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Letters to the Editor

EVALUATION PROTOCOL FOR SULFONYLUREA EXPOSURES IN TODDLERS

To the Editor:

I enjoy the series of toxicology articles, "Are One or Two Dangerous?" being published periodically within the *Journal of Emergency Medicine*. I agree with the recent conclusion by Little and Boniface that exploratory ingestions of sulfonylureas by young children can cause profound hypoglycemia (1). I am aware of even non-diabetic adults who have become profoundly hypoglycemic after only one sulfonylurea pill administered via medication error (2).

I would like to make a couple of comments related to the discussion of the recent *Journal of Emergency Medicine* article. First, the authors point out that only one pediatric death from oral hypoglycemic poisoning can be found in the American Association of Poison Control Centers database. Although I believe that this data review is valid, it should be kept in mind that selection bias is inherent in this database, and that investigation has shown that fatal poisonings may be severely underrepresented (3,4). Hypoglycemic children should fare well once brought to medical attention—emphasizing the important role of Poison Control Centers in this regard. The true incidence of mortality in this scenario is currently unknown.

Secondly, the authors have offered that children thought to have possibly ingested a sulfonylurea agent be subjected to q1–2 h fingerstick blood glucose determinations regardless of the degree of medical supervision, discount the ability of "ad lib" oral feeding to mask hypoglycemia similar to the manner described for intravenous dextrose, and don't mention the possible impact of normal physiologic variations in the blood glucose regulation of young children. It is possible that the pharmacokinetics of glyburide and glipizide (nicely presented) don't always match their pharmacodynamics. I have recently reviewed these issues, and presented a slightly different evaluation algorithm agreed upon by the medical toxicologists consulting at the Philadelphia Poison Control Center (5). This algorithmic discussion, although not experimentally validated, might still be of interest for emergency physicians to consider.

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RESPONSE TO "PREVENTION OF CS 'TEAR GAS' EYE AND SKIN EFFECTS AND ACTIVE DECONTAMINATION WITH DIPHOTERINE: PRELIMINARY STUDIES IN 5 FRENCH GENDARMES"

To the Editor:

We read with interest the recent article on the prevention of CS-induced skin and eye effects (1). Although we appreciate the authors' efforts to investigate a novel decontamination agent, we have serious concerns that their conclusions are not supported by the data. The

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study uses only 5 participants divided into three treatment groups. All of the endpoints are subjective and there is no blinding, placebo, or control. Because the symptoms of CS exposure always resolve spontaneously, the role of Diphoterine® is unclear at best, and potentially worse than either water or no treatment at all.

We are also concerned that potential biases and financial interests of the authors need to be more clearly disclosed. Although the article acknowledges that funding came from "Laboratoire Prevor," it omits that the very same company manufactures Diphoterine®. Before routine use, this agent requires further study using acceptable scientific methodology.

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☐ RE: LETTER TO THE EDITOR IN RESPONSE TO "PREVENTION OF CS 'TEAR GAS' EYE AND SKIN EFFECTS AND ACTIVE DECONTAMINATION WITH DIPHOTERINE: PRELIMINARY STUDIES IN 5 FRENCH GENDARMES"

☐ **To the Editor:**

We are in receipt of the letter by Luka et al. (1) regarding our recent publication of preliminary results of Diphoterine® decontamination or prophylaxis in 5 French Gendarmes exposed to CS "tear gas" during required routine training exercises (2). The objectives of this preliminary study in, as Luka et al. note, only 5 subjects, were to demonstrate in an empirical and practical manner that these law enforcement personnel could either be rapidly decontaminated and return to operational status (crucial in potentially violent tactical situations) or could be protected against the incapacitating effects of CS and remain operational in such situations.

This was, naturally, not a definitive blinded placebo-controlled "scientific" study, but rather one with practical application and, as is implicit in the title of the article, *preliminary*. Further studies are certainly warranted, as it was adequately pointed out in the final sentence of our article. This was a small case series and our conclusions were that preliminary data suggested that Diphoterine® may be useful and that further studies are needed for understanding, as Luka et al. note, the mechanism of decontamination with Diphoterine® compared to other rinsing solutions and, then performing a comparative clinical study. As we stated: "Based on the preliminary data presented here, Diphoterine® may be an efficacious eye and skin prophylactic and decontamination solution for CS exposure and further studies are warranted" (2).

