Abstract:
Drug overdoses and therapeutic misadventures, whether intentional or inadvertent, are a common cause of presentation to pediatric emergency departments. Timely administration of antidotes is often an important component of treatment for these patients, and in many cases, this can be life-saving. Because randomized control trials are very difficult to perform in the realm of medical toxicology, there is often a paucity of information regarding efficacy and best use of antidotes, and it is important to continually examine the literature for new data and evidence. We review the current evidence and indications for some newer antidotes and therapies for selected common pediatric poisonings, as well as recent data regarding use of a well-known and commonly used antidote.

Keywords:
antidote; poisoning; n-acetylcysteine; glucarpidase; high-dose insulin euglycemic therapy; intravenous lipid emulsion therapy

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Antidotes: Familiar Friends and New Approaches for the Treatment of Select Pediatric Toxicological Exposures

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The timely administration of antidotes is often a critical component of emergency department treatment for drug overdoses and for patients experiencing therapeutic misadventures. In many cases, these antidotes can be life-saving. Because of limited available data from prospective clinical trials, there may be a paucity of evidence regarding efficacy and best use of antidotes, particularly for the pediatric population. In this article, we review 4 antidotes/therapies that are relevant to current pediatric emergency medicine clinical practice.

N-ACETYLCYSTEINE FOR TREATMENT OF ACETAMINOPHEN TOXICITY

Analgesic exposures, whether intentional or accidental, continue to be one of the leading reasons for calls to poison centers in the United States, with most recent data showing them to be the most common cause for calls in adults and the third most common in children.[1] Acetaminophen exposure makes up a large percentage of these cases.[1] In general, acetaminophen toxicity can be described in 2 broad categories: (1) acute toxicity, which occurs after a single acute ingestion, or 3 or fewer ingestions within an 8-hour period or (2) chronic toxicity, which involves multiple exposures over time.

Following ingestion, acetaminophen undergoes rapid absorption and distribution, with the majority remaining in the intravascular compartment.[2] It is primarily metabolized in the liver, most of it being metabolized via glucuronidation and sulfonation.[2] However, a small amount is metabolized by the cytochrome P450 enzymatic system, with 2E1 being the predominant enzyme involved.[2] This process creates a metabolite called *N-acetyl-p-benzoquinone imine*, which is directly hepatotoxic.[2] In sufficiently large exposure, whether acute or chronic, this can lead to hepatic injury.

N-acetylcysteine (NAC) is a well-described antidote that is the primary treatment for acetaminophen toxicity. It exerts its therapeutic effects via multiple mechanisms including direct detoxification of *N*-acetyl-*p*-benzoquinone imine, providing substrate for glutathione synthesis, free radical scavenging, increasing oxygen delivery to hepatocytes, and altering microvascular tone.[2] When given within 8 hours of acute acetaminophen overdose, NAC leads to recovery in nearly 100% of cases,[3] with recovery also occurring in a high percentage of late-presenting acute overdoses and chronic toxic exposures as well.

NAC is usually administered as either a 72-hour oral course or a 21-hour intravenous (IV) course. Despite years of experience with NAC, there continues to be discussion about route of administration, as well as correct treatment course to optimize therapy and safety while minimizing adverse effects and hospital length of stay.

Several studies have addressed the question of whether oral or IV NAC should be the preferred method of treatment. In general, these studies have found equal efficacy between the 2 treatments in both acute and chronic acetaminophen toxicity, with rates of progression to hepatic failure and death being statistically indistinguishable.[4,5] However, when acute toxicity is further stratified into early presenting and late presenting, some literature does suggest a difference in outcomes, with IV NAC being more efficacious in acute overdose presenting within 12 hours and oral NAC being more effective in patients presenting greater than 18 hours from time of ingestion.[6] Although the reasons for these findings are not entirely clear, they may have to do with the more rapid increase in serum concentration of NAC with IV dosing[6] and the greater amount of first-pass metabolism with oral dosing.[6,7]

Oral NAC existed and was used for many years prior to US Food and Drug Administration (FDA) approval of IV NAC in 2004. As previously noted, it has generally been given as a 3-day course requiring lengthy hospitalization. However, there is little evidence that a full 72 hours of therapy is actually necessary. A retrospective evaluation of 3303 patients who received oral NAC for acetaminophen toxicity, with 1932 of them qualifying for early discontinuation of NAC based on acetaminophen concentration of less than 10 μg/mL, international normalized ratio less than or equal to 1.3, and aspartate aminotransferase and alanine aminotransferase both less than or equal to 60.[8] Minimum length of treatment was 20 hours (140 mg/kg loading dose followed by 70 mg/kg every 4 hours), with mean treatment duration of approximately 35-38 hours between various subgroups. None of the patients in whom oral NAC was discontinued early went on to develop subsequent hepatotoxicity or death. A prospective study by many of the same authors showed similar results.[3] Another retrospective analysis showed equivalency between 36 and 72 hours of oral NAC when treatment was started within 8 hours of acute ingestion.[9] These findings indicate that 72 hours of oral NAC administration does not seem to be necessary in many cases, and patients who meet criteria for early discontinuation can be safely discharged. This practice could decrease hospital length of stay by as much as 70%.[8]

Recently approved flavored effervescent oral NAC tablets have been shown to have equal bioavailability to traditional oral NAC in healthy fasting adult patients and are likely to be more palatable and better tolerated than traditional oral NAC.[10] However, more data are needed to assess whether there is actually a decrease in rates of nausea and vomiting and whether it would be cost effective when compared with other NAC products.

New IV NAC protocols are also emerging with the hope that they will decrease the rates of adverse events including dosing errors and anaphylactoid reactions. The 3-bag IV NAC protocol lends itself to the potential for both dosing errors and interruption of treatment.[11] Recent studies examining 2-bag protocols in both adults[12] and pediatric patients[11] demonstrated equal overall clinical outcomes with a