TITLE: Nutritional adequacy therapeutic enhancement in the critically ill: A randomized double blind, placebo controlled trial of the motilin receptor agonist camicinal (GSK962040): The NUTRIATE Study.

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Conflict of interest

AMD has received honoraria from Medtronic, Baxter and Takeda. GED is a paid consultant for Takeda. All other authors have no conflicts of interest to declare.

ABSTRACT

Background

Camicinal is a novel, non-macrolide, motilin receptor agonist that accelerates the rate of gastric emptying when administered to critically ill patients with established feed-intolerance. The primary question was whether the pre-emptive administration of camicinal increased the provision of goal enteral nutrition to critically ill patients with risk factors that predisposed to feed-intolerance.

Methods

This was an international, multi-center, parallel-group, blinded, randomized controlled trial. Patients at risk of feed-intolerance, defined as receiving moderate to high doses of vasopressors or opiates, or admitted because of multiple traumatic injuries, or with brain injury, received either enteral camicinal 50 mg or placebo daily for a maximum of 7 days, along with enteral nutrition administered according to a standardized feeding protocol. The primary outcome was the daily adequacy of enteral feed delivered, as assessed by percentage of goal volume (delivered/prescribed * 100) prior to the development of intolerance.

Results

Eighty-four patients participated. The administration of camicinal did not result in a statistically significant clinical difference in the daily average percentage goal volume delivered (camicinal: 77% (95% CI 71, 83) vs. placebo: 68% (58, 78); mean difference 9% (-5, 23); $P=0.21$). Similarly, there were no differences in the percentage goal calories (76% (65, 88) vs. 68% (60, 77) and protein (76% (66, 86) vs. 70% (61, 80) administered, or the incidence of feed-intolerance (15% vs. 14%).

Conclusion

The incidence of feed-intolerance was low in both groups. In this cohort the pre-emptive administration of enteral camicinal did not significantly augment the provision of goal enteral nutrition.

CLINICAL RELEVANCY STATEMENT

In this trial the pre-emptive administration of enteral camicinal did not augment the percentage goal volume of enteral nutrient received by 15% or greater. This trial does not support the administration of pre-emptive camicinal to critically ill patients receiving enteral nutrition.

BACKGROUND

Inadequate provision of protein and energy to critically ill patients is associated with increased complications, such as prolonged duration of mechanical ventilation and hospital admission, impaired physical recovery, increased health care costs and increased mortality (1-5). Once enteral feeding is commenced a major determinant of nutritional adequacy is disordered gastrointestinal motility, specifically slow gastric emptying (6, 7).

Pro-motility drugs, such as metoclopramide and the macrolide antibiotic erythromycin, have been shown to accelerate gastric emptying, improve feed tolerance, and increase the delivery of calories administered via the gastric route (8-12). As part of the PEP uP protocol the use of metoclopramide, when commencing enteral nutrition, contributed to a 15% absolute increase in the average percentage of goal calories delivered in a cohort of patients that were receiving < 50% of their caloric requirements (13). However, even when patients have established feed-intolerance, the use of pro-motility drugs is not widespread (14), possibly because of concerns regarding adverse drug reactions. Accordingly, there is considerable interest in the development of effective pro-motility drugs that have an acceptable benefit-risk profile (15-17).

Motilin is a peptide secreted from endocrine cells in the upper small intestine, and motilin receptors are found throughout the gastrointestinal tract (18). Exogenous motilin substantially accelerate gastric emptying in healthy individuals and patients with gastroparesis (19). Furthermore, macrolide antibiotics such as erythromycin exert pro-motility effects via stimulation of motilin receptors (19).

Camicinal is a first-in-class non-macrolide motilin receptor agonist. Camicinal was designed to enhance the specificity for the recombinant human motilin receptor and avoid the adverse effects associated with the use of macrolide antibiotics. In a single center study of 23 critically ill patients with established feed intolerance, a single 50 mg dose of camicinal (n=15) when compared to placebo (n=8), appeared to accelerate gastric emptying, quantified using an isotope breath test and increased carbohydrate absorption (20).

The objective of the NUTRIATE study was to determine whether, in a cohort of patients with risk factors predisposing them to feed-intolerance, the pre-emptive administration of repeated doses of camicinal improves the provision of enteral nutrient, quantified as the average percentage of goal volume delivered. Secondary outcomes included: (i) the effect of camicinal on the provision of enteral nutrient when quantified as the time to delivery of 80% of prescribed calories; (ii) the effect of camicinal on prevention of feed intolerance, quantified as time to development of two consecutive gastric residual volumes (GRVs) $\geq$ 250ml; (iii) the effect of camicinal on gastric emptying, assessed via absorption of acetaminophen and 3-O-methylglucose (3-OMG); and (iv) the safety and tolerability of camicinal.