Luka et al.'s statement that the symptoms of CS *always* resolve spontaneously must be questioned (1). Recently published literature, as well as those references cited in our article, suggests that CS exposure is not necessarily as benign as generally supposed (3–10). Such effects as contact allergy, leukoderma, initiation or exacerbation of seborrheic dermatitis, and aggravation of rosacea after CS exposure have been described (3). Marked laryngospasm was noted during extubation after surgical treatment in a patient exposed to CS several hours before surgery, and re-intubation was difficult (4). Dermatitis and blisters with adverse effects occurring more than 6 h post-exposure have been reported (5). Long-term psychiatric sequelae (post-traumatic stress disorder) occurred in just over 25% of 30 individuals exposed to CS in one study (6). Some effects may last for 1 h, but others may persist as long as 8–10 months (7). Not only cough and shortness of breath, but also hemoptysis and hypoxia, which resolved over 72 h, have been described during a military training exercise (8). Severe contact dermatitis has occurred after CS exposure, as well as actual skin burns (9,10).

Luka et al.'s concerns "that potential biases and financial interests of the authors need to be more fully disclosed . . ." (1) seems misplaced. We believe that full disclosure occurred, as the affiliations of the authors at the time of final submission of the article are clearly listed on the first page. That Diphoterine® was provided by Laboratoire Prevor, Valmondois, France is noted in the first sentence of the Materials and Methods section, and in the Acknowledgements section, the funding source is clearly identified.

Since this article was published, some other studies of the beneficial effects of Diphoterine®, especially with eye exposure to caustic substances, have been published

(11–13). The manufacturer and affiliated researchers are continuously involved in collecting new data and performing new studies, as is the case for other research laboratories.

As well, the beneficial effects of water for eye/skin decontamination are poorly documented in "scientific" studies. Interested readers should anticipate publication of a critical review on this topic: Hall AH, Maibach HI: Water decontamination: a critical review, accepted for publication in the *Journal of Toxicology: Cutaneous and Ocular Toxicology*. These review data have also been presented at the Medichem 2004 (Paris) and Medichem 2005 (Goa, India) Congresses.

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INVALID CORRECTION OF "FALSELY" ELEVATED OSMOL GAP

To the Editor:

Sztaznkrycer and Scaglione present two case reports of patients with metabolic acidosis, elevated anion (28 and 30 mmol/L) and osmol (14 and 26 mOsm/kg H_2O) gaps who also have hypertonic hyponatremia secondary to hyperglycemia (700 and 650 mg/dL) (1). In the absence of assays for methanol and ethylene glycol, an elevated osmol gap associated with elevated anion gap-metabolic acidosis may be an indication of their ingestion. The osmol gap is the difference between measured (freezing point depression) and calculated (generally based on sodium, glucose, and urea concentrations) osmolality.

The authors correctly ascribe hyponatremia in these two cases to a physiologic shift of intracellular water to the extracellular volume in response to the osmotic pressure gradient imposed by hyperglycemia. Consequently, the osmolality of serum is somewhat dampened and the sodium concentration is decreased. It is commonly accepted that the serum sodium concentration decreases approximately 1.6 mmol/L for each 100 mg/dL increase in glucose above a nominal value of 100 mg/dL (2). However, a value of 2.4 mmol/L decrease in sodium per 100 mg/dL increase in glucose may be more appropriate (3). Moreover, the authors accurately state that sodium measurements in such cases are true and reflect the physiologic dilutional effect of the hyperosmolality. Our data confirm analytical accuracy (± 1 mmol/L) for sodium at glucose concentrations up to 2500 mg/dL (unpublished data). In contrast, falsely low sodium values (pseudohyponatremia) may result from the volume exclusion effect due to very elevated triglycerides or protein when sodium is measured by indirect methods (those requiring a dilution step) but not when measured by direct (no dilution) methods (4).

After accurately distinguishing true hypertonic hyponatremia from pseudohyponatremia, the authors curiously and erroneously "correct" the sodium concentration for hyperglycemia (1.6 mmol/L per 100 mg/dL

increase in glucose). After this correction, the calculated osmol gaps normalized (<10 mOsm/kg H_2O) for both patients. Whether the observed osmol gaps for these patients are accurate or meaningful is debatable, but this correction of the sodium concentration for hyperglycemia is clearly inappropriate.

"Correction" of serum sodium concentration for hyperglycemia has been recommended for an entirely different purpose. In states of hyperglycemia, "correction" of the serum sodium concentration to the value expected after resolution of hyperglycemia allows assessment of the nature of fluid loss (isotonic or hypotonic) due to osmotic diuresis and thus helps guide appropriate fluid and electrolyte management (5).

