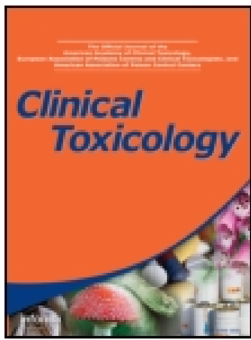

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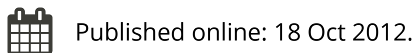
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RESEARCH ARTICLE

Analytical interferences resulting from intravenous lipid emulsion

AMI M. GRUNBAUM,[1] BRIAN M. GILFIX,[1] SOPHIE GOSSELIN,[2] and DAVID W. BLANK[1]

[1]*Division of Medical Biochemistry, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada*
[2]*Department of Emergency Medicine and Clinical Toxicology Service, McGill University Health Centre, Montreal, QC, Canada*

Context. Lipid resuscitation therapy using intravenous lipid emulsion (IVLE) for drug overdoses has gained widespread use. However, there is little information regarding its adverse effects. *Objectives*. We performed lipemic interference studies on typical automated platforms to investigate the potential of lipid resuscitation therapy to interfere with the reliability and turnaround time of analytes that would be of interest in acute intoxications. We also tested methods to minimize interferences. *Materials and methods*. Serum pools were supplemented with increasing concentrations of Intralipid-20%® (0–30%). Analyses were performed on Beckman-Coulter DXC800 and DXI and Roche Modular-P. Analytes demonstrating significant interference were re-measured after centrifugation (14 000 × g for 10 minutes). *Results*. Triglyceride and glycerol-blanked triglyceride concentrations were similar in IVLE-free samples. However, with addition of IVLE, concentrations were markedly different (139 vs. 76 mmol/L). There was no appreciable interference on the troponin-I, sodium, potassium, chloride, calcium, bicarbonate or urea assays. Albumin and magnesium assays demonstrated significant interference. Amylase, lipase, phosphate, creatinine, total protein, ALT, CK and bilirubin became unmeasurable in IVLE-supplemented samples. Whereas glucose measurement by potentiometry was free of interference, colorimetric methodology was error prone. Centrifugation removed $>90\%$ of glycerol-blanked triglyceride (max = 5.8 mmol/L), dramatically reducing lipid interferences. *Discussion*. IVLE results in appreciable analytical interferences at concentrations demonstrated in lipid resuscitation therapy. Of particular concern is the marked interference on glucose and magnesium, which may result in unsuccessful and potentially harmful interventions. Major implications for patient care include reporting of incorrect results and delays in the reporting of time-sensitive results. Whenever possible, blood samples should be collected prior to initiating lipid therapy. Interferences can be minimized by brief centrifugation at relatively low speeds on equipment readily available in most core labs.

Keywords Lipid resuscitation therapy; Lipemia; Drug overdose; Laboratory measurements

Introduction

Lipid resuscitation therapy refers to the use of intravenous lipid emulsion infusions (IVLE) for the purpose of treating intoxications from a variety of acute drug overdoses. While lipid resuscitation therapy is increasingly popular, the data from human reports are predominantly anecdotal and in the form of case reports.[1] Furthermore, there has been little investigation of the possible analytical interferences that may arise from the supra-physiologic doses of IVLE that are used. It is important to consider these potential interferences in order to better estimate the risk-benefit ratio of lipid resuscitation therapy as they may negatively impact other aspects of patient care.

Dosing protocols approved by the American College of Medical Toxicology (ACMT) call for 1.5 mL/kg of 20% IVLE (such as Intralipid-20%®, containing 200 grams of triglyceride per liter) as a bolus (repeatable), followed by infusion at a rate of 0.25 mL/kg/min.[2] For a 70 kg individual, this would be 250 grams (or 290 mmol) of soybean oil-derived triglycerides (molecular mass of approximately 870 g/mol)[3] over the course of 1 hour. This is over ten times the recommended infusion rates of 12–24 g/hr in parenteral nutrition therapy.[3]

Interference indices are used by assay manufacturers to determine if a method is valid in the face of interfering substances such as lipids, bilirubin or hemoglobin. The lipemic interference index corresponds to the concentration of lipid where a test analyte (e.g., sodium) differs by a predetermined amount from that measured in the absence of the interferent.[4,5] Lipemic interference indices generally go up to 4 g/L of IVLE,[6] far below the levels attained in lipid resuscitation therapy.

