Intralipid therapy does not improve level of consciousness in overdoses with sedating drugs : A case series

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ABSTRACT

Objective

To assess the effect of Intralipid emulsion therapy (ILE) in sedating drugs presenting to an urban Emergency department.

Methods

Following the introduction of a clinical protocol for the use of ILE a retrospective chart review was undertaken which describes the use of ILE in treating sedating drug overdose in a facility with a tertiary referral level clinical toxicology unit. Demographic data as well as details of drug ingested, physiological parameters and disposition were extracted from the medical record.

Results

Over a 7 month period 9 cases were treated with intralipid of which two were male and the median age was 33 years (17-52 y). Endotracheal intubation was required in seven cases and of the other two, one required a nasopharyngeal airway for several hours whilst being observed in a critical care area. One patients was managed in the intensive care unit without intubation. The median duration of ventilation in the seven patients was 31 hours **(**22-82hr**)** and median length of stay for all 9 cases was 63 hours (24-133hr).

Conclusion

This study does not support any clinically significant effect of intralipid in sedating drug overdose.

INTRODUCTION

Intralipid Emulsion Therapy (ILE) has become the accepted treatment for local anaesthetic related cardiac toxicity such that guidelines of professional bodies advocate it's use for this purpose.[1] Although several mechanisms have been suggested [2] the most commonly postulated hypothesis proposes the creation of a "lipid sink" compartment within the plasma such that lipid soluble drugs diffuse down a concentration gradient into this compartment and thus away from potential sites of toxicity.

Since the initial suggestion that ILE may be effective in treating local anaesthetic drug toxicity, the protagonists have advocated that ILE may have a role beyond local anaesthetic toxicity in other drug poisonings where the toxins are lipid soluble as determined by the Octanol/Water coefficient (log P). [3] Case reports advocate success in cardiotoxic cardiac arrest, a relatively uncommon clinical scenario. However more recently reports have suggested that ILE may be potentially useful in reversing sedative effects of medication, in particular quetiapine and possibly also quetiapine related QTc prolongation .[4] [5]Such sedative effects will be encountered more commonly in emergency departments than refractory cardiovascular collapse and thus effectiveness in such cases make ILE a clinically much more useful treatment, particularly if it prevents the need for invasive procedures such as endotracheal intubation.

In 2009 our department introduced a clinical protocol to allow the use of ILE in lipophilic drug ingestions. The aim of this study was to investigate the effect of ILE in a small series of cases with predominantly sedating drug overdoses, to ascertain the effect of ILE in improving LOC and other aspects of toxicity.

METHODS

This was a retrospective chart review of all presentations who received ILE as a treatment for sedating drug overdose between September 2009 and May 2010. The study was approved by the local human research ethics committee as a quality assurance project.

The study was undertaken at an urban district hospital with an annual census of 32,000 acute presentations to the emergency department. In addition to providing acute care adult medical and surgical services to the local area, the hospital provides a regional clinical toxicology service which admits all cases of poisoning and serves as a tertiary referral service for a region with a population of approximately 650,000.

In 2009 the clinical toxicology service introduced an ILE treatment protocol for cardiac and sedative toxicity caused by drug overdose. These drugs included commonly ingested agents such as quetiapine, olanzapine, benzodiazepines, tricyclic antidepressants or any other sedative hypnotic agent that was lipid soluble. ILE was only administered in cases deemed to be at high risk of requiring active airway management for airway protection purposes, or at significant risk of cardiac toxicity (significant arrhythmia or cardiogenic shock). ILE was administered as a 500 ml infusion of a 20% solution over a 20 minute period by the treating doctor in the emergency department. During this time patients received continuous cardiac and oxygen saturation (SpO_2) monitoring in a critical care area with regular recording of vital signs. Any decision to intubate the patient or pursue any other airway intervention, was made in the emergency department by either the senior emergency department doctor on duty or a clinician from the intensive care unit based on level of consciousness (LOC) using the Glasgow Coma Scale (GCS) and clinical assessment of the ability of the patient to protect their airway. All other treatments were determined by the admitting clinical toxicologist. Details were recorded for all cases where ILE was administered for subsequent review.

After a 7 month period of using ILE, the medical records for all cases were retrieved and reviewed by the investigators. Data collected included demographic details, length of stay, drug ingested and amount. Clinical parameters recorded included GCS, with the lowest GCS pre-intubation recorded for ventilated patients and the lowest value recorded prior to ILE for non-ventilated patients. Cardiovascular parameters such as tachycardia, defined as heart rate greater than 100, hypotension defined as a systolic blood

pressure less than 90 mmHg were also recorded as well as the occurrence of delirium. Treatment parameters included need for intubation or ventilation, the use of inotropes or pressor agents, and length of stay. ECG data was also collected with QRS length greater than 120 ms recorded and QT interval manually measured as previously described with subsequent plotting of the QT and HR pairs on the QT nomogram.[6]

Descriptive statistics were calculated using Microsoft excel. Medians with ranges are reported as well as percentages.

