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Effects of lipase inhibition on gastric emptying and alcohol absorption in healthy subjects

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The rate of alcohol absorption is dependent on gastric emptying (GE). As the slowing of GE by fat is dependent on lipolysis, orlistat may increase the rise in blood alcohol when alcohol is consumed with, or after, fat. The aim of the study was to evaluate the effects of orlistat on GE and blood alcohol after an alcohol-containing drink following a fat 'preload', in healthy subjects. Ten healthy males consumed 120 ml cream with or without 120 mg orlistat, 30 min before an alcohol-containing drink labelled with 20 MBq [^{99m}Tc]sulfur colloid on 2 d. GE, plasma alcohol and blood glucose were measured. GE was slightly faster with orlistat ($P<0{\cdot}05$) compared with control. Plasma alcohol at 15 min was slightly higher with orlistat (0·034 (SEM 0·006) g/100 ml) *v.* control (0·029 (SEM 0·005) g/100 ml) ($P<0{\cdot}05$), but there was no effect on the area under the curve 0–240 min. The increase in blood glucose was greater with orlistat, for example, at 15 min (1·07 (SEM 0·2) mmol/l) *v.* control (0·75 (SEM 0·2) mmol/l) ($P=0{\cdot}05$). The rise in blood glucose and plasma alcohol were related (for example, at 15 min r 0·49; $P=0{\cdot}03$). In conclusion, lipase inhibition accelerates GE of an alcohol-containing drink following a fat 'preload' with a minor increase in the initial rise in plasma alcohol.

Gastric emptying: Orlistat: Plasma alcohol: Blood glucose

The rate of gastric emptying is regulated primarily by feedback inhibition generated by the interaction of nutrients with the small intestine (Hunt *et al.* 1985; Lin *et al.* 1989; Borovicka *et al.* 2000; Rayner *et al.* 2001); the magnitude of this feedback is dependent on the length of small intestine exposed (Lin *et al.* 1989). Of the three macronutrients, fat is the most potent in slowing gastric emptying, primarily because of its higher energy density, and potentially also because its absorption rate is relatively slower (Lin *et al.* 1996). Accordingly, consumption of fat before, or with, a meal slows gastric emptying (Cunningham & Read, 1989; Stacher *et al.* 1990, 1991; Davidson *et al.* 1999), and delays the absorption of orally administered nutrients (Welch *et al.* 1987; Cunningham & Read, 1989; Hebbard *et al.* 1995). For example, when lipid is infused directly into the small intestine before the consumption of, or incorporated into, a carbohydrate-containing (potato) meal, the glycaemic response to that meal is substantially less (Welch *et al.* 1987; Cunningham & Read, 1989). Fat appears to be most potent in slowing gastric emptying when given before, rather than with, a meal (Cunningham & Read, 1989). This is to be expected; it takes some time for small-intestinal feedback mechanisms induced by fat to become established (Feinle *et al.* 2003), and administration of fat before a meal ensures that it would empty preferentially and be partially digested in the small intestine before the meal is consumed.

Like most drugs, alcohol is absorbed predominantly from the small intestine; hence, pharmacological (Nimmo, 1976; Johnson *et al.* 1991) or dietary (Horowitz *et al.* 1989; Hebbard *et al.* 1995) factors that modify gastric emptying may affect the rate of alcohol absorption (Holt, 1981). In particular, interventions that slow gastric emptying have the potential to minimise the rise in blood alcohol concentrations, mainly by decreasing the access of alcohol to the small-intestinal mucosa and, possibly, by increasing 'first-pass' alcohol metabolism by the liver and, possibly, the stomach (DiPadova *et al.* 1987; Caballeria *et al.* 1989; Frezza *et al.* 1990). Anecdotal evidence that ingestion of fat (for example, olive oil) before the consumption of alcohol may reduce inebriation is consistent with this concept.

The lipase inhibitor, orlistat, is now used widely in the treatment of obesity. As a result of inhibition of gastric and pancreatic lipase, orlistat, when given in a dose of 120 mg with a meal, reduces dietary fat absorption by about 40 % (Davidson *et al.* 1999). We have recently reported, in patients with type 2 diabetes managed by diet, that acute administration of orlistat potentiates the initial postprandial rise in blood glucose after both an oil or aqueous drink containing glucose (Pilichiewicz *et al.* 2003) and a high-fat, mashed potato, meal (O'Donovan *et al.* 2004*a*). These observations were not surprising, given that the slowing of gastric emptying by fat is dependent on lipolysis (Carney *et al.* 1995;

Abbreviations: AUC, area under the curve; NH&MRC, National Health and Medical Research Council.

