＜考察＞

今回の初回の KANA の得点は金子らの報告とほぼ同じでありテストの施行方法に問題はないと思われた。しかし、今回の個人成績の経時変化を調べると 3 回目、4 回目で有意な得点の増加が認められた。一方 MMSE の成績は減少傾向が認められた。KANA 成績の増加は実際に認知機能が改善したというより、KANA を繰り返し施行することによる学習効果だと考えられる。これは同時に行った MMSE の点数との相関が 2 回目までは認められるものの、3 回目、4 回目での相関がなくなることと矛盾しない。これらの結果は KANA が個人の知的機能の経時変化を正しく反映しないことを示唆している。おそらく、3 回目の施行から文の内容を追わずに文字列から「あいうえお」だけをピックアップする方略をとるようになった結果だと考えられる。今後、テストの後に問題文の内容を理解しているかどうかを問う質問を追加して得点の補正を行うなどの工夫が必要である。しかし、今回の結果は必ずしも KANA の有用性を否定するものではない。初回の KANA 成績は MMSE 得点と相関が認められたことは、少なくとも初回の施行であればその利便性からスクリーニングテストとしての有用性は明らかである。これまで同じ母集団について野口らは KANA の成績と UCLA 孤独感尺度得点と有意な負の相関を見出している 9)。また原岡は先行研究のなかで、5 年間で KANA の得点が上昇した群は下降した群に比べて、生き甲斐満足度が有意に高いことを報告している 1)。

　　　MMSE は世界的に共通して行われている知的機能検査で信頼性も高い。Jacqmin-Gadda H らは 2537 名の健常高齢者に対して MMSE の 5 年間の経時変化を調べ、初回テストでは緊張により低得点となり、2 回目では慣れや学習効果により得点は増加し、2 年から 5 年目にかけて若干低下する（65 歳に開始した場合 0.02 点、85 歳に開始した場合 0.57 点低下）ことを報告している 3)。また別の研究では 75 歳以上の一般高齢者 924 名の MMSE 得点の低下は年間平均 0.4 点と報告されており、加齢、女性、教育程度、脳血管障害、収縮期血圧の低下等の様々な因子が関与している 11)。今回の MMSE の結果では得点の低下は認められたもののその幅は 6-8 年間で 1.325 点の減少に留まり Zhu らの報告に比べ少なかった。これは MMSE を希望者のみに施行したことから、特に成績の低下傾向にある参加者ほど検査を忌避する傾向が多く、8 年間で 4 回以上 MMSE が施行されたのは 8 名と少数になったことが影響していると思われる。すなわち今回認められた MMSE の経時変化には参加者のバイアスがかかり、MMSE 得点の低下は Zhu らの報告より少なくなったと思われる。このように MMSE の施行に際し多数の脱落者が出たことは MMSE 検査が精神的苦痛や緊張を伴うことを示唆している。

　　　知的機能の経時変化を追跡するための効果的な認知症のスクリーニング法には被験者の負担が少なく複数の対象者に同時に施行できる簡便なテストバッテリーが求められている 7)。

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A 8 years longitudinal study of Kana-pick out test in non-demented elderly subjects

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The aim of this study is to compare the course of the performance of two psychometric tests during a eight-year period in a cohort of non-demented elderly subjects. We studied Kana-pick out test (KANA) which pick out vowel letters in a fable written by Japanese within 2 minuets and the Mini-Mental State Examination (MMSE) 4 times at baseline(T0), 2 to 3 years(T2), 4 to 5 years(T3) and 6 to 8 years(T4). One Way Analysis of variance with repeated measure showed the improvement of the performance of KANA at T3 and T4. The improvement of the KANA performance at T3 and T4 may be explained by a practice effect induced by repetition of the test. On the other hand, the MMSE performance showed gradually decline with time passes. There was a significant correlation between the score of MMSE and that of KANA at T0 (r=0.44, P<0.0001, n=313).　However, the significance of the correlation was disappeared at T3 and T4. Theses data indicate that KANA used at a first time was a useful screening tool for dementia from general population. However, KANA was inappropriate for observing longitudinal change of cognitive function in a cohort study, because of the improvement of the KANA performance with repetitive use of KANA.

総　説
Overview

特集●総合病院精神医学とメンタルヘルス

Mental Health among Students in Information-oriented Society:

Prevalence and psychological status in relation to Internet addiction

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【要約】　To understand the current prevalence and psychological status of Internet addiction among college students, we evaluated them using the Internet Addiction Test (IAT), the STAI-state, the STAI-trait, the SDS, and the BDI. The first study was performed in a sample of 93 freshmen (78 males and 15 females) of the department of Science and Engineering at Saga University. The second study was performed in a sample of 118 students (42 males and 76 females) of the department of Culture and Education or Agriculture at Saga University. The prevalence rates of Internet addiction among students at the Science and Engineering, and Culture and Education or Agriculture were 7.5%, 17.0%, respectively. Based on our result from four psychological test performed in the second study, a significantly higher score was observed in the Internet addiction group based on the STAI-state, the STAI-trait and the SDS, but no significant difference was found in the BDI score.

