Biomedical Research 2017; 28 (16): 7060-7069 *ISSN 0970-938X*
www.biomedres.info

The impact of intravenous lipid emulsion on lipophilicity in poisoned patients: A systematic review.

Evvah Karakılıç[1*], Elif Kaya[2], Ahmet Erdem[2], Engin Deniz Arslan[3], Tamer Durdu[2], Serkan Tulgar[4], Doğan Işcanlı[2]

[1]Department of Emergency Medicine, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

[2]Ankara Numune Training and Research Hospital, Emergency Medicine Clinic, Altındağ, Ankara, Turkey

[3]Ankara Dışkapı Yıldırım Beyazıt Education and Research Hospital, Emergency Medicine Clinic, Altındağ, Ankara, Turkey

[4]Department of Anesthesia and Reanimation, Faculty of Medicine, Maltepe University, İstanbul, Turkey

Abstract

Objective: Although the action mechanism of intravenous lipid emulsion has not been fully elucidated yet, its use in liposoluble drugs intoxications. In this study, we examined the lipophilic features of causative agents and the success of the treatment ILE therapy in intoxication cases.
Methods: We reviewed 765 cases published in PubMed between 1966 and June, 2015. After applying exclusion criteria, totally 141 cases ingested single substance and received ILE therapy with 20% ILE solution were included in present study. Amount of lipid solutions given and the results were recorded. Success rate was statistically assessed according to log p values of the substances taken and the amount of lipid emulsion used.
Results: 141 patients were involved in this study; log p values were calculated for all drugs regardless of the success of ILE therapy. ILE therapy under the amount of 100 ml failed to achieve successful outcome. ALOGPS and ChemAxon log P values were higher in cases, which received ILE therapy ≤ 500 ml and showed successful results. It was found that log p value had no contribution to the treatment success in the group received ILE therapy>500 ml.
Conclusions: It was found that ILE therapy<500 ml was successful in drugs with higher lipophilicity while success rate was higher in ILE therapy>500 ml and that liposolubility had no significant contribution to treatment success.

Keywords: Intravenous lipid emulsion, Lipophilicity, Poisoning.

Accepted on July 17, 2017

Introduction

In recent years, the lipid emulsions used for nutrition were introduced as an antidote in life-threatening drug intoxications. Weinberg et al. reported the Intravenous Lipid Emulsion (ILE) therapy given after severe bupivacaine intoxication to be effective in resuscitation in intact rats [1]. Since then, it was shown that lipid emulsions are effective in the treatment of accidental or intentional drug intoxications in many case reports and animal studies [2-7].

Although many studies were carried out on ILE, its mechanism of action couldn't be completely understood. However, various theories were proposed on the pharmacodynamics and pharmacokinetic aspects. First of all, a theory proposing pharmacological sink for liposoluble drugs, which is also termed as lipid sink theory, was considered [8,9]. In lipid sink theory, it is proposed that the lipid emulsion creates an expanded lipid phase, resulting in redistribution; thus, lipid emulsion leads the toxic drugs to pass into the plasma, where they then pass to the lipid phase [9,10]. In a rat study, it was found that ILE given after bupivacaine injection decreased the concentration of bupivacaine in heart, brain, lung, kidney and spleen *via* redistribution [11]. In this theory, liposoluble drugs would better pass into lipid phase. Liposolubility of a drug is generally represented by logarithmic presentation (log10) of distribution between octanol and water (octanol-water partition coefficients; log p or log d (distribution-coefficient) [12]. According to this statement, drugs with higher log p value would be more lipophilic. Second theory is the enhancement of cardiac energy support. Fatty acids are primary energy source in non-stressed, resting heart. In previous studies, it was shown that supplementation with fatty acids increased the performance in ischemic, hypo-dynamic heart [8,13]. Another action mechanism that was proposed is the direct cardiotonic

effect. In a study on rats, it was demonstrated that lipid emulsions had positive inotropic and lusitropic effects, although underlying mechanism couldn't be clarified [14]. Besides these mechanisms of action, it is also known that free fatty acid has some effects on ion channels [10]. In cardiomyocytes, long-chain fatty acids contribute to positive inotropic effect by increasing the calcium level *via* the calcium channels [15,16]. In recent studies, it was reported that long-chain fatty acids in lipid emulsions exerted cardioprotective effects *via* signaling pathway that regulates calcium homeostasis and opening of mitochondrial pores [17].

When considering above-mentioned mechanisms of action, it is anticipated to achieve successful outcome with ILE therapy in many types of intoxication. However, there are case reports indicating the failure of ILE therapy, including those demonstrating different outcomes in different drug classes or those demonstrating failure or success in same drug classes [2,18-20]. Such inconsistencies could be influenced by many factors such as amount of drug ingested, lipophilicity of drug and dose of ILE given. According to lipid sink theory, log p values of drugs can be helpful in predicting the clinical effectiveness of ILE therapy in lipophilic drug intoxications [21].