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Schwizer *et al.* 1997; Borovicka *et al.* 2000), i.e. NEFA are responsible for mediating small-intestinal feedback inhibition (Feinle *et al.* 2003), and the rate of gastric emptying is a major determinant of the glycaemic response to carbohydrate-containing meals (Horowitz *et al.* 1993*a*; Jones *et al.* 1996; Rayner *et al.* 2001). Accordingly, we reasoned that orlistat has the potential to increase the magnitude of the rise in blood alcohol when an alcohol-containing beverage is consumed with fat, and that these effects were likely to be most marked when fat was consumed before the alcohol. Perhaps surprisingly, this concept has not been evaluated previously – one study reported that orlistat had no effect on alcohol absorption, but the drink contained carbohydrate only (Melia *et al.* 1998).

We have now evaluated the effects of lipase inhibition on gastric emptying and blood alcohol and glucose concentrations after ingestion of an alcohol-containing drink consumed after a fat 'preload', in healthy subjects.

Materials and methods

Subjects

Ten healthy adult males (age 29·5 (SE 3·7) years; BMI 23·1 (SE 0·8) kg/m^2) were recruited by advertisement. No subject had a history of gastrointestinal disease or surgery, significant respiratory or cardiac disease, alcohol abuse, or epilepsy and none smoked more than ten cigarettes per d, or was taking medication known to affect gastrointestinal function. The protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital, and each subject gave written, informed consent.

Protocol

Each subject was studied on two occasions, separated by an interval of 4–7 d in randomised, single-blind order. Each study commenced at 08.30 hours, following an overnight fast (14 h for solids, 12 h for liquids), when an intravenous cannula was inserted into an antecubital vein for blood sampling. On both days, subjects consumed 120 ml full-fat cream (Bulla Thick cream; Bulla Dairy Foods, Derrimut, Victoria, Australia; carbohydrate 55·3 kJ (13·2 kcal), fat 1398 kJ (333·9 kcal), protein 44·4 kJ (10·6 kcal)) with or without 120 mg orlistat (Xenical™; Roche Products Pty., Dee Why, NSW, Australia), which was mixed thoroughly into the cream, 30 min before consuming a 230 ml drink comprising 97 ml 'Feel Good' iced chocolate (Farmers Union; National Foods Limited, Melbourne, Victoria, Australia; carbohydrate 94·6 kJ (22·6 kcal), fat 19·3 kJ (4·6 kcal), protein 82·9 kJ (19·8 kcal)), low-energy sweetener (SPLENDA®; Johnson and Johnson Pacific, Broadway, NSW, Australia; carbohydrate 77·9 kJ (18·6 kcal) and 66·5 ml vodka (Premium Vodka 2000 Millennium product; Wyborowa SA Poznan, Poland; 20 g alcohol; 334·9 kJ (80 kcal)) and 66·5 ml water labelled with 20 MBq [^{99m}Tc]sulfur colloid, while sitting in front of a γ camera (Collins *et al.* 1983; Horowitz *et al.* 1989; Johnson *et al.* 1991). Accordingly, the energy content of the cream 'preload' was 1497·6 kJ (357·7 kcal) and the drink contained 606·2 kJ (144·8 kcal), i.e. total energy 2103·9 kJ (502·5 kcal). The drink was consumed over 5 min, and radioisotopic data were acquired between 0 and 240 min (60 s frames for the first 60 min, 3 min frames thereafter, with time 0 (t 0 min) defined as the time of completion of the drink. Venous blood samples (5–10 ml in volume) were collected at t −5, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 min. Blood glucose was measured on all of the samples; plasma alcohol was measured on the samples obtained at t −5, 15, 30, 60, 90, 120, 150 and 240 min. Subjects were allowed to leave the laboratory after 5 h and were asked to record any gastrointestinal symptoms and their bowel habit over the following 48 h.

Measurements

Gastric emptying. Data were corrected for subject movement, radionuclide decay and γ-ray attenuation (Collins *et al.* 1983; Pilichiewicz *et al.* 2003). Gastric emptying curves were derived by drawing a region-of-interest around the total stomach, from which the intragastric content at t 0, 15, 30, 45, 60, 75, 90, 120, 150, 180 and 240 min and the 50 % gastric emptying time were calculated (Collins *et al.* 1983).