Triglyceride concentrations of 25–30 mmol/L have been measured in two published case reports (three patients total) of lipid resuscitation therapy.[7,8] However, the amount of

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Address correspondence to Ami M. Grunbaum, Division of Medical Biochemistry, Department of Medicine, McGill University Health Centre, Royal Victoria Hospital, Room C6.78, 687 Pine Avenue West, Montreal, QC H3A 1A1, Canada. Tel: +514-934-1934 x34409. Fax: +514-843-1499. E-mail: ami.grunbaum@mail.mcgill.ca

IVLE administered was not reported for two of the patients, while the third patient received only a fraction of the maximum amount approved by the ACMT protocol (140 grams). Most other human case reports and the original animal studies advocating its use for local anesthetic toxicity have reported neither triglyceride levels nor other laboratory parameters that could be affected by lipemia.[9]

In a series of kinetic studies on exogenous lipid clearance rates,[10–12] Hallberg's group demonstrated that IVLE clearance can be estimated by a two-phase model. For triglycerides greater than 1.1 mmol/L, a constant *amount* of triglyceride was eliminated per unit time (i.e. zero order kinetics), removing 25–90 μmol/L blood/minute in young healthy males. Below this concentration, a constant *fraction* was removed per unit time (i.e. first order kinetics), eliminating 5–11%/minute in young healthy males.

Thus, the maximum clearance rate of exogenous lipids from blood is approximately 6 mmol/L per hour. With a typical plasma volume of 3 L, we would expect serum triglyceride levels to reach approximately 80 mmol/L (70 g/L) after 1 hour of treatment using the ACMT recommended lipid resuscitation therapy protocol, and take several hours to return to baseline. The impact of such high concentrations on laboratory measurements has not been explored.

The primary objective of this study was to investigate the degree of analytical interferences from lipid resuscitation therapy on blood tests that are of interest in acute intoxications. We also investigated methods to minimize such interferences.

Methods

Our study design was an ex-vivo model of expected intravenous lipid emulsion concentrations post-lipid therapy.

Measurements were performed on three independent pools of serum or plasma that were prepared and analyzed on separate days. Each pool was prepared from patient specimens analyzed at the McGill University Health Centre central laboratory that had triglyceride concentration < 1.0 mmol/L. Two mL aliquots were prepared from each pool, and supplemented with increasing volumes of Intralipid-20%® (Fresenius Kabi AB, Uppsala, Sweden) (0–855 μL) in order to approximate final triglyceride concentrations of 1–80 mmol/L. For each analyte, a single determination was performed on each aliquot. In order to demonstrate the interference effects separately from the experimental dilutional effects, the mean of the three measures was normalized for dilution by the IVLE volume (by multiplying by a factor of dilution volume/neat volume).

The mean and standard deviation for each normalized set of three measures was calculated. One-way ANOVA with post hoc Student t-test using Tukey's adjustment was used to determine statistically significant differences (SAS version 9.3, SAS Institute Inc.).

Sodium, potassium, chloride and calcium were measured by indirect potentiometry on a Beckman-Coulter DXC800.

Creatinine, amylase, lipase, creatine kinase (CK), urea, total protein, bicarbonate, magnesium, albumin, phosphate, alanine aminotransferase (ALT), bilirubin and triglycerides were measured by colorimetric or UV absorbance methods on a DXC800.

Troponin-I was measured by an immuno-luminescent method on a Beckman-Coulter DXI.

Glucose was measured by two methods: a colorimetric glucose oxidase method on a Roche Modular-P and a potentiometric method on a DXC800.

In order to investigate the potential for misdiagnosis in pathological states, separate plasma pools with either elevated troponin-I (0.4–0.9 μg/L) (reference range: 0–0.06 μg/L) or low glucose (2.3–3.3 mmol/L) were similarly prepared and measured.

