The Journal of Emergency Medicine, Vol. 45, No. 1, pp. 53–56, 2013

0736-4679/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.jemermed.2012.11.081

Selected Topics: Emergency Radiology

EFFECT OF LOW-OSMOLALITY INTRAVENOUS CONTRAST ON SERUM OSMOLAL GAP IN ADULTS

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□ **Abstract—Background: Contrast media used today is considered "low-osmolality." No study has evaluated the effect of intravenous contrast media on the measurement of the osmolal gap in adult patients. Objective: To determine if "low-osmolality" intravenous contrast media administered to adult patients undergoing computed tomography (CT) of the abdomen and pelvis affects the osmolal gap. Methods: We performed a prospective pilot study in the Emergency Department of a university-affiliated tertiary care center. Patients were enrolled if they were age ≥18 years and <60 years and the treatment team had ordered an abdomen and pelvis CT with intravenous (i.v.) contrast procedure and a serum basic metabolic panel (BMP) that included serum glucose, blood urea nitrogen, and sodium. Once enrolled, a serum osmolality and serum ethanol level was ordered and obtained on the same blood draw as the BMP before the CT. Patients were excluded if they had detectable ethanol on laboratory screen, if they were suspected to have ingested methanol, ethylene glycol, isopropanol, mannitol, or underwent CT with i.v. contrast within the prior 24 h. Paired samples were compared using the Wilcoxon signed-rank test. Results: Of the 100 patients screened, 18 patients were lost due to withdrawal of consent or missing data. The median of the osmolal gap pre-CT was 8.18 with an interquartile range of 4.76–11.15. The median of the osmolal gap post-CT was 11.23 with an interquartile range of 7.29–14.83. The difference in the osmolal gap was a median of 2.34 ($p = 0.0003$) with an interquartile range of −1.32–5.97. Conclusion: Although the effect in our study was small, clinicians should be aware of the ability of contrast media to increase the osmolal gap.** © **2013 Elsevier Inc.**

□ **Keywords—intravenous contrast; computed tomography; serum osmolality; osmolal gap; toxic alcohols**

INTRODUCTION

As the number of Emergency Department (ED) visits has increased, so has the number of visits that involve the use of computed tomography (CT) imaging. The National Hospital Ambulatory Care Survey estimated that during the years of 1995–2007, the number of ED visits in which a CT study was performed increased from 2.8% to 13.9% (1). The most common chief complaints associated with obtaining CT studies were abdominal pain, headache, and chest pain. When trauma was excluded, over 50% of imaging was for "other" chief complaints, suggesting liberal use of CT for the undifferentiated ill patient (1).

As a result of increased use of CT studies, more ED patients are receiving intravenous (i.v.) contrast media. Currently used contrast media is considered "low-osmolality" (2). Although usually given in small volumes, the osmolality of the contrast media may theoretically raise the serum osmolality. In the majority of patients, this change in serum osmolality is not clinically significant. However, in certain patients, the calculated osmolal gap may be important information for making

RECEIVED: 17 July 2012; FINAL SUBMISSION RECEIVED: 27 October 2012;
ACCEPTED: 18 November 2012

management decisions. For instance, methanol and ethylene glycol poisonings are serious medical emergencies in which the osmolal gap is often utilized as a surrogate marker for ingestion in lieu of measuring serum toxic alcohol concentrations due to limited laboratory capability (3).

To date, only one study has evaluated the effect of new "low osmolality" i.v. contrast media on the determination of the osmolal gap (4). In this study, the authors evaluated the effect of Optiray 320 (Tyco Healthcare, Mallinckrodt, Hazelwood, MO) (ioversol 68%) administered at 2 mL/kg to patients undergoing CT of the abdomen and pelvis. The authors did not find a significant difference in the pre-contrast and post-contrast osmolal gap, but the study was limited to 14 pediatric patients. Given that the contrast was administered as a volume per kilogram, and sample size was small, it is difficult to extrapolate the data to the adult population. Because more imaging studies using i.v. contrast dye are being used for the evaluation of the undifferentiated ill patient, clinicians must know if this study will have an impact on further diagnostic testing. The goal of this study is to evaluate how i.v. contrast media given to adult patients undergoing CT of the abdomen and pelvis affects the osmolal gap.

METHODS

We performed a prospective pilot study of a convenience sample of patients in the ED of a university-affiliated tertiary care center from January 2009 to January 2010. Eligible patients were screened and consented by trained research coordinators between the hours of 7:00 a.m. and 7:00 p.m., Monday through Friday. Patients were enrolled if they were age $\geq$18 years and <60 years and the treatment team had ordered an abdomen and pelvis CT scan with i.v. contrast procedure and a serum basic metabolic panel (BMP) that included serum glucose, blood urea nitrogen (BUN), and sodium. Once enrolled, serum osmolality and serum ethanol level were ordered and obtained on the same blood draw as the BMP before the CT scan. Patients were excluded if they had detectable ethanol on laboratory screen, if they were suspected to have ingested methanol, ethylene glycol, isopropanol, mannitol, or underwent CT with i.v. contrast within the prior 24 h. Serum osmolality and a BMP were then measured as soon as possible after completion of the CT scan. Serum osmolality was measured using the freezing point depression method. Serum osmolarity was calculated using the formula $2 \times Na + BUN/2.8 + glucose/18$. To test our hypothesis, the change in osmolal gap was calculated using before-and-after contrast laboratory data for each patient. The osmolal gap was calculated as the difference between the measured osmolality and calculated osmolality.

