Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic©) in chronic intestinal failure

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Summary Background & aims: Injectable lipid emulsion is an important component of parenteral nutrition. ClinOleic© is a lipid emulsion composed of olive oil (80%) and soybean oil (20%). This study evaluated the efficacy and safety of ClinOleic in adults already receiving parenteral nutrition, comparing it to their usual lipid (soybean-oil-based).

Methods: Thirteen adults dependent on home parenteral nutrition were recruited from a single hospital. ClinOleic was administered for 6 months. Two-monthly assessments were made. In addition, clinical and adverse events were recorded for 6-month periods before, during and after the study.

Results: Total numbers of important complications for the 6 months before, during and after the study were 13, 9 and 9, respectively. There were, respectively, 5, 3 and 2 line infections, and 2, 0 and 5 thrombotic episodes in the 3 periods. The numbers of unplanned admissions were, respectively, 8, 5 and 7, with in-patient days accounting for 3.4%, 1.5%, and 2.6% of feeding days, respectively. One patient died (pneumonia). One new case of cholecystolithiasis appeared.

Conclusion: ClinOleic may be used as a safe alternative to standard soybean-oil-based lipid emulsions.

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Introduction

Intravenous lipid is an important component of the prescription for patients dependent on long-term home parenteral nutrition (HPN). Injectable lipid emulsions (ILE) provide an energy-dense source of calories and reduce the potential side effects of a high glucose intake.\textsuperscript{1-3} They provide the two essential fatty acids (EFA), linoleic and linolenic acids, which are needed for the synthesis of the important eicosanoid lipid mediators.\textsuperscript{4-6} There are two types of ILE in general use at present. The first ILEs were soya based; these consist of long-chain triglycerides (LCT) and have a greater proportion of
polysaturated fatty acids (PUFA) than monounsaturated fatty acids (MUFA)—typically around 60% PUFA; these yield a high concentration of EFA. Soybean oil is especially rich in the n-6 fatty acid linoleic acid (18:2n-6) which is the precursor of arachidonic acid (20:4n-6). There are also the medium-chain triglyceride (MCT) admixtures consisting of 50% LCT (30% PUFA), as soybean oil, and 50% MCT.

A normal healthy western diet provides saturated fatty acids (SFA), MUFA and PUFA in proportions of approximately 30%:40%-30%, respectively, depending on fat intake. These are LCTs; the normal diet does not include medium or short chain triglycerides.

It is thought that an excessive intake of PUFA—particularly when this is in the form of linoleic acid—may lead to alteration of membrane structures, impaired immune function, increased lipid peroxidation and decreased synthesis of protective EFA derivatives. It would therefore be logical to construct and examine lipid emulsions which bear a lower proportion of PUFA. It might be hoped also that such emulsions would be less likely to provoke cholestasis.

A new olive oil-based lipid emulsion (ClinOleic) consisting of purified olive oil (80%) and soybean oil (20%), and containing only LCTs, has been devised. It has 65% MUFA, and a lower proportion of PUFA (20%) than the conventional more heavily soya-based formulations. It has previously been shown that, despite the lower proportion of PUFAs in ClinOleic, there is no significant change in the plasma fatty acid profile, and in particular, that EFA deficiency does not occur. It is known that an excess of the EFAs, linoleic and linolenic acids, will inhibit Δ6-desaturase. This is a rate-limiting enzyme in the biosynthesis of eicosanoids such as arachidonic acid and other inflammatory response mediators. The double bonds in PUFAs are targets for free radical attack, which can result in cell death (cell membrane PUFAs), and in the production of potentially toxic peroxide derivatives. If there is an overproduction of free radicals, as for example in the acute inflammatory syndromes, or a deficiency in anti-oxidants that neutralise free radicals, then the presence of double bonds will result in oxidative stress. Olive oil is rich in α-tocopherol (active vitamin E) which is a major anti-oxidant. This, together with the fact that oleic acid, the principal component of ClinOleic is a MUFA and therefore resistant to lipid peroxidation, should render ClinOleic potentially beneficial in subjects at risk of oxidative stress.

The efficacy and safety of ClinOleic have been demonstrated in a number of studies, but further evidence is required before it can be widely accepted as an alternative to established ILEs, and especially so in patients on long-term therapy. The present study assesses the use of the new ILE in adult patients on HPN and compares their clinical status with that whilst on their usual ILE before and after the intervention period.

Materials and methods

The study was performed in two parts: a prospective open trial of ILE treatment in adult patients lasting 6 months, and a retrospective case notes review of the study patients for 6-month periods before, during and after the study.