Blood glucose and plasma alcohol concentrations. Blood glucose concentrations were determined immediately using a portable glucose meter (Medisense Precision QID; Abbott Laboratories, Bedford, MA, USA). The accuracy of this method has been confirmed in our laboratory using the hexokinase technique (Horowitz *et al.* 1996). The maximum increase in blood glucose from baseline (i.e. t −5 min), and the areas under the curve (AUC) for the change in blood glucose between −5 to 30 min, −5 to 60 min and −5 to 240 min, were calculated. Blood samples for determination of plasma alcohol were collected in ice-chilled tubes. Plasma was separated by centrifugation and stored at −70°C for subsequent analysis by chromatography (Cooper, 1971). The maximum increase in blood alcohol from baseline, and the AUC between −5 to 30 min, −5 to 60 min and −5 to 240 min, were calculated.

Statistical analysis

Data were evaluated using repeated-measures ANOVA and are presented as means with their standard errors. Mean contrasts were used to analyse individual point-by-point comparisons. AUC for blood glucose and plasma alcohol were calculated using the trapezoidal rule and compared using Student's paired *t* test. Relationships between gastric emptying and the early rise in blood glucose and plasma alcohol concentrations were assessed using linear regression analysis. $P < 0{\cdot}05$ was considered significant in all analyses.

Results

All subjects tolerated the study well; two subjects reported loose bowel actions after orlistat – in both cases the symptoms were mild and resolved within 48 h. All subjects experienced no gastrointestinal symptoms.

Gastric emptying

Gastric emptying was faster with orlistat ($P < 0{\cdot}05$) when compared with the drink without orlistat (Fig. 1(a)), although

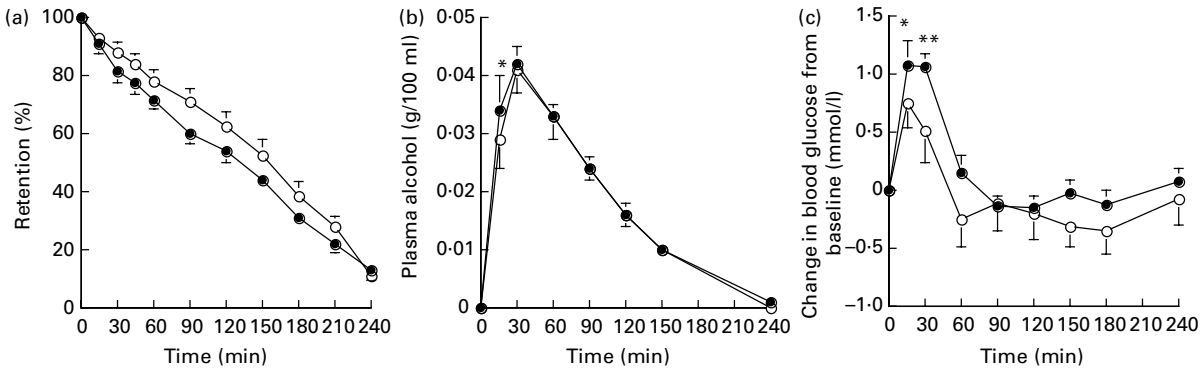

Fig. 1. (a) Gastric emptying, (b) plasma alcohol and (c) blood glucose concentrations in response to a drink containing 20 g alcohol, consumed 30 min after ingestion of 120 ml cream with (– ● –) or without (–○–; control) orlistat. Data are means, with their standard errors represented by vertical bars. Mean value was significantly different from that of control: $^{*}P<0{\cdot}05$, $^{**}P=0{\cdot}001$. The presence of orlistat had a significant effect on gastric emptying (ANOVA); $P<0{\cdot}05$. For details of subjects and procedures, see p. 884

there was no significant difference in the 50 % gastric emptying time (orlistat 102·8 (SEM 8·3) min *v.* control 116·0 (SEM 10·9) min).

Plasma alcohol and blood glucose concentrations

Plasma alcohol concentrations increased after the drinks on both study days ($P<0{\cdot}05$). The plasma alcohol concentration at t 15 min was slightly higher with orlistat (orlistat 0·034 (SEM 0·006) g/100 ml *v.* control 0·029 (SEM 0·005) g/100 ml; $P<0{\cdot}05$). There was no overall difference in plasma alcohol concentrations ($P=0{\cdot}65$), or peak blood alcohol (orlistat 0·045 (SEM 0·003) g/100 ml *v.* control 0·044 (SEM 0·004) g/100 ml) between the two study days (Fig. 1(b)). There was no significant difference between orlistat and control in the AUC between −5 to 30 min (orlistat 0·82 (SEM 0·11) g/100 ml × min *v.* control 0·74 (SEM 0·10) g/100 ml × min, −5 to 60 min (orlistat 1·94 (SEM 0·15) g/100 ml × min *v.* control 1·86 (SEM 0·19) g/100 ml × min and −5 to 240 min (orlistat 4·30 (SEM 0·32) g/100 ml × min *v.* control 4·22 (SEM 0·40) g/100 ml × min).