METHODS

This was a multi-center, parallel group, placebo-controlled, blinded, randomized controlled trial conducted in 12 centers in Australia, Canada and the United States. The study was designed and supervised by a steering committee, coordinated by the Clinical Evaluation Research Unit (Queen's University, Kingston, Canada), and was sponsored by GSK (GSK protocol 113445). Data were collected by sites using specific Case Report Forms, which were collated by the sponsor. Site monitoring was performed by the sponsor. Both the Clinical Evaluation Research Unit and sponsor had full access to the database to verify and analyse the results. The protocol was approved by the relevant local institutional review boards and ethics committees and was registered with ClinicalTrials.gov (NCT01934192). Written informed consent was obtained from a surrogate decision maker for each patient in accordance with local laws and regulations before any study specific procedures were performed.

Patients

Patients were eligible for inclusion if they were admitted to a participating intensive care unit (ICU) within the previous 48 hours, were invasively mechanically ventilated, were receiving enteral nutrition or this was just about to commence, and were between the ages of 18 and 85 years. In addition, to identify those predisposed to feed-intolerance, eligible patients had to have at least one of: (i) clinical evidence of cardiovascular dysfunction, defined as the need for continuous vasopressor agents (e.g. any dose of norepinephrine, epinephrine or vasopressin, > 5 µg/kg/min dopamine, or > 50 µg/min phenylephrine) for ≥ 2 hours; (ii) be admitted because of trauma with multiple injuries and an injury severity score ≥ 15 points; (iii) be admitted because of acute traumatic or non-traumatic brain injury with a Glasgow Coma Scale score ≤ 12 prior to the initiation of sedation; or (iv) be the recipient of moderate to high doses of opioid, defined as continuous opioid infusion ≥ 2 mg/hr morphine (or equivalent) and expected to continue on the infusion at any dose for at least another day (6, 7). Major exclusion criteria included established feed intolerance, those patients not expected to be alive and in the ICU for at least 48 hours, QT corrected >480 ms, acute hepatitis or chronic liver disease and those who has received a pro-motility drug in the previous 12 hours. Detailed exclusion criteria are provided as Text S1 in Supplementary Materials.

Following consent, patients were randomized via centralized web-based randomization in a 1:1 ratio within permuted blocks of eight. Patients were stratified by country (Australia, Canada and USA). Randomization was based on an undisclosed computer generated list created, maintained and implemented by the Clinical Evaluation Research Unit. This system notified the local pharmacist of the treatment allocated but maintained blinding for everyone else.

Study drug

The study drug, camicalin (50 mg diluted in 10ml 5% dextrose or saline (5 mg/ml)) or placebo (10 ml 5% dextrose or saline), was prepared at each site by the unblinded pharmacist. All other study and clinical personnel were blinded, as study drug and placebo were identical in appearance. Study drug was administered via gastric feeding tube (i.e. enteral) followed by a 20 ml 'flush' of water once a day for a maximum of 7 days.

Protocol

All patients had a gastric tube (14 French or larger) with the distal tip 10 cm below the gastro-esophageal junction, or clearly visualized in the stomach on plain abdominal radiograph. If the location of the feeding tube was uncertain at any point during the study period the tip of the tube was reconfirmed by x-ray (21). Individual patient nutritional requirements were determined or calculated as per standard practice for each site. A standardized feeding protocol was used to determine the initial rate and adjustment of nutrient infusion based on gastric residual volumes conducted 6-hourly (Figure 1) and the recommended formula was Jevity Promote (1 kcal/ml, 5.6 g protein and 1.7 g fibre per 100 ml) or equivalent. Following baseline assessment of gastric emptying rate, the study drug was administered. All interventions other than the study drug, such as the feeding protocol and the use of concomitant drugs, were left to the discretion of the treating physician. Other pro-motility agents were disallowed during the study period. Withdrawal and stopping criteria were predefined and included established feed-intolerance (two consecutive GRV measurements ≥ 250 ml), transition to small bowel feeding, enteral nutrition discontinued, initiation of renal replacement therapy or estimated glomerular filtration rate < 20 ml/min, impaired liver chemistry, or QT prolongation. Patients who were extubated but continued tube enteral nutrition remained eligible to continue study medication.

