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REVIEW ARTICLE

Review of the effect of intravenous lipid emulsion on laboratory analyses

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ABSTRACT

Context Although the clinical use of intravenous lipid emulsion therapy for the treatment of lipophilic drug toxicity is increasing, the focus of most publications is on outcome in laboratory animals or in patients. An unintended consequence of intravenous lipid emulsion is the creation of extremely lipemic blood, which may interfere with the laboratory analysis or interpretation of common analytes. **Objective** The American Academy of Clinical Toxicology has established a lipid emulsion workgroup to review the evidence and produce recommendations on the use of this novel therapy for drug toxicity. The aim of this subgroup is to review the available evidence regarding the effect of intravenous lipid emulsion on common laboratory testing, which often forms the basis of the appraisal of the balance between benefits and potential adverse events. **Methods** We performed a comprehensive review of the literature. Relevant articles were determined based upon a predefined methodology. Package inserts of manufacturers' assays were collected. Article inclusion required that the article met predefined inclusion criteria with the agreement of at least two members of the subgroup. **Results** We included thirty-six articles in the final analysis. Evaluation of the reviewed analytes revealed heterogeneity with regards to the assessment of the effect of intravenous lipid emulsion in terms of consistency and magnitude of effect across the different analytic platforms. **Conclusions** The measurements of a number of common analytes can be markedly affected by the lipemia produced by lipid emulsions such that they cannot always be interpreted in the way that most physicians use this information in typical clinical situations. In fact, a lack of appreciation of this effect may lead to unintentional treatment errors. Because the effect of the lipemia produced is dependent on the reagents and laboratory platform used, it would be useful for all future reports to clearly document sample handling, reagents and laboratory platform used, as well as any procedures employed to reduce the lipid content.

KEYWORDS

Analytical interference;
Laboratory measurements;
Lipemia; Lipid emulsion

HISTORY

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Introduction

The use of intravenous lipid emulsion as a treatment for acute drug toxicity was first reported in human cases of local anesthetic systemic toxicity (LAST) in 2006.[1,2] Subsequently, it has gained vast acceptance with potential indications broadening to include many other lipophilic drugs and patients with less severe toxicity.[3–5] Guidance for the use of intravenous lipid emulsion is published in both the anesthesia and medical toxicology literature.[6,7] However, the transient production of hyperlipidemia or excess lipid in patient's blood is an unintended consequence of intravenous lipid emulsion.[8–11] Unfortunately, lipemia, or the presence of excess lipid *in vitro* affects the measurement of various analytes of clinical significance in serum.[12] As reviewed by Nikolac, this effect can be attributed to a number of factors (e.g. increasing light scattering, increasing the non-aqueous

phase, and altering the partitioning between the polar and non-polar phases) and can produce erroneous results.[13] The phenomenon is well known to the manufacturers of analytical instruments and of their reagents. With some exceptions, most manufacturers provide data as to the effect of lipemia up to levels of 10 mmol/L (8.8 g/L) (measured in terms of triglyceride equivalents). The administration of intravenous lipid emulsion as a treatment for poisoning typically produces lipid concentrations far in excess of 10 mmol/L.[14]

When treating a patient with drug toxicity, measurement of various analytes (e.g. sodium, potassium, creatinine, calcium, glucose, etc.) is important for the appropriate management of the patient. The concentrations of lipids obtained during lipid emulsion therapy can alter the measured values,[14,15] and unless this process is thoroughly understood, it could lead to

incorrect treatment decisions for the patient. The American Academy of Clinical Toxicology (AACT)¹ initiated a collaboration between the European Association of Poison Centres and Clinical Toxicologists (EAPCCT), the Asia Pacific Association of Medical Toxicology (APAMT), the Canadian Association of Poison Control Centres (CAPCC), the American College of Medical Toxicology (ACMT) and the American Association of Poison Control Centers (AAPCC) to create the Lipid Emulsion Therapy in Clinical Toxicology Workgroup in order to review all appropriate evidence pertaining to the use of lipid emulsion in toxicology, with the ultimate goal of providing evidence and consensus-based recommendations.[16] We present the results of this comprehensive review of the literature that was undertaken in order to determine the effect of lipid emulsions on the measurement of the clinically relevant analytes.

Methods

A subgroup of the Lipid Emulsion Therapy In Clinical Toxicology Workgroup was formed to gather and review the evidence on the effect of lipid emulsions on pertinent laboratory analyses. In addition to expert clinical toxicologists, members of this subgroup included two medical biochemists, an epidemiologist with expertise in conducting systematic reviews and two medical librarians who assisted in conducting the searches and in the retrieval of potentially eligible publications.

A complete methodology for the various systematic reviews was previously published and describes all the methodological aspects of this review.[16] This includes the clinical question, search strategy, eligibility of publications, poison selection, data extraction and summary. The search strategy (shown in Appendix 1) was conducted in Medline (Ovid), and translated to Embase (Ovid), BIOSIS (Ovid) and CINAHL, from inception to 15 December 2014. For the purposes of this comprehensive review we applied the following inclusion criteria:

- (1) Papers containing original data only.
- (2) Evaluations reporting triglyceride concentrations that are obtained when lipid emulsions are used (i.e. >5 mmol/L).
- (3) Increases in serum lipid that result from the addition of lipid emulsion and not by the addition of exogenous lipids in any other form or from endogenous hyperlipidemia syndromes as the nature of the lipids differ and could produce different responses.[17,18]
- (4) Evaluation of analytes relevant in the acute management of drug toxicity and the use of intravenous lipid emulsion in critical care settings as selected by our reviewing toxicologists and biochemists to include analytes for which critical value reporting exists and that are typically requested in poisoning cases. (Table 1).
- (5) Evaluation using currently available equipment.
- (6) Evaluations measuring the response as a function of added triglyceride and not as a lipemic index as the relationship between the two is complex.[17–19]

We retrieved additional results through hand searching in PubMed, and by citation tracking based on highly relevant

articles that had already been retrieved. Package inserts of manufacturers' assays were also collected.