There was no significant difference in the baseline (i.e. t −5 min) blood glucose concentration between the two study days. Blood glucose increased ($P<0{\cdot}05$) after the drink on both days (Fig. 1(c)). The magnitude of the rise from baseline was greater at both 15 min (orlistat 1·07 (SEM 0·2) mmol/l *v.* control 0·75 (SEM 0·2) mmol/l; $P=0{\cdot}05$) and at 30 min (orlistat 1·06 (SEM 0·1) mmol/l *v.* control 0·51 (SEM 0·3) mmol/l; $P=0{\cdot}001$) after orlistat. There was no overall difference in the rise from baseline ($P=0{\cdot}31$) or peak blood glucose (orlistat 6·87 (SEM 0·17) mmol/l *v.* control 6·97 (SEM 0·28) mmol/l) between the 2 d (Fig. 1(c)). There was also no significant difference between orlistat and control in the AUC between −5 to 30 min (orlistat 22·83 (SEM 3·87) mmol/l × min *v.* control 12·90 (SEM 4·56) mmol/l × min), −5 to 60 min (orlistat 37·90 (SEM 3·39) mmol/l × min *v.* control 17·85 (SEM 11·70) mmol/l × min) and −5 to 240 min (orlistat 31·83 (SEM 13·04) mmol/l × min *v.* control −18·53 (SEM 39·70) mmol/l × min).

Relationships between plasma alcohol and blood glucose concentrations and gastric emptying

There was a significant inverse relationship between plasma alcohol concentrations and the 50 % gastric emptying time in the total group; for example, at t 30 min (r −0·65; $P=0{\cdot}002$), which was not significant in the orlistat (r −0·57; $P=0{\cdot}08$), but significant in the control (r −0·65; $P=0{\cdot}02$), group (Fig. 2(a)). There was a significant inverse relationship between the blood glucose concentration and gastric emptying in the total group; for example, at t 15 min

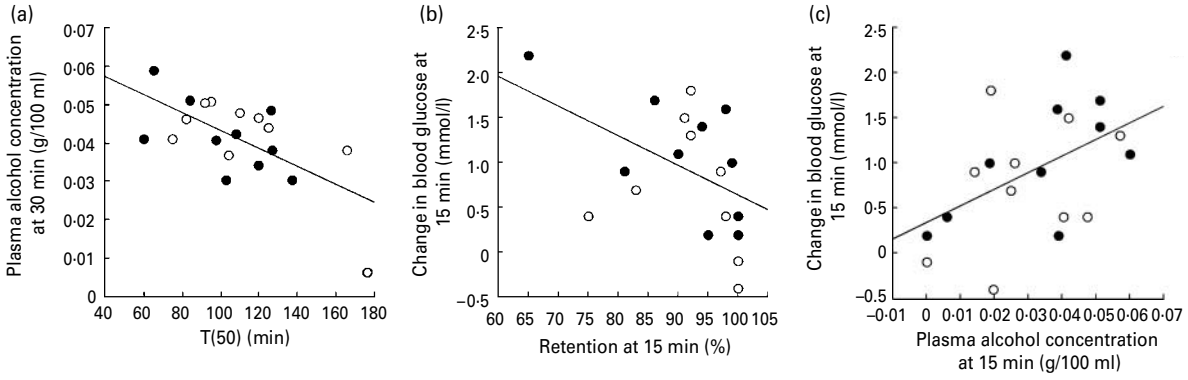

Fig. 2. Relationships between (a) plasma alcohol concentrations at 30 min and the 50 % emptying time (T50) for gastric emptying (r −0·65; $P=0{\cdot}002$), (b) the rise in blood glucose from baseline and the intragastric retention at 15 min (r −0·46; $P=0{\cdot}04$) and (c) the plasma alcohol concentration at 15 min and the rise in blood glucose from baseline at 15 min (r 0·49; $P=0{\cdot}03$) in the total group. (●), Orlistat; (○), control. For details of subjects and procedures, see p. 884.

(r − 0·46; P=0·04), which was significant in the orlistat (r − 0·66; P=0·03), but not the control (r − 0·24; P=0·3) group (Fig. 2(b)). There was a direct relationship between blood glucose and plasma alcohol concentrations in the total group; for example, at t 15 min (r 0·49; P=0·03), which was not significant in the orlistat (r 0·61; P=0·06) or control (r 0·34; P=0·34), groups (Fig. 2(c)).