Inclusion criteria were: age 18–80 years; anticipated need of HPN for at least 6 months from the start of the trial; greater than 50% of the total energy requirement provided by parenteral nutrition and lipid required two or more times per week. Exclusion criteria were: active malignant disease or acquired immunodeficiency syndrome; pregnancy or lactation; serious disease other than that for which they required parenteral nutrition; established cholestasis (bilirubin > 0.3 mmol/l); prior exposure to ClinOleic; and expected survival of less than 6 months from the start of the trial.

The study had the approval of the Harrow Research Ethics Committee and all patients provided written informed consent.

Thirteen patients were recruited and fulfilled the inclusion criteria. The patients had a median age of 44 (range 25–68) (9 females, 4 males). The underlying diagnoses of recruited patients were: anatomical short bowel syndrome (Crohn's disease: n = 5; ischaemia: n = 2; volvulus: n = 2), other intestinal failure (scleroderma: n = 1; visceral myopathy: n = 2), and pseudo-obstruction secondary to idiopathic sclerosing peritonitis (n = 1). The median body mass index at baseline was 20.3 kg/m² (range 13.7–25.0).

Parenteral nutrition

The mean period of previous parenteral nutrition intake was 3.8 ± 0.8 years (n = 13). Prior to the central study period, patients' lipid provision was from soybean-oil-based lipid emulsions: Ivelip® 20% (n = 5), Ivelip 10% (n = 4), Intralipid® 10% (n = 1), or Intralipid 20% (n = 1). Two patients were not already on regular lipid infusions, but were slowly losing weight on their existing regimes. They were due to receive a prescription modification to include lipid, in line with standard clinical practice.
It was felt reasonable to include them in the study and they were therefore recruited (with ClinOleic 20% 500ml twice weekly). Prior parenteral feeding provided a median of 85.4 kcal/kg/day (range 69.8-92.4) % of estimated total non-protein energy intake, or 25.7 kcal/kg/day. Glucose provided a median of 20.3 kcal/kg/day (range 11.1-38.5). Lipid provided a median of 4.3 kcal/kg/day (range 1.23-8.63) (n = 11). For many years we have had a policy of limiting lipid administration to a maximum of 1 g/kg/day (or 9 kcallkg) in patients on long-term intravenous nutrition. The amino acid source for all patients was FreAmine 111 (8.5% or 10%).

Intravenous trace elements were administered daily. Multivitamins— as Multibionta© twice or thrice weekly—and folic acid 15 mg weekly were also given to all patients. Vitamin B₁₂ and vitamin D (calciferol) were given every 2 months by the intramuscular route. Vitamin K was given when indicated on the basis of coagulation studies (other than in patients on oral anticoagulants for prior thrombotic disease); it is also present in Intralipid and Ivelip. Vitamin E was present in all of the lipid emulsions; it is thought that ClinOleic has considerably greater availability of the biologically most active alpha-tocopherol than conventional soy-predominant emulsions (approximately 8.75 mg/l total tocopherol in Intralipid). Additional sodium chloride 0.9% was made available to be given as required. A home-care service provider delivered intravenous nutrition supplies to the patients' homes.

Study treatment and duration

At the initial visit demographic characteristics, medical history, and concomitant therapies were recorded. Clinical, nutritional and biological assessments were made. The selection and inclusion criteria were checked. Patients were seen at recruitment (~15 days), after which there was a lipid-free interval until the day zero visit. ClinOleic 20% (500 ml) was then prescribed for administration two or three times per week in exact replacement of the usual lipid preparation and to provide appropriate or equivalent energy content, with the exception of the 2 patients starting lipid anew, who are referred to above. Patients previously on 10% emulsions had the same provision of calories, but in a smaller weekly volume.

A patient record diary was provided. Follow-up assessments were made at 2, 4 and 6 months (or their final visit whilst on ClinOleic if this was sooner). After the 6-month period of intervention with ClinOleic all patients reverted to their pre-study lipid prescription, with the exception of the 2 patients newly started on lipid who were switched to Intralipid 20% 500 ml twice weekly. In other respects the nutritional and pharmacological regime was left unaltered during this time. Routine follow-up comprised continuing 2-monthly outpatient visits with clinical and biochemical monitoring.