We extracted data using predefined fields, including analytes, assay platforms and methods, lipid sources and ranges of concentration and percent bias due to lipemia (i.e. level of interference). The percent bias was calculated as follows:

$$\left[\frac{(\text{control result} - \text{lipemic result})}{\text{control result}} \right] \times 100\%$$

The "control result" is the measurement of the native sample without lipid emulsion, and the "lipemic result" is the measurement with lipid emulsion added to the sample.

Results

The flow diagram for the article search is shown in Fig. 1. We obtained a total of 243 full text articles for evaluation, of which 36 met the inclusion criteria and were therefore analyzed in this review. The most common reasons for excluding articles were insufficient detail of interference, use of endogenous lipids as the interfering agents, outdated methods and studies of analytes not relevant in the emergent toxicology setting. In contrast to the systematic reviews undertaken by the lipid emulsion workgroup, which focus on the clinical reports of intravenous lipid emulsion use, this review extracted data from evaluations of analytical methods.

The inherent advantage of these studies is that they are designed to investigate analytical interferences. Typically, analytical measurements are made on serum samples both before (control sample) and after (test sample) addition of varying concentrations of lipid emulsion. Analytical bias (i.e. degree of interference) due to the emulsions can then be calculated. While this has the disadvantage of being an *in vitro* study, it affords the opportunity of making measurements on a lipid emulsion-free sample and to control for the concentration of lipid emulsion.

Table 2 summarizes the 36 peer-reviewed methodological evaluations that were included in this comprehensive review of interferences by exogenous lipids on serum measurements.

Analytes included were selected by consensus of the 4 medical toxicologists and medical biochemists in this subgroup for their potential clinical impact on decisions to be made in the emergent toxicology setting.

Intra-individual biological variation (CV_i) alone does not take into consideration analytical imprecision (CV_a). Furthermore, the former can be increased in the acute clinical setting when patients in critical conditions such as poisoning have rapidly changing biological markers due to their evolving physiological and biochemical status. In order to make our extrapolation more clinically relevant and to get a good estimate of clinical interference thresholds, we added 2% to the CV_i.

We acknowledge that using 2% as an estimate of CV_a for all analytical methods of endogenous analytes reviewed in this article is an oversimplification. However, in most cases, the CV_a is smaller than the CV_i, such that the clinical interference

1. The AACT lipid emulsion workgroup also includes the following members:

Benoit Bailey, Theodore C. Bania, Ashish Bhalla, Diane P. Calello, Ryan Chuang, Andis Graudins, Bryan Hayes, Lotte C. G. Hoeberg, Michael Levine, Sheldon Magder, Bruno Mégarbane, Jose A. Morais, Carol Rollins, Samuel J. Stelplflug, Christine M. Stork, Simon H.L. Thomas and Alexis F. Turgeon

Table 1. Summary of reported interferences for endogenous analytes in serum due to exogenous lipid as reported in the literature.

Analyte	CVi*	Clinical interference threshold [†]	# Platform evaluations	# Evaluations with interference	Max reported interference	References [‡]
ALT	19.4%	21.4%	5	5	n/r	[14,23,24]
albumin	3.2%	5.2%	7	6	48%	[14,23,24,26,27]
ALP	6.5%	8.5%	4	0	-7%	[23,24]
amylase	8.7%	10.7%	6	1	n/r	[14,23,24,26]
AST	12.3%	14.3%	4	4	n/r	[23,24]
bicarbonate	4.0%	6.0%	2	1	6%	[14,21]
biliD	36.8%	38.8%	7	4	1150%	[23,24,60]
biliT	21.8%	23.8%	10	8	n/r	[14,21,23,24,60]
Ca	2.1%	4.1%	11	6	-21%	[14,21,23,24,26,43,53,59]
carbamazepine	n/a	10.0%	1	0	-3%	[21]
carboxy-hemoglobin	n/a	2.0%	1	1	-10%	[69]
Cl	1.2%	3.2%	9	8	-19%	[14,21,24,55]
CKMb	19.7%	21.7%	5	2	n/r	[21,23,24,50]
CK	22.8%	24.8%	6	1	n/r	[14,21,23,24]
creatinine	6.0%	8.0%	10	9	n/r	[14,21,23,24,26,48,55]
cystatin C	5.0%	7.0%	2	0	x	[56,57]
D-dimer	23.3%	25.3%	2	1	-43%	[54,63]
digitoxin	n/a	10.0%	1	0	6%	[21]
digoxin	n/a	10.0%	1	0	0%	[21]
GGT	13.4%	15.4%	6	2	-54%	[21,24,26]
gentamycin	n/a	10.0%	1	0	x	[21]
glucose	5.6%	7.6%	9	4	377%	[14,21,23,24,26,27]
hematocrit	2.7%	4.7%	1	1	-6%	[49]
hemoglobin	2.9%	4.9%	4	3	125%	[49,61,69]
iron	26.5%	28.5%	5	1	78%	[21,24,64]
lactate	27.2%	29.2%	4	2	100%	[21,26,29,64]
lipase	32.2%	34.2%	6	2	n/r	[14,21,24,71]
Mg	3.6%	5.6%	7	4	322%	[14,24,28,29]
methemoglobin	n/a	2.0%	1	1	50%	[69]
O ₂ content	n/a	2.0%	1	0	x	[69]
osmolality	1.3%	3.3%	1	0	x	[67]
oxyhemoglobin	n/a	2.0%	1	1	-60%	[69]
PTT	3.4%	5.4%	2	0	x	[65,68]
phenobarbital	n/a	10.0%	1	1	-17%	[21]
phenytoin	n/a	10.0%	3	1	18%	[21,52,66]
phosphate	8.2%	10.2%	8	5	n/r	[14,21,23,24,26]
platelets	9.1%	11.1%	8	4	300%	[49,51,61,62]
K	4.6%	6.6%	8	4	-17%	[14,21,24,55]
PT	4.0%	6.0%	2	1	n/r	[65,68]
RBC	3.2%	5.2%	5	2	43%	[49,51,61]
Na	0.6%	2.6%	12	8	-18%	[14,21,24,55,58]
theophylline	n/a	10.0%	1	1	-20%	[21]
tobramycin	n/a	10.0%	1	0	4%	[21]
total protein	2.8%	4.8%	8	3	n/r	[14,21,23,24,26,29]
troponin I	14.1%	16.1%	3	0	x	[14,50,72]
troponin T	30.5%	32.5%	1	0	x	[25]
urate	8.6%	10.6%	2	1	n/r	[21,23]
urea	12.1%	14.1%	8	4	n/r	[14,23,24,26,55]
valproate	n/a	10.0%	1	0	5%	[21]
WBC	11.4%	13.4%	7	1	25%	[49,51,61,71]