RESULTS

Over the 7 month study period there were nine patients who received ILE treatment. In eight cases ILE was administered because of concerns about potential airway compromise and one case received ILE whilst in ICU as a potential treatment for both persistent coma and haemodynamic instability requiring treatment with a pressor agent. Of the nine cases, two were male and the median age was 33 years (17 to 52yr). Quetiapine was the commonest drug ingested in five cases. Baclofen was ingested in two cases, clonazepam and quetiapine in one case and carbamazepine and amisulpride in another case. Other coingestants were mirtazapine, sertraline, mitazapine, diazepam, codeine, paracetamol, ibuprofen and oxycodone. All drugs ingested were lipid soluble with the exception of baclofen. **Table 1** summarises the demographic details and drugs ingested.

Intubation was required in seven of the nine cases and five of these received ILE prior to intubation. In these five patients, the median time to intubation was 19 minutes (11 to 100min) from ILE administration, median duration of ventilation was 31 hours (22 to 82hr) and median LOS for all 9 cases was 59 hours (24 to 133 hr). Of those intubated, GCS ranged from 3 to 11 prior to intubation and was less than 9 in six of the seven cases. Of the seven intubated cases, three developed a delirium as the sedative effects resolved. Quetiapine was ingested in two of these cases and the third was due to an unquantified ingestion of baclofen.

Of the two cases who did not require intubation, one required a nasopharyngeal airway for several hours and had no significant increase in GCS over this period. The additional case required admission to ICU for close monitoring of airway and level of consciousness. The lowest recorded GCS values in the two non intubated patients were 9 and 11.

Tachycardia occurred in all cases except one case who ingested carbamazepine and amisulpride. Hypotension occurred in two of the quetiapine cases but neither required vasopressors or inotropes. The unquantified baclofen ingestion did develop hypotension requiring treatment with metaraminol over a ten hour period. This was initiated 4 hours prior to ILE administration and continued until 6 hours post administration.

No cases had a QRS greater than 120 ms on ECGs performed during the first 24 hours of admission, however in one case who ingested amisulpride in addition to carbamazepine, QT prolongation was evident on an ECG at approximately 5 hours post ingestion and the last recorded abnormal QT/HR pair for this case was recorded at approximately 14 hours post ingestion. Table 2 summarises the clinical details of cases.

DISCUSSION

This case series did not support a clinically significant role for ILE in sedating drug ingestion. Intubation was not avoided in the majority of patients and there was no obvious improvement in those patients not requiring intubation. The administration of ILE also had no effect on other complications of poisoning, QT prolongation and delirium in this study. The prevalence of quetiapine in this study underlies it's importance as a commonly ingested agent in overdose.

In one previous case reported of an ingestion of 4.3g quetiapine, an increase in GCS from 3 to 9 was attributed to ILE administration and it was suggested that endotracheal intubation was averted because of the ILE.[4] However there are several confounding factors in this case. In particular the variable GCS of 3 to 8 pre hospital, GCS being a measure documented previously to have significant interrater variation within an acute care environment.[7] Additionally, the initiation of a flumazenil infusion to reverse a possible benzodiazepine component of toxicity could have led to GCS variability and the recorded GCS of 12 approximately 19 hours post ingestion is still abnormal and more consistent with the redistribution kinetics of a quetiapine poisoning rather than any therapeutic effect of ILE.

Watt et al report two cases of ILE use in quetiapine poisoning which did not support a role in preventing endotracheal intubation but suggest a reduction in QTc from 550ms to 425ms shortly after administration of ILE.[5] The authors suggest this may be protective against the occurrence of arrhythmias in particular Torsades de Pointes (TdP) secondary to a prolonged QT interval. One must be cautious in using the QTc as an assessment tool as it calculates an artefactually longer QT as heart rate increases above seventy beats per minute.[8] Use of the QT nomogram and the calculation of QT/ HR pairs has been shown to give a better indication of risk.[8] Previously, a case series of 176 quetiapine poisonings showed that an abnormal QT only occurred in 8% of admissions, all of whom had tachycardia [9] supporting that quetiapine induced QTc prolongation is likely to be artificially high. The occurrence of TdP secondary to a drug or toxin induced QT prolongation has also been shown to be less likely in the presence of tachycardia [6] which is a cardinal feature of quetiapine ingestion.[9] Hence it seems unlikely that quetiapine poses any serious risk of cardiac arrhythmia in overdose.

Abnormal QT/HR pairs did occur in one of our cases, secondary to the co-ingestion of amisulpride which has been shown to prolong the QT interval and cause TdP previously in self poisoning.[10] This persisted till at least fourteen hours post ingestion despite the use of ILE.

