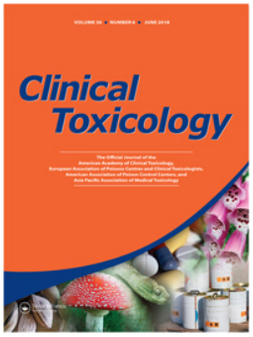

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CLINICAL RESEARCH

The safety of high-dose insulin euglycaemia therapy in toxin-induced cardiac toxicity

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ABSTRACT

Context: High-dose insulin euglycaemia (HIE) is recommended in the management of toxin-induced cardiac toxicity, with increasing insulin doses now being used. We aimed to investigate the safety of HIE in toxin-induced cardiac toxicity.

Methods: This was a retrospective review of cases from two clinical toxicology units. Demographics, toxin(s) ingested, clinical effects, investigations (serum glucose, electrolytes), treatments (insulin, glucose, electrolyte replacement), length of stay (LOS) and outcomes were extracted from the patients' medical records. Associations between insulin and glucose/electrolyte homeostasis were explored by comparing insulin administration and glucose or electrolyte concentrations and replacement.

Results: There were 22 patients (12 females), median age 57 years (15–88 years) treated with HIE. There were 12 beta-blocker, six calcium channel blocker and three combined beta-blocker and calcium channel blocker ingestions. A total of 19 patients had a systolic blood pressure <80mmHg and 18 patients required inotropes in addition to HIE. There were three deaths. Despite glucose and electrolyte replacement, 16 patients (73%) developed hypoglycaemia (Reference range [RR] < 3.5 mmol/L or <63 mg/dl). In 7 patients, hypoglycaemia was mild (2.5–3.4 mmol/L or 45–62 mg/dl) and in nine was severe (<2.5 mmol/L or <45 mg/dl). There were no neurological effects from hypoglycaemia. A total of 18 patients (82%) developed hypokalaemia (<3.5 mEq/L). In 16 patients, this was mild (2.5–3.4 mEq/L). There were no cardiac arrhythmias associated with this hypokalaemia.

There was no apparent association between insulin dosing and severity of hypoglycaemia or hypokalaemia, or in glucose or potassium replacement. Median insulin loading dose was 80U (range 50–125 U) and the median maximum insulin infusion rate was 150 U/h (range 38–1500 U/h). Median glucose infusions rates were 37.5g/h (range 4–75g/h). There was no apparent association between insulin and glucose administration. Glucose was administered for a median of 18h after ceasing insulin. The duration of glucose administration after ceasing insulin increased with the rate and total insulin administered during HIE.

Discussion: Despite the benefits of HIE in toxin-induced cardiac toxicity, it caused significant disruption to glucose and electrolyte homeostasis, although there were no apparent complications from this. There was no association by comparing the amount of insulin administered on adverse effects or glucose administered, suggesting higher doses of insulin are associated with no more adverse effects.

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Insulin euglycaemia; cardiac toxicity; overdose; poisoning

Introduction

High-dose insulin euglycaemia (HIE) for toxin-induced cardiac toxicity was first reported in canine models of verapamil toxicity in the 1990s [1–3]. Its first reported use in humans for drug overdose was in a small case series of five verapamil and amlodipine overdoses published in 1999 [4]. Since this time, there have been further case reports and case series of the benefit of HIE therapy in calcium channel blocker toxicity [5–7], beta-blocker toxicity [8] and other toxin-induced cardiac toxicity [9–11]. It is now accepted as having an important role in toxin-induced cardiac toxicity and reviews of the management of calcium channel blocker and beta-blocker overdose now routinely include HIE therapy in their recommendations [12–14].

Early clinical reports of HIE used insulin loading doses of 0.1–1 U/kg [4,7] followed by infusions ranging from 0.1 to 2 U/kg/h, which will be referred to as low-dose HIE. Few of these specifically report the safety of HIE therapy. In a series of 7 patients with calcium channel blocker overdose, HIE appeared to be relatively safe in the lower dose ranges and adverse effects were related to those known to be associated with insulin [7]. These included hypoglycaemia (2.4 mmol/L or 43 mg/dl) in 1 patient, which was not clinically significant, and hypokalaemia (2.5–3.5 mEq/L) in 2 patients with no arrhythmias. Hypoglycaemia is thought to occur less frequently in calcium channel blocker overdoses, compared to beta-blockers, because they impair glucose-induced pancreatic insulin release [15]. In another series of overdoses,

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hypokalaemia, hypomagnesaemia and hypophosphatemia were more commonly reported in addition to hypoglycaemia [4]. Adverse effects from hypokalaemia such as cardiac arrhythmias have not been reported [16].