The aim of this systematic review is to investigate the relationship between the log p value of pharmacological agent leading to poisoning and the success rate of ILE therapy by reviewing case series, which ILE therapy was given for intoxication cases. By these results, we tested the theory that intoxication from more lipophilic drugs has more successful outcomes with ILE therapy; additionally, we investigated the relationship with the log p values of drugs and the success rate of ILE therapy.

Methods

We performed a literature search in PubMed between 1966 and June, 2015. The search was conducted by using Medical Subject Headings terms (MeSH): "((((((toxicology) OR poisoning) OR rescue) OR arrest) OR toxic)) and ((((lipid emulsion) OR fat emulsion) OR intralipid) OR intravenous lipid emulsion)". In total, 765 publications were identified. Among them, the animal studies and those on multidrug ingestion were excluded. Finally, 323 publications involving single agent ingestion were included to the review.

Two researchers reviewed congress abstracts and articles separately. The congress abstracts, which were subsequently published as an article, were considered as a single case report. The results were assessed, and 1 case of ingestion of a drug termed "Bonzai" was excluded since there was no data about the drug composition. Again, another case was excluded due to ingestion of a drug classified as unknown TCA. In addition, 15 cases were excluded since amount of lipid given was unspecified. Overall, 141 cases (75 publications) were included to the review. There was concurrent alcohol consumption in 4 of 141 cases with single agent ingestion. These cases were included to the review as ethanol is a water-soluble substance (log p=-0.4 (ALOGPS)).

The concentration of the lipid given in all patients was 20% lipid emulsion. The amount of lipid given was stratified as<100 ml, 100-500 ml and >500 ml. Success was defined as complication-free result. Cases with complication or non-survivors were considered as failure.

Log p value for each substance was searched from "www.drugbank.ca" website. Log p values were recorded as Experimental, ALOGPS and ChemAxon data. Analyses were performed for all three parameters.

All statistical analyses were performed using SPSS 17.0 (IBM, New York, USA) and MS Office Excel. The continuous variables were expressed as mean ± SD, whereas the categorical variables were expressed as n (%). The difference between the mean values of the continuous variables was calculated using the Mann Whitney U-test. The correlations among continuous variables were calculated using Spearman's Rho correlation. Logistic regression analysis was performed in order to determine the independent effect of the log p values. $P \leq 0.05$ was considered statistically significant.

Results

Among 141 cases, 15 drug classes and 31 drugs were identified. Table 1 presents log p values and number patients for 31 drugs identified. In Table 2, log p values and number of patients for 15 drug classes are presented. Table 3 summarizes the amount of lipid given and success rates.

The cases were stratified according to the treatment outcome as successful and failure regardless of amount of lipid given. Mean log p values (Experimental, ALOGPS, ChemAxon) were calculated for drugs, in which the lipid emulsion therapy was successful. In addition, mean log p values were calculated for all drugs regardless of treatment outcome with ILE therapy. Moreover, mean log p values were calculated according to the reasons for failure. When groups were compared, it was found that mean ChemAxon and Experimental log p values were higher in the group, in which ILE therapy failed (Table 4).

Amount of ILE therapy given was ≤ 100 ml in 14 (9.9%), 100-500 ml in 73 (51.8%) and >500 ml in 54 (38.3%) of the cases. The amount of lipid emulsion was <100 ml in only one case, in which treatment outcome was found to be successful; thus, we stratified the amount of the lipid emulsion as ≤ 500 ml and >500 ml. The success rate was 85.1% in patients received ILE therapy ≤ 500 ml, whereas the same rate was 92.6% in patients that received ILE therapy>500 ml. There was no significant difference between groups received ILE therapy ≤ 500 ml or >500 ml (p=0.142).

When amount of lipid emulsion given was below 500 ml (1-500 ml), the log p value, especially the ALOGPS and ChemAxon data, becomes more important. In cases that received ILE therapy ≤ 500 ml, the ALOGPS and ChemAxon log p values were higher in the group with successful outcome than those observed in cases, in which ILE therapy failed (p

values are 0.043 and 0.008). In addition, Experimental log p value was higher, indicating a trend towards statistical significance (p=0.071). Thus, we can argue that log p value has significant effect on treatment success when amount of lipid emulsion is equal or below 500 ml. But, there is no significant effect of treatment outcome when amount of lipid emulsion is higher than 500 ml (Table 5). The summary of the 141 human case reports treated with ILE is given in Table 6.

Table 1. Log P values of medication or toxic agents of survey.