Outcome measures

Gastric emptying, glucose absorption and test meal

At baseline (i.e. before study drug was administered) and 90 minutes after the second dose of study drug was administered, assessments of gastric emptying and glucose absorption were performed. Gastric emptying was measured with patients in the supine position and the head of the bed elevated to 30° . Ninety minutes prior to measurement of gastric emptying the gastric tube was aspirated and the gastric residual volume recorded and discarded. Administration of enteral nutrition then continued at the previous rate. At T=0 minutes enteral nutrient was stopped and the test meal administered over 5 minutes (22). The test meal comprised 100 ml of the patient's liquid nutrient, labelled with 2 g 3 -OMG (Sigma-Aldrich, Castle

Hill, NSW, Australia) and 500 mg acetaminophen (Children's Panadol; GSK). Blood was sampled at T=15, 30, 45, 60, 120 and 240 minutes. Enteral nutrition was recommenced at the previous rate at T=120 minutes.

Blood samples

Blood samples were collected in chilled ethylenediaminetetraacetic acid (EDTA) tubes and separated within 30 minutes of collection for assessment of camical and acetaminophen concentrations. Blood was also collected into serum tubes for subsequent measurement of 3-OMG concentrations which is a previously validated technique in the critically ill to quantify glucose absorption (23, 24). Both serum and plasma were separated by centrifugation (3200 rpm for 15 minutes at 4°C). Samples were then stored at -70°C and were analyzed in batches for acetaminophen, camical and 3-OMG samples using respective validated analytical methods that were based on protein precipitation, followed by high performance liquid chromatography-mass spectrometry analyses. The lower and higher limits of quantification were: 3-OMG 1 µg/ml and 1000 µg/ml; acetaminophen 25 ng/ml and 5000 ng/ml; and camical 1 ng/ml and 1000 ng/ml. Quality control was determined using comparison against calibration standards and re-analysis to establish reproducibility.

Provision of enteral nutrient

The primary outcome was the daily adequacy of enteral feed delivered, as assessed by average percentage goal volume (delivered/prescribed * 100), prior to the development of intolerance (25), from the first study dose until permanent discontinuation of enteral nutrition - due to discharge, or removal of enteral feeding tube - or the development of enteral feed intolerance, defined as two consecutive gastric residual volumes (GRVs ≥ 250 ml) (26), or censored on the last dosing day if the participant did not develop intolerance. A study day was a day on which the participant received study drug and there was available nutritional data (including no nutrition), with the first day being a partial day from dose administration to midnight. If the participant died or was discharged on a day that they were dosed this was counted as a study day. The secondary outcomes included the effect of the intervention on delivered calorie and protein relative to what was prescribed, the proportion of patients who received ≥ 80% goal calories on at least one day, the time to delivery of 80% of prescribed calories (i.e. number of days from first dose of study drug to the first day on which the subject received ≥ 80% goal calories) and incidence of feed-intolerance (25).

Clinical outcomes

Duration of ICU and hospital admission and all-cause mortality were recorded, with all variables censored at the time of study completion/withdrawal, or at 90 days after randomization. Duration of ICU and

hospital admissions were only calculated for participants who were alive when data were censored. Ventilator free days were calculated as the number of days within 28 days from randomization that the participant was alive and mechanical ventilator was permanently discontinued.

Statistical analysis

Data are presented as frequencies and proportions for categorical variables and mean (standard deviation or 95% confidence intervals as appropriate) for continuous variables. The primary outcome, daily adequacy of enteral feed delivered as assessed by average percentage goal volume delivered prior to intolerance, was compared based on a modified intention to treat analysis (i.e. randomized and received at least one dose of study drug) and using an ANCOVA model, fitting treatment as the main effect and number of days used to calculate the average as the covariate. Paracetamol and 3-OMG pharmacokinetic parameters were log-transformed and then compared with an ANCOVA model fitting treatment as the main effect and baseline values as the covariant. The time to delivery time of 80% of prescribed calories and time to develop feed-intolerance are presented as Kaplan-Meier curves. Imputation for missing data was not performed. A two-sided p-value < 0.05 was considered statistically significant. All analyses were conducted using SAS V9.4.

Sample size

The proposed sample size was 150 patients. This would provide 90% power (5% alpha) based on the assumption that the observed mean (standard deviation) average percentage of goal volume for placebo is 60% (27) and between patient standard deviation of 28% (28), with an absolute increase in percentage goal volume of 15% representing a clinically meaningful difference.