All measurements were made using analytical equipment in regular use, maintenance and validation at a tertiary care academic hospital centre (McGill University Hospital Centre). For further method specifications the reader is invited to consult the vendors' literature, available online at www.beckmancoulter.com.

Analytical variability was estimated from intra-laboratory quality control data collected at least twice daily from January through July 2012. These data were used to calculate the analytical coefficient of variation (CVanal):

$$\text{CVanal} = \text{standard deviation} \div \text{mean}$$

Typical intra-individual biological variability (CVindiv) of blood tests is compiled in an online database maintained by Ricos et al.[13] The coefficient of variation incorporating both CVanal and CVindiv (CVcomb) was then calculated:

$$\text{CVcomb} = (\text{CVanal}^2 + \text{CVindiv}^2)^{1/2}$$

The confidence interval (CI) was then calculated from CVcomb:

$$\text{CI} = [\text{unsupplemented concentration}] \pm 2 \times \text{CVcomb} \times [\text{unsupplemented concentration}]$$

Significant interference was defined as measurement falling outside the confidence interval. Analytes that demonstrated significant interferences were re-measured after centrifugation.

For centrifugation, approximately 1–1.5 mL of sample was transferred to an Eppendorf-type tube and centrifuged at 14 000 × g on a desktop centrifuge with a fixed-angle rotor (Sigma 1–14 microcentrifuge, SIGMA Laborzentrifugen GmbH) for 10 minutes. The lipid layer was discarded and the infranatant was re-measured.

Results

Triglyceride and glycerol-blanked triglyceride concentrations were similar in Intralipid®-free serum samples. However, with addition of Intralipid®, concentrations of triglyceride were markedly different (139 vs. 76 mmol/L with addition of 30% Intralipid-20%® by volume) (Table 1, top).

There was no appreciable interference on the sodium (except at the highest lipid concentration), potassium, chloride, calcium, bicarbonate, urea or troponin-I assays (Table 1).

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The albumin and magnesium assays demonstrated significant interference when supplemented with as little as 10% and 5% Intralipid®, respectively.

Amylase, lipase, phosphate, creatinine, CK, total protein, ALT and bilirubin became unmeasurable in Intralipid®-supplemented samples at different lipid concentrations.

Whereas glucose measurement by potentiometry was interference free, colorimetric methodology was prone to significant positive interference when supplemented with as little as 15% Intralipid®.

Centrifugation removed > 90% of glycerol-blanked triglyceride (i.e. the maximum triglyceride concentration after centrifugation was 5.8 mmol/L), dramatically reducing lipid interferences (Table 2).

The CVanal and CVindiv for all analytes measured are shown in Supplementary Table 3 to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2012.731509.

Discussion

The results have at least two major implications for patient care. First, erroneous results will be reported and might be used to guide therapy. Second, there will be a significant delay in the reporting of time-sensitive results.[7,14,15]

The impact of IVLE interference on measures of analyte concentrations is summarized in Table 1, and can be qualitatively grouped into three categories: minimal effect, false result or not measurable. While the inability to make a measurement may frustrate the clinical teams and delay reporting of results, a false report may result in incorrect diagnoses and flawed clinical interventions.

To determine if statistically significant results also represent clinically significant results, we have utilized both analytical and biological variability to define a confidence interval. Biological variability is in almost all cases the larger of the two. If the lipemic interference is within this confidence interval, its clinical impact is negligible as it would be lost in the test "noise". In all cases except for sodium, wherever the effect was statistically significant it also proved to be clinically significant; that is, outside of the confidence interval.

The clinician still needs to determine whether the differences in results are clinically relevant to the care of the patient. For example, while a blood glucose of 3.3 mmol/L may be different from 2.6 mmol/L, the clinical team may not alter their management of the patient (i.e. the patient would be treated for suspected hypoglycemia in both instances). However, a reported result of 4.7 mmol/L may falsely reassure the team. In order to make optimal use of lab tests, especially in uncommon situations, it is imperative that there be good communication between the clinicians and the laboratory.

Analytical interferences from lipid emulsions can be due to several mechanisms, including:

Table 1. IVLE Analytical interference – impact on measures of analyte concentrations.