Medication or chemical agent		n	Log P		
			Experimental	ALOGPS	ChemAxon
Beta blocker	Metoprolol	2	1.880	1.800	1.760
	Propranolol	6	3.480	3.030	2.580
Ca^{2+} channel blocker	Diltiazem	2	2.800	3.090	2.730
	Amlodipine	6	3.000	2.220	1.640
	Verapamil	6	3.790	5.230	5.040
Local anesthetic	Ropivacaine	10	2.900	2.910	4.070
	Bupivacaine	27	3.410	3.310	4.520
	Lidocaine	1	2.440	1.810	2.840
	Levobupivacaine	2	3.600	3.310	4.520
	Mepivacaine	1	1.950	2.160	3.190
Narcoticagents	Cocaine	3	2.300	1.970	2.280
Alpha and beta blocker	Carvedilol	5	4.190	3.050	3.420
TCA	Amitriptyline	11	4.920	5.100	4.810
	Dosulepin	3	4.200		
	Doxepin	2	4.290	4.080	3.840
	Imipramine	2	4.800	4.530	4.280
Antipsychotic	Quetiapine	7	2.800	2.930	2.810
	Haloperidol	1	4.300	3.700	3.660
	Olanzapine	2	2.000	3.610	3.390
Antiepileptic	Lamotrigine	2	2.500	1.870	1.930
	Carbamazepine	1	2.450	2.100	2.770
Herbicide	MCPA	1	3.25	-	-
	Glycophosate	25	-4.000	0.040	-3.100
Central muscular blocker	Baclofenone	2	1.300	-0.820	-0.780
Na^{+} channel blocker	Propafenone	1	3.200	3.100	3.540
	Flecainide	3	3.780	2.980	3.190
Insecticide	Endosulphan	1	-	-	-
	Ivermectin	1	-	-	5.830
Antimalarial	Hydroxychloroquine	1	-	3.870	2.890
Antidiabetic	Metformin	1	-0.500	-1.800	-0.920

Table 2. Log P values of agent types.

	n	Log P		Log P	Log P

		Experimental (mean ± SD)*	ALOGPS (mean ± SD)*	ChemAxon (mean ± SD)*
Beta blocker	8	3.080 ± 0.741	2.723 ± 0.569	2.375 ± 0.380
Ca^{2+} channel blocker	14	3.302 ± 0.426	3.562 ± 1.465	3.168 ± 1.651
Na channel blocker	4	3.635 ± 0.290	3.010 ± 0.060	3.278 ± 0.175
Local anesthetic	41	3.244 ± 0.329	3.155 ± 0.314	4.345 ± 0.355
TCA	18	4.727 ± 0.305	4.901 ± 0.374	4.623 ± 0.354
Antipsychotic	10	2.790 ± 0.626	3.143 ± 0.344	3.011 ± 0.332
Antiepileptic	3	2.483 ± 0.029	1.947 ± 0.133	2.210 ± 0.485
Herbicide	26	-3.731 ± 1.395	0.04	-3.1
DNRI	3	3.6	3.28	3.27
Central muscle relaxator	2	1.3	-0.82	-0.78
Narcotic agents	3	2.3	1.97	2.28
Alpha and beta blocker	5	4.19	3.05	3.42
Insecticide	2	-	-	5.830
Antimalarial	1	-	3.870	2.890
Antidiabetic	1	-0.5	-1.800	-0.920

*SD: Standard Deviation; SD=0.000 values not written

Table 3. *Given amount of lipid emulsion therapies and success rates.*

	≤ 100 ml	100-500 ml	>500 ml	Success
Beta blocker	-	6 (75%)	2 (25%)	7 (87.5%)
Ca^{2+} channel blocker	1 (7.1%)	9 (64.3%)	4 (28.6%)	10 (71.4%)
Local anesthetic	12 (29.3%)	22 (53.7%)	7 (17.1%)	40 (97.7%)
Narcotic agents	1 (33%)	1 (33%)	1 (33%)	2 (66.7%)
Alpha and beta blocker	-	5 (100%)	-	5 (100%)
TCA	-	10 (55.6%)	8 (44.4%)	18 (100%)
Antipsychotic	-	7 (70%)	3 (30%)	8 (80%)
Antiepileptic	-	1 (33%)	2 (67%)	2 (66.7%)
Herbicide	-	3 (11.5%)	23 (88.5%)	26 (100%)
DNRI	-	2 (67%)	1 (33%)	2 (66.7%)
Central muscle relaxator	-	2 (100%)	-	1 (50%)
Na channel blocker	-	1 (25%)	3 (75%)	2 (50%)
Insecticide	-	2 (100%)	-	1 (50%)
Antimalarial	-	1 (100%)	-	0 (0%)
Antidiabetic	-	1 (100%)	-	0 (0%)

Table 4. *Log P values according to success rate.*

		Log P	Log P	Log P
		Experimental (mean ± SD)*	ALOGPS (mean ± SD)*	ChemAxon (mean ± SD)*
Successful		1.970 ± 3.108	2.663 ± 1.621	2.364 ± 2.975
Unsuccessful		2.676 ± 1.131	2.495 ± 1.814	2.513 ± 1.688
	Exitus	2.520 ± 1.372	2.259 ± 1.661	2.413 ± 1.489
	Hypoxic ischemic encephalopathy	3.395 ± 0.559	3.725 ± 2.128	3.340 ± 2.404
	Quadriplegia**	2.5	1.87	1.93
	Delirium	2.300 ± 0.866	1.680 ± 2.165	1.613 ± 2.073
	Ischemic colitis**	3.79	5.23	5.04

*SD: Standard Deviation; **Only one sample present.

Table 5. Log P values according to success and given amount of lipid emulsion.