Interim Analysis

According to the protocol and pre-specified interim analysis charter, a futility analysis was conducted after approximately 70 patients were randomized. The analysis evaluated the predictive probability of the trial demonstrating the pre-defined clinically meaningful treatment difference of 15% if recruitment continued to reach 150 participants. Given the observed difference between groups at the interim analysis, i.e. if true population difference was $\leq 9\%$, the probability of observing a difference at 150 participants was very low (<0.01%). Furthermore, if the true population was that which was predefined as clinically meaningful (15%), there was only an 11% chance of observing a difference of this magnitude at 150 participants. Because it

was unlikely that even if all 150 participants were enrolled the primary null hypothesis would be rejected, the sponsor terminated the study because of futility.

Results

Eighty-four patients were enrolled (n=44 and n = 40 respectively randomized to camical and placebo) but two participants in each group reached predefined stopping criteria of feed-intolerance (i.e. 2 GRVs $\geq$ 250 ml) post randomization and prior to receiving the first dose of drug dosing (Figure 2). Baseline demographic data and nutrition prescription did not appear to be grossly imbalanced across treatment groups (Table 1). The mean number of doses of study drug administered prior to development of intolerance (camical: 4.1 (2.3) vs. placebo: 4.3 (2.3) doses) and the number of patients who received seven doses of study drug (camical: 29% vs. placebo: 29%) were similar between groups.

Provision of enteral nutrition

The raw daily average percentage goal volume delivered via the enteral route was not statistically significantly different between the two groups (camical: 77% (95% CI 71, 83) vs. placebo: 68% (95% CI 58, 78); mean difference 9% (95% CI -5, 23); $P=0.21$). Likewise, there were no significant differences in the adjusted means of daily % goal volume (Figure 3), percentage goal calories (camical: 76% (95% CI 65, 88) vs. placebo: 68% (95% CI 60, 77); mean difference 9% (95% CI -5, 23), and protein (camical: 76% (95% CI 66, 86) vs. placebo: 70% (95% CI 61, 80); mean difference: 7% (95% CI -7, 20)) administered.

In both groups, over two thirds of the patients received $\geq$ 80% of prescribed calories (camical: 67% vs. placebo: 74%) and the time to delivery of 80% of prescribed calories was similar between groups (Figure 4A). The incidence of feed-intolerance (camical: 15% vs. placebo: 14%) and the time to develop feed-intolerance were also similar (Figure 4B).

Gastric emptying and glucose absorption (Acetaminophen and 3-O-Methylglucose concentrations)

Gastric emptying and glucose absorption (acetaminophen and 3-O-Methylglucose concentrations) were similar between groups (Tables 2, 3).

Plasma camical concentrations

Twenty-five patients who received camical provided pharmacokinetic data on day 2 (Supplementary Figure S1). Camical plasma concentrations observed were within the anticipated range based on previous study data and modeling and simulation for a 50 mg dose administered orally, suggesting the drug was absorbed.

Safety and adverse events

Serious adverse events were reported for four camical treated participants: acute respiratory distress syndrome (n = 2), pulmonary haemorrhage (n = 1) and blood stream infection (n = 1). A Serious adverse event was reported for one participant treated with placebo who developed intestinal ischemia. None of these events were considered by the investigators related to study treatment. Non-serious adverse events were reported in 33% of participants receiving camical and 26% receiving placebo (Supplementary Text S2). None of the adverse events led to treatment discontinuation. Within the limitations of this relatively small study no clear differences in the incidence of adverse events between treatment groups was apparent.

Clinical outcomes

Clinical outcomes were similar in both groups (Supplementary Table S1).

DISCUSSION

The primary finding is that in critically ill patients at risk of feed intolerance, the administration of enteral camicinal did not augment by at least 15% the average percentage of goal volume of enteral nutrition delivered. Secondary observations are that camicinal did not significantly increase or decrease the percentage goal delivery of calories or protein, time to deliver $\geq 80\%$ of calories or time to feed intolerance, rate of gastric emptying – when measured using either plasma 3-OMG or acetaminophen – or glucose absorption. Finally, there were no investigator-reported drug-related serious adverse events with camicinal (50 mg, once daily for a maximum of 7 days).