According to these results, we emphasized that Internet addiction might be associated with anxiety and depression as it may reflect stressful situations experienced by the subjects. We also introduced psychological problems concerned with mobile phone e-mail addiction encountered in a primary care practice.

INTRODUCTION

The explosive growth of the Internet in the last decade has had a huge impact on communication and interpersonal behavior. Psychological research during the same period has sought to increase understanding of this impact. The Internet was originally designed to facilitate communication and research activities. However, the dramatic increase in the use of the Internet in recent years has led to pathological use (Internet addiction). The effect of Internet addiction includes the impairment of academic performance, psychological well-being, and interaction with peers and family members.

To understand the current status of Internet addiction among college students, this study aims to clarify the prevalence of Internet addiction among students and compares with that in foreign countries. Next, we will evaluate the psychological problems with Internet addiction using several psychological instruments. Third,

it also introduces psychological problems concerned with Internet addiction and mobile phone e-mail encountered in a primary care practice.

SUBJECTS AND METHODS

Subjects

The first study consisted of the 93 first-year students in 2005 of the Saga University who were Science and Engineering students (average age 18.3 ± 0.7 years, 78 men and 15 women). On the other hand, the second study consisted of the 118 first-year students in 2005 of the Saga University who were Culture and Education, or Agriculture students (average age 18.6 ± 1.3 years, 42 men and 76 women). They had attended our lecture of Health Science.

All students provided their fully informed consent to the aims of this research.

Methods

First, we examined that the rate of Internet addiction at the department of Science and Engineering, or culture and education or its of agriculture. Second, we investigated whether there was the relationship between Internet addiction, anxiety and depression.

We selected four types of questionnaire for this study and described below.

Internet Addiction Test (IAT): The Internet Addiction Test (IAT) developed by Young[1] appears in his book, Caught in the Net. This is a simple exercise that helps people in two ways: (1) If patients already know or strongly believe they are addicted to the Internet, this guide will assist them in identifying the areas in their life most impacted by their excessive Net use; and (2) If they are not sure whether they are addicted or not, this will help determine the answer and begin to assess the damage done. When answering, respondents should only consider the time they spent on-line for non-academic or non-job related purposes. The IAT has been already translated into Japanese and can be used by clinicians for screening in their clinic if they want to rule out Internet addiction (Appendix). After patients have answered all the questions, a final score can be obtained by the numbers they selected. The higher their score, the greater their level of addiction and the greater the number of problems their Internet usage causes. Here's a general scale to help measure their score:

20-49 points: You are an average on-line user. You may surf the Web a bit too long at times, but you have control over your usage.

50-79 points: You are experiencing occasional or frequent problems because of the Internet. You should consider itstheir full impact on your life.

80-100 points: Your Internet usage is causing significant problems in your life. You should evaluate the impact of the Internet on your life and address the problems directly caused by your Internet usage.

State-Trait Anxiety Inventory (STAI): The STAI[2] is a measure of trait and state anxiety. The validity of the Japanese version of the STAI was developed and its reliability was highly estimated. It includes two scales: the state form and the trait form. Each scales consists of 20 items that indicate the absent or not of the anxiety symptoms.

Zung Self-rating Depression Scale (SDS): The SDS[3] is a self-report test that was designed as a short simple way of quantifying the severity of depression among patients. Items that were developed to reflect common clinical symptoms among the depressed are balanced: half are positively worded and half are negatively worded. The primary use of the SDS has been in clinical research to monitor treatment effectiveness, but it has also been used in general medical practice as a screening test. The severity of depression was assessed using it for depression ranging 20-80. More than 48 in this SDS indicates a depressive state, 42-47 a borderline state, and 41 or less a normal state.

Beck Depression Inventory (BDI): The BDI[4] is a 22-item questionnaire that emphsizes cognitive rather than somatic symptoms of depression over the past 2 weeks. It is reliable and correlates well with other measures of depression, but may in part assess a general distress or neuroticism factor.

Table 1. Internet addiction and psychological tests

	Control group (N = 73)	Internet addiction group (N = 15)		
	mean (SD)	mean (SD)	t value	p value
STAI-state	42.7 (9.6)	50.8 (16.4)	− 2.101	0.0396
STAI-trait	48.5 (8.9)	59.0 (14.8)	− 2.986	0.0040
SDS	41.4 (6.2)	50.7 (8.7)	− 3.335	0.0015
BDI	7.2 (6.7)	10.8 (7.5)	− 1.786	0.0778

Data analysis

In statistical analysis, the two-tailed χ^2 test, Fisher's Exact test, and two-tailed Student's t test were used. Tests were at the 0.05 level of significance.

RESULTS

The first study

In the assessment of the Science and Engineering students, it was found that the mean IAT score (± standard deviation [SD]) was 26.5 ± 8.6. In this study, we classified them into two group according the total score of the IAT: Internet addiction group (IAT is 40 or more) and control group (IAT is less than 40). Of the 93 students eligible for the study, 7 students (7.5%) were diagnosed as Internet addiction according to this classification. On the other hand, the rate found at the same department performed in 2004 was 5.0% (5 among 100 students). There was not found significant increase in the rate of Internet addiction between the two year ($\chi^2 =$ 0.528, p = 0.5575, using Fisher's exact test).