		Successful	Unsuccessful	p
≤ 500 ml lipid emulsion	Experimental Log P	3.107 ± 1.644	2.577 ± 1.269	0.071
	ALOGPS Log P	3.087 ± 1.074	2.313 ± 1.917	0.043
	ChemAxon Log P	3.483 ± 1.745	2.285 ± 1.765	0.008
>500 ml lipid emulsion	Experimental Log P	0.310 ± 3.917	2.948 ± 0.681	0.577
	ALOGPS Log P	2.040 ± 2.056	3.043 ± 1.561	0.302
	ChemAxon Log P	0.741 ± 3.600	3.198 ± 1.410	0.286

Discussion

Besides the use for nutritional purposes, intravenous lipid emulsions were introduced into treatment of serious intoxications. There is limited number of studies on the use of lipid emulsion therapy in poisoned patients as antidote, and majority of available studies are animal studies and case reports. Although it was shown that lipid emulsions are effective in many intoxication cases caused from liposoluble drugs, they were also shown to be ineffective in some drug intoxications with high liposolubility [22]. In addition, there are also case reports indicating that lipid emulsions are successful in drug intoxications with low liposolubility [23]. In this review, we focused on the intoxication caused from a single agent. Because, in mixed drug intoxications, it is difficult to identify which drug is responsible for clinical picture and to confirm which drug was affected by therapy given. Given this, we performed our analysis in patients with single agent ingestion according to amount of lipid given and log p values, which indicate liposolubility of drugs leading to the intoxication. According to our study until 500 ml ILE treatment liposolubulity is important and ILE therapy is more effective in highly liposoluble drugs. Liposolubility does not affect the success rate.

In a study on healthy volunteers, Litonius et al. suggested that there was no significant decrease in plasma-free bupivacaine levels before and after intravenous lipid administration and that no lipid sink effect was observed [24]. Litonius et al. reported the lack of lipid sink phenomenon despite lipophilic structure of bupivacaine (ALOGPS log p: 3.31) but positive response to ILE therapy at toxic levels, and also we reported that over 500 ml of ILE therapy the liposolubility has no effect. When our systematic review and the study by Litonius et al. were considered together, we can argue that there may be some additional action mechanisms besides the lipid sink phenomenon.

It is thought that lipid sink effect occurs *via* uptake of liposoluble drug molecule from aqueous compartment to lipid compartment [25]. In this systematic review, we compared success rate according to amount of lipid given. Successful outcome was observed in only one out of 14 patients received ILE therapy<100 ml. Based on this finding, it was concluded that ILE therapy given less than 100 ml was ineffective. Among the patients that received ILE therapy>500 ml, no significant difference was found in mean log p values of drug between cases with successful outcome and those with failure.

Among the patients that received ILE therapy ≤ 500, ChemAxon log p and ALOGPS log p values were significantly higher in the group successfully treated when compared to those with treatment failure. Experimental log p value was significantly higher. Based on these findings, ILE therapy ≤ 500 ml was more successful in drugs with high log p value, while log p value had no contribution to clinical outcomes in cases received ILE therapy>500 ml.

Table 6. References of the 141 human case reports treated with ILE [26-97].

Drugs	References [26-97]		References [26-97]	
	ILE ≤ 500 ml		ILE>500 ml	
	Success	Failed	Success	Failed
Metoprolol		[26]	[28]	
Propranolol	[26,56,91]		[58]	

Diltiazem	[26,71]			
Amlodipine	[26]	[26]	[37]	
Verapamil	[26,68]	[26]	[40,63]	[46]
Ropivacaine	[27,38,53,67,78,82,87,97]	[80]		
Bupivacaine	[3,33,38,65,70,72,75-77,79,81,83,84,86,89,90,97]		[2,36,38,40]	
Lidocaine			[69]	
Levobupivacaine	[47,85]			
Mepivacaine	[88]			
Cocaine	[48,55]			[41]
Carvedilol	[26,57,91]			
Amitriptyline	[32,73,93]		[28,39,42,50,66]	
Dosulepin	[45,54,64]			
Doxepin	[91,92]			
Imipramine	[92,95]			
Quetiapine	[28,35]	[35]	[43,91]	
Haloperidol	[31]			
Olanzapine	[51,96]			
Lamotrigine			[62]	[29]
Carbamazepine	[91]			
MCPA			[30]	
Glycophosate	[34,52,74]		[23]	
Bupropion	[91]	[32]	[61]	
Baclofenone	[93]	[35]		
Propafenone				[60]
Flecainide		[91]	[49,59]	
Endosulphan		[44]		
Ivermectin	[97]			
Hydroxychloroquine		[91]		
Metformin		[94]		

Conclusion

According to lipid sink theory, it is anticipated that ILE therapy should be associated to more effective outcomes in lipophilic group ≤ 500 ml ILE therapy. It could be thought that additional action mechanisms other than lipid sink phenomenon are more active in ILE therapy. When amount of ILE therapy given was assessed, it was found that ILE therapy<100 ml failed to achieve successful outcome, and that there was no association between success rate and lipophilicity of drug in cases receiving ILE therapy>500 ml.