Numerous equations have been proposed for calculating serum osmolality and thus the osmol gap (6). Most incorporate the concentrations (molarity) of sodium (×2 to account for associated anions), glucose, and urea as major contributors to normal serum osmolality. It is generally assumed that serum osmolarity (osmol/L) is equivalent to serum osmolality (osmol/kg H_2O). For glucose, this assumption allows the conversion of measured glucose molarity (mmol/L; mg/dL ÷ 18) to calculated osmolality (mOsm/kg H_2O). However, a liter of serum contains about 0.93 kg H_2O (7). Thus, some equations divide measured molarity by 0.93 (multiply by 1.08) to account for the water content of serum. Recent data suggest that glucose and ethanol do not behave as ideal solutions, but instead contribute to serum osmolality to a greater extent than that predicted by their molarity (8). For glucose, a factor of 1.15 was required to convert measured molarity to effective osmolality. Applying this factor to the two reported cases lowered the osmol gaps by 6–7 mOsm/kg H_2O. Thus, a correction may be required to account for hyperglycemia when calculating the osmol gap, but not for the reason nor to the magnitude suggested by Sztaznkrycer and Scaglione. Whereas the osmol gap may be helpful to identify probable ethylene glycol or methanol ingestion in some cases, its limitations in both sensitivity and specificity must always be considered. The osmol gap may be normal if presentation is delayed, a result of metabolism of ethylene glycol or methanol to glycolic and formic acids, respectively (9). Substances other than ethylene glycol and methanol may cause an elevated osmol gap. Included among these are ethanol (easily measured; should be included in calculated osmolality), acetone in alcoholic (10) and diabetic ketoacidosis (11), propylene glycol (12), glycerol (endogenous and exogenous), mannitol, and neutral or basic amino acids plus unknown substances in patients with multiple organ failure (13), or unknown osmolutes in chronic but not acute renal failure (14).

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☐ To the Editor:

We would like to thank Dr. Porter for his excellent discussion regarding serum osmolality and the osmol gap, as well as for his concerns regarding our brief report. The impetus for our discussion was to highlight a potential for misdiagnosis and therefore delay in patient care, and certainly not to disseminate erroneous information.

Although analytically accurate, the apparent hyponatremia measured in the setting of hyperglycemia is physiologically inconsequential, and will correct as the hyperglycemia resolves (1,2). As Dr. Porter notes, the role of the correction factor has traditionally been to provide a more physiologically accurate picture of serum sodium upon which to make subsequent management decisions. Therefore, Dr. Porter raises a valid criticism concerning the appropriateness of using corrected sodium values in calculating the osmol gap. Although the corrected sodium more accurately reflects the physiological state, the measured sodium in these cases remains analytically accurate. This is problematic as the calculated osmolality, and therefore the osmol gap, is strongly influenced by the reported serum sodium value.

Multiple methods of calculating the serum osmolality have been suggested in the past (3–5). The most commonly used method in clinical practice remains the formula quoted in our discussion:

$$\text{Osmolality} = 2 \times \text{Na (mEq/L)} + \text{BUN (mg/dL)}/2.8 + \text{Glucose (mg/dL)}/18$$

This formula, although simple and easy to remember, does not account for the additional contribution of glucose beyond its molar basis, a failure that more significantly effects the osmolality calculation with increasing degrees of hyperglycemia. As a consequence, the problem in our cases may lie not so much with the reported serum sodium, but rather with the formula's inability to accurately reflect the additional impact of hyperglycemia, with resultant discordancy between measured and calculated serum osmolality. More accurate glucose correction factors have been suggested in the past, but simply have not achieved mainstream acceptance (6). We therefore read with interest Dr. Porter's comments regarding the contribution of glucose to measured sodium, and the suggested revised glucose calculations based upon these findings (7).

Osmol gap calculation is fraught with problems, and interpretation should be performed cautiously at best. Multiple confounders affect osmol calculation, may in fact have played a role in the osmol gaps noted in each of these patients, and may have distracted away from the actual clinical diagnoses (6,8–10). The currently accepted formula for calculating osmolality, biased toward serum sodium concentration and failing to fully account for the effects of glucose, simply may not accurately reflect the actual osmolality measured in hyperglycemic hyponatremia. As Dr. Porter notes, whether the observed osmol gaps are accurate or meaningful is debatable. Unfortunately, clinical decisions continue to be made based upon these observed osmol gaps, and in our cases led to potential delays in patient care.

In an ideal world, a surrogate marker for the presence of toxic alcohols would not be necessary, as real-time quantification of suspect agents would be available. However, this capability simply does not exist for many institutions (11). In the meantime, it seems fairest to say that when a patient is assessed clinically for evidence of toxic alcohol ingestion, the calculated osmol gap should be interpreted cautiously. This would seem especially true in the setting of hyperglycemia, given its effects on both measured sodium levels and serum osmolality, effects the calculated osmolality formula seems ill-designed to handle.

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