% IVLE added (by volume)	[Initial]	CI	5%	10%	15%	20%	25%	30%
TG (mmol/L)	1 ± 0		25 ± 2	48 ± 3	74 ± 5	99 ± 10	118 ± 4	139 ± 5
glycerol-blanked TG (mmol/L)	1 ± 0		14 ± 1	26 ± 2	39 ± 2	50 ± 4	59 ± 3	76 ± 4
Analyte					Normalized concentration			
Sodium (mmol/L)	139 ± 1	135–143	140 ± 1	140 ± 1	141 ± 1	141 ± 1	142 ± 1*	142 ± 2*
Potassium (mmol/L)	4.5 ± 0.2	4.0–5.0	4.6 ± 0.2	4.6 ± 0.1	4.6 ± 0.2	4.7 ± 0.1	4.8 ± 0.2	4.8 ± 0.2
Chloride (mmol/L)	106 ± 2	103–109	107 ± 2	107 ± 1	107 ± 1	107 ± 1	107 ± 1	108 ± 1
Calcium (mmol/L)	2.26 ± 0.06	2.14–2.38	2.28 ± 0.05	2.31 ± 0.05	2.33 ± 0.05	2.33 ± 0.06	2.35 ± 0.04	2.36 ± 0.05
Bicarbonate (mmol/L)	21 ± 0	17–25	21 ± 1	21 ± 1	21 ± 0	21 ± 0	21 ± 1	21 ± 1
Urea (mmol/L)	4.8 ± 0.6	3.2–6.4	4.9 ± 0.7	5.0 ± 0.5	4.7 ± 0.4	5.0 ± 0.6	5.2 ± 0.5	5.2 ± 0.7
Troponin-I (μg/L)	0.40 ± 0.02	0.31–0.49	0.38 ± 0.03	0.39 ± 0.03	0.39 ± 0.02	0.38 ± 0.01	0.38 ± 0.03	0.39 ± 0.04
	0.82 ± 0.08	0.63–1.01	0.82 ± 0.03	0.83 ± 0.04	0.83 ± 0.02	0.84 ± 0.01	0.85 ± 0.02	0.84 ± 0.04
	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Glucose (potentiometric) (mmol/L)	5.2 ± 0.8	4.5–5.9	5.2 ± 0.8	5.1 ± 1.0	5.3 ± 0.8	5.3 ± 0.9	5.2 ± 0.7	5.2 ± 0.8
	2.7 ± 0.5	2.3–3.1	2.7 ± 0.5	2.7 ± 0.5	2.8 ± 0.4	2.8 ± 0.4	2.7 ± 0.4	2.8 ± 0.4
Glucose (colorimetric) (mmol/L)	5.6 ± 0.8	4.8–6.4	6.1 ± 0.7	7.0 ± 0.9	8.4 ± 0.6*	10.4 ± 0.4*	11.8 ± 0.7*	14.9 ± 0.6*
	2.6 ± 0.7	2.3–2.9	2.9 ± 0.8	3.3 ± 0.7	4.7 ± 0.7*	8.2 ± 0.6*	10.8 ± 0.3*	12.4 ± 0.4*
Albumin (g/L)	42 ± 2	39–45	45 ± 2	47 ± 2*	50 ± 2*	54 ± 1*	58 ± 2*	62 ± 2*
Lipase (U/L)	25 ± 3	13–37	41 ± 9	41 ± 10	38 ± 10	33 ± 8	31 ± 6	x
Magnesium (mmol/L)	0.93 ± 0.01	0.84–1.02	1.43 ± 0.03*	1.93 ± 0.02*	2.57 ± 0.01*	3.19 ± 0.01*	3.92*	x
Amylase (U/L)	80 ± 6	65–95	82 ± 7	79 ± 5	74 ± 8	x	x	x
Phosphate (mmol/L)	1.20 ± 0.08	0.97–1.43	1.15 ± 0.06	1.13 ± 0.06	x	x	x	x
Creatinine (μmol/L)	68 ± 7	55–81	52 ± 4	x	x	x	x	x
Creatine Kinase (U/L)	100 ± 22	54–146	90 ± 15	x	x	x	x	x
Total Protein (g/L)	67	63–71	x	x	x	x	x	x
Alanine Aminotransferase (U/L)	21	13–29	x	x	x	x	x	x
Total Bilirubin (μmol/L)	12	6–18	x	x	x	x	x	x