Limitations

Many cases were excluded due to the fact that the amount of ILE was not indicated. On the other hand, using the one database for scanning the literature is limitation of this study.

Conflict of Interest

Authors warrant that no conflicts of interest.

References

1. Weinberg GL, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-

induced asystole in rats. Anesthesiology 1998; 88: 1071-1075.

2. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology 2006; 105: 217-218.
3. Warren JA, Thoma RB, Georgescu A, Shah SJ. Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. Anesth Analg 2008; 106: 1578-1580.
4. Weinberg GL, Di Gregorio G, Ripper R, Kelly K, Massad M, Edelman L. Resuscitation with lipid versus epinephrine in a rat model of bupivacaine overdose. Anesthesiology 2008; 108: 907-913.
5. Kang C, Kim DH, Kim SC, Lee SH, Jeong JH, Kang TS. The effects of intravenous lipid emulsion on prolongation of survival in a rat model of calcium channel blocker toxicity. Clin Toxicol (Phila) 2015; 53: 540-544.
6. Udelsmann A, Melo Mde S. Hemodynamic changes with two lipid emulsions for treatment of bupivacaine toxicity in swines. Acta Cir Bras 2015; 30: 87-93.
7. Arslan ED, Demir A, Yilmaz F, Kavalci C, Karakilic E. Treatment of quetiapine overdose with intravenous lipid emulsion. Keio J Med 2013; 62: 53-57.
8. Turner-Lawrence DE, Kerns Ii W. Intravenous fat emulsion: a potential novel antidote. J Med Toxicol 2008; 4: 109-114.
9. Rothschild L, Bern S, Oswald S, Weinberg G. Intravenous lipid emulsion in clinical toxicology. Scand J Trauma Resusc Emerg Med 2010; 18: 51.
10. Cave G, Harvey MG. Should we consider the infusion of lipid emulsion in the resuscitation of poisoned patients? Crit Care 2014; 18: 457.
11. Shi K, Xia Y, Wang Q, Wu Y, Dong X. The effect of lipid emulsion on pharmacokinetics and tissue distribution of bupivacaine in rats. Anesth Analg 2013; 116: 804-809.
12. Kokate A, Li X, Jasti B. Effect of drug lipophilicity and ionization on permeability across the buccal mucosa: a technical note. AAPS Pharm Sci Tech 2008; 9: 501-504.
13. Weinberg GL, Palmer JW, VadeBoncouer TR, Zuechner MB, Edelman G, Hoppel CL. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. Anesthesiology 2000; 92: 523-528.
14. Fettiplace MR, Ripper R, Lis K, Lin B, Lang J. Rapid cardiotonic effects of lipid emulsion infusion. Crit Care Med 2013; 41: 156-162.
15. Pennec JP, Guillouet M, Rannou F, Arvieux CC, Gueret G. Hemodynamic effects of lipid emulsion after local anesthetic intoxication may be due to a direct effect of fatty acids on myocardial voltage-dependent calcium channels. Can J Anaesth 2010; 57: 947.
16. Huang JM, Xian H, Bacaner M. Long-chain fatty acids activate calcium channels in ventricular myocytes. Proc Natl Acad Sci USA 1992; 89: 6452-6456.
17. Partownavid P, Umar S, Li J, Rahman S, Eghbali M. Fatty-acid oxidation and calcium homeostasis are involved in the rescue of bupivacaine-induced cardiotoxicity by lipid emulsion in rats. Crit Care Med 2012; 40: 2431-2437.
18. Litonius ES, Niiya T, Neuvonen PJ, Rosenberg PH. Intravenous lipid emulsion only minimally influences bupivacaine and mepivacaine distribution in plasma and does not enhance recovery from intoxication in pigs. Anesth Analg 2012; 114: 901-906.
19. Heinonen JA, Skrifvars MB, Haasio J, Backman JT, Rosenberg PH, Litonius E. Intravenous lipid emulsion for levobupivacaine intoxication in acidotic and hypoxaemic pigs. Anaesth Intensive Care 2016; 44: 270-277.
20. Heinonen JA, Litonius E, Salmi T, Haasio J, Tarkkila P. Intravenous lipid emulsion given to volunteers does not affect symptoms of lidocaine brain toxicity. Basic Clin Pharmacol Toxicol 2015; 116: 378-383.
21. French D, Smollin C, Ruan W, Wong A, Drasner K, Wu AH. Partition constant and volume of distribution as predictors of clinical efficacy of lipid rescue for toxicological emergencies. Clin Toxicol (Phila) 2011; 49: 801-809.
22. Varney SM, Bebarta VS, Vargas TE, Boudreau S, Castaneda M. Intravenous lipid emulsion therapy does not improve hypotension compared to sodium bicarbonate for tricyclic antidepressant toxicity: a randomized, controlled pilot study in a swine model. Acad Emerg Med 2014; 21: 1212-1219.
23. Gil HW, Park JS, Park SH, Hong SY. Effect of intravenous lipid emulsion in patients with acute glyphosate intoxication. Clin Toxicol (Phila) 2013; 51: 767-771.
24. Litonius E, Tarkkila P, Neuvonen PJ, Rosenberg PH. Effect of intravenous lipid emulsion on bupivacaine plasma concentration in humans. Anaesthesia 2012; 67: 600-605.
25. Ozcan MS, Weinberg G. Intravenous lipid emulsion for the treatment of drug toxicity. J Intensive Care Med 2014; 29: 59-70.
26. Sebe A, Disel NR, Acikalin Akpinar A, Karakoc E. Role of intravenous lipid emulsions in the management of calcium channel blocker and beta-blocker overdose: 3 years' experience of a university hospital. Postgrad Med 2015; 127: 119-124.
27. Scherrer V, Compere V, Loisel C, Dureuil B. Cardiac arrest from local anesthetic toxicity after a field block and transversus abdominis plane block: a consequence of miscommunication between the anesthesiologist and surgeon. Case Rep 2013; 1: 75-76.
28. Eren Cevik S, Tasyurek T, Guneysel O. Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. Am J Emerg Med 2014; 32: 1103-1108.
29. Chavez P, Casso Dominguez A, Herzog E. Evolving electrocardiographic changes in lamotrigine overdose: a case report and literature review. Cardiovasc Toxicol 2015; 15: 394-398.
30. Hwang I, Lee JW, Kim JS, Gil HW, Song HY, Hong SY. Surfactant toxicity in a case of (4-chloro-2-methylphenoxy)

