The effect of protein composition in liquid meals on gastric emptying rate in children with cerebral palsy

Anne C. Brun a,⁎, Ketil Størdal b, Groa B. Johannesdottir c, Beint S. Bentsen d, Asle W. Medhus d

a Paediatric Department, Vestfold Hospital, N-3103 Tønsberg, Norway
bOslo Hospital Trust, Fredrikstad, Norway
b Akureyri Hospital, Iceland
d Oslo University Hospital, Ullevål, Norway

Summary

Background & aim: Dysmotility, nausea and vomiting are common among children with cerebral palsy. This study aimed to evaluate influence of protein composition on rate of gastric emptying and study the relation between gastric emptying and postprandial gastrointestinal symptoms.

Methods: 15 children with cerebral palsy, using gastrostomy, received four liquid test meals on separate days in random order. The meals contained a standard carbohydrate and fat base plus one of four protein modules (100% casein (A), hydrolysed whey (B), amino acids (C) and 40% casein/60% whey (D)) with a total energy of 1 kcal/ml. The 13C octanoic acid breath test was applied to assess gastric emptying.

Results: When comparing half emptying time (T½) of the fast emptying meals (meal B, C and D) with the slowest emptying meal (meal A), more rapid emptying was demonstrated for meal D (p < 0.001). For meal D, emptying was significantly faster in children with postprandial symptoms than in those without (p < 0.01).

Conclusion: In children with cerebral palsy using gastrostomy, gastric emptying is influenced by type of protein in the meal. The present results also suggest that there is a relation between rapid gastric emptying and postprandial gastrointestinal symptoms.

ClinicalTrials.gov: U1001K28200706.

© 2011 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

1. Introduction

The prevalence of cerebral palsy (CP) in Norway is 2.1/1000 live births. This is similar to other populations in Europe. Children most at risk for feeding problems are those with severe total body involvement of CP (spastic quadriplegic and dystonic type), and account for one third of all cases of CP in developed countries. They involve one third of all cases of CP in developed countries and are disabilities, and may be related to dysphagia, vomiting, symptoms of pulmonary aspiration, gastroesophageal reflux and constipation. Moreover, children with disorders of the central nervous system and GI symptoms may have delayed gastric emptying (GE) and symptoms possibly related to gastric dysmotility.

Gastrostomy tube feeding is increasingly used for nutritional support in children with neurodevelopmental disabilities and is associated with improved height and weight in the most disabled patients with CP. Persisting feeding difficulties among disabled children with gastrostomy is, however, a common and well known problem in paediatric medicine. The relevance of dysmotility for GI symptoms and need for nutritional support in these patients is at present unclear. However, changes in formula composition of the enteral feed administered through the gastrostomy may, according to clinical observations, result in relief of GI symptoms. This might be related to an altered rate of GE, since meal volume, fat content, caloric content, and meal viscosity all may influence GE. At present, there are no available studies addressing the influence on rate of GE by changing only the protein composition of a meal. If an influence on rate of GE by protein composition in meals and a relation to postprandial symptoms can be demonstrated, then
meal composition could have consequences for nutritional status. The aim of the present study was thus to examine the influence of protein composition in liquid meals on rate of GE in children with CP and gastrostomy. In addition, the relation between GE and postprandial GI symptoms was studied.

2. Materials and methods

2.1. Patients

Fifteen children with CP (7 girls), using gastrostomy as their main route of feeding, were examined. Mean age was 10.7 years (range 4–15 years) (Table 1). Five of the children had undergone a Nissen fundoplication (NF). The children were selected from four different hospitals in the southern part of Norway (Oslo University Hospital, Ullevål, Akershus University Hospital, Ostfold Hospital Trust, Fredrikstad, and Hospital Innlandet, Elverum). Children with CP with age below 16 years and gastrostomy for at least one year (range 4–15 years) (Table 1). Five of the children had undergone a Nissen fundoplication (NF). The children were selected from four different hospitals in the southern part of Norway (Oslo University Hospital, Ullevål, Akershus University Hospital, Ostfold Hospital Trust, Fredrikstad, and Hospital Innlandet, Elverum). Children with CP with age below 16 years and gastrostomy for at least one year were identified in the patient registers. The diagnosis of CP was verified by review of the medical record of the patient. Patients with information in the records indicating problems with breath test sampling (confer below), known or suspected immunological reactions against dietary proteins, in need for continuous treatment with prokinetic medication or use of valproic acid (interferes with reactions against dietary proteins, in need for continuous treatment with prokinetic medication or use of valproic acid (interferes with) were not eligible for inclusion. Families of eligible patients were contacted by telephone for information and asked to participate in the study. If willing to participate, the parents/legal guardian received written information by mail and informed consent was signed before inclusion in the study.