x = no significant interference, n/r = no values reportable due to lipid interference

alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), bilirubin direct (biliD), bilirubin total (biliT), calcium (Ca), chloride (Cl), creatine kinase (CK), creatine kinase-myoglobin (CKMb), gamma-glutamyl transferase (GGT), magnesium (Mg), partial thromboplastin (PTT), potassium (K), prothrombin time (PT), red blood cells (RBC), sodium (Na), white blood cells (WBC).

*CVi = intraindividual biological variation. (<https://www.westgard.com/biodatabase1.htm>) (Accessed 2015-06-10)

[†]For endogenous analytes, in order to account for the analytical imprecision of the assay methodologies, 2% was added to the CVi (interference if %difference > CVi + 2). For exogenous drugs, an analytical bias of 10% was considered significant.

[‡]Several references included evaluations of multiple platforms (i.e. the number of references need not necessarily match the number of studies).

threshold is largely dependent on biological variability. In cases with large biological variability (e.g. troponin T), the CVa is rendered comparatively insignificant. For tightly regulated analytes with small biological variability (e.g. sodium), CVa has greater impact. In these cases, 2% is an appropriate estimate of CVa. For this reason and due to the tremendous variability in methods reviewed for each analyte (e.g. at least 7 different analytical methods for calcium), we chose to use a fixed and conservative estimate for CVa.

For example, in the case of sodium with a reported CVi of 0.6%, a difference of 1 mmol/L (141 versus 140) would be

considered a significant interference. However, a variation of 2.6% (or a 4 mmol/L difference) is more likely to be clinically relevant.

There is no universally accepted definition of significant interference, with considerable variation reported amongst proposed acceptable clinical interference thresholds (Table 3). Most manufacturers still use the arbitrarily chosen criteria of 10% suggested by Glick et al nearly 30 years ago.[20]. Sonntag and Scholer used a group consensus derived from analytical performance data on external quality control assessments and clinical significance.[21] Dimeski and Jones,[22] and Fleming