To date, only one randomised control clinical trial in humans has studied the issue of GCS changes post ILE administration. This study enrolled thirty cases using ILE plus standard care versus standard care alone and suggested a greater increase in GCS with ILE therapy of 1 or 2 points which reached statistical significance.[11] No benefit was demonstrated however, in terms of patients intubated and ventilated thus making it difficult to infer any clinical significance to this finding. This study also had a number of limitations including a lack of detail on how many patients ingested which particular types of drugs, as well as including agents such as the selective serotonin receptor inhibitors (SSRIs) which rarely cause a significant depression of level of consciousness in overdose.[12]

The occurrence of delirium due to anticholinergic activity is also well documented in quetiapine poisoning,[13] most often being manifested in the latter stages of poisoning when the sedative effects have worn off. This occurred in two cases despite the use of ILE in our case series thus also suggesting ILE is not likely to be effective in preventing delirium in quetiapine poisoning.

Whilst our study did not support a beneficial effect of ILE, there were no harmful effects that could be definitively attributed to it's administration. However recent animal evidence raises the possibility of a worse outcome if ILE is administered with a rodent study showing a significantly shorter time to respiratory arrest and death following sodium thiopentone administration if ILE was used, compared with both saline and octreotide in three treatment arms.[14] Another study looking at amitriptyline, administered oro-gastrically, in rodents showed a survival rate of 10% at one hundred and twenty minutes post administration with ILE versus a 70% rate in the sodium bicarbonate and hartmanns solution treatment arms.[15] Hence caution must be exercised in the use of ILE as these studies suggest that ILE may lead to an increase in drug absorbed and thus potentially expose patients to increased quantities of toxin. The timing of ILE administration in relation to toxin ingestion may influence the effect that ILE may have on toxin absorption. [16]

There are some limitations which must be borne in mind when interpreting our data. The decision to initiate ILE was done on the basis of the treating clinician deciding that airway compromise was highly

likely and thus may potentially be subject to practice variation as well as the observer bias that may be experienced when multiple individuals assess the GCS of the same patient [7]**.** Due to the focus placed on the need for active airway protection it also cannot be excluded that small improvements in level of consciousness, such as an increase in GCS by 1 or 2 points, did not occur post ILE administration. The GCS is not recorded post ILE administration, which theoretically makes an evaluation of effect difficult, for some patients however this reflects a perceived need for urgent airway intervention which in clinical practice would likely render further GCS measurements superfluous. Our data do however refute an end of needle effect of ILE similar to that of naloxone reversal of opioid toxicity.

Whilst dosing regimens for ILE use in local anaesthetic toxicity are standardised via guidelines, this is not the case for other toxins where different regimens have been used. It could therefore be argued that another dosing regimen may yield different results. Likewise this study contained sedative drug ingestions where the effect of ILE would require diffusion of toxin across two compartments from CNS to the vascular system and from the vascular system into the lipid sink.

Lack of confirmatory serum concentrations of drugs ingested is another potential limitation, however the history of ingestion has proven to be reliable in previous studies of self poisoning in Australia. [9]

In conclusion, this case series of sedative drug overdoses did not support a role for ILE in preventing the consequences of sedation nor the later complications such as delirium. Further research is required looking at the use of ILE for specific poisoning indications so that it’s place in management can be defined.

Competing Interests

No external funding and no competing interests declared.

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Table 1

Demographic details and drugs ingested

Case	Sex	Age (years)	Drug ingested	Log P	Amount	Coingestants
1	F	17	Baclofen	- 1.0	1g	Oxycodone, ibuprofen, diazepam
2	M	32	Baclofen	- 1.0	Unknown	-
3	F	39	Carbamazepine	2.45	7.2g	Amisulpride
4	M	33	Clonazepam	2.5	Unknown amount	Quetiapine
5	F	46	Quetiapine	2.5	8g	-
6	F	27	Quetiapine	2.5	5g	-
7	F	43	Quetiapine	2.5	11g	-
8	F	52	Quetiapine	2.5	4.8g	Mirtazapine
9	F	20	Quetiapine	2.5	6g	-

Table 2

Clinical effects of toxicity

Case	Intubated	GCS pre ILE	GCS post ILE	Comments
1	Yes	7	7	-
2	Yes	NA*	No change	Required pressors for further 6 hours post ILE
3	Yes	3	Intubated ¶	QT prolongation persisted between 11 and 17 hours post ILE#
4	Yes	NA*	No change	-
5	Yes	3	Intubated¶	Prolonged ventilation due to delirium
6	No	11	10	Stayed overnight in ED resuscitation bay with Naso-pharyngeal airway in situ
7	No	9	11	Admitted to ICU without intubation due to airway concerns
8	Yes	8	Intubated ¶	-
9	Yes	7	Intubated ¶	Prolonged ventilation due to delirium

*NA, ILE administered post intubation
¶ No formal GCS recorded post ILE, however clinical decision made to intubate patient due to airway concerns
# As per the QT nomogram [8]