Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Orlistat treatment is safe in overweight and obese liver transplant recipients: a prospective, open label trial

David Cassiman,[1] Mieke Roelants,[2] Gerda Vandenplas,[1] Schalk W. Van der Merwe,[3] Ann Mertens,[2] Louis Libbrecht,[4] Chris Verslype,[1] Johan Fevery,[1] Raymond Aerts,[5] Jacques Pirenne,[5] Erik Muls[2] and Frederik Nevens[1]

1 Department of Hepatology, University Hospital Gasthuisberg, University of Leuven, Belgium
2 Department of Endocrinology, University Hospital Gasthuisberg, University of Leuven, Belgium
3 Department of Internal Medicine and Gastroenterology, University of Pretoria, Pretoria, South Africa
4 Department of Morphology and Molecular Pathology, University Hospital Gasthuisberg, University of Leuven, Belgium
5 Department of Abdominal Transplantation, University Hospital Gasthuisberg, University of Leuven, Belgium

Keywords
cyclosporin, drug interaction, nonalcoholic fatty liver disease, tacrolimus, weight loss.

Correspondence
David Cassiman MD, PhD, Department of Hepatology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Tel.: 0032 16 344 299; fax: 0032 16 345 846; e-mail: david.cassiman@med.kuleuven.be

Received: 23 May 2006
Revision requested: 20 June 2006
Accepted: 13 July 2006

doi:10.1111/j.1432-2277.2006.00379.x

Summary

Obesity is a frequent complication following liver transplantation and is insufficiently responsive to dietary and life style advice. We studied the safety of orlistat treatment in obese and overweight liver transplant recipients ($n = 15$) on a stable tacrolimus-based immunosuppressive regimen. For safety reasons, the treatment period was restricted (6 months 120 mg t.i.d., 3 months 120 mg daily). Three patients dropped out, tacrolimus dose was adjusted in six of 12 remaining patients (dose reduction in 4, increase in 2, $P =$ N.S.). All dose adjustments occurred during the 6 months of orlistat 120 mg t.i.d. therapy. No drug intolerance, adverse events or episodes of rejection occurred during the study. Efficacy of orlistat treatment in this population could not be shown, because a formal control population was not included in this safety trial. Moreover, only a significant decrease of waist circumference ($P < 0.01$ versus start of the study), but not of weight or body mass index, was achieved in the treated group. Orlistat treatment is well tolerated in liver transplant recipients and can be started safely, provided immunosuppressive drug levels and dietary adherence are closely monitored.

Introduction

Weight gain occurs quite often in liver transplant recipients and 20–70% of liver transplant recipients become significantly obese following transplantation [1–3]. The exact cause of this high prevalence of obesity following liver transplantation is unknown, but the post-transplant weight gain has been attributed to appetite increase because of recovery from chronic disease, immunosuppressive drug effects and autonomic denervation of the transplanted liver [4,5].

Obesity is an important risk factor for cardiovascular disease and other major health problems including diabetes, cirrhosis, cancer and osteoarthritis, as much in the post-transplant patient as in the general population. In addition, immunosuppressive drugs – such as corticosteroids, cyclosporin and tacrolimus which are commonly used in liver transplantation – may increase the risk of developing diabetes, hyperlipidemia and hypertension, further accelerating atherosclerosis [3].

The cornerstone of therapy for obesity remains dietary and life style advice. However, as in obesity unrelated to the transplant settings, this form of therapy often fails. Given the excessive risk of accelerated atherosclerosis, diabetes, (recurrence of) liver fibrosis and cirrhosis in liver transplant recipients, the necessity to explore additional treatment options in this population is high.

Orlistat (Xenical®, N.V. Roche S.A., Brussels, Belgium) is a reversible inhibitor of pancreatic lipase. By preventing the digestion of triglycerides, their absorption is prevented and the relative contribution of fat to the caloric content of the diet is effectively reduced [6]. Studies evaluating the pharmacological effect of orlistat show a maximum effect on faecal fat excretion at about 120 mg [7]. Approximately 30% of dietary fat is excreted at this dose. To minimize side-effect such as steatorrhoea, the dietary fat content is kept at 30% of the total caloric intake and the drug is combined with a calory-restricting diet. In double-blind randomized multicenter studies the efficacy and safety of orlistat 120 mg t.i.d., given as adjunctive therapy to a moderately calory-reduced diet (containing approximately 30% of calories as fat), was compared with placebo for weight loss and effect on co-morbidity parameters. More than 10 000 patients have participated in phase III and phase IV trials. Orlistat 120 mg t.i.d. resulted in a more pronounced weight loss than diet or placebo alone [8–10].