For all measurements, each point represents the mean ± SD (n = 3); x = not measurable due to excessive interference.
CI = confidence interval incorporating both analytical & biological variability; IVLE = intravenous lipid emulsion; TG = triglyceride.
*$p < 0.05$ compared to unsupplemented concentrations using ANOVA with post-hoc Tukey adjustment.

Table 2. IVLE analytical interference – effect of centrifugation.

% IVLE added (by volume)	[Initial]	CI	5%	10%	15%	20%	25%	30%
TG (mmol/L)	1 ± 1		14 ± 1	28 ± 2	42 ± 2	55 ± 1	68 ± 4	86 ± 2
glycerol-blanked TG (mmol/L)	1 ± 0		2 ± 0	2 ± 0	2 ± 0	2 ± 1	4 ± 1	5 ± 1
Analyte					Normalized concentration			
Glucose (colorimetric) (mmol/L)	2.7 ± 0.7	2.3–3.0	2.7 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	2.9 ± 0.7	3.0 ± 0.7	3.0 ± 0.7
Albumin (g/L)	39 ± 7	37–42	40 ± 7	41 ± 8	42 ± 8	43 ± 8	43 ± 8	44 ± 8
Lipase (U/L)	36 ± 14	19–53	37 ± 16	37 ± 13	38 ± 15	38 ± 15	40 ± 16	41 ± 15
Magnesium (mmol/L)	0.94 ± 0.03	0.85–1.02	1.00 ± 0.05	1.00 ± 0.02	0.99 ± 0.02	1.00 ± 0.04	1.03 ± 0.02*	1.07 ± 0.03*
Amylase (U/L)	80 ± 3	66–95	81 ± 2	84 ± 1	84 ± 2	85 ± 2	88 ± 3*	88 ± 2*
Phosphate (mmol/L)	1.18 ± 0.09	0.96–1.40	1.24 ± 0.12	1.22 ± 0.11	1.26 ± 0.13	1.27 ± 0.12	1.30 ± 0.12	1.31 ± 0.13
Creatinine (μ/L)	94 ± 47	76–112	100 ± 49	98 ± 48	100 ± 47	100 ± 51	102 ± 50	104 ± 49
Creatine Kinase (U/L)	249 ± 242	134–364	250 ± 248	256 ± 248	256 ± 251	263 ± 256	270 ± 261	272 ± 264
Total Protein (g/L)	61 ± 9	56–65	61 ± 11	65 ± 10	66 ± 10	67 ± 11	69 ± 9*	69 ± 10*
Alanine Aminotranferase (U/L)	23 ± 5	15–32	23 ± 5	23 ± 6	24 ± 5	26 ± 5	26 ± 4	26 ± 5
Total Bilirubin (μmol/L)	11 ± 1	6–17	8 ± 1	8 ± 1	10 ± 1	9 ± 2	9 ± 2	9 ± 1

For all measurements, each point represents the mean ± SD n = 3.
CI = confidence interval incorporating both analytical & biological variability; IVLE = intravenous lipid emulsion; TG = triglyceride.
*$p < 0.05$ compared to unsupplemented concentrations using ANOVA with post-hoc Tukey adjustment.

Light scattering

Lipid particles suspended in solution scatter light, producing a cloudiness or turbidity similar to that seen in milk. Lipemia may interfere in any assay that uses the transmission of light as part of the detection scheme, such as colorimetric or turbidometric methods.

Electrolyte exclusion effect

This is the exclusion of electrolytes from the fraction of total plasma volume occupied by solids (e.g., lipids). Lipids decrease the apparent concentrations of electrolytes that are restricted to the aqueous phase when an aqueous dilution is performed before the measurement (as with indirect potentiometry).