In a relatively small cohort of critically ill patients with established feed intolerance it was previously observed that a single dose of camicinal accelerated gastric emptying and increased glucose absorption (17). However, in the current study, the pre-emptive administration of camicinal did not significantly increase the provision of nutrient or accelerate gastric emptying. There are plausible mechanisms to explain the absence of a detectable difference observed in the current study. The most likely explanation is that the current study enrolled patients at *risk* of feed intolerance, whereas the previous study enrolled patients with established feed intolerance. In health, ambulatory patients with gastroparesis, and in the critically ill, erythromycin accelerates gastric emptying, via stronger and more frequent antral contractions, a reduction in the frequency of pyloric pressure waves and pyloric tone (8, 12, 19, 29). However, at least in the critically ill, the effect of erythromycin to accelerate gastric emptying is most pronounced when the baseline gastric emptying rate is slow (30), and in the previous single center study a dose of 75 mg of camicinal did not appear to accelerate gastric emptying in a cohort of critically ill patients who had a relatively normal rate of emptying at baseline (20). Accordingly, an effect of camicinal may have been apparent if the patient cohort had slower gastric emptying at baseline.

The inclusion criteria of the current study were expected to identify a cohort that were predisposed to slow gastric emptying and so would be difficult to feed. However nutritional intake was greater and the incidence of enteral feeding intolerance much lower in the placebo group than anticipated. The better than anticipated provision of enteral nutrition to those receiving placebo may be that the ICUs participating in this study prioritized nutritional therapy and/or the use of standardized feeding protocols (31, 32). It is also possible that the inclusion criteria, may have failed to identify patients predisposed to delayed gastric emptying. These criteria were based on observational data and expert opinion. Moreover, recent changes in processes of care - such as reduction in sedation, limiting excessive fluid administration and blood glucose control - may have reduced the incidence of feed intolerance in this sample (19).

There were a number of methodological features that provide confidence that the results obtained in this cohort reflect population data. Consecutively admitted patients were screened and web-based randomization ensured allocation concealment to limit selection bias. Furthermore, the use of both

physiological endpoints and clinical endpoints, such as percentage delivery/prescribed and feed intolerance, and actual indirect measurement of gastric emptying, such as 3-OMG and acetaminophen, along with camical PK data – is reassuring that a large effect of camical was not missed. Finally, the current study was performed at a large number of centers in three countries, ensuring external validity to patients admitted to ICUs in academic hospitals in developed countries.

There were, however, limitations. Despite the inclusion criteria to identify those at risk of delayed gastric emptying and feed intolerance, relatively few patients in either cohort developed feed intolerance. The study was ceased after interim analysis because the likelihood of showing a statistical difference between groups for the primary outcome was low. While the current study is informative, in that the administration of camical as a pre-emptive agent to a cohort that is already receiving close to 70% of nutritional adequacy may reduce daily average percentage goal volume delivery by up to 5% or augment delivery up to 23%, it may be that camical is more useful for treating patients with established feed-intolerance. **The development of enteral feed intolerance was defined as two consecutive gastric residual volumes (GRVs $\geq$ 250 ml) and the results may have differed if a larger volume (e.g. 500 ml) was selected as the threshold.** It should also be noted that while clinical outcomes were reported, the study was not powered to determine differences in these. **The majority of the study cohort were admitted due to medical issues, and these data may not reflect outcomes in patients admitted following surgery.** Lastly this was a relatively heterogeneous cohort and other interventions that affect gastric motility, e.g. such as opiates, were not protocolized.

In summary, in a cohort of critically ill patients who were receiving approximately 70% of nutritional adequacy, the pre-emptive administration of enteral camical did not augment, or reduce, the percentage goal volume of enteral nutrient received by 15% or greater.

SUPPLEMENTARY MATERIAL

Supplemental materials (Text S1-S2, Figure S1, Table S1) are available online at <http://pen.sagepub.com>

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FIGURE LEGENDS

Figure 1. Protocol for administration of enteral nutrition

GRV – gastric residual volume

Figure 2. Randomization and follow-up of study participants

*patients may have > 1 exclusion criteria recorded

§reasons not approached for consent included surrogate decision maker not contactable in timely fashion or patient was no longer eligible by the time that a physician was able to discuss participation with the surrogate decision maker.

Figure 3. Daily percentage of goal nutrition delivered according to study drug

Figure 4A. Time to deliver $\geq$ 80% goal calories

If a subject did not reach delivery of 80% prescribed calories, they were censored at the last day on which they received study drug.

Figure 4B. Time to develop feed intolerance

If a subject did not develop intolerance, they were censored at the time of the last available GRV measurement. Note: Two subjects in the camicinal group and one subject in the placebo group had their last available GRV assessment done prior to first dose and are therefore excluded from this summary

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