Orlistat treatment, however, is not recommended for organ transplant patients because it is thought to interfere with the absorption and therefore the serum levels of calcineurin inhibitors. Interactions with tacrolimus absorption and serum levels have not been studied or described yet, but one randomized trial and several case reports do suggest orlistat interferes with gastrointestinal cyclosporin absorption and hence could cause acute rejection [11–19]. Moreover, orlistat has been described to cause acute to fulminant hepatitis in nontransplanted patients, which is also a deterrent for its use in liver transplant patients [20–23]. On the other hand, the alternatives for the treatment of obesity and its consequences in liver transplant patients are limited. Sibutramine is a serotonin-noradrenalin reuptake inhibitor, currently successfully used with the purpose of inducing weight loss in obese patients. Sibutramine has systemic side-effects (hypertension, increased heart rate) and has also been associated with hepatotoxicity [24]. The experience with bariatric surgery in liver transplant recipients is limited and gastrointestinal bypass surgery, especially the older techniques, is associated with an increased risk of developing acute steatohepatitis and liver failure [25]. The aim of the present study therefore was to explore the safety of orlistat treatment in overweight and obese liver transplant recipients.

Materials and methods

Subjects

Fifteen overweight and obese liver transplant patients were recruited from a single transplant centre (University Hospital Gasthuisberg, University of Leuven, Belgium) during the time period between 31 July to 31 December 2001. All patients signed a written informed consent form prior to their inclusion in the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the University Hospital Gasthuisberg Ethical Committee.

Inclusion and exclusion criteria

Patients included were transplanted at least 1 year prior to start of the study [time since transplantation 52.3 ± 29.5 months (mean ± S.D.)] and were on stable immunosuppressive therapy that did not include corticosteroids. Stable immunosuppressive regimen was defined as <25% dose adjustment over the last 3 months prior to inclusion and either a fixed combination of immunosuppressants or unchanged tacrolimus monotherapy. Patients were between the ages of 18 and 70 years, had a body mass index (BMI) > 28.5, had been unsuccessful at losing weight during the past year, despite repeated instruction on healthy, low-fat, hypocaloric dieting by the clinician and dietician and had stable weight measurements over the last month. Patients with a history of unstable disease or psychiatric illness (bulimia, substance abuse) were excluded. Patients were also excluded if they had previously undergone surgery for weight loss purposes or if they had a history of bowel adhesions. For safety reasons and lack of data on pharmacological interactions at the time the study was initiated, diabetic patients taking oral antidiabetic drugs were excluded. Also patients with a history of malignancy except for successfully treated malignancies of the skin such as squamous or basal carcinoma and cervix carcinoma in females were excluded for safety reasons.

Study protocol

Patients included in the study were extensively evaluated at baseline: a comprehensive clinical and drug history was taken and physical examination was performed. Body weight was measured and standing waist circumference determined using a tape-measure. Blood pressure was taken with a standard mercury sphygmomanometer with the patient in the sitting position after an initial adaptation period of at least 5 min. Blood and serum were obtained for routine biochemical analysis, using standard laboratory protocols. Tests included urea, creatinine and electrolytes, liver function tests, serum glucose and standard blood count. In addition, blood lipids were determined, tacrolimus level assessed and pregnancy tests performed in females in their reproductive years. The patients were assessed by a dietician and a low calory diet was prescribed (reduction of 600 kcal of their diet, adapted to their total daily expenditure with a minimum daily intake of

1200 kcal, with no more than 30% of calories as fat and a maximum of 300 mg cholesterol/day). All patients were started on orlistat 120 mg t.i.d., taken 15–30 min before the meal. In patients not showing weight loss exceeding 5% at week 12, therapy was considered to fail and was discontinued to avoid unnecessary exposure to the hypothetical drug toxicity or adverse reactions ('safety stopping rule'). These patients nevertheless remained in follow-up afterwards.