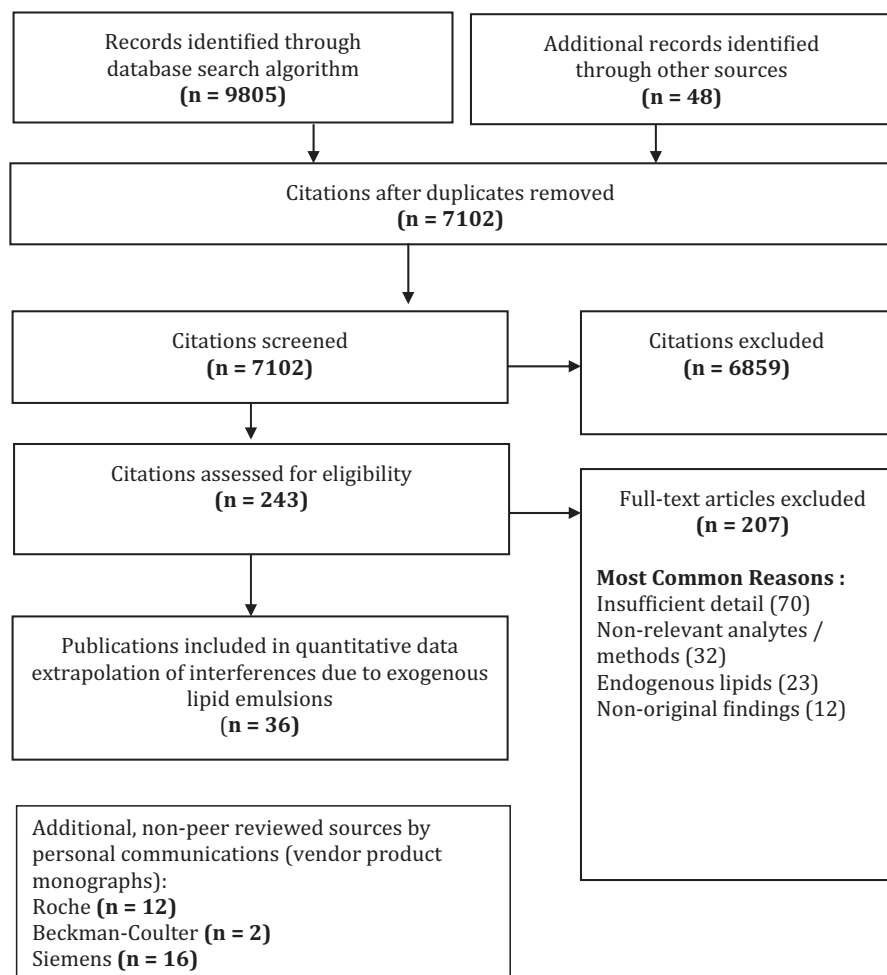


Fig. 1. Study selection flow diagram.

and Swaminathan,[23] used differing multiples of assay imprecision ($2.8 \cdot (CVa)^{1/2}$ and $2.8 \cdot CVa$, respectively). Nikolac et al,[24] and Saracevic et al,[25] both used the concept of Desirable Specification for Imprecision (DSI, where $DSI = 0.5 \cdot CVi$). Grunbaum et al,[14] used a combination of CVi and experimentally derived CVa.

Table 1 summarizes the reported interferences for given serum analytes that result from administration of exogenous lipids. There are many different platforms and analytical methods in use in clinical laboratories, as well as a lack of standardization regarding the concentration of lipid emulsion used in the study measurements. As a consequence, there is often a lack of agreement between studies regarding the effects of lipid emulsion on analytical interferences. For example, glucose can be measured by several different enzymatic assays as well as by an indirect potentiometric method.[14,21,23–26] While 6 of 10 evaluated platforms demonstrated acceptable bias,[14,21,24,27] 4 other platforms reported significant interference.[14,23,24,26] Grunbaum et al.[14] found a colorimetric method (glucose oxidase on a Roche platform) to be prone to as much as 377% positive bias at both normoglycemic (5.6 mmol/L, or 100 mg/dL) and hypoglycemic (2.6 mmol/L, or 47 mg/dL) concentrations. This could potentially result in failure to identify and appropriately

treat a clinically significant hypoglycemic event. Similarly for magnesium, while three evaluated platforms reported negligible interferences,[24,28] results were elevated on four other platforms[14,24,28,29] by as much as 320%.[14] This is true of other analytes found in Table 1 as well.

Fig. 2 is a graphical representation of the lipemic interferences described in the 36 peer-reviewed reports included in this review. It highlights the considerable variability in the reporting of interferences. Of all the analytes with at least two evaluations, only four (alkaline phosphatase, cystatin C, PTT and troponin) demonstrated no significant interference. For most analytes, both positive and negative interferences were observed and often of quite differing degree.

With regards to lipid emulsion interferences concerning therapeutic and toxic drugs, there is very little information available in the peer-reviewed literature. Therefore, we evaluated additional data not otherwise available in our database search that was found in product inserts provided from the assay vendors.[30–32] Table 4 is a summary of vendor-reported interferences for a selection of commonly available commercial assays. Instead of biological variation (a concept of limited applicability for exogenous drugs), we considered an analytical bias of 10% to be of significance for these measures. Unfortunately, manufacturers' claims cannot

Table 2. Summary of 36 peer-reviewed methodological evaluations included in the comprehensive review.