The second study

The mean IAT score among Culture and Education, or Agriculture students was 31.0 ± 12.9. The rate of Internet addiction was 17.0% (15 among 88 students). There was significant difference between Science and Engineering students and Culture and Education, or Agriculture students ($\chi^2 = 4.571$, p = 0.0325).

According to the psychological tests, the score of STAI-state (men/women), STAI-trait(men/women), SDS, and BDI were 45.2 ± 8.4/42.3 ± 10.7, 49.3 ± 8.0/49.7 ± 10.8, 42.1 ± 7.0, 7.7 ± 6.4, respectively.

With regard to the comparison between the IAT group and control group on the psychological tests, the results were shown in **Table 1**. There were significant differences between the two groups on the following tests: STAI-state, t = − 2.101, p = 0.0396; STAI-trait, t = − 2.986, p = 0.0040; SDS, t = − 3.335, p = 0.0015). Significant difference on the BDI was not observed (t = − 1.786, p = 0.0778).

Overall, college students with Internet addiction or with the tendency of Internet addiction had high level of state and/or trait anxiety. In addition, they also had depressive symptoms from the perspective of the SDS.

DISCUSSION

Addictive use of the Internet is a new phenomenon that many practitioners are unaware of and consequently unprepared to treat. Some practitioners are unfamiliar with the Internet, making its seductive powers difficult to understand. Sometimes its impact on the afflicted person's life is underestimated as many practitioners do not recognize the legitimacy of the disorder. Hence, this paper starts with a review of the diagnostic criteria of Internet addiction to help prepare clinicians for this issue.

Definition of Internet addiction

The best method clinically to detect compulsive use of the internet is to compare it with criteria for other established addictions. Of all the diagnoses referenced in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[5] pathological gambling was viewed

Table 2. Diagnostic criteria for Internet addiction according to DSM-IV[1]

1. Do you feel preoccupied with the internet (think about previous online activity or anticipate the next online session)?
2. Do you feel the need to use the internet with increasing amounts of time in order to achieve satisfaction?
3. Have you repeatedly made unsuccessful efforts to control, cut back, or stop internet use?
4. Do you feel restless, moody, depressed, or irritable when attempting to cut down or stop internet use?
5. Do you stay online longer than originally intended?
6. Have you jeopardized or risked the loss of a significant relationship, job, educational or career opportunity because of the internet?
7. Have you lied to family members, therapist, or others to conceal the extent of your involvement with the internet?
8. Do you use the internet as a way of escaping from problems or of relieving a dysphoric mood (for example, feelings of helplessness, guilt, anxiety, depression)?

as most akin to this phenomenon. Prior research defined internet addiction as an impulse control disorder that does not entail an intoxicant.

Using pathological gambling as a model, Young[2] developed eight items of criteria of Internet dependency that modified the DSM-IV criteria to be used as a screening device to differentiate "dependent" from "non-dependent" users. The questions are shown in **Table 2**.

Patients are considered "addicted" when answering "yes" to five or more of the questions and when their behavior cannot be better accounted for by a manic episode. The cut off score of "five" is consistent with the number of criteria used for pathological gambling and seen as an adequate number of criteria to differentiate normal from pathological Internet use. Official criteria for the diagnosis of Internet Addiction Disorder (IAD) along with more information on IAD and subscription information for the Internet Addiction Support Group (IASG) on Ivan Goldberg's website[6].

Screening devices for Internet addiction

How do patients know if they are already addicted or rapidly tumbling toward trouble? Everyone's situation is different, and it's not simply a matter of time spent on-line. Some patients feel they are addicted with only twenty hours of Internet use, while others who spent forty hours on-line insist it is not a problem to them. It's more important to measure the damage their Internet use causes in their life. What conflicts have emerged in family, relationships, work, or school?

In this study we used the Internet Addiction Test

(IAT) developed by Young for screening. Another scale includes Pathological Internet Use Scale (PIUS) developed by Morahan-Martin and Schumacher[7].

Prevalence of Internet addiction

The prevalence of Internet addiction is shown in **Table 3**. These studies were undertaken using varying instruments, and show that 8-10% of college students have Internet dependence[7-17]. These results were obtained from many college student population studies and are similar to results in this study. However, the prevalence of Internet addiction among college students differed from the department. To compare our data with that in Korea, prevalence rate in Korea is about four times as high as our result in Japan. Further studies are necessary to clarify the factors associated with the prevalence rate of Internet addiction. In addition, primary care physicians may also need data based on community samples.

It is difficult to predict the future prospects of Internet dependence. It might be on the increase, or it may fade out. Before drawing any conclusions about this study, it is necessary to perform a prevalence study of Internet addiction on a large scale in Japan.