Safety and efficacy assessments

Compliance was checked at each assessment from the patient diary, supplemented by information from the home care service provider on unused supplies. Anthropometric data (weight, body mass index, mid arm circumference, and triceps skinfold thickness) were measured. Adverse events were recorded according to the latest International Committee on Harmonization (ICH) guidelines' definitions, graded for severity and treatment relationship. We considered that any event responsible for an unscheduled hospital visit was a complication. If documented pyrexia (>38°C) occurred this was assumed to be of infective origin whether or not there was microbiological confirmation. Septic episodes were categorised on clinical grounds as to the most probable site and source of those infections.

With specific respect to feeding catheter related sepsis, the unit has for years recorded this on a "confirmed/probable" basis. Confirmed sepsis requires the same organism to be cultured from blood cultures and from the tip of a removed catheter. As our strategy is normally to attempt treatment without catheter removal many infective episodes are classified as probably catheter related sepsis on the basis of culture of the same organism from central and peripheral venous blood in a clinical context in which infection of the feeding catheter is thought the probable cause.

Central vein thrombosis was diagnosed in the presence of clinical signs supported by ultrasonographic Doppler studies or venography.

Blood samples were drawn at each visit and the following recorded: haemoglobin (as part of a full blood count), total protein, albumin, triglycerides, and cholesterol (total and HDL), sodium, potassium, calcium, phosphate, urea, creatinine, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin, conjugated bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST).

Ultrasound scans were obtained to assess the presence of gallstones and/or sludge, at baseline and on follow-up through the study. Gall bladder
motility was assessed in appropriate patients. Scintigraphic assessment of biliary outflow efficiency by HIDA scan was also assessed at baseline and completion, working to the premise that this is sufficiently sensitive to detect clinically important but biochemically inapparent changes in biliary excretion.¹²

**Retrospective study**

A retrospective case notes review recorded all important clinical events for the 6-month periods preceding, and following the trial intervention. Comparable analysis for the trial period was made without reference to the trial documentation. The following clinical adverse events were recorded systematically: sepsis (of any source including line infections), thrombotic episodes affecting any site, admissions to hospital, and the duration of any inpatient stay. The retrospective nature of this part of the study necessitated simple recording of events considered at the time to be of septic or thrombotic origin. The unit's criteria for catheter related sepsis did not change during the study period. Blood results from the 6-month periods before and after the study were also considered.

**Analysis and statistics**

Comparative analysis of changes within patients during the interventional part of the study and comparison with events in the pre- and post-trial periods were made with paired non-parametric statistics (Wilcoxon signed rank test). In the case of premature study termination, investigatory criteria were judged evaluable after no less than 2 months of active treatment, provided both assessments were performed. All data were used for safety analysis.

**Results**

Of the thirteen recruited patients, four patients left the trial prematurely, two because of significant sepsis (fatal in one), one because of abnormal liver function tests and sepsis, and one withdrew consent after 15 days. Median duration of ClinOleic therapy was 5.7 months (mean 5.0 months, range 0.5–7.0). Data from patient diaries and delivery records indicated that median compliance with ClinOleic infusions was better than 90% of intended administration in the 12 patients who completed more than 2 months (range 75–100% compliance). Delivery drivers regularly checked patient fridges and equipment stores with telephone feedback to the hospital base. The reasons for omitted feeds generally reflected concerns about infection and periods whilst blood cultures were obtained.

In the 12 patients who completed more than 2 months' treatment, the baseline total protein, albumin, cholesterol, and bilirubin fell globally within the normal range or, in the case of AST, was no more than 15% outside it. Baseline haemoglobin was in the normal range or within 15% of it in 11 of the 12 patients. In two patients the ALP, GGT or ALT was elevated greater than twice normal at baseline, but with otherwise normal laboratory parameters. There were transient rises in some of the liver chemistry tests in 4 patients, but they only remained persistently abnormal in one severely septic patient who also had abnormal tests at baseline. The median platelet count remained stable: 259 cells/mm³ (range 145–392) at the start of the trial period; 224 (range 122–383) at the end of ClinOleic administration.

Six patients were found to have biliary disease at baseline, two had a cholecystectomy, three were known currently to have gall stones and one had biliary sludge. One new case of cholelithiasis was identified. Scintigraphic assessment of biliary outflow efficiency by HIDA scanning demonstrated no abnormality at baseline (n = 12) or at the trial endpoint (n = 8) despite the high prevalence of and overt biliary disease.

The median BMI at the end of the intervention period was 20.0 (range 14.6–25.0) (n = 12). There was no important (±2.5%) weight change in any individual during the study intervention, other than in the two patients newly commencing lipid infusion, both of whom gained weight.