Porcine animal models [17,18] using HIE with higher doses of insulin (up to 10 U/kg/h or high-dose HIE) in beta-blocker toxicity have led to high-dose HIE therapy being used in humans [8–11]. A review of HIE [19] and more recent reviews of the management of beta-blocker and calcium channel blocker overdose have incorporated these reports and now recommend these higher insulin doses [14]. Similar to low-dose HIE, hypoglycaemia and hypokalaemia have been reported with these higher doses of insulin but the safety of insulin has not been the primary focus of these reports or reviews. One small animal study (16 pigs) of propranolol toxicity compared glucose administration between three different doses of insulin (1, 5 and 10 U/kg/h) and reported no statistically significant difference in the average glucose cumulative dose administered between any two individual arms over the study [18]. In addition potassium was allowed to fall to 2.5 mEq/L before replacement was given and no sequelae was reported. No such comparison has been reported in human cases. It is therefore not known if hypoglycaemia and hypokalaemia are more common or severe with higher insulin doses or if there is a relationship between increasing doses of insulin and its effect on glucose, potassium and other electrolyte homeostasis and required replacement therapy.

In this study, we aimed to report the use and safety of HIE in a case series of toxin-induced cardiac toxicity. In addition, we aimed to explore the relationship between insulin dosing and its effect on glucose and electrolyte concentrations and homeostasis.

Methods

Study design and setting

This is a retrospective observational study of HIE use in cases of toxin-induced cardiac toxicity. Cases were identified from the databases of two clinical toxicology units. One toxicology unit admits all overdoses or poisonings either as primary presentations or hospital referrals (>15 years of age) from a population of over 500,000 people. All patients managed by the toxicology unit have demographic and clinical information recorded on a specifically designed data collection form that is part of the patient's medical record. Research assistants then enter this information into a purpose designed database.

The second toxicology unit is based in a large tertiary adult (>16 years of age) referral hospital with an emergency department that has approximately 60,000 presentations each year. All overdoses and poisonings managed by the toxicology unit are entered into a purpose built relational database by the units medical staff, which undergoes weekly audit. Both toxicology units managed their intensive care patients in conjunction with intensive care physicians. Neither unit uses a HIE protocol to guide insulin dosing or glucose and electrolyte testing and replacement. The change from traditional low-dose HIE to high-dose HIE occurred in 2007. Both toxicology units have approval by their respective local area health service Human Research Ethics Committees to use their databases and patient medical records for research.

Selection of patients

Both toxicology databases were searched from their commencement date (January 1987 and May 2014, respectively, to December 2016) for all presentations in which HIE therapy was used in the treatment of toxin-induced cardiac toxicity.

Data collection

Presentations in which HIE was used were extracted from each toxicology unit database. Medical records for each patient were then reviewed and data extracted onto a data collection sheet piloted by two of the authors prior to data extraction. The data collection sheet included demographics (sex, age), ingestion (drug[s] and dose ingested) or toxin, time of ingestion or exposure, heart rate (HR), minimum systolic blood pressure (SBP), use of inotropes and ventilation, decontamination, commencement of HIE post ingestion/exposure, insulin loading dose, maintenance dose and duration, glucose concentration, doses and duration, blood sugar levels (BSL), presence of hypoglycaemia (BSL <3.5 mmol/L or 63 mg/dl) and serum electrolytes (potassium, magnesium and phosphate), electrolyte replacement, length of stay (LOS) and deaths. Double data extraction was first performed on one of the toxicology units cases (75% of total records extracted) and the remaining cases were extracted by one extractor. The severity of poisoning or toxicity is reported as the number with bradycardia (HR <60 beats per minute [bpm], hypotension (SBP <80mmHg), requirement for inotropes and/or ventilation, and death. The details of HIE treatment included time to commencement of insulin post admission, insulin loading dose, insulin maintenance rate, duration of insulin administration, amount of glucose administered (total and maximum g/h of glucose) during insulin administration, and duration of glucose administration after insulin was ceased.

Outcomes

Predefined outcomes aimed to assess the safety of HIE treatment and included all adverse effects of insulin administration: hypoglycaemia both during and after insulin administration, hypokalaemia (< 3.5 mEq/L) and potassium replacement, hypomagnesaemia (< 0.7 mmol/L or < 1.7 mg/dl), hypophosphatemia (< 0.8 mmol/L or < 2.5 mg/dl) and complications of electrolyte abnormalities such as cardiac dysrhythmias. In addition, we investigated associations between the rate and amount of insulin administered and both the amount of glucose administered and adverse effects.

Analysis

Continuous variables are reported as medians, interquartile ranges (IQRs) and ranges and dichotomous variables as

percentages. The differences in continuous variables were assessed with Mann–Whitney *U* tests. Linear regression and non-linear regression were used to determine if there was any associations/correlations between glucose requirements, serum electrolytes (potassium, magnesium, phosphate) and potassium replacement versus insulin given during HIE therapy. A p value of < 0.05 was considered statistically significant. All analysis and graphics were performed in GraphPad Prism 6.0h for Mac OS X (GraphPad Software, La Jolla California CA, U.S.A.; www.graphpad.com).

Results

There were 22 non-diabetic patients (12 females; 55%), median age 57 years (range 15–88 years) treated with HIE therapy over a 15 year period from 2002 to 2016 (Table 1). There were 12 beta-blocker overdoses (propranolol [4], metoprolol [4], atenolol [2], bisoprolol [1], sotalol [1]), six calcium channel blocker overdoses (verapamil [4], amlodipine [1], nifedipine [1]) and three combined beta-blocker and calcium channel blocker overdoses (metoprolol and amlodipine [2], atenolol and verapamil [1]). One patient had funnel-web spider envenomation resulting in a catecholamine-induced cardiomyopathy. Decontamination with single-dose activated charcoal was undertaken in 5 patients. No patients received whole bowel irrigation. Median doses (range) ingested of the three most common drugs taken in overdose were metoprolol 2.5g (0.075–5g), propranolol 3.6g (1–16g) and verapamil 3.6g (1–7.2g). The median LOS was 4.2 days (IQR 1.8–8 days, range: 0.7–27 days).