Characteristics of Internet addiction

With regard to gender and addiction, Greenberg et al.[18] reported an interesting pattern of gender differences in addictive tendencies (**Table 4**). Analyses on the individual substances and activities revealed that men reported greater level of addiction to cigarettes,

Table 3. Prevalence of Internet addiction among students

Year	Authors	Country	Subjects	Number of Subjects	Percentage of Internet Addiction	Assessment tool
1997	Scherer[8]	South America	college	531	13.0	Internet dependence
2000	Chou & Hsiao[9]	Taiwan	college	910	5.9	IAT
2000	Morahan-Martin & Schumacher[7]	US	college	283	8.1	PIU scale
2001	Anderson[10]	US	college	1,300	9.8	Internet dependence
2001	Wang[11]	Australia	college	293	9.6	IAD
2002	Mingyi[12]	China	college	500	6.4	IAD
2002	Lin & Tsai[13]	Taiwan	high school	753	11.7	Chinese IAS
2004	" Johansson & Gotestam[14]	Norway	12-18 years	3,237	10.7	IAT 40 or more
2004	Sato[15]	Japan	college	242	9.1	IAT 40 or more
2005	Niemz et al[16]	UK	college	371	18.3	PIU scale
2006	Kim et al[17]	Korea	high school	1,573	39.6	IAT 40 or more

(IAT : Internet Addiction Test, PIU : Pathological Internet Use, IAD : Internet Addiction Disorder)

Table 4. Gender Difference in Addiction[18]

Addiction	Gender difference	Addiction	Gender difference
Substances		Activities	
Alcohol	M > W	Exercise	M = W
Cigarettes	M > W	Television	M = W
Caffeine	M < W	Internet use	M > W
Chocolate	M < W	Video games	M > W
		Gambling	M > W

alcohol, video games, gambling, and internet use. On the other hand, women reported greater levels of addiction to chocolate and caffeine. No significant differences were found for exercise or television. Men tend to be addicted to the Internet.

Furthermore, low self-esteem has been linked to addictive behaviors. Armstrong et al. investigated whether low self-esteem was associated with Internet addiction, and found that self-esteem was a good predictor of Internet addiction and amount of time spent online per week. According to Kim et al.[17] the level of depression and suicidal ideation were highest in the Internet-addicts group. Our study indicates that Internet addiction group had significantly high level of anxiety and depression. It might reflect their interpersonal relationship or stressful situation among college students in Japan. Further studies should investigate the direct relationship between psychological health problems and Internet dependence.

Future problems of Internet addiction in primary care practice in Japan

Recently, the use of e-mail on mobile phones among adolescents in Japan has been increasing. New and serious psychological problems have arisen relative to the spread of mobile phones (keitai). Some Japanese adolescents with school refusal use the mobile phone e-mail to communicate with their friends excessively. I encountered two cases of high school students with school refusal in a primary care practice. They sent e-mail to their friends more than 200 times a day. They could not stop using mobile phone e-mail, and then were

Appendix

Internet Addiction Test（IAT）[1]

To assess level of addiction, answer the following questions using this scale: 1 = Rarely, 2 = Occasionally, 3 = Frequently, 4 = Often, 5 = Always.

1. How often do you find that you stay on-line longer than you intended?
2. How often do you neglect household chores to spend more time on-line?
3. How often do you prefer the excitement of the Internet to intimacy with your partner?
4. How often do you form new relationships with fellow on-line users?
5. How often do others in your life complain to you about the amount of time you spend on-line?
6. How often do your grades or school work suffer because of the amount of time you spend on-line?
7. How often do you check your e-mail before something else that you need to do?
8. How often does your job performance or productivity suffer because of the Internet?
9. How often do you become defensive or secretive when anyone asks you what you do on-line?
10. How often do you block out disturbing thoughts about your life with soothing thoughts of the Internet?
11. How often do you find yourself anticipating when you will go on-line again?
12. How often do you fear that life without the Internet would be boring, empty, and joyless?
13. How often do you snap, yell, or act annoyed if someone bothers you while you are on-line?
14. How often do you lose sleep due to late-night log-ins?
15. How often do you feel preoccupied with the Internet when off-line, or fantasize about being on-line?
16. How often do you find yourself saying "just a few more minutes" when on-line?
17. How often do you try to cut down the amount of time you spend on-line and fail?
18. How often do you try to hide how long you've been on-line?
19. How often do you choose to spend more time on-line over going out with others?
20. How often do you feel depressed, moody, or nervous when you are off-line, which goes away once you are back on-line?

exhausted from sending mail all day, which resulted in depression. Kamibeppu and Sugiura [19] found that they used it much more frequently for e-mail than as a phone. Most of them exchanged e-mails between schoolmates, and more than a half of them exchanged e-mails more than 10 times a day. Sociable students estimated that their own keitai was useful for their friendship. But they experienced some insecurity or started staying up late at night engaged in e-mail exchanges, and they thought that they could not live without their own keitai. They had developed addictive and compulsive behavior to e-mail use on mobile phones, which impaired academic performance, psychological well-being, and interpersonal relationships with friends and family members.