**Retrospective analysis**

The retrospective review revealed similar complication rates in the 6-month periods before, during and after the use of ClinOleic, with the exception of thromboses, none of which occurred during the trial period (Table 1). In the pre-trial period, of nine septic episodes, five were line infections requiring in-patient management for between 2 and 33 days. Other infections were of the urinary tract (n = 1), unspecified viral illnesses (n = 2), and pneumonia (n = 1). The two thrombotic episodes were respectively a cerebrovascular infarct, and pulmonary embolism. One patient had a grand-mal convolution shortly before the first infusion of ClinOleic. There was an episode of dehydration with significant electrolyte imbalance requiring in-patient stay.
There were a total of eight unplanned admissions during this period, with a median duration of stay of 10 days (range 2–50) (Table 1).

Nine adverse clinical events during the trial period were identified retrospectively. Seven of these were septic episodes (3 line infection; 2 pneumonias; 1 urinary tract infection; and one of unknown source). In one patient aseptic necrosis of the femoral head required surgery, and the patient who had suffered a cerebrovascular infarct in the pre-trial period died from septicemia complicated by hyperosmolar diabetic coma and adult respiratory distress syndrome. No thrombotic episodes were identified during the trial period. There were five unplanned admissions, in each case relating to one of the above complicating conditions. The median duration of in-patient stay was 7 days (range 3–27) (Table 1). One patient withdrew consent during the trial period whilst septic. None of the adverse events was thought to have been related to the new lipid emulsion.

There were nine adverse clinical events in the 6 months following the trial. There were four septic episodes (2 line infections; 1 fungal stomal infection; 1 urinary tract infection). There were five thrombotic episodes (pulmonary embolus, axillary vein thrombosis, superior vena cava thrombosis, line-associated thrombosis, and subclavian vein thrombosis). The patient with thrombosis of the superior vena cava had suffered a pulmonary embolus in the pre-trial period and was on oral anti-coagulants throughout the 18 months of interest. The mean duration between stopping ClinOleic and the diagnosis of the thrombotic episodes was 69.2 days (median 55, range 11–135). The number of thrombotic episodes during the trial period was lower than in the periods off ClinOleic. There were seven unplanned admissions for the above problems, with a median duration of in-patient stay of 8 days (range 1–19) (Table 1).

Amongst 11 patients who completed more than 2 months’ treatment and who were fully evaluable, there were no significant changes in the laboratory investigations in the 6 months following the trial period. Nine patients completed all three phases of the study and received the full 6 months of ClinOleic therapy. Analysis—by treatment given—of these 9 patients indicates rates for thrombotic events of 11% and 55% for the periods before and after ClinOleic, and 0% whilst on ClinOleic.

Three patients in the study felt strongly that they had experienced symptomatic improvement whilst on ClinOleic compared to their habitual lipid. The features described were non-specific, but included a reduction in lipid-associated nausea and headaches. These 3 patients each requested a permanent change in prescription and now receive ClinOleic. No patient expressed a preference in the opposite direction.

Discussion

The aim of this study was further to evaluate an olive oil-based ILE, ClinOleic. There have been several previous studies in adults and children but there have been no data on long-term usage in adults. The current study did not identify any problems with tolerability or safety in prolonged use of ClinOleic. The patients were all dependent on lipid-containing parenteral nutrition, and therefore a placebo-controlled trial would have been unethical. We took the opportunity, nevertheless, to evaluate each patient as his or her own control by comparing the clinical response to, and overall
status whilst on ClinOleic, to equivalent data for that patient in the 6-month periods before and after the time on ClinOleic. We acknowledge that retrospective case-note reviews have their limitations, and in view of this compared the data pertinent to the 6-month trial period as retrieved retrospectively, with those for the same period collected prospectively for the study. These data closely (almost identically) matched, and we are confident that important bias has not been introduced in our comparison of these clinical data with those for the pre- and post-trial periods.

The patients in the trial were representative of the North European patient population requiring long-term parenteral nutrition, with regard to demographics and underlying diagnoses. All patients were stable in terms of their underlying medical condition, although two patients were slowly losing weight at the onset of the study. The overall complication rate proved higher for this group than for our patients on HPN in general. All patients receiving lipid immediately prior to the trial were receiving one of two established soybean-oil-based ILEs. The 15-day equilibration period aimed to achieve ‘washout’ of any lipid from their previous regimen.