Clinical effects and severity of poisoning/toxicity

A total of 16 patients had a HR $<$ 60bpm, 19 patients had a SBP $<$ 80mmHg, 18 patients required inotropes in addition to HIE therapy and 12 patients were ventilated. There were three deaths, one in a large propranolol ingestion of 16g who was retrieved from a small peripheral hospital whose HIE was commenced approximately 12 h post ingestion. The other two deaths involved an ingestion of 7.2g verapamil and an unknown dose of metoprolol.

HIE treatment safety

A total of 16 patients developed hypoglycaemia ($<$ 3.5 mmol/L or 63 mg/dl) during HIE therapy. In 7 patients, hypoglycaemia was mild (2.5–3.4 mmol/L or 45–61 mg/dl) and in nine it was severe ($<$ 2.5 mmol/L or $<$ 45 mg/dl). There was no relationship between the minimum BSL and the maximum insulin infusion rate (Figure 1a) or the total insulin administered during HIE therapy (Figure 1b). Minimum BSLs appeared to be lower in the 12 beta-blocker ingestions (median 2.5 mmol/L, range 0.9–9.1 mmol/L, 9 patients $<$ 3.5 mmol/L) compared to the four verapamil ingestions (median 3.8 mmol/L, range 1.9–9.9 mmol/L, 2 patients $<$ 3.5 mmol/L), although this was not statistically significant $p = 0.22$ (Figure 2). A total of 15 patients developed hypoglycaemia (median 2.6 mmol/L or 47 mg/dl, range 0.9–3.4 mmol/L or 16–62 mg/dl) after insulin administration was ceased. This was managed with a 50% dextrose bolus and infusion. There were no neurological sequelae. There were no episodes of rebound hyperglycaemia (BSL $>$7.5 mmol/L or 135 mg/dl).

A total of 18 patients developed hypokalaemia ($<$ 3.5 mEq/L) during HIE therapy. In 16 patients, this was mild (2.5–3.4 mEq/L). The two remaining patients had minimum serum potassium's of 1.6 and 2.1 mEq/L. Potassium was replaced in 21 patients. There was no relationship between the minimum serum potassium (Figure 3a) or the rate (mmol/h) of potassium replacement (Figure 3b) and the total insulin administered during HIE therapy. Three patients developed rebound hyperkalaemia ($>$5.0 mEq/L; range: 5.3–6.9 mEq/L) after insulin was ceased. No complications were observed and no treatment was required for the hyperkalaemia. No cardiac arrhythmias that could be attributed directly to hypokalaemia were observed, although arrhythmias consistent with the ingested drug toxicity did occur.

Serum magnesium and phosphate were recorded in 20 of the 22 patients. A total of 16 patients developed hypomagnesaemia [20] ($<$ 0.7 mmol/L or $<$ 1.7 mg/dl) during HIE therapy. In 10 patients this was mild [20] (0.5–0.69 mmol/L or 1.2–1.68 mg/dl) and in 6 patients this was severe [20] ($<$ 0.5 mmol/L or $<$ 1.2 mg/dl) with the lowest recorded magnesium of 0.24 mmol/L or 0.58 mg/dl. Magnesium was replaced in 13 patients. There did not appear to be a relationship between the minimum serum magnesium during HIE therapy and the total insulin administered during HIE therapy (Figure 3c). A total of 15 patients developed hypophosphatemia [21] ($<$ 0.8 mmol/L or $<$ 2.5 mg/dl) during HIE therapy. In 7 patients, this was severe [21] ($<$ 0.32 mmol/L or $<$ 0.99 mg/dl). Phosphate was replaced in 13 patients. Again there was no apparent relationship between the minimum serum phosphate during HIE therapy and the total insulin administered during HIE therapy (Figure 3d).

HIE treatment

Insulin was commenced at a median time of 3.5 h after admission (range 0.75–12.5 h). The median loading dose of insulin in 19 of the 22 patients who received a loading dose was 80 U (range 50–125 U) or 1 U/kg. The median maximum infusion rate of insulin for all 22 patients was 150 U/h (IQR: 79–650 U/h; range: 38–1500 U/h or 0.5–15 U/kg/h) for a median duration of 21 h (range 4.3–44 h). The median maximum glucose infusion rate was 37.5g/h (IQR: 25–50g/h; range: 4–75g/h). There did not appear to be an association (Pearson correlation 0.06) between the maximum insulin infusion rate and maximum glucose infusion rate (Figure 4a). The total insulin given and the total glucose administered during HIE therapy appears to show a maximal or ceiling effect of insulin on glucose administration (Figure 4b). Vasopressors were administered in 12 patients (55%) and in 4 patients this was started soon after (within 1 h) of the commencement of the insulin.