References	LE used	Max LE concentration (in TG equivalents)*	Analytical platform(s)	Analyte(s) [†]
[27]	Intralipid 20%	23	Vitros 5600	albumin, glucose
[48]	Intralipid	11	ABL837 FLEX blood gas analyzer	creatinine
[49]	Clinic Oleic 20%	30	Coulter LH 750	hemoglobin, hematocrit, platelets, RBC, WBC
[28]	Intralipid	23	Abbot ARCHITECT c800 (2 methods reported)	Mg
[50]	Intralipid	7	Stratus CS	CKMb, troponin I
[‡] [15]	Lipofundin 20%	14	Multiple (26 laboratories reporting)	albumin, AST, biliT, Ca, creatinine, glucose, iron, phosphate, total protein, urate, urea
[51]	Intralipid 20%	26	Technicon H3, Coulter JS	platelets, RBC, WBC
[52]	Intralipid 20%	9	ADVIA 1650	phenytoin
[53]	Intralipid 20%	11	ADVIA 1650	Ca
[54]	Intralipid	31	Roche CARDIAC POC	D-dimer
[55]	ClinOleic 20%	86	Beckman DXC800, Roche Modular DP, Siemens RapidLab 1265	Cl, creatinine, K, Na, urea
[29]	Intralipid 20%	11	Abbott c16000	lactate, Mg, total protein
[56]	Intralipid	23	Dade Behring Nephelometer II	cystatin C
[57]	Intralipid	23	Roche Modular Analytics P	cystatin C
[58]	Tutolipid 10%	10	IL 943, SMAC II, Jokoo-ION 150	Na
[23]	Intralipid 10%	26	Hitachi 912	albumin, ALP, ALT, amylase, AST, biliD, biliT, urea, Ca, CK, CKMb, creatinine, glucose, phosphate, total protein, urate
[59]	Intralipid	3	Precision Systems Calcette	Ca
[60]	lvelip 20%	8	Advia 1650 (3 methods reported)	BiliD, BiliT
[61]	Intralipid	51	Abbott CELL_DYN 4000	hemoglobin, platelets, WBC
[62]	Intralipid	25	Abbot Cell-Dyn Sapphire (3 methods reported)	platelets
[14]	Intralipid 20%	76	Beckman DXC800, Beckman DXI, Roche Modular DP	albumin, ALT, amylase, bicarbonate, biliT, Ca, CK, Cl, creatinine, glucose, lipase, Mg, phosphate, K, Na, total protein, troponin I, urea
[63]	Intralipid	47	Abbott AxSYM	D-dimer
[43]	Intralipid 20%	11	Hitachi 704	Ca
[64]	Intralipid	46	Kodak Ektachem 700XR	iron, lactate
[65]	Lipofundin 20%	23	Coagulometer KC-10	PT, PTT
[26]	Intralipid	11	Beckman AU5800	albumin, amylase, Ca, creatinine, GGT, glucose, lactate, phosphate, total protein, urea
[24]	Intralipid 20%	11	Beckman AU6800, Roche Cobas6000, Siemens Vista1500	albumin, ALP, ALT, amylase, AST, biliD, biliT, Ca, Cl, CK, CKMb, creat, GGT, glucose, iron, lipase, Mg, phosphate, K, Na, total protein, urea
[66]	Intralipid 20%	11	ADVIA 1800	phenytoin
[67]	Intralipid	18	Advanced 3250	osmolality
[68]	Intralipid	11	MDA 180	PTT, PT
[¶] [25]	Intralipid 20%	6	Beckman AU680	troponin T
[69]	Intralipid	23	Instrument Laboratories 282	carboxyhemoglobin, hemoglobin, methemoglobin, O ₂ content, oxyhemoglobin
[21, Sonntag, personal communication, 2015]	Intralipid 20%	11	Roche Hitachi 917	bicarbonate, biliT, Ca, carbamazepine, Cl, CK, CKMb, creatinine, digitoxin, digoxin, gentamycin, GGT, glucose, iron, lactate, lipase, phenobarbital, phenytoin, phosphate, K, Na, theophylline, tobramycin, total protein, urate, valproate
[70]	Liposyn	26	Roche Cobas E411	lipase
[71]	Intralipid 20%	57	Sysmex XE-2100, Sysmex NX-2000	WBC
[72]	Intralipid 20%	11	Abbott AxSYM	troponin I

Lipid emulsion (LE), triglyceride (TG), alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), bilirubin direct (biliD), bilirubin total (biliT), calcium (Ca), chloride (Cl), creatine kinase (CK), creatine kinase-myoglobin (CKMb), gamma-glutamyl transferase (GGT), magnesium (Mg), partial thromboplastin (PTT), potassium (K), prothrombin time (PT), red blood cells (RBC), sodium (Na), white blood cells (WBC).

*1 g/L lipid = 1.14 mmol/L

[†]Analytes are restricted to those of clinical relevance in the acute emergent toxicological setting.

[‡]Data extraction for Brady, 1994 is summarized in Table 5.

[¶]Aside from TnT, all other relevant analytes were obtained from the same data set summarized in Nikolac, 2013. Accordingly, they are not re-included in this review.

always be confirmed, nor do they always report them in a uniform manner, which limits the usefulness of such information.[24]

Vendors, in accordance with CLIA (Clinical Laboratory Improvement Amendment) recommendations, typically

report lipemic interferences in terms of “turbidity indices” that are not concordant with triglyceride concentrations in lipid emulsion preparations.[19] Furthermore, the amount and source of triglyceride added are often not explicitly given.

Table 3. Variability in definitions of analytical interference significance.

Analyte	Glick [20]	Grunbaum [14]	Sonntag [21]	Saracevic [25]	Fleming [23]	This review
ALT	10%	18%	20%	9.0%	5.6%	21.4%
albumin	10%	3%	10%	1.6%	4.2%	5.2%
ALP	10%	–	20%	3.2%	7%	5.2%
amylase	10%	9%	20%	4.4%	9.8%	11.7%
AST	10%	–	20%	6.0%	5.6%	14.3%
bicarbonate	10%	8%	15%	–	–	6.0%
biliD	10%	–	–	18.4%	25.2%	38.8%
biliT	10%	26%	10%	11.9%	25.2%	23.8%
Ca	10%	3%	5%	1.0%	7%	4.1%
Cl	10%	2%	5%	0.6%	–	3.2%
CK	10%	23%	20%	11.4%	14%	24.8%
creatinine	10%	10%	10%	3.0%	8.4%	8.0%
GGT	10%	–	20%	6.9%	–	15.4%
glucose	10%	7%	10%	2.3%	5.6%	7.6%
Iron	10%	–	5%	13.3%	–	28.5%
lactate	10%	–	10%	–	–	29.2%
lipase	10%	24%	20%	11.6%	–	34.0%
Mg	10%	5%	5%	1.8%	–	5.6%
phosphate	10%	9%	5%	4.3%	7%	10.2%
K	10%	6%	5%	2.4%	–	6.6%
Na	10%	2%	5%	0.4%	–	2.6%
total protein	10%	3%	10%	1.4%	2.5%	4.8%
troponin I	10%	12%	–	–	–	16.1%
urea	10%	17%	10%	6.2%	5%	14.1%

alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), bilirubin direct (biliD), bilirubin total (biliT), calcium (Ca), chloride (Cl), creatine kinase (CK), gamma-glutamyl transferase (GGT), magnesium (Mg), potassium (K), sodium (Na)

Discussion

The use of intravenous lipid emulsion is becoming more frequent in the treatment of various poisonings. The effect of this treatment is measured most importantly by clinical outcomes. However, laboratory measurements of various analytes are often used to gauge the response of the patient during treatment or as surrogate markers of clinical response.

