Br J Clin Pharmacol 1996; **42**: 313–318

Taste loss to terbinafine: a case-control study of potential risk factors

B. H. Ch. STRICKER[1,2], M. M. VAN RIEMSDIJK[3], M. C. J. M. STURKENBOOM[1] & J. P. OTTERVANGER[4]
[1]Pharmaco-epidemiology Unit, Department of Epidemiology & Biostatistics, Erasmus University Medical School, Rotterdam, [2]Drug Safety Unit, Inspectorate for Health Care, Rijswijk, [3]Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht and [4]Department of Internal Medicine II, Erasmus University Medical School, Rotterdam, The Netherlands

1 To identify risk factors associated with taste loss to terbinafine, we performed a case-control study of 87 reports of probable terbinafine-induced taste loss and 362 controls on terbinafine without taste loss, who had filled prescriptions from the same pharmacy and GP. Data on general health, diet, alcohol, smoking, drug use and medical history were collected by means of a self-administered questionnaire.

2 The mean latent period between first intake of terbinafine and taste loss was 35 days. Most patients recovered within 4 months after discontinuation. Cases were significantly older than controls. The odds ratio of taste loss in patients of 65 years and older was 4.4 in comparison with persons younger than 35 years of age (95% CI: 1.4–16.1). The risk in persons with a body mass index (BMI) below 21 kg m^{-2} was 4.4 times higher than in those with a BMI of more than 27 kg m^{-2} (95% CI: 1.6–14.2). The risk of taste loss in patients of 55 years and older with a BMI below 21 kg m^{-2} was 12.8 times higher than that in patients below 35 years of age (95% CI: 1.9–88.6).

3 A low BMI, a history of taste loss, and ageing are risk factors for developing taste loss to terbinafine. Prescription of this drug to elderly patients with low BMI and low daily intake of nutrients requires careful follow-up.

Keywords taste terbinafine antimycotic

Introduction

Terbinafine is a new antimycotic agent for the oral treatment of dermato- and onychomycosis which inhibits the enzyme squalene-epoxidase [1]. Adverse reactions are usually mild with gastrointestinal disturbances as a relatively common effect [2]. Skin reactions and cholestatic hepatitis [3] may occur. One of the adverse reactions is taste loss [4–8].

Because little is known about risk factors for taste loss to terbinafine, we performed a case-control study in which we compared characteristics of patients with terbinafine-attributed taste loss with those of users of the drug who did not suffer from this adverse effect.

Methods

Setting

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs (NARD) runs a nationwide voluntary reporting scheme for adverse reactions to drugs. All reports are evaluated by a medical officer and discussed during monthly meetings of the Advisory Board. Of each report full details are requested about: age and sex of the patient, dose and duration of use of the suspected drug, concomitantly used drugs, underlying illness, events preceding the onset of taste loss, all clinical signs and symptoms, and—if performed—the results of laboratory investigations or imaging pro-

Correspondence: Dr B.H.Ch. Stricker, Department of Epidemiology & Biostatistics, Pharmaco-epidemiology Unit, Erasmus University Medical School, Dr Molewaterplein 50, 3015 GE Rotterdam, The Netherlands

cedures. On the basis of these data causality is assessed on a case-by-case basis, according to previously defined criteria [9].

Cases and controls

All reports of terbinafine-associated taste loss, as reported to the NARD in the period 1 June 1992 through 31 December 1993 were eligible for enrolment in the study. The causal relationship was considered as 'probable' if there was a compatible temporal relationship between the intake of terbinafine and the onset of taste loss, and if no other likely causes were present. These 'probable' cases were enrolled. After obtaining permission from the reporting general practitioner (GP), we approached the pharmacy of the patient to ask for a complete printout of all users of terbinafine who had been prescribed terbinafine by the same GP. Controls were all users of terbinafine without taste loss who had filled one or more prescriptions from the same pharmacy and GP. All drug exposure and medical data of patients were anonymized, and hence no formal informed consent of patients was required according to the Dutch privacy legislation.