2.2. Test meals

In all patients, four different meal formulas were used. The main criterion for the selection of proteins was that formulas with fast or slow proteins should be applied and the selected formulas should be commercially available. The meal formulas were made up of a standardised carbohydrate and fat base (Energivit (SHS), Liverpool, United Kingdom), which was added one of four protein sources (confer below) resulting in a meal formula containing a total energy of 1 kcal/ml with protein equivalent 2.8 g/100 ml, carbohydrate 12.0 g/100 ml and fat 4.5 g/100 ml. The protein sources were (A) 100% casein, (B) hydrolysed whey, (C) amino acids and (D) 40% casein/60% whey. The protein fractions were packed by a pharmacist and were blinded for the investigator and patients.13C octanoic acid was added to the meal formula prior to administration.

2.3. Gastric emptying (GE) – 13C breath test

The test meals were labelled with 91 mg 13C octanoic acid (EUROISO-TOP, Saint-Aubin, Cedex, France) as marker to measure GE. The fraction of 13CO2 content in exhaled CO2 was determined by gas chromatographic purification isotope ratio mass spectrometry (Analytical Precision, Cheshire, UK). This technique is based on that GE is the rate-limiting step for the appearance of 13C in exhaled CO2.13 Three variables of GE were calculated; the half-time of GE (T1/2), the GE coefficient (GEC) and time until maximum excretion of 13C (Tmax).14

2.4. Experimental protocol

All patients were studied in the morning after an overnight fast on four consecutive days. The tests were performed at the outpatient/daycare ward, with a parent, legal guardian or other adult caretaker present.

Prior to administration of the first test meal, age, sex, height, weight, current feeding regimen and medications were recorded. Furthermore, history of symptoms of gastroesophageal reflux disease (GERD), constipation and other GI symptoms were obtained and a history of previous abdominal surgery was recorded. The frequency of general GI symptoms were assessed by using a standardised questionnaire.

Meals were administered with a feeding pump, randomised and double blinded, and administered at a rate of 600 ml/h for 20 min (total 200 ml). Prior to meal administration, a baseline breath sample was collected. Thereafter, breath samples were collected at 5 min intervals during the first 30 min after start of meal administration followed by sampling at 15 min intervals for 4 h. Most of the children had difficulties with breath sampling due to their handicap. In most cases samples had to be collected through a face mask into a breath sampling bag (Quintron, Milwaukee, WI 53215, USA). The sampling bag had a valve to avoid leaks.

After receiving the test meal, the children were allowed to perform their usual physical activity. No other meals were allowed during the test period with breath sampling. The children received their ordinary meal formulas in the periods between the test meals.

GI symptoms occurring in the test period (4.5 h after meal administration) were recorded by the physician conducting the study (ACB).

2.5. Statistics

Summary data are given as median with 25 and 75 percentiles in brackets, unless otherwise stated. Wilcoxon test, Mann Whitney test, Fisher exact test, and Friedman test were applied. Level of statistical significance was set at 5%.

The sample size was calculated using a standard deviation of 18.6 min of T1/2 based on data from preterm infants15 and adult volunteers.16 With a significance level of 0.05 (α), power of 80% (β) and 15 min regarded as clinically important differences in T1/2, at least 12 patients should be included.

2.6. Ethics

Written, informed consents were obtained from the parents of all patients.

The protocol was approved by the Regional Medical Ethics Committee and the Local data protection supervisor. The methods used are well known and do not imply risk or discomfort for the children.

3. Results

3.1. Rate of gastric emptying (GE) and protein source

The rate of GE differed significantly between the four meals for all GE variables (Table 1). When comparing T1/2 of the fast emptying

<table>
<thead>
<tr>
<th>Variables of gastric emptying in relation to type of meal.</th>
<th>Meal A</th>
<th>Meal B</th>
<th>Meal C</th>
<th>Meal D</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (min)</td>
<td>153.9</td>
<td>82.0</td>
<td>74.4</td>
<td>63.3</td>
<td>0.02</td>
</tr>
<tr>
<td>(76.4–230.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying coefficient (1.8–2.1)</td>
<td>1.9</td>
<td>2.4</td>
<td>2.5</td>
<td>2.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>135</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>0.04</td>
</tr>
<tr>
<td>(30–195)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are median with 25 and 75 percentiles in brackets. *Friedman test.
meals (meal B, C and D) with the slowest emptying meal (meal A), meal D emptied significantly faster than meal A. (Figs. 1 and 2).