As shown in case vignettes of these two high school students, new psychological problems have developed as a result of the change of communication media in Japan. We should pay more attention to adolescents' feelings and then propose possible solutions for problematic behavior among adolescents and students.

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Abstract

情報化社会における学生のメンタルヘルス
—インターネット中毒の有病率と心理的状態—

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　大学生におけるインターネット中毒の有病率と心理状態を理解するために，インターネット中毒度テスト Internet Addiction Test（IAT, Young, 1998），STAI状態不安尺度および特性不安尺度，SDSうつ性自己評価尺度，BDIベック抑うつ質問票を用いて評価した。第1の研究では佐賀大学新入生（理工学部）93名（男性78名，女性15名）を対象に，第2の研究では佐賀大学新入生（文化教育学部＋農学部）118名（男性42名，女性76名）を対象に調査を行った。その結果，インターネット中毒群をIATスコアが40以上と定義した場合，第1および第2の対象のインターネット中毒の有病率は，それぞれ7.5％と17.0％であった。次に，第2の研究対象をインターネット中毒群（IAT≧40）およびコントロール群（IAT＜40）の2群に分け，4つの心理検査の結果を比較検討した。その結果，インターネット中毒群では有意にSTAI-state，STAI-trait，SDSが高く，BDIでは有意差はみられなかった。
　以上の結果から，インターネット中毒は不安や抑うつと関連があり，それは学生がかなりストレスフルな状況を感じている可能性が示唆された。また，最近のプライマリケアの診療場面でみられた不登校児における携帯電話電子メール中毒の問題も紹介した。

Key words：インターネット中毒，有病率，不安，抑うつ，大学生，メンタルヘルス

[Original Article]

Determination of Paroxetine in Human Saliva by Reversed-Phase High-Performance Liquid Chromatography with UV Detection

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Abstract: A rapid and sensitive high-performance liquid chromatographic method was validated and described for determination of paroxetine in human saliva. Following liquid-liquid extraction of the drug and an internal standard (dibucaine), chromatographic separation was accomplished using a C18 analytical column with a mobile phase consisting of 0.05 mol/L sodium phosphate buffer, pH 5.0, and acetonitrile (A 30:70, v/v; B 60:40, v/v). Paroxetine and the internal standard were detected by ultraviolet absorbance at 205 nm. The average recoveries of the drug and internal standard were 92.5% and 89%, respectively. The lower limits of detection and quantification were 1 and 4 ng/ml, respectively, and the calibration curve was linear over a concentration range of 4 ng/ml. The saliva level of paroxetine in patients with depression taking 10 to 40 mg/day of the drug was significantly correlated with the plasma level of paroxetine in each patient ($r=0.617$, $P<0.004$, $n=19$). These data indicate that the saliva level of paroxetine could be a useful marker to predict the plasma level of the drug.

Key words: Paroxetine, Saliva, High-performance liquid chromatography, Fluorescence detection

Paroxetine,(3S-trans)-3((1,3-Benzodioxol-5-yloxy)methyl)-4-(4-fluorophenyl)-piperidine hydrochloride, is a member of class of serotonin selective reuptake inhibitors (SSRI), which an usually used as antidepressants for patients with depression. As paroxetine is metabolized by Cytochrome P450 (CYP) 2D6 and also simultaneously inhibits the CYP2D6 activity, it is easy for the plasma paroxetine to attain a toxic level, resulting in serious adverse effects in patients with depression.

When paroxetine was given with decipramine or imipramine, these concentrations were apt to rise. When the dose of paroxetine rose, its concentration in plasma was liable to rise disproportionately. For example, a patient given 20 mg/day of paroxetine was detected to have 3.3 times the concentration of a patient given 10 mg/day as the max concentration in plasma. A patient given 40 mg/day of paroxetine was detected to have 14 times the concentration of a patient given 10 mg/day as the max concentration in plasma. Thus it is necessary to monitor the plasma level of paroxetine to prevent a toxic level of the drug. Moreover, the monitoring of the drug concentration should be a useful tool to check the drug compliance of the patients. There are several reports to determine the plasma level of paroxetine (Härtter et al, 1994). In the present study, we intended to measure paroxetine concentration in human saliva from patients is a noninvasive way.

MATERIALS AND METHODS

1. Paroxetine and reagents

Paroxetine was kindly donated by Smithkline Beecham Pharmaceuticals (Rio de Janeiro, Brazil). Metanol, HPLC grade, was obtained from J.T. Baker (Phillipsburg, USA). Omnisolv acetonitorile, hexane and isoamyl alcohol were HPLC grade and purchased from Merck (Darmstadt, Germany). Water was deionized and filtered with a Milli-Q water processing system. All other chemicals were purchased from Merck.

A stock solution of paroxetine was prepared at the concentration of 0.1 mg/1 ml in acetontril and 0.05 mol/L sodiumphosphate buffer, pH 5.0, (50:50, v/v), and stored at $-20\pm5°C$.