Risk factors

The date of first symptoms of the case was defined as the index date. Controls from the same pharmacy and GP were allocated the index date of the case. Potential risk factors were sought in concomitant intake of other drugs, daily nutrient intake, alcohol intake, smoking, general health and medical history prior to the index date, as obtained through a self-administered questionnaire sent to cases and controls. Anonymous computerized drug dispensing histories of cases and controls served to investigate exposure to inhibitors of cytochrome P450 (e.g. cimetidine, ketoconazole), or to other drugs which have been associated with taste loss, and to confirm use of terbinafine and prescription dates. For each prescription of a specific drug other than terbinafine, the duration of use (exposure window) was estimated from the number of dispensed tablets divided by the prescribed number of tablets or capsules per day. A case or control was considered as exposed to a concomitantly used drug if the index date fell within the exposure window as defined above, or if the index date followed the last day of the exposure window with a maximum of 30 days in order to correct for carry-over effects and undercompliance.

Data analysis

Cases and controls were only included in the analysis if we received both the questionnaire and the computerized drug history and if the case or control confirmed current or past use of terbinafine. A comparison was made of basic characteristics between cases and controls, e.g. as to age, gender, body mass index (BMI), dose and duration of use of terbinafine, dietary habits, and potential risk factors for taste loss or alteration. In a second analysis, cases were only included if their taste had recovered for at least 2 months at the time of the questionnaire. This was done because taste loss itself might have led to a reduced intake of nutrients.

The analysis of nutrient intake was based on previously defined criteria [10, 11] and Dutch validated food tables [12–14]. Energy-adjusted nutrient intake values were calculated as the specific nutrient intake divided by the total daily intake of kjoules, and analysed according to the multivariate nutrient density model [11, 15]. Questionnaires were considered unacceptably incomplete if more than 56 (out of 141) of the items were left blank *and* less than 32 items were eaten at least once a month [16]. The prevalence of risk factors was compared between cases and controls and expressed as an odds ratio with a 95% confidence interval [17]. Variables for which the distribution was significantly different between cases and controls in the univariate analysis, were included in the stratified analysis, and in a multivariate analysis according to both unconditional and conditional logistic regression models. As there were no substantial differences between the conditional and unconditional regression analyses, only the results of the unconditional one are given below. All analyses were done on a microcomputer with SPSSPC (version 5.0.2) as a statistical package. One-tailed chi-square trend analyses were performed with EpiInfo (version 5).

Results

From 1st June 1992, the NARD received 117 reports of taste loss or alteration probably caused by terbinafine. Questionnaires were sent to all 115 cases and 622 controls of which computerized drug dispensing data were available. A response was received from 506 (68.7%) of which 22 were incomplete. There was no difference in age and gender between responders and non-responders.

Questionnaires were returned by 87 cases (75.6%) and 397 (63.7%) controls. Thirty-five controls were excluded: 22 because they mentioned taste loss as an adverse effect to terbinafine in the questionnaire but were unvalidated as they did not consult their general practitioner, and could therefore not be included in the group of cases; the rest because they stated that they had never used terbinafine. Hence, the total study population consisted of 87 cases and 362 controls.

The study population comprised 171 men and 278 women with a mean age of 49 and 48 years respectively. Basic characteristics of cases and controls are given in Table 1. There was an age-related risk increase with an odds ratio of 4–5 in patients of 55 years and older as compared to those with an age of up to 35 years. Cases had a lower weight and BMI than controls. In a second analysis in the 84 cases who had recovered from taste loss for at least 2 months when completing the questionnaire, patients with a BMI below 21 kg m^{-2} had a fourfold increase in the risk of developing taste

Table 1 Description of the study population

	Cases (*n*=87)	*Controls* (*n*=362)	*Odds ratio* (*95% CI*) P *value*
Women/men	62/25	216/146	1.6 (0.98–2.9)
Age (years)	53	48	
<35 years	5 (5.7%)	61 (16.9%)	1.0 (reference)
35–44 years	23 (26.5%)	85 (23.4%)	**3.3 (1.1–11.7)**
45–54 years	17 (19.5%)	105 (29.0%)	2.0 (0.7–7.2)
55–64 years	24 (27.6%)	61 (16.9%)	**4.8 (1.6–17.0)**
≥65 years	18 (20.7%)	50 (13.8%)	**4.4 (1.4–16.1)**
		Chi-square trend: ***P*=0.004**	
Height (cm)	171.4 (s.d.: 8.2)	172.0 (s.d.: 9.4)	
Weight (kg)	68.9 (s.d.: 11.0)	72.5 (s.d.:14.4)	
Body mass index (BMI)	23.4 (s.d.: 2.8)	24.6 (s.d.: 4.4)	
BMI > 27.0 kg m^{-2}	6 (7.1%)	68 (19.3%)	1.0 (reference)
BMI 24.1–27.0 kg m^{-2}	25 (29.8%)	105 (29.7%)	**2.7 (1.01–8.4)**
BMI 21.1–24.0 kg m^{-2}	32 (38.1%)	126 (35.7%)	**2.9 (1.1–8.8)**
BMI < 21.1 kg m^{-2}	21 (25.0%)	54 (15.3%)	**4.4 (1.6–14.2)**
		Chi-square trend: ***P*=0.004**	
Caucasian race	85 (97.7%)	342 (94.5%)	2.5 (0.6–22.3)
Higher education	29 (33.3%)	84 (23.2%)	1.7 (0.96–2.8)
Read product leaflet	85 (97.7%)	346 (95.8%)	2.0 (0.5–17.9)
Sucked/bit tablets	4 (4.6%)	11 (3.0%)	1.5 (0.4–9.4)
History of taste loss	3 (3.4%)	—	***P*=0.007**
Concurrent use of			
Cytochrome P_{450} inhibitors	—	4 (1.1%)	*P*=0.7
Character of taste loss			
Sweet perception	71 (81.6%)		
Salt perception	69 (79.3%)		
Sour perception	64 (73.6%)		
Spicy food perception	64 (73.6%)		
Bitter perception	62 (71.3%)		
Foul taste	35 (40.2%)		

