known, would they have been referred to an ED or left at home with a follow up phone call? Is the use of a 20-minute window (defined as onset of effect for glucagon according to the package insert) appropriate for all routes of administration? Is the goal of antidotal therapy to achieve a fixed dose or a specific clinical response? Are these results adequate to discourage the unsupported yet conveniently efficient use of bolus followed by continuous infusion of antidote?

The authors do a good job of self-identifying some of these issues with a candid discussion on confounding factors in their dosing assessment due to the high number of "suboptimal" doses (52% received only 1-2 mg of glucagon). They also note doses of >5 mg glucagon were only administered 4 times and thus were not analyzed as a subgroup. Did treating physicians order one or more therapies (e.g., IV fluids) prior to glucagon whose onset or peak may have occurred in the 20 minute period post glucagon dose? We only know that cases where atropine was administered were excluded. Was the glucagon dosing secondary to stocking practices at individual practice sites? Retrospective chart review studies are often plagued with inadequate documentation, and the medical decision making that is important for assessing antidotal effect can be lacking or difficult for an investigator to interpret [4]. In this study, the authors acknowledge that 5 hospitals were included but half of all glucagon administrations occurred in the academic medical center with relatively few administrations in the other 4 community sites. While retrospective studies are appropriate for infrequent or rare forms of poisonings, they are best done using a population-based cohort and or registries, but these may also lack adequate information across all sites and patients to offer truly illuminating information and typically offer broad bland conservative conclusions that, perhaps, inadvertently lead to a recommendation for consultation.

It may be time to standardize the sepsis of terms and or analyses used in assessing antidotal or focused therapy assessment in clinical toxicity. We should adhere to retrospective study guidelines and objective scoring instruments like the Naranjo scale when studying antidotes such as glucagon, methylene blue, or even ECMO for the treatment of poisonings to minimize bias and address confounders appropriately [4].

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The study of antidotes is notoriously difficult due to the relatively small number of patients presenting with a single, acute ingestion of a poison compared to the greater patient population, the relative lack of data on safety and efficacy of antidotes in animal and healthy human populations, and the ethical considerations of prospective, randomized controlled study. In addition, clinical practice varies, and even antidotes which are "current standard of care" may be utilized improperly (or not at all) by clinicians as was observed here with the majority receiving "sub-optimal" glucagon. Furthermore, shortages of many antidotes, such as methylene blue, physostigmine, and glucagon in the USA, limit the use of these antidotes [5]. Shortages not only impact bedside care as most references have discussed, but these shortages actually interfere with the ability to perform rigorous studies that are needed to determine if some of these antidotes are indicated and in what optimal dose—because we have these shortages, we rely on old recommendations based on anecdote or expert opinion [6].

The widespread use of electronic medical records (EMR) has been viewed by many as a benefit to retrospective studies because vital signs automatically populate into the chart, medication administration is time-stamped, patient demographics are readily available for data abstraction, and most importantly because all the data in the EMR are all legible. However, EMR data is still subject to human fallacy: patients may become unhooked from machines, nurses may inaccurately record the time of medication administration because they are busy treating a sick patient, and essential demographics must still be entered correctly by registration staff or the bedside provider. Additionally, many providers copy and paste data from previous visits or other providers, use templated charting language, and apply other imperfect workaround strategies to keep up with charting in the increasingly busier and more complicated healthcare setting.

Ultimately, more intentional collaboration among multiple healthcare systems may help to solve some of the problems commonly associated with retrospective antidote studies. A larger pool of poisoned patients, and variable clinical practice patterns, might lead to more nuanced conclusions about antidotes and increase generalizability. A prospective study addressing glucagon efficacy and safety would obviously be ideal, though fraught with ethical and logistical limitations in a small and sensitive patient population.

There is a paucity of studies on the efficacy and safety of glucagon in beta blocker toxicity in the literature, and we commend the authors for their thoughtful undertaking of a difficult task.

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Declarations

Conflicts of Interest None.

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