Glucose was continued for a median of 18 h (IQR: 8–24 h; range: 0–45 h) after ceasing insulin. The duration of glucose administration in hours after ceasing insulin was associated (increased) with the maximum insulin infusion rate

Table 1. Cases of HIE use.

	Age/Sex	Drug(s) ingested & dose	Lowest heart rate (bpm)	Lowest blood pressure (systolic)	Ventilated (Yes/No)	**Inotropes used** [1]	HIE commencement post admission (hours)	Insulin bolus (units)	Insulin maximum infusion units/ hour (units/kg/hr)	Insulin duration (hours)	Lowest BSL (mmol/L)	Lowest BSL post ceasing insulin (mmol/L)	Maximum glucose infusion (g/hr)	Glucose duration post ceasing insulin (hours)	Lowest Potassium (mmol/L)	Outcome
1	30 F	Propranolol 1000mg	58	60	Yes	Metaraminol Noradrenaline	3.5	50	200 (4)	9.75	1.9	7.4	37.5	18	2.6	Alive
2	67 M	Metoprolol 1400mg Irbesartan 4200mg Amlodipine 70mg	54	71	No	Dobutamine Metaraminol Noradrenaline	1.16	80	400 (5)	15.5	1.6	1.6	37.5	24	3.5	Alive
3	65 F	Atenolol 175mg Trandolapril 56mg	44	60	Yes	Adrenaline Metaraminol Noradrenaline	1.75	80	800 (10)	15	0.9	0.9	25	30	2.6	Alive
4	33 M	Funnel web spider	75	80	No	Dobutamine Noradrenaline	9	100	1500 (15)	43.75	3.7	3.7	60	34	3.2	Alive
5	87 F	Metoprolol 75mg	25	63	No		0.75	70	70 (1)	6	3.0	1.2	25	13.5	3.2	Alive
6	56 F	Metoprolol 3500mg	62	54	Yes	Adrenaline Metaraminol	0.75	80	800 (10)	30.5	4.6	5.6	30	15	3.4	Alive
7	24 F	Propranolol 3200mg	65	99	No		4.33	75	38 (0.5)	10.5	2.6	2.6	75	5	2.8	Alive
8	15 F	Verapamil 4000mg	70	75	No	Calcium	6	64	128 (2)	24	1.9	3.7	20	4	2.6	Alive
9	45 F	Metoprolol 5000mg	54	52	No	Isoprenaline	2.33	60	500 (5)	13.5	1.4	2.9	50	28	2.6	Alive
10	88 M	Metoprolol unknown	20	45	Yes	Dobutamine Isoprenaline Noradrenaline	3.5	80	600 (6)	4.25	2.2	2.2	20	25	2.6	Died
11[a]	64 M	Propranolol 16000mg	35	55	Yes	Adrenaline Calcium Glucagon Isoprenaline Noradrenaline	11.75	0	150 (2)	30	2.8	2.6	22.5	18	3.5	Died
12	57 F	Amlodipine 300mg Perindopril 300mg	52	63	No	Adrenaline Calcium Noradrenaline Vasopressin	2.33	100	200 (4)	44	2.5	3.3	25	11	2.1	Alive
13	57 M	Verapamil 7200mg Telmisartan 560mg	45	75	Yes	Adrenaline Calcium Noradrenaline	2.5	90	880 (10)	34.66	4.3		20		1.6	Died
14	17 F	Verapamil 1000mg	55	69	No	Adrenaline Calcium	4.33	80	100 (1)	5.5	9.9	2.6	4	0	2.9	Alive
15	51 M	Atenolol 2100mg	60	72	No	Noradrenaline	3.75	75	50 (0.5)	4.75	2.4	2.8	40	6	3.5	Alive
16	69 M	Sotalol 4200mg Irbesartan 2700mg	52	68	Yes	Glucagon Isoprenaline Milrinone	12.5	60	90 (1)	37.5	3.8	1.8	30	45	3.7	Alive
17	33 M	Verapamil 3600mg Atenolol 750mg Fosinopril 200mg	45	68	No	Adrenaline Calcium	4	0	150 (2)	36	2.2	2.6	55	9	3.2	Alive
18	79 F	Metoprolol 700mg Amlodipine 70mg	30	94	Yes	Adrenaline Calcium	11.5	0	120 (2)	20	2.6	3.4	50	15	3.4	Alive
19	37 F	Verapamil 3600mg Irbesartan 4500mg	54	60	Yes	Calcium Dopamine	5	70	72 (1)	29	3.4	3.7	37.5	24	3.1	Alive
20	75 M	Nifedipine 3000mg	55	78	Yes	Calcium Noradrenaline	3	80	80 (1)	22	3.3	2.2	60	21	2.6	Alive
21	33 F	Propranolol 3920mg	70	75	Yes		0.75	100	65 (1)	15	1.7	5.5	50	21	2.7	Alive
22	64 M	Bispropolol 45mg Perindopril 48mg	40	52	Yes	Noradrenaline	3	125	900 (10)	40	9.1	2.2	37.5	24	3.4	Alive

[a]HIE commencement was delayed (transfer logistics), other agents were commenced soon after ingestion.