In one of the first comprehensive studies on the effect of lipid emulsions, Brady and O'Leary[15] noted that the advent of automated clinical laboratory analytical platforms has increased the difficulty in dealing with interferents such as lipemia. Whereas previously such samples could be treated by various manual methods (e.g. dialysis, deproteination), modern automated hospital-based labs are poorly equipped for such manipulations. In their 1994 study, they reported on lipid emulsion interferences across 26 different hospital laboratories in Ireland using lyophilized external quality control samples that were reconstituted in soybean oil-based lipid emulsion containing diluent (Lipofundin™ 20%, for a final triglyceride concentration of 14 mmol/L (12.3 g/L)). While this report does not lend itself well to our data extraction methodology, the findings merit analysis and discussion. Over a diverse array of automated analyzers (including 12 Hitachi, 6 Roche Cobas and several other platforms), they demonstrated marked increases in inter-laboratory variation of various analyte concentrations (Table 5), such as iron (55% with lipid emulsion versus 6% without), bilirubin (105% versus 10%) and phosphate (54% versus 6%). In contrast, calcium was relatively free of interference (6% versus 3%).

Similarly, as we document in this review, laboratory measurements can be so markedly affected by the lipemia produced by lipid emulsions that the resulting analyte concentrations and enzyme activities are no longer representative of the levels

that they are meant to approximate. For example, the measured potassium can be decreased by as much as 17%, iron increased 78%, magnesium increased 322%, and glucose increased as much as 377% in comparison to their actual values (Table 1). The assessment of a potential iron overdose, the failure to provide magnesium supplementation or to recognize true hypoglycemia would be affected in these cases. Moreover, as demonstrated in Fig. 1, the degree of interference can differ among platforms and reagents. Assessment is further complicated by the fact that analytical platforms undergo continual technological change, so what was true yesterday is not necessarily what is true today or what will be tomorrow. Even the manufacturers' own assessment may not be reliable.[24,33] Clearly, physician awareness and education on this matter is of paramount importance.

Glucose merits special consideration as testing is often done at bedside with point of care (POC) devices. Whereas in-lab methods are typically performed on serum or plasma samples, POC tests are usually carried out on whole blood. In these POC instruments, glucose oxidase and hexokinase methods predominate with detection based on reflectance photometry or electrochemistry.[12] While our review did not reveal any reports of lipid emulsion interferences on POC glucometers, it may be prudent to formally evaluate these methods.

The clinical impact of analytical interferences due to the extreme lipemia generated by intravenous lipid emulsion as a rescue therapy is highlighted in the recent clinical toxicology literature. Despite the publication bias inherent to the case reports as well as a dearth of analytical information that would otherwise be required for inclusion in this analytical review, several cases of interest merit discussion in order to emphasize the potential clinical problems. Bucklin et al.[9] reported on a 14-year-old girl who presented actively seizing after ingesting multiple pharmaceuticals. She received a total dose of 4000 mL

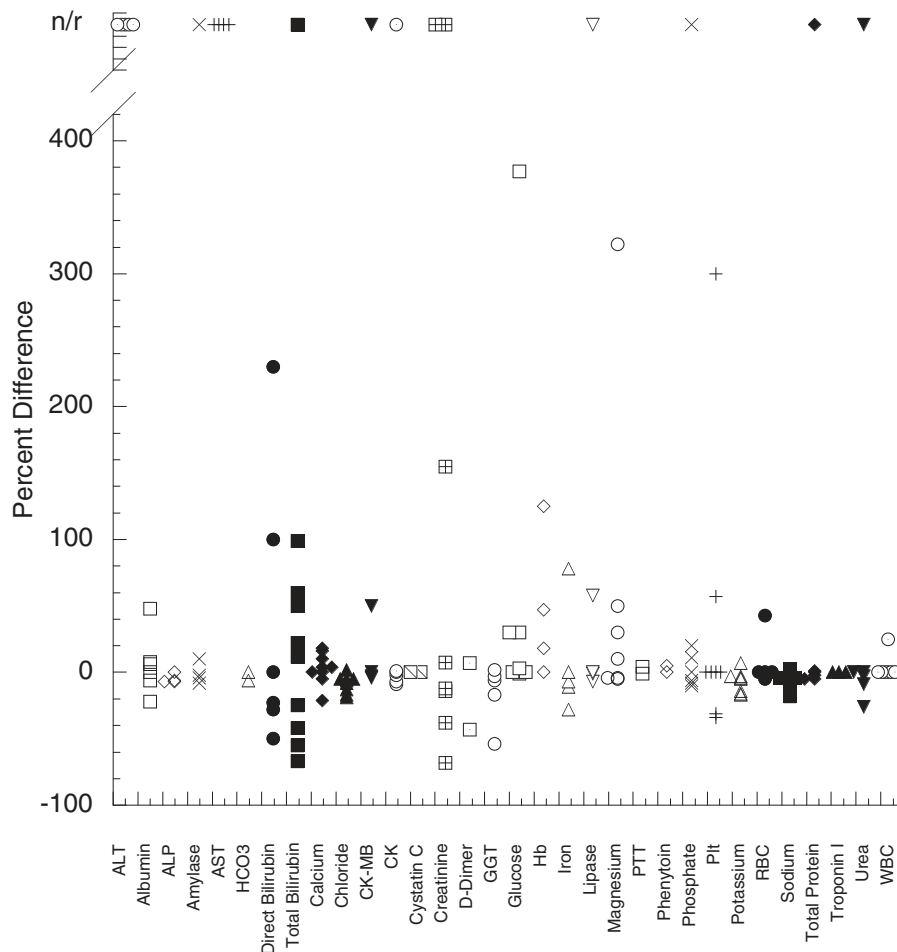


Fig. 2. Summary plot of lipemic interferences reported in the 36 reviewed studies.