2. Methods

Saliva samples was obtained from depressed patients who were treated with paroxetine (Aropax, Smithkline Beecham, Rio de Janeiro, Brazil) at daily doses of 30 mg. The extract

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Abbreviations **CYP2D6:** cytochrome P450 2D6, **CV:** coefficient of variation, **HPLC:** high-performance liquid chromatography, **min:** minute, **n:** number of samples, **PAX:** paroxetine, **P value:** probability less than point 0.05 statistically significant, **r:** correlation coefficient, **SSRI:** serotonin selective reuptake inhibitor, **UV detection:** ultraviolet detection, **V:** voltage, **V.s.:** voltage/second

consisted of the addition of 200 mg NaCl, 200 μl of 0.1 mol/L NaOH, 5 ml hexane: isoamyl alcohol (99:1, v/v) and 10 μl of 0.001% dibucaine as internal standard (Gupta,1994) to 1 ml saliva. After shaking in a mechanical horizontal shaker (220 ±10 cycles/min) and after centrifugation at 3,000 rpm for 10 min, 4.4 ml of the organic phase was transferred to conic 10 ml tubes and the organic solvent was evaporated in a centrifugal concentrator (TOMY CC-105) with the addition of 50 μl of 1 M HCl. Paroxetine was reconstituted in 50 μl of the mobile phase, 0.05 mol/L sodium phosphate buffer, pH 5.0, and acetonitrile (50:50, v/v), and 50 μl of hexane by shaking for 1 min in a vortex mixer and 25 μl from the aqueous phase was injected into the HPLC system.

3.　HPLC system

The analysis was performed on an HPLC system consisting of an Eicom Model EPC-300 data processor, an Eicom Model NOD-10 NOx-detector, an Eicom Model column, an Eicom Model Ep-300G liquid chromatograph and an Eicom Model DG-300 degasser. Chromatographic separation was achieved at 30°C on an Eicompak SC-50DS column (3 mmΦ ×150 mm) with a precolumn.

The mobile phase, 0.05 mol/L sodium phosphate buffer, pH 5.0, and acetonitrile (A 30:70, v/v; B 60:40, v/v), was delivered into the HPLC system at a flow-rate of 0.3 ml/min. The ultraviolet detector was set at 205 nm (Zainaghi et al, 2003; Foglia et al, 1997). The retention time of PAX (paroxetine) was 8.87 min.

4.　Calibration curve

The calibration curve was prepared by the addition of 25 μl of standard paroxetine solutions at concentrations of 0.8, 1.6, 2.4, 3.2 and 4 ng/μl of paroxetine in the mobile phase, 0.05 mol/L sodium phosphate buffer, pH 5.0, and acetonitrile (50:50, v/v), to 1 ml of control saliva aliquots with 100 ng of dibucaine as an internal standard, resulting in saliva paroxetine concentrations of 20, 40, 60, 80, 100 and 120 ng/ml. The height ratio of paroxetine versus dibucaine was used for the determination of the paroxetine concentration. Each of spiked saliva was processed as described previously.

5.　Validation of the method

The recovery of paroxetine was determined at three different concentrations in blank saliva 40, 80, and 120 ng/ml. Saliva samples with the drug added at the above concentrations were analyzed according to the procedure proposed. The concentrations of these samples were calculated on the basis of calibration curves constructed from the data for the drugs.

To determine the intra-assay precision, aliquots (n=7) of blank saliva containing the standard solution of paroxetine at concentrations of 40 and 120 ng/ml were analyzed by the method proposed. To determine the inter-assay precision, blank saliva containing the standard solution at the same concentration was analyzed on four consecutive days.

Nineteen patients with major depression disorder taking 10 to 40 mg/day of paroxetine were recruited. Ten to 19 were outpatients and 9 were inpatients. After obtaining informed consent, 10 ml of blood was drawn by venopuncture and saliva was collected with a salivette as previously reported.

Pearson's correlation was used to calculate the relationship between the saliva and the plasma level of paroxetine. A P value less than 0.05 was assessed as statistically significant.

The institutional audit board gave us recognition for this study.

RESULTS

As shown in Fig 1, the chromatogram of a blank saliva extract showed no peaks between 8.5 and 9.5 min. The retention time of paroxetine and dibucaine was 8.87 min and 9.26 min, respectively, as shown in Fig 2. The chromatogram of a saliva extract containing 20 ng/μl of a paroxetine and dibucaine is shown in Fig 3. The peaks of paroxetine and dibucaine in the chromatogram could be clearly detected without any concomitant peak. Paroxetine was detected in the saliva extract of a patient given 30 mg/day at the retention time of 9.0 min and the peak area of 0.53 V.s.

The calibration curve is shown in following linear equation (Fig 4). According to this linear equation, the concentration of paroxetine in his patient has been measured at 5 ng/ml. The recovery rate was 91.5%.

Table 1 shows that other drugs such as flunitrazepam, zopiclone, rebamipide, nizatidine, rilmazafone hydrochloride and etizolam taken by the patient did not interfere with the paroxetine or dibucaine.