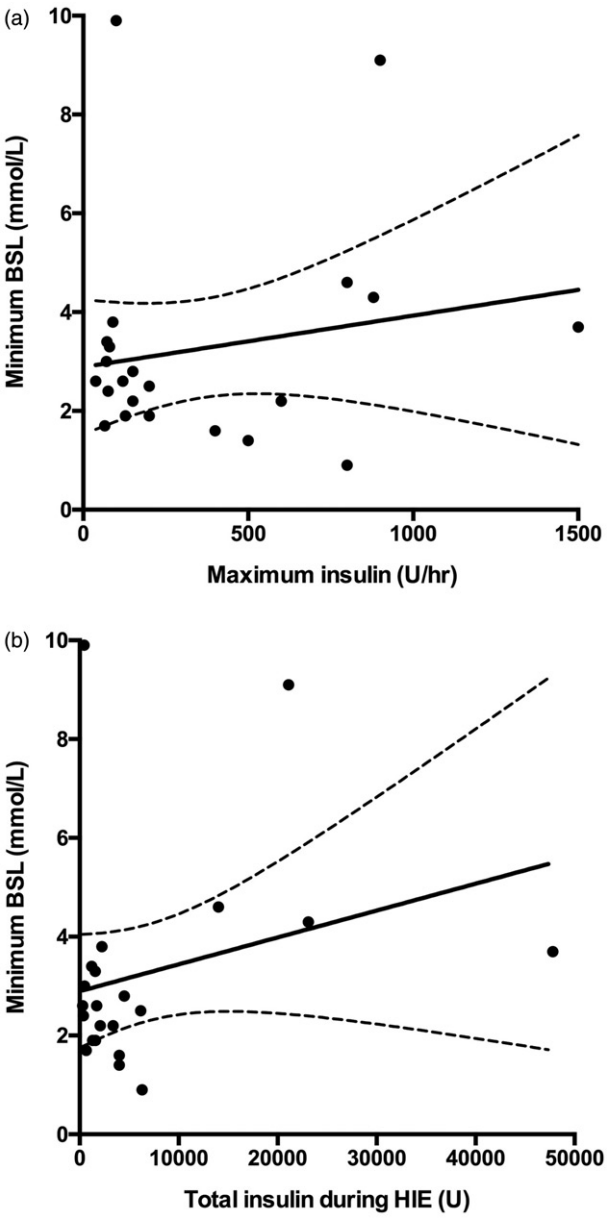

Figure 1. Minimum BSL vs maximum insulin infusion rate (a) and total insulin (b). Mean regression line (thick black) and 95% confidence intervals (dashed black).

(Figure 5a) and total insulin dose (Figure 5b). There was no apparent association between the duration of HIE and the duration of glucose administration after ceasing insulin (data not shown).

Discussion

This study demonstrates that despite the apparent beneficial effect of HIE therapy in the management of toxin-induced cardiac toxicity, it causes significant disruption to glucose and electrolyte homeostasis. Hypoglycaemia was common and occurred just as frequently during insulin therapy as after it was ceased. Hypokalaemia was also common and rebound hyperkalaemia after cessation of insulin therapy occurred in a small proportion. Hypomagnesaemia and hypophosphatemia were common.

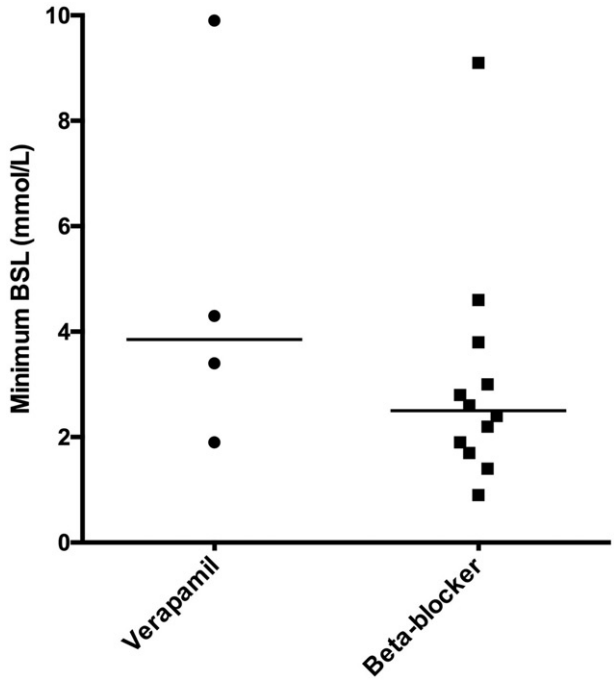

Figure 2. Minimum BSL in verapamil and beta blocker overdose patients p value = 0.22.