Odds ratios significantly different from unity are printed in bold.

loss when compared with those with a BMI of more than 27 kg m^{-2}. This risk increased to 12.8 in patients of 55 years and older with low BMI, showing that age acted as an effect modifier (Table 2). The risk of taste loss in patients of 55 years and more with a BMI below 21 kg m^{-2} was 15.8 times higher than in patients below 35 years of age with a similar BMI (95% CI: 1.8–190.8). Additional stratification by gender showed a similar risk in females in the high risk group above 55 years of age with a BMI below 21 kg m^{-2}. Due to low numbers, a stratified risk assessment in males could not be made. Three out of the 87 patients had a history of taste loss before using terbinafine, compared with none of the controls. There were no differences between cases and controls regarding the number of concurrent symptoms or preceding illnesses and operative procedures, as associated with taste or smell loss in the medical literature [18, 19]. The mean latent period between first intake of terbinafine and taste loss or alteration was 35 days (s.d.: 18.7; median latent period: 35 days). The duration of use in cases was shorter than in controls as most cases stopped terbinafine because of taste loss. There was no difference in dose between cases and controls as almost all patients were treated with 250 mg daily. Although the duration of taste loss was not exactly known in most of the patients, all recovered within 4 months of discontinuation of terbinafine. Concurrent smell loss occurred in 12 cases (13.8%) and one (0.3%) control (odds ratio 57.8; 95% CI: [8.2–2475]). Four cases and 11 controls did not swallow their tablets with a glass of water but bit or sucked on the tablets. There were no cases in wich other drugs associated with taste loss [18] were used in the risk window. None of the cases and four controls had used potential inhibitors of cytochrome P450, mainly erythromycins and H_2-receptor blocking antihistamines (e.g. cimetidine). Of the cases, 32% were smokers as against 37% of the controls ($P=0.36$).

As a low BMI may result from anorexia and subsequent weight loss due to taste loss, we conducted a separate analysis of all patients who had completed the questionnaire later than 2 months after complete recovery of their taste perception. Also in this group of 61 cases, however, BMI was significantly lower in cases than in controls. The overall intake of food nutrients in cases and controls was not significantly different. The absolute intake of total protein and zinc, however, was lower in cases than in controls (Table 3). In an unconditional logistic regression model with all variables which were significantly associated with taste loss in the

Table 2 Stratification by age and body mass index (BMI)

	Cases (n=84)	*Controls (n=353)*	*Odds ratio (95% CI)*
<35 years			
BMI > 27.0 kg m^{-2}	—	5	—
BMI 24.1–27.0 kg m^{-2}	1	9	1.0 (Reference)
BMI 21.1–24.0 kg m^{-2}	2	24	0.8 (0.04–49.1)
BMI < 21.1 kg m^{-2}	2	21	0.9 (0.04–56.1)
35–54 years			
BMI > 27.0 kg m^{-2}	2	29	1.0 (Reference)
BMI 24.1–27.0 kg m^{-2}	11	56	2.9 (0.6–27.9)
BMI 21.1–24.0 kg m^{-2}	14	74	2.7 (0.6–26.2)
BMI < 21.1 kg m^{-2}	13	29	**6.5 (1.3–63.0)**
≥55 years			
BMI > 27.0 kg m^{-2}	4	34	1.0 (Reference)
BMI 24.1–27.0 kg m^{-2}	13	40	2.8 (0.8–12.6)
BMI 21.1–24.0 kg m^{-2}	16	28	**4.9 (1.3–21.9)**
BMI < 21.1 kg m^{-2}	6	4	**12.8 (1.9–88.6)**