Table 4. Summary of reported interferences for pharmaceuticals in serum due to exogenous lipids as reported by assay vendors.

Analyte	# Evaluations	# Evaluations with interference	References
acetaminophen	2	1	[30,31]
carbamazepine	2	0	[30,31]
cyclosporine	1	0	[31]
digoxin	4	1	[30–32]
ethanol	2	0	[30,31]
gentamycin	2	1	[30,31]
lidocaine	1	1	[31]
lithium	2	0	[30,31]
phenobarbital	1	0	[31]
phenytoin	2	1	[30,31]
procainamide	1	1	[31]
salicylate	2	1	[30,31]
theophylline	3	1	[30–32]
tobramycin	2	0	[30,31]
valproate	2	0	[30,31]
vancomycin	2	0	[30,31]

Table 5. Interlaboratory variation with and without addition of lipid emulsion (14 mmol/L TG equivalent) (adapted from Brady, 1994) [15].

Analyte	%CV without LE	%CV with LE
albumin	5%	13%
AST	15%	49%
bilirubin (total)	10%	105%
calcium	3%	6%
creatinine	7%	25%
glucose	5%	26%
iron	8%	55%
phosphate	6%	53%
total protein	4%	28%
urate	11%	32%
urea	5%	11%

aspartate transaminase (AST), coefficient of variation (CV), lipid emulsion (LE)

of lipid emulsion (800 g of TG) in less than 12 h and subsequently developed a profound lipemia, which delayed critical laboratory results by four hours. Levine et al.[10] reported a case series of nine patients treated with intravenous lipid emulsion. Laboratory results were delayed in three of the patients (by 3, 16 and 25 hours). A profound lipemia in the fourth patient resulted in laboratory interferences that

ultimately precluded organ donation. Similar cases of delayed laboratory results were recently reported [11,34–36]. Punja et al.[37] described a case of multi-drug toxicity that included acetaminophen and amitriptyline. Initial evaluation revealed an AST of 138 U/L, an acetaminophen of 177 µg/mL (1170 µmol/L), and a prolonged QRS interval on the ECG. Acetylcysteine (NAC), sodium bicarbonate, and intravenous lipid emulsion therapy were started. Subsequent laboratory test results less than 6 hours later showed an undetectable AST. Consequently, NAC

and LE infusions were stopped. Eight hours later, the serum AST was measured at 488 U/L and increased over the next 2 days to a peak of 1600 U/L before recovery. The erroneous AST led to premature discontinuation of NAC therapy, possibly contributing to development of hepatotoxicity.

The observations summarized in this review should also be of interest to those using lipid emulsions in Total Parenteral Nutrition (TPN), which is subject to the same phenomena and in which similar alterations in measured parameters were noted.[38–40]

Numerous procedures can be used to reduce the effect of lipemia (e.g. high speed centrifugation, ultracentrifugation, clearing agents, organic solvents, spectral measurements at multiple wavelengths)[13,14,25,41–43] (NB: Ultracentrifugation is a term typically reserved for centrifugation at forces exceeding 100,000 $\times g$). From these attempts, it is clear that there is no single procedure that can be used for all analytical methods. For example, Saracevic et al reported significant interference even after centrifugation for calcium, total protein, sodium and chloride and after use of LipoClear™ (lipemia clearing reagent) for glucose, calcium, phosphate, magnesium, sodium, potassium, chloride, ALP, GGT, CK-MB, total protein, albumin and troponin T.[25] Vermeer et al also reported heterogeneity in response depending on the analyte.[41] Organic solvent extraction would be of limited utility in a rapid response laboratory.[42]

The mechanisms for the interference of lipids and lipemia on laboratory measurements were recently reviewed and are numerous.[44,45] These mechanisms involved include: volume depletion (electrolyte exclusion effect); turbidity (light absorption and scattering from 300–700 nm); physico-chemical interferences (e.g. altered lipid-antibody interaction and differential partitioning of analyte due to interaction with lipids (e.g. lipid extraction), and sample non-homogeneity), and excipients within the lipid emulsion product (e.g. cross-reactivity of glycerol on lipase and triglyceride methods).

The degree of lipemia of a patient sample was traditionally determined by visual inspection. To replace this subjective assessment, many manufacturers use a lipemic index to quantify lipemia (an automated assessment of interfering substances in samples based on light absorbance at different wavelengths, conversion of these wavelengths into a concentration and assignment of an index value – the lipemic index). Not surprisingly, visual inspection performs poorly against the automated methods.[33] What many do not realize is that there also is a poor correlation between the triglyceride concentration and turbidity in patient lipemic samples as measured by the lipemic index.[19] The response of an assay can differ whether the lipemia is native or due to added lipid emulsion.[17,18] Bornhorst et al. performed correlations of triglyceride concentration versus lipemic index for a soybean oil-based lipid emulsion (Intralipid 20%™) ($r^2=0.7056$) and native triglycerides ($r^2=0.7744$), demonstrating poor correlation, between lipemic index and triglyceride concentration for both native and lipid emulsion supplementation.[17] In contrast, Twomey et al demonstrated a poor correlation between the lipemic index and native triglyceride for turbid samples ($r^2=0.2399$), but a very high degree of correlation in samples supplemented with Ivelip™ lipid emulsion (another soybean