Glucose administration during HIE therapy did not show a dose relationship with the maximum insulin infusion rate or total insulin dose administered during HIE therapy. Median glucose administered was approximately 0.5g/kg/h (or 1mL/kg/h of 50% glucose) with no patients administered more than 1g/kg/h (2mL/kg/h of 50% glucose). After insulin cessation, hypoglycaemia was common and glucose supplementation was required for a prolonged time. One possible theory for this finding is that large doses of glucose administered during exogenous insulin therapy appear to stimulate endogenous insulin secretion resulting in hypoglycaemia when exogenous insulin is ceased and glucose weaning is attempted. This is analogous to the non-diabetic patient taking a large insulin overdose requiring a glucose infusion. As the exogenous insulin is metabolised, euglycaemia is maintained in the normal patient by endogenous insulin secretion, resulting in hypoglycaemia and prolonged glucose infusions as the glucose is weaned and pancreatic homeostasis is restored. Measuring both endogenous and exogenous insulin levels (C-peptide concentrations) would be required to confirm if this was an ongoing effect from the HIE or from pancreatic insulin secretion. Finally, a higher insulin infusion rate and administered total insulin were associated with a longer duration of glucose administration post ceasing insulin, suggesting that higher insulin doses were associated with a greater disruption in insulin/glucose homeostasis.

Previous smaller case series [4,7,10] have described similar adverse effects to those reported here. The first case series published of HIE therapy using only low-dose HIE ($\leq$0.5unit/kg/h) by Yuan et al. [4] of five calcium channel blocker overdoses reported hypoglycaemia (1.4–3.2 mmol/L or 26–58 mg/dl), hypokalaemia (2.2–2.8 mEq/L), hypomagnesaemia (0.4–0.6 mmol/L or 0.97–1.46 mg/dl) and

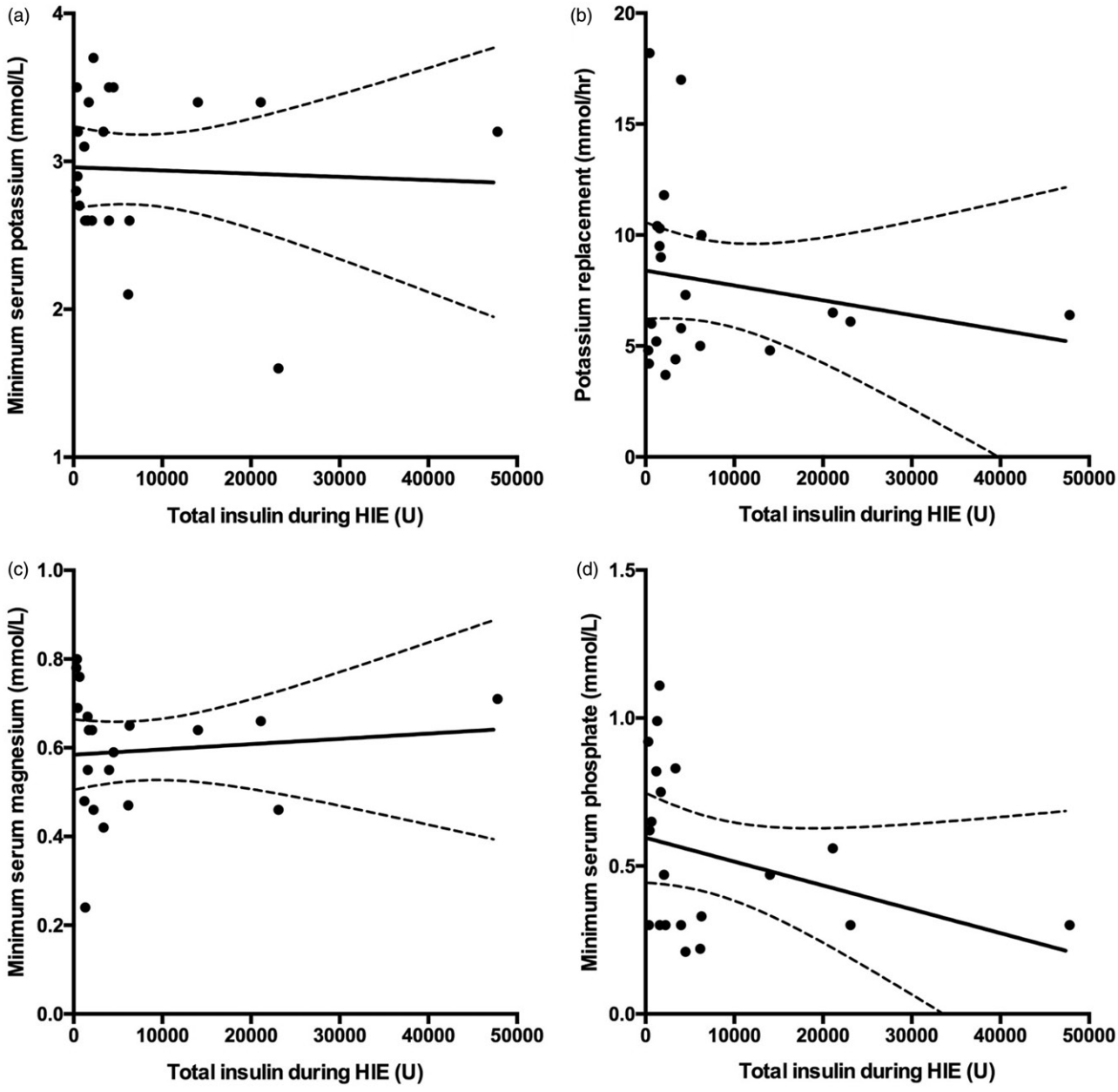

Figure 3. Total insulin administered versus minimum serum potassium (a), potassium replacement (b), minimum serum magnesium (c) and minimum serum phosphate (d). Mean regression line (thick black) and 95% confidence intervals (dashed black).