Odds ratios significantly different from unity are printed in bold

Table 3 Stratified daily intake of kjoules, protein, nicotinic acid and zinc

	Cases (n=61)	*Controls (n=326)*	*Odds ratio (95% CI)*
Kjoules			
Upper tertile	14	116	1.0 (Reference)
Middle tertile	25	104	2.0 (0.9–4.4)
Lower tertile	22	107	1.7 (0.8–3.8)
Protein			
Upper tertile	12	119	1.0 (Reference)
Middle tertile	22	105	2.1 (0.9–4.8)
Lower tertile	21	108	**2.6 (1.2–5.8)**
Nicotinic acid			
Upper tertile	20	110	1.0 (Reference)
Middle tertile	16	117	0.8 (0.4–1.6)
Lower tertile	25	100	1.4 (0.7–2.8)
Zinc			
Upper tertile	12	118	1.0 (Reference)
Middle tertile	18	111	1.6 (0.7–3.8)
Lower tertile	31	98	**3.1 (1.5–7.0)**

Odds ratios significantly different from unity are printed in bold

	Upper tertile:	*Median:*	*Lower tertile:*
Kjoules	> 10 925	9182	< 8057
Protein	> 105.5 g	90.9 g	< 79.4 g
Nicotinic acid	> 11.8 mg	9.6 mg	< 8.3 mg
Zinc	> 11.7 mg	9.8 mg	< 8.6 mg

univariate analysis, only age and BMI remained significant risk factors. In this model the odds ratio increased up to 22 for patients of 55 years of age and older with a BMI below 21.1 compared with those of the same age group with a BMI beyond 27.0 (95% CI: 4.4–106.8). In this final model, every year of age increased the risk for taste loss by 6% (95% CI: 3–9%) and every decrease of BMI-units of 1 kg m^{-2} increased the risk by 18% (95% CI: 8–27%).

Discussion

Unlike the approach which is followed in a traditional case-control study, it was not our intention to study whether terbinafine may cause taste loss. The reason is that its relatively high frequency of 0.1 to 1% [8], the close temporal relationship with its intake, and the absence of other likely explanations mean that this adverse effect to terbinafine may be considered as

proven. Instead, we studied other determinants by comparing those in patients with taste loss on terbinafine with those in patients on terbinafine without taste loss, in order to gain insight into potential risk factors and mechanisms.

In this case-control study, cases were of older age and had a lower weight and BMI than controls. Weight loss has been attributed to taste distortion but seems to be less common with taste loss [20]. As some of our patients had taste loss whereas others had incomplete taste loss with alteration and taste distortion, we decided to restrict the analysis to the cases in which a complete recovery had occurred at least 2 months earlier. Hence, this excluded the possibility that a relatively low BMI was explained by the fact that patients with taste disturbances might tend to suffer from weight loss due to anorexia, as refeeding after temporary weight loss usually results in regaining one's original weight within 2 months [21]. No other conditions or recognized drug-induced causes were associated with taste loss in our patients. This is not surprising, as the assessment of the 'probable' causal relationship required a temporal relationship with the intake of terbinafine and the exclusion of other likely causes. Cases had, however, a lower absolute daily intake of protein and zinc which might be meaningful as protein and zinc deficiencies are well-known causes of taste disturbances [18]. Although the daily intake of zinc of 9.7 mg is below the daily requirement of 15 mg in adults [22], it should be noted that controls also consumed less than this requirement. Moreover it should be emphasized that food questionnaires are not reliable for the assessment of absolute daily intake. Even so, there was a dose-response relationship as the risk increased with declining daily intake of zinc and protein.