Of the 13 patients evaluated, 4 left the trial prematurely. One departure followed elective withdrawal of consent during a period of sepsis; this was not felt to be related to the lipid and did not otherwise necessitate termination according to the study protocol. In two patients the trial was terminated as a result of adverse events. In one patient there were deteriorating abnormal liver function tests, and it was felt that this required further investigation; no definitive cause was found, but the abnormalities continued in an intermittent but very slowly progressive fashion over the succeeding 2 years of follow-up. The synthetic function remained good and no treatment was required. Examination of the biochemistry results across a total of 4 years failed to indicate any “frameshift” deterioration at the time of ClinOleic exposure. In another patient there were episodes of fitting (grand-mal seizures) which pre-dated the start of ClinOleic. The novel lipid was therefore not considered responsible for either of these adverse events by the investigators, but the trial sponsors felt that the patient should be withdrawn. The fourth patient had septicaemia complicated by hyperosmolar non-ketotic diabetic coma and died within the study period. Again this was considered unrelated to lipid administration.

Baseline biological parameters were homogeneous between subjects. The moderate abnormalities in liver function tests were compatible with those associated with long-term parenteral nutrition. Biliary dysfunction is known to occur in association with parenteral nutrition and the conditions which make it necessary. We hypothesised that ClinOleic would have less tendency to aggravate hepatobiliary dysfunction than conventional ILEs. Six of our patients were identified as having pre-existing biliary disease. Ultrasound together with HIDA scanning was used to evaluate the development of biliary disease and to measure biliary outflow. We found no significant change in outflow. This is in line with the findings of Goulet et al.11 Comparable studies of the administration of PUFA-rich ILEs13,14 have shown a decrease in biliary flow with time, and another study (still presented only in abstract form) demonstrated stability of established steatosis or cholestasis whilst on ClinOleic when compared to soybean oil ILE.15 It is probable that HIDA scanning is a poor investigation in the present context, and it would clearly be premature to conclude that ClinOleic prevents progression of hepatobiliary disease.

The retrospective review examined all entries in the medical records of the subjects for the 6-month periods preceding, during, and following the trial. All comments were reviewed and any clinical symptoms noted were recorded. In particular, all episodes of sepsis, (serious or not, feeding catheter or other), thrombotic episodes and in-patient admissions were detailed. For the trial period this information was compared to that retrieved prospectively. Minor symptoms and those that occurred both before and during the study were not analysed in detail (e.g. backache, and symptoms related to the underlying disease, such as Crohn’s disease fistula drainage). Minor symptoms were greater in number for the study period, which is to be expected as patients were followed more closely and specifically asked to report all symptoms; these were all trivial however. The retrospective data analysis nonetheless identified all the serious adverse and clinically important events that were identified prospectively. This implies reasonable reliability of the case notes for the periods before and after the trial period. The results suggest that there is no clinical disadvantage from the long-term use of ClinOleic. Indeed the overall proportion of in-patient days and the frequency of thrombotic episodes were favourable. In particular, one of the patients who experienced a thrombotic episode during the prior 6-month period, had no thrombosis whilst on ClinOleic, and then was among the five with a serious thrombotic episode during the 6 months after the trial. Patients who expressed a preference all preferred ClinOleic to their usual lipid.
The size of the study and the absence of a randomised control group preclude meaningful statistical analysis. A confident statement in respect of the lower frequency of thrombotic episodes observed whilst patients were on ClinOleic is not warranted, but such an effect is biologically plausible and deserves further exploration.

The apparently lower rate of thrombotic episodes during the trial period suggests that ClinOleic may be less thrombogenic than conventional ILEs. While this may reflect the lower exposure to vitamin K in the ClinOleic phase than with the conventional lipid emulsions, it is known that free radicals induce tissue damage by reacting primarily with PUFAs in cellular membranes, and peroxidised free fatty acids have been shown to be responsible for increased platelet aggregation. This noxious effect on platelets can be blocked by antioxidants such as vitamin E. Reactive oxygen metabolites also have several other pro-thrombotic properties. A nutritional lipid admixture which has a low percentage of PUFA, but which is rich in vitamin E could be expected to be associated with less platelet aggregation and fewer consequent thrombotic episodes than conventional ILEs. The small reduction in platelet count observed during the time on ClinOleic is likewise of potential benefit.

The results of this trial are consistent with the hypotheses posed, and with the results of laboratory investigation and short-term clinical studies. ClinOleic appears to be a safe and well-tolerated alternative intravenous lipid emulsion for prolonged use in adult patients.

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References


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