acetic acid herbicide intoxication. Hum Exp Toxicol 2015; 34: 848-855.

31. Weinberg G, Di Gregorio G, Hiller D, Hewett A, Sirianni A. Reversal of haloperidol-induced cardiac arrest by using lipid emulsion. Ann Intern Med 2009; 150: 737-738.
32. Geib AJ, Liebelt E, Manini AF, Toxicology Investigators C. Clinical experience with intravenous lipid emulsion for drug-induced cardiovascular collapse. J Med Toxicol 2012; 8: 10-14.
33. Buck D, Kreeger R, Spaeth J. Case discussion and root cause analysis: bupivacaine overdose in an infant leading to ventricular tachycardia. Anesth Analg 2014; 119: 137-140.
34. Mahendrakar K, Venkategowda PM, Rao SM, Mutkule DP. Glyphosate surfactant herbicide poisoning and management. Indian J Crit Care Med 2014; 18: 328-330.
35. Downes MA, Calver LA, Isbister GK. Intralipid therapy does not improve level of consciousness in overdoses with sedating drugs: a case series. Emerg Med Australas 2014; 26: 286-290.
36. Whiteman DM, Kushins SI. Successful resuscitation with intralipid after marcaine overdose. Aesthet Surg J 2014; 34: 738-740.
37. Meaney CJ, Sareh H, Hayes BD, Gonzales JP. Intravenous lipid emulsion in the management of amlodipine overdose. Hosp Pharm 2013; 48: 848-854.
38. Cave G, Harvey M, Willers J, Uncles D, Meek T, Picard J. LIPAEMIC report: results of clinical use of intravenous lipid emulsion in drug toxicity reported to an online lipid registry. J Med Toxicol 2014; 10: 133-142.
39. Levine M, Brooks DE, Franken A, Graham R. Delayed-onset seizure and cardiac arrest after amitriptyline overdose, treated with intravenous lipid emulsion therapy. Pediatrics 2012; 130: 432-438.
40. Levine M, Skolnik AB, Ruha AM, Bosak A, Menke N, Pizon AF. Complications following antidotal use of intravenous lipid emulsion therapy. J Med Toxicol 2014; 10: 10-14.
41. Kundu R, Almasri H, Moza A, Ghose A, Assaly R. Intravenous lipid emulsion in wide complex arrhythmia with alternating bundle branch block pattern from cocaine overdose. Kardiol Pol 2013; 71: 1073-1075.
42. Agarwala R, Ahmed SZ, Wiegand TJ. Prolonged use of intravenous lipid emulsion in a severe tricyclic antidepressant overdose. J Med Toxicol 2014; 10: 210-214.
43. Bartos M, Knudsen K. Use of intravenous lipid emulsion in the resuscitation of a patient with cardiovascular collapse after a severe overdose of quetiapine. Clin Toxicol (Phila) 2013; 51: 501-504.
44. Moon HJ, Lee JW. Availability of intravenous lipid emulsion therapy on endosulfan-induced cardiovascular collapse. Am J Emerg Med 2013; 31: 886.
45. Hendron D, Menagh G, Sandilands EA, Scullion D. Tricyclic antidepressant overdose in a toddler treated with intravenous lipid emulsion. Pediatrics 2011; 128: 1628-1632.
46. Liang CW, Diamond SJ, Hagg DS. Lipid rescue of massive verapamil overdose: a case report. J Med Case Rep 2011; 5: 399.
47. Lange DB, Schwartz D, DaRoza G, Gair R. Use of intravenous lipid emulsion to reverse central nervous system toxicity of an iatrogenic local anesthetic overdose in a patient on peritoneal dialysis. Ann Pharmacother 2012; 46: 37.
48. Arora NP, Berk WA, Aaron CK, Williams KA. Usefulness of intravenous lipid emulsion for cardiac toxicity from cocaine overdose. Am J Cardiol 2013; 111: 445-447.
49. Ellsworth H, Stellpflug SJ, Cole JB, Dolan JA, Harris CR. A life-threatening flecainide overdose treated with intravenous fat emulsion. Pacing Clin Electrophysiol 2013; 36: 87-89.
50. Kiberd MB, Minor SF. Lipid therapy for the treatment of a refractory amitriptyline overdose. CJEM 2012; 14: 193-197.
51. Yurtlu BS, Hanci V, Gur A, Turan IO. Intravenous lipid infusion restores consciousness associated with olanzapine overdose. Anesth Analg 2012; 114: 914-915.
52. You Y, Jung WJ, Lee MJ. Effect of intravenous fat emulsion therapy on glyphosate-surfactant-induced cardiovascular collapse. Am J Emerg Med 2012; 30: 2097.
53. Nguyen VH, White JL. Further support for the early administration of lipid emulsion in the treatment of ropivacaine-induced central nervous system toxicity. J Anesth 2012; 26: 479-480.
54. Blaber MS, Khan JN, Brebner JA, McColm R. Lipid rescue for tricyclic antidepressant cardiotoxicity. J Emerg Med 2012; 43: 465-467.
55. Jakkala-Saibaba R, Morgan PG, Morton GL. Treatment of cocaine overdose with lipid emulsion. Anaesthesia 2011; 66: 1168-1170.
56. Dean P, Ruddy JP, Marshall S. Intravenous lipid emulsion in propranolol overdose. Anaesthesia 2010; 65: 1148-1150.
57. [No authors listed]. Bet 2: intralipid/lipid emulsion in beta-blocker overdose. Emerg Med J 2011; 28: 991-993.
58. Jovic-Stosic J, Gligic B, Putic V, Brajkovic G, Spasic R. Severe propranolol and ethanol overdose with wide complex tachycardia treated with intravenous lipid emulsion: a case report. Clin Toxicol (Phila) 2011; 49: 426-430.
59. Moussot PE, Marhar F, Minville V, Valle B, Dehours E, Bounes V. Use of intravenous lipid 20% emulsion for the treatment of a voluntary intoxication of flecainide with refractory shock. Clin Toxicol (Phila) 2011; 49: 514.
60. ten Tusscher BL, Beishuizen A, Girbes AR, Swart EL, van Leeuwen RW. Intravenous fat emulsion therapy for intentional propafenone intoxication. Clin Toxicol (Phila) 2011; 49: 701.
61. Livshits Z, Feng Q, Chowdhury F, Amdo TD, Nelson LS, Hoffman RS. Life-threatening bupropion ingestion: is there a role for intravenous fat emulsion? Basic Clin Pharmacol Toxicol 2011; 109: 418-422.