The treatment period was limited to 6 months, to allow the study of drug safety and interaction with immunosuppressant serum levels. After 6 months of orlistat 120 mg t.i.d., patients were switched to orlistat 120 mg daily, taken 15–30 min before the main meal for a further 3 months, then orlistat was stopped. Patients were followed up for another 3 months after cessation of therapy.

Patients were seen in the outpatient clinic weekly until week 4, monthly until week 24 and every 3 months thereafter until 1 year after the study was started. Patients underwent routine physical examination by a clinician on week 24 and 48. Weight, blood pressure and waist circumference were noted on every visit. Routine biochemical analyses were repeated at week 24 and 48 of the study. Blood lipids [total cholesterol, triglycerides, low density lipoprotein (LDL) and high density lipoprotein (HDL)] were assessed at weeks 4, 8, 24 and 48. Tacrolimus levels were assessed at every visit. Tacrolimus was ingested separate from meals (1 h before the meal or more than 2 h after). In practice, in the morning patients took tacrolimus, waited 30 min, then took orlistat, followed by breakfast 30 min later; in the evening patients took orlistat and 30 min later had their dinner, 2 h later they took their evening dose of tacrolimus. Tacrolimus target trough levels were determined individually as they are multifactorial and depended on time elapsed since transplantation, immunosuppressive scheme (monotherapy tacrolimus or bitherapy with tacrolimus plus azathioprine or mycophenolate mofetil), past episodes of rejection, kidney function, cause of transplantation and absence or presence of intercurrent liver disease. Target trough levels remained unchanged during the study. Patients received dietary advice every second visit. Adverse events were assessed by interview and recorded at every visit.

Statistical analysis

Weight, BMI, waist circumference, biochemical test results and blood pressure at the different time points ($t = 0$, 24 weeks, 36 weeks, 48 weeks) were compared by ANOVA and Fisher protected least-significant difference (PSLD) test (Statview, Abacus, Berkley, CA, USA). Significance was accepted when $P < 0.05$.

Results

The baseline characteristics of the transplanted patients and the indications for liver transplantation are summarized in Table 1. None of the patients discontinued therapy because of intolerance. Most notably, there were no episodes of rejection. None of the patients developed diarrhoea, steatorrhoea, abdominal complaints or flatulence during the study period, with the exception of an infectious episode of diarrhoea in one patient. Other events during the study period included hyperventilation attacks in one predisposed patient, a subarachnoidal haemorrhage in one (in week 36 of the study, when on orlistat 120 mg/day) and minor musculoskeletal complaints in two patients. One patient could no longer be followed up during the study, because of an unrelated intercurrent problem (hip fracture), which precluded standard weight measurement beyond the 12th week of the study. Two patients were taken off medication at week 12, per protocol, because they had not reached 5% weight loss by that time ('safety stopping rule').

'Intention-to-treat' analysis (i.e. including one patient that dropped out and two patients that discontinued treatment) showed significant decrease in waist circumference at 6, 9 and 12 months after start of therapy (109.7 ± 11.9 cm at start; 97.3 ± 11.2 cm at 24 weeks;

Table 1. Patient characteristics.

Male/female	8/7
Age range (mean)	40–71 (55)
Indication for liver transplantation	
Viral cirrhosis	8
Alcoholic cirrhosis	2
Other	5
Immunosuppressive regimen	
Tacrolimus + azathioprine	7
Tacrolimus + MMF	6
Tacrolimus monotherapy	2
Tacrolimus dose (mg)	3.7 ± 2
Blood pressure (mmHg)	
Systolic	132.9 ± 16
Diastolic	80 ± 8
Body weight (kg)	91.0 ± 14
BMI (kg/m^2)	33.9 ± 4
Waist circumference (cm)	109.7 ± 12
Triglyceride level (mg/dl, ULN 180)	198.8 ± 160
Total cholesterol level (mg/dl, ULN 190)	201 ± 46
HDL (ULN 40)	49.4 ± 17
LDL (ULN 115)	127.7 ± 38
Glucose (mg/dl, 55–110)	123 ± 69

The baseline characteristics (T = 0) are listed here. 'Other' indications for liver transplantation: one primary biliary cirrhosis, one primary sclerosing cholangitis, two cryptogenic, one sarcoidosis. ULN: upper limit of normal.