Detection at 205 nm, solvent extract with hexane and isoamyl alcohol (99:1, v/v) and the mobile phase, 0.05 mol/L sodium phosphate buffer, pH 5.0, and acetonitrile (A 30:70, v/v; B 60:40, v/v) yielded saliva residue free from interference and showed high values for validation of the method, presented in Table 2, and guaranteed highly precise results.
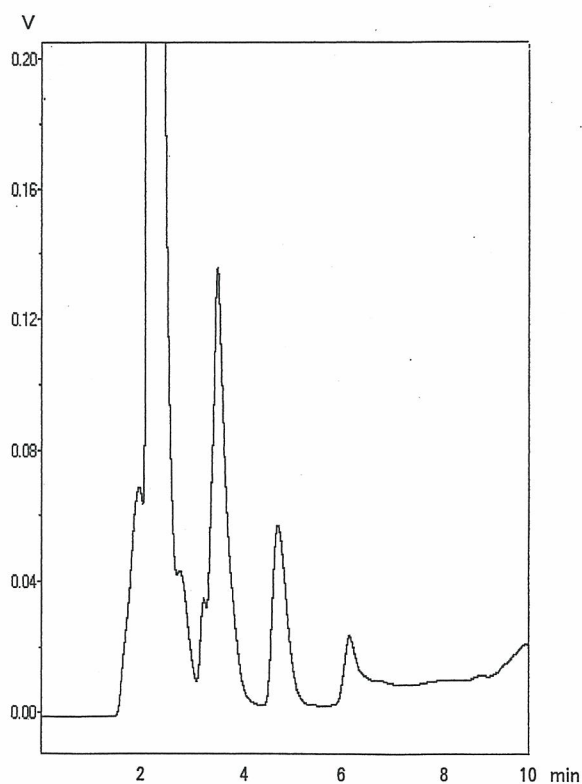

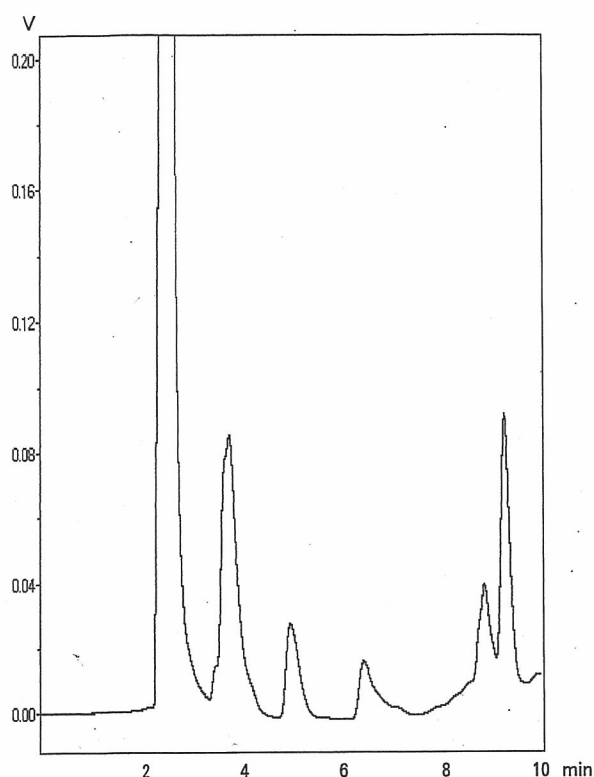Fig. 1　Chromatogram of a blank saliva extract.

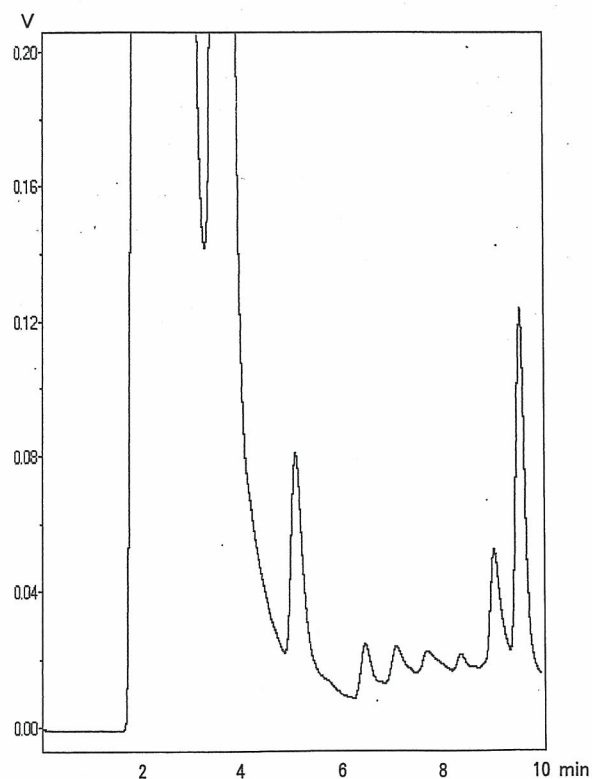Fig. 2   Chromatogram of a saliva extract of paroxetine at the concentration of 20 ng/ml.