62. Castanares-Zapatero D, Wittebole X, Huberlant V, Morunglav M, Hantson P. Lipid emulsion as rescue therapy in lamotrigine overdose. J Emerg Med 2012; 42: 48-51.
63. French D, Armenian P, Ruan W, Wong A, Drasner K, Olson KR. Serum verapamil concentrations before and after Intralipid(R) therapy during treatment of an overdose. Clin Toxicol (Phila) 2011; 49: 340-344.
64. Boegevig S, Rothe A, Tfelt-Hansen J, Hoegberg LC. Successful reversal of life threatening cardiac effect following dosulepin overdose using intravenous lipid emulsion. Clin Toxicol (Phila) 2011; 49: 337-339.
65. Harvey M, Cave G, Chanwai G, Nicholson T. Successful resuscitation from bupivacaine-induced cardiovascular collapse with intravenous lipid emulsion following femoral nerve block in an emergency department. Emerg Med Australas 2011; 23: 209-214.
66. Huge V, Baschnegger H, Moehnle P, Peraud A, Briegel J. Amitriptyline-induced cardiac arrest : treatment with fat emulsion. Anaesthesist 2011; 60: 541-545.
67. Mizutani K, Oda Y, Sato H. Successful treatment of ropivacaine-induced central nervous system toxicity by use of lipid emulsion: effect on total and unbound plasma fractions. J Anesth 2011; 25: 442-445.
68. Franxman TJ, Al-Nabhan M, Cavallazzi RS, Speak AJ. Lipid emulsion therapy for verapamil overdose. Ann Intern Med 2011; 154: 292.
69. Dix SK, Rosner GF, Nayar M, Harris JJ, Guglin ME, Winterfield JR. Intractable cardiac arrest due to lidocaine toxicity successfully resuscitated with lipid emulsion. Crit Care Med 2011; 39: 872-874.
70. Shah S, Gopalakrishnan S, Apuya J, Shah S, Martin T. Use of Intralipid in an infant with impending cardiovascular collapse due to local anesthetic toxicity. J Anesth 2009; 23: 439-441.
71. Montiel V, Gougnard T, Hantson P. Diltiazem poisoning treated with hyperinsulinemic euglycemia therapy and intravenous lipid emulsion. Eur J Emerg Med 2011; 18: 121-123.
72. Admani B, Essajee F. Successful resuscitation of a three month old child with intralipid infusion, presumed to have bupivacaine induced seizures and cardiovascular complications: case report. East Afr Med J 2010; 87: 354-356.
73. Engels PT, Davidow JS. Intravenous fat emulsion to reverse haemodynamic instability from intentional amitriptyline overdose. Resuscitation 2010; 81: 1037-1039.
74. Han SK, Jeong J, Yeom S, Ryu J, Park S. Use of a lipid emulsion in a patient with refractory hypotension caused by glyphosate-surfactant herbicide. Clin Toxicol (Phila) 2010; 48: 566-568.
75. Gallagher C, Tan JM, Foster CG. Lipid rescue for bupivacaine toxicity during cardiovascular procedures. Heart Int 2010; 5: 5.
76. Cordell CL, Schubkegel T, Light TR, Ahmad F. Lipid infusion rescue for bupivacaine-induced cardiac arrest after axillary block. J Hand Surg Am 2010; 35: 144-146.
77. Wong GK, Joo DT, McDonnell C. Lipid resuscitation in a carnitine deficient child following intravascular migration of an epidural catheter. Anaesthesia 2010; 65: 192-195.
78. Gnaho A, Eyrieux S, Gentili M. Cardiac arrest during an ultrasound-guided sciatic nerve block combined with nerve stimulation. Reg Anesth Pain Med 2009; 34: 278.