Contaminants

This is the cause of the discrepancy between the two triglyceride methods (traditional and glycerol-blanked). Intralipid-20%® contains 2.25% glycerol in order to maintain a physiologic osmolality in the IVLE solution. Most commonly used clinical methods for determining triglyceride concentration measure the glycerol that has been chemically or enzymatically hydrolyzed from triglyceride, rather than the triglyceride itself.[16] Overestimation of triglyceride occurs when glycerol from sources other than from hydrolyzed triglyceride is measured, as is the case with addition of Intralipid®. Glycerol blanking corrects for the free glycerol load in solution by performing two measurements (i.e., before and after glycerol hydrolysis) and subtracting the initial measurement to obtain the following result:

[glycerol-blanked triglyceride] = [post-hydrolysis triglyceride] − [pre-hydrolysis triglyceride]

In our study, analytes measured by colorimetric methods were much more affected by lipemic interference than those measured by potentiometric methods. This is readily appreciable when comparing the results of the two glucose methods (Fig. 1).

Magnesium, which was also measured colorimetrically was the other analyte that had over a two-fold error (Fig. 2). In order to demonstrate that this was due to lipemic interference and not from the addition of a contaminant, we measured the magnesium content of Intralipid® by inductively coupled plasma mass spectrometry (Toxicology Laboratory, Institut National de Santé Publique du Québec) and found it to be < 1 mg/L (< 0.0411 mmol/L).

Interestingly, while we expected significant negative interferences on the indirect potentiometric methods (i.e., sodium, potassium, chloride and calcium), these tests demonstrated small positive interferences. This is explained by the fact that while Intralipid-20%® contains 200 g/L of lipid, it is an aqueous-based solution (approximately 80% water phase compared to 93% in serum), and analyzers employing indirect potentiometric methodology use a correction factor of 93% when calculating ion concentrations.

Using sodium measurements in serum supplemented with 30% Intralipid® as an example, we can calculate the expected deviation due to the electrolyte exclusion effect using calculations suggested by Klinke et al.[17]:

Serum fraction of solution = 2000 μL of 2855 μL (70%); serum water content = 93%.

Intralipid® fraction of solution = 855 μL of 2855 μL (30%); Intralipid® water content = 80%.

Water content of serum supplemented with 30% Intralipid® = $0.3 \times 80\% + 0.7 \times 93\% = 89.1\%$.

Sodium concentration in aqueous phase = reported serum sodium÷0.93 = 139 mmol/L÷0.93 = 149 mmol/L.

Similarly, the predicted concentration of sodium in the aqueous phase of the Intralipid®-supplemented serum before volume and phase corrections is 109 mmol/L. The application of the volume correction factor (2.855/2) and the phase correction factor programmed into the analyzers (0.93) yields a value of 145 mmol/L, close to what was observed (142 mmol/L). The use of the more appropriate phase correction factor of 0.89 yields a value of 139 mmol/L.

So it would seem that in addition to the electrolyte exclusion effect, there is a second type of interference involved in the indirect potentiometric methods, possibly matrix effects

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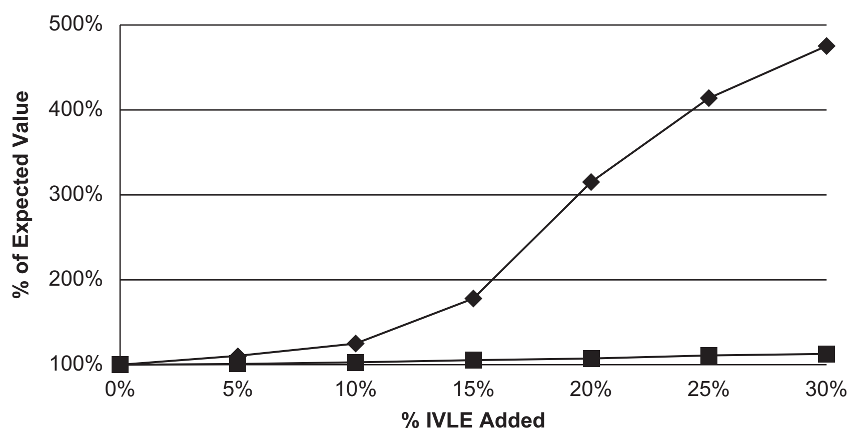

Fig. 1. The effect of IVLE interference and centrifugation on determination of glucose by colorimetry. Each point represents the mean of three determinations. Initial concentration = 2.6 mmol/L. ◆ = uncentrifuged serum; ■ = serum post-centrifugation.

at the membrane level. In any case, the sum of these interferences is not clinically significant.