Fig. 3   Chromatogram of a saliva extract of a patient given 30 mg/day of paroxetine.
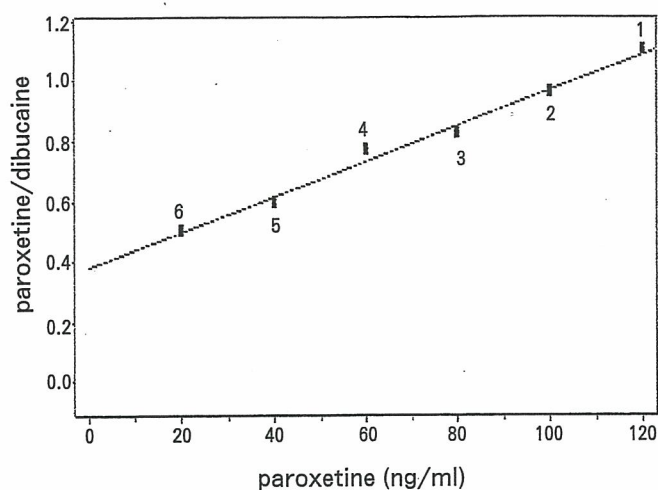

Fig. 4   Calibration curve $Y=0.006X+0.37$. Y: peak-area ratios (paroxetine/dibucaine). X: concentration of paroxetine (ng/ml).

Table 1   Retention time of other drugs besides paroxetine which a patient was prescribed

Durg	Retention time (min)
Flunitrazepam	15.02
Zopiclone	4.33
Rebamipide	3.33
Nizatidine	3.73
Rilmazafone hydrochloride	7.80
Etizolam	12.56

Table 2   Parameter in validation of the method for analysis of paroxetine and dibucaine in saliva samples

Mean (ng/ml)	Precision	
	n	cv (%)
Intra-assay		
40	7	4.3
120	7	2.3
Interassay		
40	4	3.3
120	4	2.0

The saliva level of paroxetine was 32.0 ± 13.0, and the plasma level of paroxetine was 175.3 ± 128.5.

Furthermore, the saliva level of paroxetine in patients with depression taking 10 to 40 mg/day of the drug was significantly correlated with the plasma level of paroxetine in each patient ($r=0.617$, $P<0.004$, $n=19$).

DISCUSSION

There have been many reports about the measurement of paroxetine concentration in breast milk (Spigset et al, 1996; Begg et al, 1999; Hagg et al, 1999; Misri et al, 2000; Stowe et al, 2000; Hallberg et al, 2005). Öhman et al (1999) reported that excretion of paroxetine in breast milk was 25 ng/ml after taking 20 mg/day of paroxetine. The concentration of paroxetine in breast milk was highest at 8 hours after
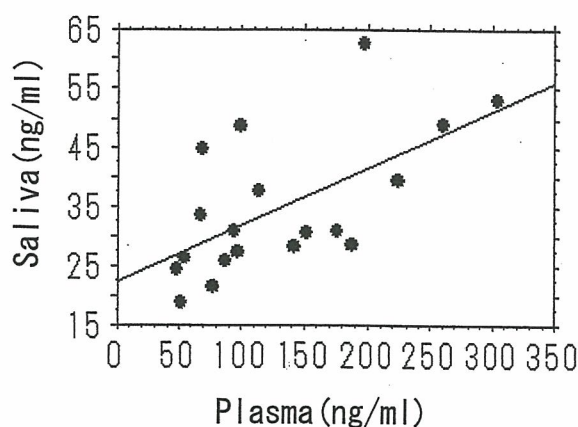
Fig. 5 Correlation between saliva and plasma.

paroxetine intake. The condition of this study was changed from breast milk to saliva. Extract of paroxetine in saliva was 5 ng/ml at a paroxetine intake of 30 mg/day.

Drugs in saliva such as phenytoin and phenobarbital have been detected by arranged UV spectrophotometry (Honda et al, 1978). However, it has not been popular to determine the concentration of drugs in saliva. In this study, we have measured paroxetine concentration in human saliva, which is a noninvasive way to take it from the patients. This is a first report to measure the saliva concentration of paroxetine in patients with depression.

The original mobile phase was used only once in HPLC. But for our new mobile phase two different types of liquid consisting of 0.05 mol/L sodiumphosphate buffer and acetonitrile (A 30:30%, B60:40%) were invented in this study.

These were extremely useful for the present study to detect extracts of paroxetine in saliva by the HPLC method. Furthermore it was important to avoid fluorescence detection. Both the easy way to collect the sample and the low cost may facilitate the measurement and ascertainment of the concentration of paroxetine in saliva more quickly and more frequently in order to provide suitable antidepressant medications.

High linearity was found between the saliva and the plasma

level of paroxetine in patients with depression. These data indicate the saliva level of paroxetine could be a useful marker to predict the plasma level of the drug.

It is necessary to collect a lot of case studies for such subjects to investigate and discover the correlation between concentrations in saliva and amounts of SSRI drug intake which causes serious adverse effects.

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