79. Markowitz S, Neal JM. Immediate lipid emulsion therapy in the successful treatment of bupivacaine systemic toxicity. Reg Anesth Pain Med 2009; 34: 276.
80. Sonsino DH, Fischler M. Immediate intravenous lipid infusion in the successful resuscitation of ropivacaine-induced cardiac arrest after infraclavicular brachial plexus block. Reg Anesth Pain Med 2009; 34: 276-277.
81. Marwick PC, Levin AI, Coetzee AR. Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest. Anesth Analg 2009; 108: 1344-1346.
82. ter Horst M, Tjiang GC, Luitwieler RL, van Velzen C, Stolker RJ, de Quelerij M. Antidote against local anaesthetic intoxication: new use of lipid emulsion for intravenous administration. Ned Tijdschr Geneeskd 2010; 154: 1302.
83. Smith HM, Jacob AK, Segura LG, Dilger JA, Torsher LC. Simulation education in anesthesia training: a case report of successful resuscitation of bupivacaine-induced cardiac arrest linked to recent simulation training. Anesth Analg 2008; 106: 1581-1584.
84. McCutchen T, Gerancher JC. Early intralipid therapy may have prevented bupivacaine-associated cardiac arrest. Reg Anesth Pain Med 2008; 33: 178-180.
85. Foxall G, McCahon R, Lamb J, Hardman JG, Bedforth NM. Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. Anaesthesia 2007; 62: 516-518.
86. Zimmer C, Piepenbrink K, Riest G, Peters J. Cardiotoxic and neurotoxic effects after accidental intravascular bupivacaine administration. Therapy with lidocaine propofol and lipid emulsion. Anaesthesist 2007; 56: 449-453.
87. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia 2006; 61: 800-801.
88. Charbonneau H, Marcou TA, Mazoit JX, Zetlaoui PJ, Benhamou D. Early use of lipid emulsion to treat incipient mepivacaine intoxication. Reg Anesth Pain Med 2009; 34: 277-278.
89. Spence AG. Lipid reversal of central nervous system symptoms of bupivacaine toxicity. Anesthesiology 2007; 107: 516-517.
90. Whiteside J. Reversal of local anaesthetic induced CNS toxicity with lipid emulsion. Anaesthesia 2008; 63: 203-204.
91. Abstracts of the 2009 North American Congress of Clinical Toxicology Annual Meeting September 21–26, 2009, San Antonio, Texas, USA. Clin Toxicol 2009; 47: 702-765.
92. NACCT 2010 Abstracts. Clin Toxicol 2010; 48: 604-667.

93. 2012 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT) October 1-6, 2012 Las Vegas, NV, USA. Clin Toxicol 2012; 50: 574-720.
94. Abstracts: North American Congress of Clinical Toxicology. Clin Toxicol 2011; 49: 515-627.
95. Abstracts of the XXIX International Congress of the European Association of Poison Centres and Clinical Toxicologists, May 12-15, 2009, Stockholm, Sweden. Clin Toxicol 2009; 47: 436-510.
96. McAllister RK, Tutt CD, Colvin CS. Lipid 20% emulsion ameliorates the symptoms of olanzapine toxicity in a 4-year-old. Am J Emerg Med 2012; 30: 1012.
97. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila) 2010; 48: 1-27.

*Correspondence to

Evvah Karakılıç

Department of Emergency Medicine

Faculty of Medicine

Eskisehir Osmangazi University

Turkey