97.7 ± 9.1 cm at 36 weeks; 97.7 ± 9.4 cm at 48 weeks; $P < 0.01$ versus start; values represented as mean ± SD; Fig. 1). Weight and BMI decreased, but this decrease did not reach statistical significance at any of the time points. Weight loss amounted to −9.8 ± 2.7 kg at 6 months, −10.2 ± 4.3 kg at 9 months and −9.2 ± 5.5 kg at 1 year (mean ± SD; P = NS; Fig. 2 and data not shown).

Dosage of immunosuppressive agents in the entire group ($n = 14$, one dropout with loss of data) was adapted to serum trough levels, as described in the Materials and Methods section. Mycophenolate mofetil and azathioprine doses were kept constant throughout the study. All tacrolimus dose adjustments occurred during the first 24 weeks of treatment (orlistat 120 mg t.i.d. period). Dose adjustments were necessary in six of 14 patients (dose reduction in four, increase in two). None of the tacrolimus dose adjustments exceeded 4 mg tacrolimus/day. No statistically significant differences could be recorded in tacrolimus dosage (either expressed as daily dose, as daily dose per kilogram of body weight, or as the ratio of trough level to daily dose), in the patient subgroup that received full treatment with orlistat ($n = 12$), at any of the recorded time points (data not shown).

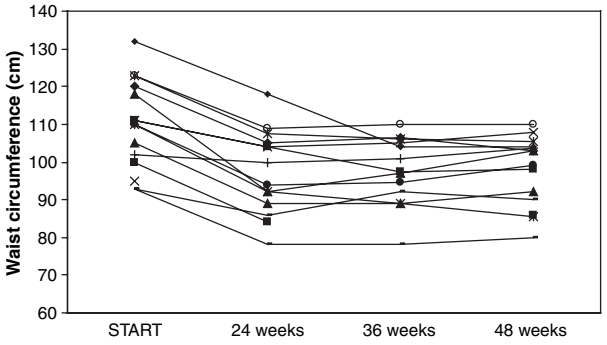

Figure 1 Changes in waist circumference (intention-to-treat analysis). Orlistat treatment resulted in a significant decrease in waist circumference at 6, 9 and 12 months after start of therapy (109.7 ± 11.9 cm at start; 97.3 ± 11.2 cm at 24 weeks; 97.7 ± 9.1 cm at 36 weeks; 97.7 ± 9.4 cm at 48 weeks) (mean ± SD; $P < 0.01$ versus start).

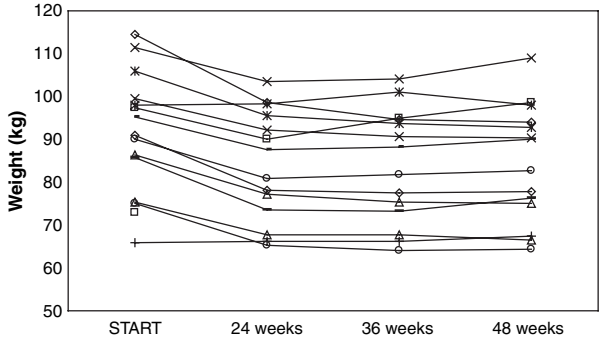

Figure 2 Weight changes during the study (intention-to-treat analysis). The patients that received the entire schedule of orlistat treatment ($n = 14$), showed a nonsignificant decrease in weight: at 24 weeks (end of orlistat 120 mg t.i.d.; −9.8 ± 2.7 kg), at 36 weeks (end of orlistat 120 mg daily; −10.2 ± 4.3 kg) and at 48 weeks (end of study; −9.2 ± 5.5 kg) (mean ± SD; P = NS for all time points).