In this study, we had no prior specific hypotheses as to the mechanism of taste loss to terbinafine. Taste loss may result from local atrophy or injury by physical or chemical causes, damage to neural projections (e.g. by trauma or surgery), a disturbance in the cycle of regeneration (e.g. by malnutrition, metabolic disturbances or radiation), or from a modification in receptor cell population (e.g. by drugs or altered saliva). Also, ageing is known to lead to a decrease in taste and smell acuity by a decrease in receptor population and function [19]. Although the mechanism of taste loss to terbinafine is unknown, it is likely that it concerns an idiosyncratic reaction as this adverse effect is fairly uncommon. A recent estimate by the manufacturer is 1 : 800 treated patients [8]. As this was based on spontaneous reports, however, the true incidence may be higher. Apparently, such patients are relatively vulnerable to a toxic effect of terbinafine or one of its metabolites. Terbinafine is extensively metabolised in humans, mainly by *N*-demethylation, *N*-oxidation, alkyl side-chain oxidation or arene oxide formation, and subsequent conjugation and renal excretion [1]. Although impaired hepatic function does not appear to affect C_{max} and t_{max}, plasma clearance was decreased by approximately 30% in such patients as compared to healthy volunteers, resulting in markedly increased AUC values. In patients with impaired renal function, the terminal plasma elimination half-life was longer than in healthy volunteers (23.8 *vs* 16.8 h) [1]. In view of the low number of patients reporting renal or liver disease, it is unlikely that a decrease in liver or kidney function explains the risk for taste loss by a decreased excretion. Alternatively, the lower BMI in our elderly patients could be in line with a distribution which differs from young patients with a high BMI. As terbinafine is highly lipophilic, one might speculate that a lower BMI is associated with higher levels at the site of injury. As there is an intrasubject variability of 36.8% of the elimination, other temporary factors (e.g. diet) may play an additional role [23, 24]. It is unlikely that terbinafine exerts its effect on taste by a direct effect on the mucosa. First, regeneration of taste buds usually takes less than 14 days whereas in most patients full recovery of taste took several months. Second, a direct injurious effect to the mucosa is not a likely explanation as the large majority of patients swallowed terbinafine with sufficient amounts of water. Neurotoxicity is unlikely in view of the absence of symptoms compatible with central or peripheral neuropathy.

Our study design has some potential limitations, i.e. potential reporting bias and the limited validity of food questionnaires. First, cases were obtained via a national voluntary reporting scheme. This might have introduced reporting bias. Reporting bias will result, for instance, from preferential reporting of cases in which no other causes were found. Since we were interested in risk factors, however, there is no reason why this should have biased our results. Also, patients who visit their GP more frequently might more readily have complained about taste loss, and the GP may have reported this. If more elderly visit their GP, this could explain the age-related effect. A re-analysis including the 22 (non-reported) controls who mentioned taste loss in the questionnaire gave similar results, however, which suggests that reporting bias did not occur. Moreover, reporting bias might result since taste loss was included in the data sheet in The Netherlands in April 1993. Although this might mean that patients tend to recognize and report this effect more readily, such a recognition and reporting bias will not invalidate the assessment of risk factors as the effect of a data sheet will play a role to a similar extent in cases and controls. Even if it were a threat to the validity of our study, this would lead to a conservative risk estimate. A second limitation of our results might originate from the use of food questionnaires. For reasons of efficiency, we used a validated food questionnaire instead of a face-to-face interview. Although the mailing of such a questionnaire has the advantage that patients may complete it at a convenient moment and are not forced to react to questions to which they have no answer, it also has disadvantages. Not all questionnaires were completed as many patients clearly state what they usually eat but are much less explicit about what they never eat. By restricting the analysis to those patients who had completed at least 60% of all questions on food items, however, this problem was largely dealt with. Moreover, the average number of completed food items in cases and controls was the same. As the average daily energy intake per

individual of the population in The Netherlands in 1992 was 9278 kjoules [25], the average daily intake in our study of 8958 kjoules by cases and 10 107 kjoules by controls suggests that the estimation of daily nutritional intake was probably fairly accurate.

In conclusion, our results suggest that low weight and BMI, and ageing are risk factors for taste loss to terbinafine. Terbinafine is an effective antimycotic and taste loss is not a life-threatening disorder. Hence, we feel that these data do not mean that the drug should not be used any longer. However, prescription of the drug to the elderly with low BMI and low daily intake of nutrients should be carefully followed, especially if they have a history of taste loss.

References

1 Balfour JA, Faulds D. Terbinafine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in superficial mycoses. *Drugs* 1992; **43**: 259–284.

2 Villars VV, Jones TC. Special features of the clinical use of oral terbinafine in the treatment of fungal diseases. *Br J Dermatol* 1992; **39**: 61–69.

3 Van't Wout JW, Herrmann WA, De Vries RA, Stricker BHCh. Terbinafine-associated hepatic injury. *J Hepatol* 1994; **21**: 115–117.