3.2. GI symptoms

Seven children reported daily/weekly GI symptoms and eight rarely/never. Four out of the seven children with daily/weekly symptoms experienced symptoms during one or more of the test meals (nausea (n = 4), diarrhoea (n = 1), sweating (n = 2), retching (n = 1)). Two other children experienced nausea during the test meals despite having recorded rarely to have GI symptoms. In total, six (40%) of the 15 children reported postprandial symptoms.

Four children reported symptoms after administration of meal A, one after meal B, two after meal C, and three after meal D (Table 2).

3.3. Postprandial GI symptoms and rate of gastric emptying (GE)

When dividing the children into one group with postprandial GI symptoms and one without symptoms, $T_{1/2}$ was 16 min in subjects with and 75 min in subjects without postprandial symptoms following administration of meal D ($p < 0.01$, Fig. 3). For the other meals, no difference in rate of emptying between children with or without symptoms was found.

4. Discussion

The present study shows that protein composition in meal formulas influences rate of GE. In our study, a meal with 40% casein and 60% whey emptied significantly faster than a meal with 100% casein, and meals with hydrolysed whey and amino acids showed the same tendency towards more rapid emptying. Furthermore, a relation between rapid GE and postprandial GI symptoms was demonstrated.

There are few available studies on the influence of protein composition in meals on rate of GE. Fried et al. compared three different types of whey-based formulas with a casein-predominant formula in gastrostomy-fed children with CP. They reported that whey-based formulas reduced the number of episodes of vomiting by improving the rate of GE, which could be beneficial for the nutritional status and decrease the risk of aspiration pneumonia.17 Furthermore, Billeaud and colleagues reported that protein concentration and composition influenced GE, with breast milk and whey predominant formulas emptying faster than follow up formula and regular cows milk.18 Interestingly, breast milk contains a similar protein mixture (40% casein/60% whey) as the fastest emptying meal in the present study.19 These previous findings hence correspond with the present results. In contrast to the present study design, the previous studies did not control for other

![Fig. 1. Gastric emptying time for all four meals. Gastric emptying after intake of the four different meals (A, B, C and D) estimated by time until emptying of 50% of the meal ($T_{1/2}$). Each column represents one meal. $T_{1/2}$ of the fast emptying meals B, C and D is compared with the slowest emptying meal A, demonstrating a significantly faster emptying of meal D (40% casein & 60% whey) compared with meal A (100% casein) ($p < 0.001$).](image1)

![Fig. 2. Gastric emptying time for meal with 100% casein and 40% casein & 60% whey. Comparing gastric emptying after intake of 100% casein (meal A) and 40% casein & 60% whey (meal D) estimated by time until emptying of 50% of the meal ($T_{1/2}$). Each line represents one patient, demonstrating a significantly faster emptying of meal D compared with meal A ($p < 0.001$).](image2)

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>General GI symptoms</th>
<th>Postprandial symptoms (study days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>9</td>
<td>23</td>
<td>120</td>
<td>daily</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>12</td>
<td>22</td>
<td>130</td>
<td>weekly</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>4</td>
<td>15</td>
<td>99</td>
<td>never</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>12</td>
<td>28</td>
<td>143</td>
<td>rarely</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>11</td>
<td>29</td>
<td>131</td>
<td>rarely</td>
<td>nausea (C + D)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>13</td>
<td>22</td>
<td>132</td>
<td>rarely</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>15</td>
<td>27</td>
<td>131</td>
<td>daily</td>
<td>nausea (B), diarrhoea (D)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>15</td>
<td>30</td>
<td>150</td>
<td>weekly</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>10</td>
<td>31</td>
<td>127</td>
<td>never</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>9</td>
<td>21</td>
<td>120</td>
<td>never</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>11</td>
<td>29</td>
<td>126</td>
<td>daily</td>
<td>unwell, sweat (A)</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>6</td>
<td>15</td>
<td>101</td>
<td>daily</td>
<td>nausea (A)</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>13</td>
<td>20</td>
<td>138</td>
<td>rarely</td>
<td>unwell (A)</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>14</td>
<td>20</td>
<td>120</td>
<td>rarely</td>
<td>none</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>6</td>
<td>14</td>
<td>114</td>
<td>daily</td>
<td>nausea, sweat (A, D, C)</td>
</tr>
</tbody>
</table>

Letters in brackets refer to type of meal administered.

Table 2

Patient demographics and symptoms.