oil-based formulation similar to Intralipid) ($r^2=0.9994$).[19] The different measures of correlation are due to the difference in lipemic index methods between the analytical platforms used in each of these studies. Bornhorst et al used a Roche platform (Mod P 800) that determines lipemic index by differential absorbance at 2 different wavelengths (660 nm and 700 nm) in normal saline-diluted samples. Twomey et al performed their lipemic index measurements on an Abbott Aeroset using a combination of three pairs of wavelengths (500/524, 572/604, 524/804). Their lipemic index was developed on this Abbott platform using a lipid emulsion (Intralipid™) model of turbidity. It is not surprising that the correlation was excellent. In their review of three different analytical platforms, Fliser et al noted that each used different wavelengths to assess interference, different calculations for the conversion of the measured absorbance into concentrations, and different classification schemes for assigning a serum index value.[46] For example, the Siemens RXL Max assigned a serum index value of 1 to a triglyceride concentration of ≤ 0.28 mmol/L (0.25 g/L) (Intralipid™) while the Siemens VISTA assigned the same value to a triglyceride concentration of ≤ 0.56 mmol/L (0.5 g/L) (Intralipid™).

Nevertheless, lipemic indices may be useful for rejecting samples that have excessive interference due to turbidity, with the caveat that lipid emulsions cause interference by other mechanisms as well. The nature and magnitude of the analytical interferences caused by lipemia is dependent of the reagents and laboratory platform used. Accordingly, we advocate that any future reports clearly document sample handling, reagents and laboratory platform used, and any procedures used to reduce the lipid content. To this end, we further propose the establishment of Minimum Information for Publication of Quantitative Experiments (MIQE) guidelines to be adhered to in reporting any use of lipid emulsions analogous to those described by Bustin et al for real-time PCR.[47] The MIQE guidelines describe the minimum information necessary for evaluating reports in order to help ensure the integrity of the scientific literature, promote consistency between laboratories, and increase experimental transparency. This could include a checklist to accompany the submission of a manuscript to the publisher. By providing all relevant information, reviewers could assess the validity of the protocols used. Full disclosure of all reagents and analysis methods is necessary to enable other investigators to reproduce results. Others have similarly called for a standardization of approach for reporting lipemia interference.[24]

Limitations

The majority of analytical studies which form the basis of this review were not designed with the intent of exploring the impact of intravenous lipid emulsion therapy. Consequently, many studies had to be excluded. Even among the studies included significant limitations persisted (for example, limited amounts of added lipid emulsion). There is a lack of peer-reviewed studies of the analytical interference of lipid emulsions on pharmaceuticals or other poisons, necessitating our reliance on vendor-supplied product monographs. Finally, these analytical studies were all performed on *ex vivo* pooled samples

models rather than directly measured samples from patients' post-lipid emulsion therapy. As such, they are unable to account for patients' rates of endogenous triglyceride clearance.

Conclusion

The use of intravenous lipid emulsion is becoming more frequent in the treatment of drug toxicity. While the clinical response to treatment of the primary poisoning is what ultimately matters, laboratory measurements of various analytes are used to monitor the response of the patient to treatment, as surrogate markers of clinical progression and to detect possible co-ingestants. The lipemia produced by lipid emulsions renders many laboratory measurements suspect and prone to interference errors. The primary goal of this review is to promote awareness of this potential adverse effect of intravenous lipid emulsion therapy. We hope that our work will help guide clinicians who use intravenous lipid emulsion therapy in poisoned patients by encouraging sample collection prior to administering lipid emulsion when possible, and to help them make informed decisions regarding evaluation of post-lipid laboratory analyses.

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Declaration of interest

All members of the workgroup completed a Conflict Of Interest form for AACT and received no honoraria. Webcast conferences and rooms for meetings were provided by AACT. The workgroup does not include members with a financial or academic Conflict Of Interest preventing neutral assessment of the literature reviewed (i.e. no committee member's livelihood or academic career is depending on a grant studying lipid emulsion in poisoning).

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Appendix 1

Search Strategy for Medline (Ovid)

Search date – December 15, 2014

1. exp Fat Emulsions, Intravenous/
2. exp Lipids/
3. exp Hyperlipidemias/
4. lipid*.tw.
5. intralipid.tw.
6. ((fat or fats) adj3 emulsi*).tw.
7. liposyn.tw.
8. (lip?emia or lip?emic or lipid?emia or lipid?emic).tw.
9. (hyperlip?emia or hyperlip?emic or hyperlipid?emia or hyperlipid?emic).tw.
10. or/1-9

11. exp Blood/
12. exp Blood Cells/
13. exp Hematology/
14. exp Hyperlipidemias/
15. (blood or serum or sera or platelet* or plasma or h?ematolog*).tw.
16. (erythrocyte* or h?emocyte* or leukocyte*).tw.
17. (lip?emia or lip?emic or lipid?emia or lipid?emic).tw.
18. (hyperlip?emia or hyperlip?emic or hyperlipid?emia or hyperlipid?emic).tw.
19. bl.fs.
20. or/11-19
21. 10 and 20
22. exp Diagnostic Errors/
23. exp Delayed Diagnosis/
24. interference*.tw.
25. unreliab*.tw.
26. distort*.tw.
27. ((diagnos* or test* or laboratory or analys?s or analytic*) adj5 (false or error* or erroneous or efficien* or inefficien* or delay* or interfere* or turnaround*)).tw.
28. false positive*.tw.
29. exp False Positive Reactions/
30. exp False Negative Reactions/
31. false negative*.tw.
32. (observer\$ adj3 variation\$).tw.
33. or/22-32
34. 21 and 33