In order to address the negative analytical ramifications of lipid resuscitation therapy, we explored different means of limiting the lipemic interference. We demonstrated that brief centrifugation at relatively low speed on equipment found in most hospital labs can minimize interferences.

Another common approach when dealing with suspected interferences is to dilute the sample in either normal saline (0.9% sodium chloride) or water. In an attempt to validate this approach we diluted subsets of our lipemic samples tenfold in either saline or water. All analytes included in this study were tested at 5% and 10% IVLE-supplemented levels with both diluents. Our results demonstrated that diluting was of no benefit (data not shown).

We recommend that clinical samples that are automatically rejected for or identified as having a high lipemic index be centrifuged and re-measured. This will enable transmission of valid results in a reasonable time. Finally, whenever possible, blood samples should be collected prior to starting lipid therapy.

Our study is limited by its reliance on diluted ex-vivo pooled samples to calculate estimates of triglyceride concentrations attainable by lipid emulsion therapy rather than directly measured samples from patients' post-lipid therapy. Future analytical studies should address this point and expand investigations of interferences to include point-of-care devices (e.g., bedside glucose monitors), blood gases (lactate and pH) and common co-ingestants. Clinical pharmacotoxicology investigations should also determine IVLE clearance rates in the setting of lipid resuscitation therapy and address whether dosing regimens ought to be modified according to patients' rates of triglyceride clearance.

Conclusions

Lipemia is a well-recognized cause of analytical interference with a wide variety of laboratory tests and methods. Analytical systems and reagents are routinely tested for possible interferences, and known interferents are listed in the manufacturers' literature. However, lipid concentrations reached by lipid resuscitation therapy are far above routine physiologic lipid concentrations and evaluations of possible analytical interferences at these degrees of lipemia are not typically done. This was the impetus for our study.

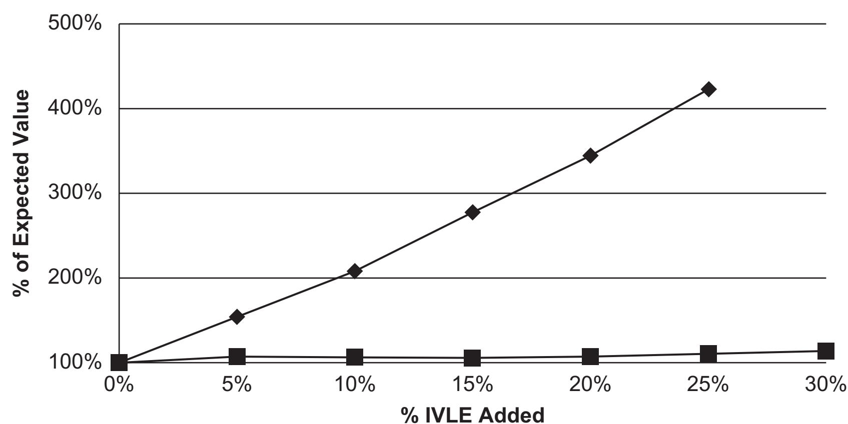

Fig. 2. The effect of IVLE interference and centrifugation on determination of magnesium by colorimetry. Each point represents the mean of three determinations. With 25% IVLE, 2 of 3 uncentrifuged determinations were not measurable due to excessive interference. Initial concentration = 0.93 mmol/L. ◆ = uncentrifuged serum; ■ = serum post-centrifugation.

Colorimetric methods are more prone to lipemic interference, whereas potentiometric methods remain relatively interference-free. We have also demonstrated how relatively brief centrifugation on commonly available equipment minimizes lipemic interference.

Hopefully, our work will sensitize clinicians to the risks of relying on lab results without collaborating with the laboratory to ensure their validity.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Table 3.

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