Children with neurodevelopmental disabilities like CP frequently have associated GI-problems including foregut dysmotility. It is possible that children with CP are more sensitive to type of protein in the meal than healthy children, thereby providing a possible explanation for the differing results. Furthermore, in the study by Thorkelsson et al., the infants did not serve as their own controls. According to the present results, the rate of GE shows a high degree of inter-individual variation, and a study design comparing two different groups of limited size might increase the risk for a statistical type II-error.

In two of the children included in the present study, there was a large difference in emptying rate when comparing the fastest with the slowest emptying meal (Fig. 2). It might hence be questioned whether the demonstrated difference in GE may rely too much on these two subjects. However, as a non-parametric test was applied, the outliers were only given a rank, and the magnitude of the difference did not influence the analysis. Furthermore, of the 15 children studied, only one subject had faster GE after administration of the meal with 100% casein.

Following administration of the fastest emptying meal with 40% casein/60% whey, the three children reporting postprandial symptoms exhibited a particularly rapid rate of emptying. Certainly, we cannot at present base patient treatment on this finding alone, but these results suggest that rapid emptying is well tolerated until a certain limit is exceeded. Tests of GE can hence be useful when a relation between symptoms and emptying is considered and in the search for the most optimal meal for each specific patient.

Scintigraphy is the gold standard for evaluation of GE. In children, this method is often avoided, since a radioactive isotope is applied and the study objects have to sit in front of a gamma camera for prolonged periods. GE breath tests with the use of octanoic acid labelled with the stable isotope $^{13}$C have in recent years been validated against scintiscans in adults as well as in infants. The method is easy to perform, involves no pain or risk for the patient and has a high reproducibility at least in the individual patient.

The main aim of the present study was to examine GE of liquid meal formulas with different proteins and relate this to GI symptoms. Children with CP were chosen because they are well known to have feeding difficulties and upper GI symptoms, and many have a gastrostomy, which allows standardised meal administration. Furthermore, children with CP are at risk of malnutrition and could benefit from data demonstrating differences in rate of GE and frequency of symptoms related to type of meal administered.

Children with CP and nutritional problems might require a Nissen fundoplication (NF) due to symptoms of GORD. Five of the present children had undergone a NF, a procedure that might accelerate GE. Three of these five children had a pattern of rapid GE after administration of meal D and also had symptoms of dumping. The five children with NF were not excluded, as patients served as their own controls. It would have been of interest to further study GE and symptoms in this subgroup of patients, but this was beyond the scope of the present study and the limited number of patients with NF does not allow sub-analyses to be performed.

The present data demonstrate that rate of GE varies considerably between subjects. It is also known that the day to day variation in GE within subjects may be large. It would therefore have been optimal if each child had been tested and retested several days in a row with every meal. This design was not chosen, as it would have been too time-consuming since each meal test required the presence of the child and parent for a day. The present design with each child being its own control avoids the influence of inter-subject
variability, and the present findings suggest that the possible con-
ounding influence of intra-individual variability has been limited.
In conclusion, the present study demonstrates that the rate of GE is influenced by the protein composition of a liquid meal, and that there might be a relation between rapid gastric emptying and postprandial symptoms. This suggests that some children might not tolerate a meal formula which is emptied at a high rate. On the other hand, a rapid emptying formula could be beneficial in children who have delayed GE. Thus, when children with CP have nutritional problems including postprandial GI symptoms, a test of GE may be helpful to reveal whether a change in type of meal administered should be considered.

Conflict of interests
Anne Charlotte Brun has been an invited speaker at three paediatric meetings arranged by Nutricia.

Acknowledgements

Funding: This project has been financially supported by the Norwegian Extra Foundation for Health and Rehabilitation through EXTRA funds. The study has also been supported by ESPEN Nutricia Research Fellowship Award 2005.

Funding made it possible for the corresponding author to carry out the present study and write the manuscript. The study sponsors had no involvement in study design, collection of data, analysis of data or writing of manuscript.

The authors wish to thank pharmacist Kjersti Helland at the Hospital Pharmacy, Oslo University Hospital, Ullevål, for performing randomisation and preparing the liquid meals. Furthermore, the authors wish to thank Jarle Rugvist and Vibeke Fossum at the Paediatric Department, Oslo University Hospital, Ullevål, for their contribution in collecting breath samples and Anne-May Schjønneberg and Grethe Keirung at the Department of Gastroenterology, Oslo University Hospital, Ullevål, for performing the 13C breath test analyses.

Statement of authorship: ACB carried out the study, data analyses and drafted the manuscript. KS, GBJ and BSB participated in the study design, applied for funding and ethical approval and wrote the study protocol. AWM carried out data analyses, performed statistical analyses and helped to draft the manuscript. All authors have given their final approval of the version to be submitted.

References