Blood pressure, blood glucose, serum lipids (total cholesterol, LDL, HDL and triglycerides) did not change significantly, when compared with baseline values, at any time point. Systolic blood pressure was 132.9 ± 16 mmHg at start, 130.6 ± 16 at 24 weeks, 126.7 ± 16 at 36 weeks and 129 ± 15 at 48 weeks (P = NS, values represent mean ± SD). Diastolic blood pressure was 80.0 ± 8 mmHg at start, 78.7 ± 8 at 24 weeks, 81.2 ± 6 at 36 weeks and 81.9 ± 9 at 48 weeks (P = NS). Glycaemia was 123 ± 69 mg/dl at start, 100 ± 15 at 24 weeks, 108 ± 26 at 36 weeks, 105 ± 12 at 48 weeks (P = NS). Triglycerides were 198.8 ± 160 mg/dl at start, 135.4 ± 45 at 24 weeks, 159 ± 75 at 36 weeks and 119.4 ± 50 at 48 weeks (P = NS). HDL was 49.4 ± 17 mg/dl at start, 52.2 ± 18 at 24 weeks, 64.7 ± 39 at 36 weeks and 57.2 ± 16 at 48 weeks (P = NS). LDL was 127.7 ± 38 mg/dl at start, 112.5 ± 33 at 24 weeks, 111.9 ± 34 at 36 weeks and 110.5 ± 27 at 48 weeks (P = NS).

During the study period, none of the patients demonstrated biochemical changes on routine lab testing (blood count, creatinine, electrolytes and clotting), beyond the limits of normal values. All patients had normal liver tests at the start of the study and none developed liver test elevations during the study period.

Discussion

We evaluated the short-term safety of orlistat in the management of overweight and obese liver transplant recipients, on tacrolimus-based immunosuppressive regimens. We further assessed the effects of orlistat on tacrolimus serum levels and dosage.

We demonstrate here that orlistat treatment was well tolerated and safe following liver transplantation. No formal or definite conclusions can be drawn with regards to the efficacy of orlistat in the liver transplant recipient population, because a double-blind randomized control population (on a similarly strict diet as the orlistat-treated group) was not included in the trial. Moreover, 'intention-to-treat' analysis showed only significant reduction of waist circumference at 6, 9 and 12 months, not of weight or BMI. The fact that we could not demonstrate significant reduction of weight or BMI is undoubtedly also related to the small sample size and short treatment duration in this trial.

In two of 15 patients (13.3%) orlistat was discontinued because of lack of effect, defined as <5% weight loss after 3 months (see 'safety stopping rule', Materials and Methods section). This is concordant with published rates of nonresponse (defined as weight loss <5%), being 31.5% of patients in the series reported by Sjostrom et al. [8] and 34.3% in the series of Davidson et al. [9]

During orlistat treatment, immunosuppressive dose adjustments were necessary in six of 14 (43%) patients, but did not reflect significant changes in tacrolimus dosage at any time point. All dose adjustments were minor and did not indicate any systematic problem in gastrointestinal absorption of the immunosuppressants, in contrast to what has been reported for cyclosporin [26]. The fact that no complaints of diarrhoea were recorded during the study period suggests successful and strict adherence to the prescribed dietary fat restrictions, in our well-motivated and closely monitored study population, but also raises questions about diet adherence in other orlistat-treated patients. Our study therefore does not exclude the possibility that transplanted patients who do not follow dietary advice and develop diarrhoea or steatorrhoea when on orlistat, will need more drastic adjustments of their immunosuppressants.

In conclusion, obesity, a common problem postliver transplantation, can safely be treated with orlistat 120 mg t.i.d., provided immunosuppressive drug levels and diet are closely monitored. This prospective, open, single arm pilot study evaluating safety of short-term orlistat treatment opens the door for larger, randomized controlled trials studying the effect of long-term orlistat treatment in transplant recipients.

Grants and financial support

David Cassiman and Louis Libbrecht are postdoctoral researchers of the FWO-Vlaanderen.

Orlistat was donated by the manufacturer (N.V. Roche S.A., Brussels, Belgium), for this otherwise investigator-initiated study.