hypophosphatemia (0.19–0.52 mmol/L or 0.59–1.6 mg/dl) in four out of 5 patients. There were no apparent adverse effects. One patient developed hyperkalaemia in the context of acute renal impairment and oliguria. The only other case series of low-dose HIE (≤2units/kg/h) was a study by Greene et al. [7] of seven calcium channel blocker overdoses who reported hypoglycaemia in 1 patient (exact value not reported) and hypokalaemia (2.8 mEq/L) in 2 patients. Finally Holger et al. [10] reported mainly high-dose HIE (eight out of 12 patients >6 U/kg/h of insulin) in a cohort of calcium channel blocker, beta-blocker and other drug-induced cardiac toxicity. Hypoglycaemia occurred in 6 patients (1.2–3.4 mmol/L or 21–63 mg/dl and hypokalaemia (2.3–3 mEq/L) in 8 patients and no adverse effects or arrhythmias were recorded. None of these three case series investigated the relationship between insulin dose and the severity of adverse effects, which our study has reported on.

Glucose administration is reported to varying detail in previous reports. No inference can be made between glucose administration (total or g/h) and insulin (total or U/h) in the case series by Yuan et al. [4] as the infusion rates were all ≤0.5 U/kg/h. In the series by Greene et al. [7], there is no individual patient data to comment on. Lastly in the case series by Holger et al. [10] with insulin rates of 0.5–14.1 U/kg/h (total insulin dose was not recorded), the data is not available to make a direct comparison because the glucose administered is only recorded as total glucose given not as g/h. Our series of a wide range of insulin rates and dose gives the best evidence to suggest that there is no relationship between glucose administration and insulin rate or dose in HIE therapy.

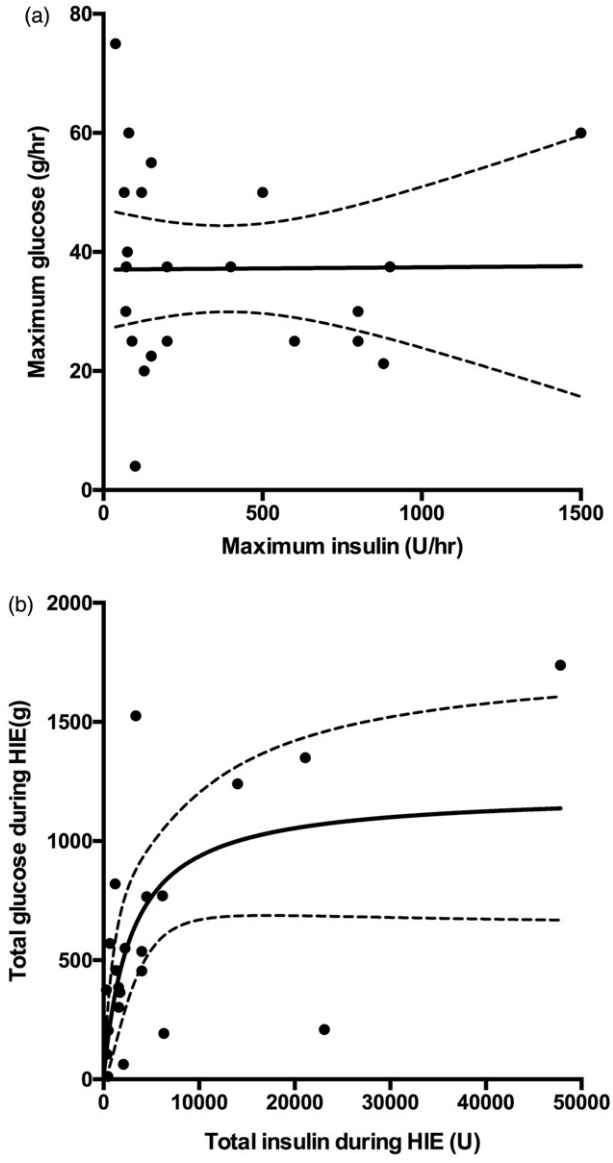

Figure 4. Maximum insulin infusion rate versus maximum glucose replacement (a), and total insulin administered versus total glucose during HIE (b). Mean regression line (thick black) and 95% confidence intervals (dashed black).