Discussion

Orlistat is a potent inhibitor of lipase in the gastrointestinal tract (Borgstrom, 1988; Drent & van der Veen, 1993; O'Donovan *et al.* 2004*a*) and is used widely in the management of obesity. The present study demonstrates that in healthy male subjects the incorporation of orlistat into a cream 'preload' accelerates gastric emptying of an alcohol-containing drink consumed 30 min later, and this is associated with an initially greater blood alcohol and glycaemic response, although these effects were all relatively modest and unlikely to be of clinical significance. Both alcohol absorption and postprandial glucose concentrations were shown to be dependent on the rate of gastric emptying, as has been noted previously (Horowitz *et al.* 1989; Rayner *et al.* 2001). Moreover, the magnitude of the elevation in blood alcohol and glucose were shown to be related, which, while not unexpected, has not to our knowledge been demonstrated previously.

Melia *et al.* (1998) reported that short-term treatment with orlistat had no effect on alcohol absorption after a drink containing 13·9 g carbohydrate and 41·7 g alcohol, which is not surprising, given the absence of fat (Melia *et al.* 1998). It has been well established that gastric emptying of carbohydrate has a major influence on postprandial glycaemia accounting for about 35 % of the variance in the initial blood glucose response to 75 g oral glucose loads in cross-sectional studies of healthy subjects (Horowitz *et al.* 1993*a*) and patients with type 2 diabetes (Jones *et al.* 1996). In our present study, subjects consumed a high-fat 'preload' before a drink that predominantly comprised carbohydrate, since the effects of fat to slow gastric emptying were likely to be more marked than if the fat was included in the drink (Welch *et al.* 1987; Cunningham & Read, 1989). If it is assumed that the cream emptied from the stomach at a rate of about 12·6 kJ/min (3 kcal/min) (Edelbroek *et al.* 1993), some 25 % should have entered the small intestine at the time of ingestion of the drink. The presence of digested and digestible fat in the small intestine would be expected to slow gastric emptying of the drink (Stacher *et al.* 1991). The observed relationships between both plasma alcohol and blood glucose responses with gastric emptying are consistent with previous reports (Nimmo, 1976; Holt, 1981; Horowitz *et al.* 1993*a*; Jones *et al.* 1996), which have established that the latter is evident even after low carbohydrate loads (O'Donovan *et al.* 2004*b*; Chaikomin *et al.* 2005). It should be acknowledged that the present study was not specifically designed to evaluate relationships. It is therefore not surprising that correlations were more evident in the total group (n 20) rather than in the individual groups (n 10).

The magnitude of the acceleration of gastric emptying by orlistat was small, as reflected in the blood alcohol and glucose responses. There are a number of possible explanations for this. The acceleration of gastric emptying by orlistat may potentially have been more marked if the fat were consumed as a liquid emulsion (Schwizer *et al.* 1997) and if the fat content of the alcohol-containing drink had been higher, given that the effects of lipase inhibition on gastric emptying are dependent on the fat load (Schwizer *et al.* 1997; Borovicka *et al.* 2000). As our subjects were studied in the sitting position it is possible that, because of its lower density, ingestion of the drink would result in 'layering' of some, or all, of the remaining intragastric fat (Horowitz *et al.* 1993*b*); if so, the carbohydrate would empty preferentially and, thereby, regulate gastric emptying. While the orlistat was mixed thoroughly into the cream, the latter is a stabilised droplet emulsion of fat in which protein encases the fat droplets, and may have limited access of orlistat to the fat surface.

Had the differences in gastric emptying been more pronounced we would have expected higher initial postprandial rises in both plasma alcohol and blood glucose concentrations (as we have shown previously in patients with type 2 diabetes (Pilichiewicz *et al.* 2003; O'Donovan *et al.* 2004*a*)), which may have significant implications for driving a motor vehicle or operating machinery, and for glycaemic control in patients with diabetes. This is of major relevance to patients with diabetes given that postprandial glycaemia affects glycated Hb (Bastyr *et al.* 2000) and may also be an independent risk factor for macrovascular disease (Saydah *et al.* 2001; Del Prato, 2002).

It could be expected that in patients with delayed gastric emptying, the potential effects of orlistat on gastric emptying, blood alcohol and postprandial glycaemia may be reduced; however, this has not been previously studied.

Because of the potential limitations to the present study the provisional conclusion that orlistat does not have any meaningful effect on alcohol absorption in healthy subjects should be treated circumspectly.

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