References

1. Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. *Transpl Int* 2005; **18**: 461.
2. Everhart JE, Lombardero M, Lake JR, Wiesner RH, Zetterman RK, Hoofnagle JH. Weight change and obesity after liver transplantation: incidence and risk factors. *Liver Transpl Surg* 1998; **4**: 285.
3. Munoz SJ, Elgenaidi H. Cardiovascular risk factors after liver transplantation. *Liver Transpl* 2005; **11**: S52.
4. la Fleur SE, Ji H, Manalo SL, Friedman MI, Dallman MF. The hepatic vagus mediates fat-induced inhibition of diabetic hyperphagia. *Diabetes* 2003; **52**: 2321.
5. la Fleur SE, Manalo SL, Roy M, Houshyar H, Dallman MF. Hepatic vagotomy alters limbic and hypothalamic neuropeptide responses to insulin-dependent diabetes and voluntary lard ingestion. *Eur J Neurosci* 2005; **21**: 2733.
6. Guerciolini R. Mode of action of orlistat. *Int J Obes Relat Metab Disord* 1997; **21**(Suppl. 3):S12.
7. Van Gaal LF, Broom JI, Enzi G, Toplak H. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Orlistat Dose-Ranging Study Group. *Eur J Clin Pharmacol* 1998; **54**: 125.
8. Sjostrom L, Rissanen A, Andersen T, *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998; **352**: 167.
9. Davidson MH, Hauptman J, DiGirolamo M, *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999; **281**: 235.
10. Muls E, Kolanowski J, Scheen A, Van Gaal L. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomized, double-blind, placebo-controlled, multicentre study. *Int J Obes Relat Metab Disord* 2001; **25**: 1713.
11. Zhi J, Moore R, Kanitra L, Mulligan TE. Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. *J Clin Pharmacol* 2002; **42**: 1011.
12. Asberg A. Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. *Drugs* 2003; **63**: 367.
13. Cailotto C, La Fleur SE, Van Heijningen C, *et al.* The suprachiasmatic nucleus controls the daily variation of plasma glucose via the autonomic output to the liver: are the clock genes involved? *Eur J Neurosci* 2005; **22**: 2531.
14. Colman E, Fossler M. Reduction in blood cyclosporine concentrations by orlistat. *N Engl J Med* 2000; **342**: 1141.
15. Errasti P, Garcia I, Lavilla J, Ballester B, Manrique J, Purroy A. Reduction in blood cyclosporine concentration by orlistat in two renal transplant patients. *Transplant Proc* 2002; **34**: 137.
16. Evans S, Michael R, Wells H, *et al.* Drug interaction in a renal transplant patient: cyclosporin-Neoral and orlistat. *Am J Kidney Dis* 2003; **41**: 493.
17. Le Beller C, Bezie Y, Chabatte C, Guillemain R, Amrein C, Billaud EM. Co-administration of orlistat and cyclosporine in a heart transplant recipient. *Transplantation* 2000; **70**: 1541.
18. Nagele H, Petersen B, Bonacker U, Rodiger W. Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. *Eur J Clin Pharmacol* 1999; **55**: 667.

19. Schnetzler B, Kondo-Oestreicher M, Vala D, Khatchatourian G, Faidutti B. Orlistat decreases the plasma level of cyclosporine and may be responsible for the development of acute rejection episodes. *Transplantation* 2000; **70**: 1540.
20. Kim DH, Lee EH, Hwang JC, *et al.* [A case of acute cholestatic hepatitis associated with Orlistat]. *Taehan Kan Hakhoe Chi* 2002; **8**: 317.
21. Lau G, Chan CL. Massive hepatocellular (correction of hepatocullular) necrosis: was it caused by Orlistat? *Med Sci Law* 2002; **42**: 309.
22. Montero JL, Muntane J, Fraga E, *et al.* Orlistat associated subacute hepatic failure. *J Hepatol* 2001; **34**: 173.
23. Thurairajah PH, Syn WK, Neil DA, Stell D, Haydon G. Orlistat (Xenical)-induced subacute liver failure. *Eur J Gastroenterol Hepatol* 2005; **17**: 1437.
24. Chounta A, Tsiodras S, Zouridakis S, Doumas M, Giamarellou H. Sibutramine use associated with reversible hepatotoxicity. *Ann Intern Med* 2005; **143**: 763.
25. Blackburn GL, Mun EC. Effects of weight loss surgeries on liver disease. *Semin Liver Dis* 2004; **24**: 371.
26. Lemahieu W, Maes B, Verbeke K, Rutgeerts P, Geboes K, Vanrenterghem Y. Cytochrome P450 3A4 and P-glycoprotein activity and assimilation of tacrolimus in transplant patients with persistent diarrhea. *Am J Transplant* 2005; **5**: 1383.