Table 1. Summary of Results

Parameter	Result
Patients	82
Male	39
Female	43
Age	Mean 36.2 years (range 19–58 years)
Pre-contrast osmolal gap	Median = 8.18 (IQR 4.47–11.15)
Post-contrast osmolal gap	Median = 11.23 (IQR 7.29–14.83)
Δ Osmolal gap	Median 2.34 (IQR −1.32–5.97) $p = 0.0003$
Time to blood draw	Mean = 109 min (SD 84 min)

IQR = interquartile range.

The CT procedure was performed by the Radiology Department using a standard "abdominal pain" protocol. This protocol consists of the bolus infusion of 125 mL of iohexol 350 (Omnipaque™ 350; GE Healthcare Ireland, Cork, Ireland) at a rate of 2 mL/s. Iohexol 350 is a nonionic water-soluble contrast medium that contains 350 mg of iodine per mL and has an osmolality of 844 mOsmol per kg of water (5). To address the controversy regarding the ideal equation to calculate the serum osmolarity, we present results as "osmolal gaps" to remove any effect that the equation would present. Continuous data are presented as medians (interquartile range [IQR]). Paired samples were compared using the Wilcoxon signed-rank test to correct for variance in the data. Statistical analysis was performed using computer software Stata 9.0 (StataCorp LP, College Station, TX). This study was approved by the Institutional Review Board.

RESULTS

One hundred patients were consented for enrollment in the study. Eighteen patients were lost because they either withdrew consent for a post-CT blood draw or refused the CT scan after initial consent. Pre- and post-contrast laboratory measurements were available for 82 patients. The demographics and time from contrast infusion until repeat laboratories are summarized in Table 1. The median of the osmolal gap pre-contrast was 8.18 (IQR 4.47–11.15). The median of the osmolal gap post-contrast was 11.23 (IQR 7.29–14.83). The difference in the osmolal gap was a median of 2.34 ($p = 0.0003$, IQR −1.32–5.97). This difference persisted after controlling for gender.

DISCUSSION

The results of our study demonstrated that the infusion of a newer "low osmolality" contrast agent, iohexol 350, at standard adult volumes and infusion rates did increase the osmolal gap with a median change of 2.34. Given that

a normal osmolar gap is −10 to 10, this represents a change of over 10%.

Clinicians often use an osmolal gap when evaluating patients with an undifferentiated metabolic acidosis or when history leads them to consider toxic ingestions. In 2009, 5470 ethylene glycol exposures and 2146 methanol exposures were reported to poison centers across the United States (6). Surrogate markers such as an elevated osmolar gap, calcium oxalate crystals in the urine, or urine fluorescence, have been used in an attempt to risk-stratify the potentially poisoned patient (7,8). The osmolal gap is neither sensitive nor specific, and there are published case reports of patients poisoned from a toxic alcohol that had a normal osmolal gap (9). Further, the osmolal gap can be elevated in such disease states as alcohol and diabetic ketoacidosis and acute or chronic kidney disease (10). Recent exposure to i.v. contrast may further limit the utility of the osmolal gap as a diagnostic aid.

Limitations

Our study had limitations. First, although all patients received normal saline, we did not control for volume administered, which may alter renal perfusion, excretion of contrast, and alterations in variables such as sodium, glucose, and BUN. To mitigate this limitation, complete serum chemistries were obtained before and after contrast and we used the same equation to calculate osmolarity. Second, the time elapsed between CT and blood draw was variable despite best efforts to obtain them as soon as possible. Finally, we studied only one contrast medium used at our institution. It is unknown if other "low osmolality" contrast media would have the same results.

CONCLUSIONS

Intravenous contrast media have a small but statistically significant effect on the serum osmolal gap in adults tested in our study. The clinical significance of the change is less clear. It may suggest that the osmolal gap is an even less reliable marker of toxic alcohol poisoning in patients who recently were administered i.v. contrast media.

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ARTICLE SUMMARY

1. Why is this topic important?

Many Emergency Department patients receive intravenous (i.v.) contrast media during computed tomography (CT) studies obtained because they are ill and undifferentiated. Some of these patients are ill due to toxic alcohol ingestion. Diagnosing a toxic alcohol ingestion is challenging for many institutions due to the fact that the laboratory test is not readily available.

2. What does this study attempt to show?

This study attempts to demonstrate that newer "low-osmolarity" i.v. contrast media may increase the osmolal gap. The osmolal gap is often used as a surrogate marker for toxic alcohol ingestion.

3. What are the key findings?

Our study found a small but statistically significant increase in the serum osmolal gap in patients who received i.v. contrast media after CT of the abdomen and pelvis.

4. How is patient care impacted?

Given the fact that the osmolal gap is highly variable, even a small change may be clinically important. This change may make diagnosing toxic alcohol ingestions more challenging as the often used surrogate marker, the osmolal gap, may be less reliable.