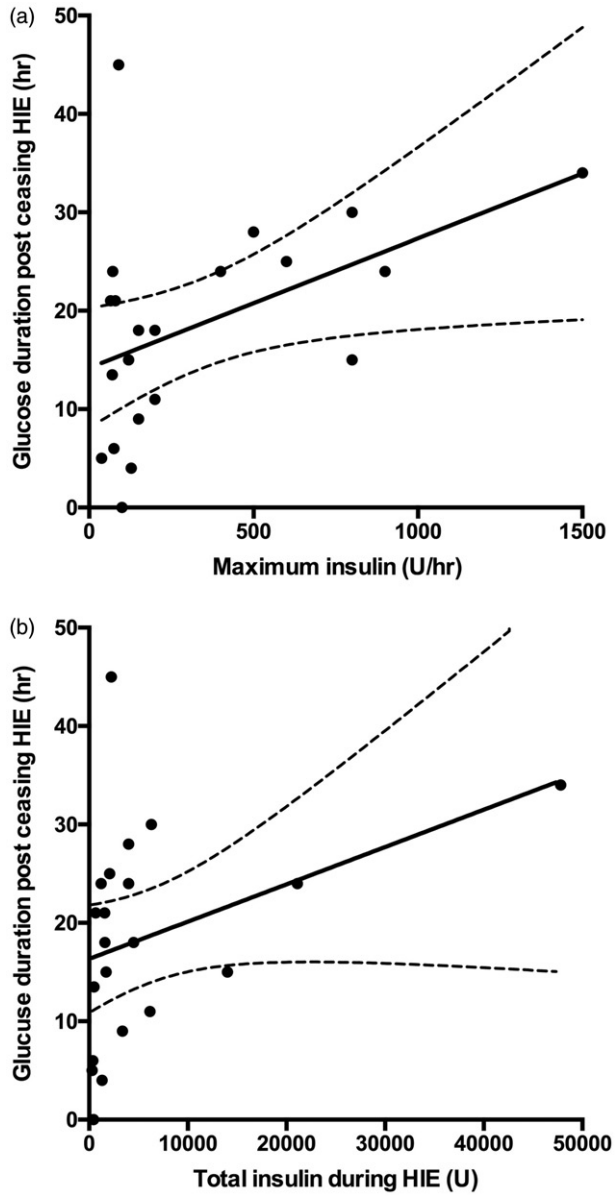

Figure 5. Glucose duration versus maximum insulin infusion rate (a) and total insulin administered (b) during HIE. Mean regression line (thick black) and 95% confidence intervals (dashed black).

Glucose duration after ceasing insulin is also variably reported. Only the case series by Yuan et al. [4] and three case reports [6,8,9] contain this information. Only two of the case reports [8,9] use insulin at rates >1 U/kg/h, so no interpretation can be made. Our series provides more definitive information and suggests that glucose is administered for longer periods with higher insulin infusion rates or doses. The most likely interpretation of this is that there is a greater disruption of insulin/glucose homeostasis with higher infusion rates and doses, as indicated by the time it takes to wean glucose supplementation.

All of the case reports and series including ours have reported very few complications of the hypoglycaemia and electrolyte disorders seen with use of HIE therapy. Neurological sequelae from the hypoglycaemia have never been reported and this may reflect the close monitoring of patients on HIE therapy who are invariably in a critical care setting. Hypokalaemia predisposes to first and second degree heart block, and atrial fibrillation. Ventricular tachycardia, torsades de pointes leading to cardiac arrest can occur in severe cases [22]. Arrhythmias that have been reported with HIE therapy are consistent with the known drug toxicity. Unlike hypokalaemia in total body potassium depletion, hypokalaemia in the setting of HIE therapy reflects intracellular shift due to the insulin and total body potassium is unchanged, which may be a protective factor. Hypomagnesaemia can cause neurological disturbances including seizures as well as atrial and ventricular arrhythmias [20] and hypophosphatemia can cause a variety of symptoms related to a decrease in intracellular adenosine triphosphate or ATP [21]. Complications from both hypomagnesaemia and hypophosphatemia were not seen in our study. As in the situation with hypokalaemia, hypomagnesaemia and hypophosphatemia in HIE therapy likely also reflects intracellular shift from insulin and total body stores are unchanged.

The study has a number of important limitations. It is a small descriptive study of 22 patients without confirmatory drug concentrations who received HIE therapy. Our findings on the relationships between insulin dosing and its effects should therefore be interpreted with this in mind. There were no comparisons made on patient outcomes e.g. mortality or on glucose or electrolyte disturbance between patients receiving or not receiving HIE in toxin-induced cardiac toxicity. No patients included in this study were managed with a HIE protocol that stipulated when glucose or electrolyte replacement should be commenced, the rate of replacement and targets for replacement. A protocol based approach for HIE may have reduced some of the disruption to glucose and electrolyte homeostasis. It is also possible that the use of a HIE protocol could have resulted in different findings to what we have found in regards to a ceiling effect of insulin dosing.

The study was a retrospective analysis of data recorded in the patient's medical record that has subsequently been extracted. Missing or inaccurate data may have occurred that a prospective study design with specific hypotheses is more likely to avoid. The extraction was performed by two of the authors (CP and GI) and although there were a small number of discrepancies e.g. total insulin dose, minimal serum electrolyte level in the extraction, these were not thought to have introduced significant errors in the study findings, which are consistent with previous studies.

Our study found that HIE therapy has a significant effect on glucose and electrolyte homeostasis, although there were no apparent complications from this effect. The large doses of insulin used in HIE therapy appear to cause a prolonged requirement for glucose even after insulin is ceased. Despite this effect, there was no evidence that increasing the insulin dose increased or worsened the adverse effects or the amount of glucose administered to maintain euglycaemia during HIE therapy. This suggests that high-dose HIE therapy with insulin infusion rates up to 10 U/kg/h is as safe as low-dose HIE therapy (1–2 U/kg/h).

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