4 Juhlin L. Loss of taste and terbinafine. *Lancet* 1992; **339**: 1483.

5 Ottervanger JP, Stricker BHCh. Loss of taste and terbinafine. *Lancet* 1992; **340**: 728.

6 Stricker BHCh, De Jong PAC, Schreuder F, Bijlmer-Iest JC, Herrmann WA, Van Ulsen J. Smaakverlies tijdens gebruik van terbinafine. *Ned Tijdschr Geneeskd* 1992; **136**: 2438–2440.

7 Van Damme PA. Smaakverlies tijdens gebruik van terbinafine. *Ned Tijdschr Geneeskd* 1992; **137**: 617.

8 Beutler M, Hartmann K, Kuhn M, Gartmann J. Taste disorders and terbinafine. *Br Med J* 1993; **307**: 26.

9 Stricker BHCh. Bijwerkingen van geneesmiddelen: de causaliteitsbeoordeling. *Ned Tijdschr Geneesk* 1989; **133**: 275–280.

10 Willett W. Food frequency methods. In *Nutritional Epidemiology*, ed Willett W. Monographs in Epidemiology and Biostatistics vol.15 1990: 69–91. Oxford University Press, New York Oxford.

11 Hulshof KFAM, Kistemaker C, Huldij JC, Meulmeester JF, Kempen-Voogd R. Validation of a food consumption study among men 35 years of age. *CIVO-TNO report no. V86.547/160513*, 1986. Zeist, The Netherlands.

12 Schneijder P, Kistemaker C, Van Erp-Baart AMJ. The compilation and processing of a questionnaire for the assessment of retinol intake among women 15–45 years of age. *CIVO-TNO report no. V92.355*, 1992. Zeist, The Netherlands.

13 Voorlichtingsbureau voor de voeding. NEVO table. *The Dutch composition table 1989–1990*. 1989. The Hague, The Netherlands.

14 Willett W. Implications of total energy intake for epidemiologic analyses. In *Nutritional Epidemiology* ed Willett W. Monographs in Epidemiology and Biostatistics vol. 15 1990: 245–271. Oxford University Press, New York Oxford.

15 Jain M, Cook GM, Davis FG, Grace MG, Howe GR, Miller AB. A case-control study of diet and colorectal cancer. *Int J Cancer* 1980; **26**: 757–768.

16 Goldbohm RA, Van den Brandt PA, Brandts HAM, Van 't Veer P, Al M, Sturmans F, Hermus RJJ. *Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer*. Doctoral thesis. Maastricht University 1994.

17 Kahn HA, Sempos CT. Statistical methods in epidemiology. *Monographs in epidemiology and biostatistics,* 1989; vol. 12. Oxford University Press. New York Oxford.

18 Schiffman S. Taste and smell in disease (part 1). *N Engl J Med* 1983; **308**: 1275–1279.

19 Schiffman S. Taste and smell in disease (part 2). *N Engl J Med* 1983; **308**: 1337–1343.

20 Mattes RD, Cowart BJ, Schiavo MA, *et al.* Dietary evaluation of patients with smell and/or taste disorders. *Am J Clin Nutr* 1990; **51**: 233–240.

21 Davidson S, Passmore R, Brock JF, Truswell AS. Starvation and anorexia nervosa. In *Human nutrition and dietetics.* ed Davidson S, Passmore R, Brock JF, Truswell AS. 7th ed. 1979: 237–243. Churchill Livingstone Edinburgh.

22 Rosenberg IH. Nutrition and nutritional requirements. In *Harrison's principles of internal medicine*. 1991; 12th ed.: 1991: 403–405. McGraw-Hill, New York.

23 Kovarik JM, Grass P, Kutz K. Inter- and intraindividual variation in terbinafine pharmacokinetics (Abstract). *Naunyn-Schmiedeberg's Arch Pharmacol* 1992; **346** (suppl 1):R37.

24 Kovarik JM, Kirkesseli S, Humbert H, Grass P, Kutz K. Dose-proportional pharmacokinetics of terbinafine and its N-demethylated metabolite in healthy volunteers. *Br J Dermatol* 1992; **126** (suppl 39): 8–13.

25 Anonymous. Zo eet Nederland, 1992. Resultaten van de voedselcomsumptiepeiling. *Voorlichtingsbureau voor de voeding*. Ten Brink, Meppel 1993.

(*Received 5 January 1996, accepted 13 March 1996*)