be considered for an exercise test. However, it is difficult to do such a test in high-risk patients like the acute ischemic stroke patients in this study, making it difficult to diagnose PAD from the ABI alone, particularly when vessels below the knee are involved. Therefore, we defined PAD as being present when either lower extremity MRA or ultrasonography showed severe stenosis or occlusion, or when at least two out of three clinical factors (ABI <0.9, a pulseless artery, and symptoms) were positive. The prevalence of PAD has varied in previous studies, depending on the age distribution of the subjects and the presence or absence of underlying disease.

The majority of patients with PAD are asymptomatic; in fact, only 22% of them have symptoms like leg pain or intermittent claudication[22]. In the present study, no attempt was made to identify PAD on the basis of symptoms such as intermittent claudication for the following two reasons: 1) it is difficult to distinguish PAD from other diseases based on symptoms alone and 2) PAD is usually asymptomatic (most of our patients had early disease).

Our findings were consistent with the results of some previous studies that have addressed the relationship between PAD and ischemic stroke. Risk factors for an abnormal ABI have been investigated by several authors. In the ARIC study, a high total cholesterol level was found to be a major risk factor for PAD[14]. In another study, the non-HDL cholesterol level was more strongly correlated with ApoproteinB than LDL cholesterol as a predictor of coronary atherosclerosis[23]. We found that both non-HDL and LDL levels were higher in men without PAD, while logistic regression analysis showed that the apoprotein A1 level was strongly correlated with the occurrence of stroke in patients who had PAD. However, this was a small sample size and cross-sectional study, so a causal relationship cannot be deduced from our results. Therefore, a large-scale investigation will be necessary to determine the relationship between PAD and ischemic strok.

PAD not only interferes with daily activities and affects QOL, but also worsens the prognosis of patients with ischemic stroke. The present study revealed that that PAD is frequently associated with ischemic stroke, suggesting that it is important to screen stroke patients for PAD.

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末梢動脈閉塞と虚血性脳卒中との関連

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【目的】脳血管障害における末梢動脈閉塞(PAD)の関与を明らかにするために，虚血性脳卒中を対象に末梢動脈閉塞合併率および動脈硬化の危険因子を検討した．

【方法】対象は平成14年7月から平成15年12月まで原三信病院救急外来に救急搬送された虚血性脳卒中と診断された70例（平均年齢71歳）である．NINDS(1990年)の分類に従ってラクナ脳梗塞(LAC)，アテローム血栓性脳梗塞(ATI)，心原性脳梗塞(CE)に分けた．採血，心電図，頭部CT，MRI･MRA，超音波(頸動脈，心，下肢動脈)，下肢造影MRA，フォルム(ABI/baPWV)，ホルター心電図等の検査を施行．下肢造影MRA，下肢動脈エコーで閉塞あるいは有意狭窄を認め，かつABI<0.9，動脈触知不良，自覚症状のうち2つ以上を満たすものをPADと診断した．

【結果】PADの合併は，70例（83.3%）と高率にみられ，病型別では，LACで51例(72.8%)，ATIで7例(10.0%)，CEで12例(17.2%)であった．Fontaine分類では，I度が38例（58.5%)，II度が29例（41.0%）でIII度が3例(0.5%)と，半数以上がI度の無症候性のPADであった．ABIはPAD群で1.09±0.13と非PAD群（1.15±0.08）比較し，低値傾向を示すも有意差は認めなかったが，baPWV，IMTはPAD群が非PAD群と比較し有意に高値を示した．血清CRP，D-D,及びTATでは有意差は認めなかったが，PAD群で高値を示し，HDL-CはPAD群が非PAD群と比較し有意に低値を示した．modified Rankin Scaleは入院時（3.21 vs 2.64）及び退院時（1.96 vs 1.78）のいずれもPAD群が高値傾向を示した．

【考察】虚血性脳卒中にPADを合併した場合，機能予後や生命予後に悪影響を及ぼす可能性があり，PADを早期診断をすることが重要であると考えられた．

Original Article

Efficacy of Intravenous Glycyrrhizin for the Treatment of Chronic Hepatitis C : A Comparison of the Original and Generic Drugs

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ABSTRACT : The utilization of generic drugs in medical practice has been promoted in Japan for the purpose of minimizing drug costs. In order to determine the clinical efficacy of the original preparation of glycyrrhizin, in comparison to its generic drug, a controlled longitudinal study was done of 82 consecutive patients with chronic hepatitis C receiving the original preparation of glycyrrhizin for 6 months. Patients treated with the original preparation of glycyrrhizin for 6 months at two hospitals were separated into two groups for study : Patients who changed from the original preparation of glycyrrhizin to a generic drug and then changed back from the generic drug to the original preparation of glycyrrhizin (Group A, n=46) ; and, patients who were continuously treated with the original preparation of glycyrrhizin (Group B, n=36). HCV RNA levels were serially determined by Cobas Amplicor HCV Monitor assay. In Group A, the ALT level significantly elevated 3 months after switching treatment from the original preparation of glycyrrhizin to the generic drug (from 65.1±22.7 IU/L to 112.4±39.9 IU/L) ($P<0.05$), then significantly decreased 3 months after the change back to the original preparation of glycyrrhizin (from 112.4±39.9 IU/L to 62.1±23.0 IU/L) ($P<0.05$). In Group B, however, the ALT level did not significantly change during the same observation period. The serum HCV RNA level did not significantly change in either group, even in Group A patients whose ALT levels significantly changed. The efficacy on ALT of the original preparation of glycyrrhizin and the generic drugs differed in patients with chronic hepatitis C.

KEY WORDS : glycyrrhizin, chronic hepatitis C, generic drug

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Chronic hepatitis C virus (HCV) infection has become the most frequent cause of chronic liver disease worldwide. Population based surveys in Japan have reported the prevalence of HCV to be 0.7-3.7%.[1-3] Chronic HCV viremia often follows a progressive course over many years and can ultimately result in cirrhosis and hepatocellular carcinoma (HCC).[4,5] Over the past decade, more than 80% of Japanese patients with HCC were found to have chronic HCV viremia.[6,7] The risk of HCC development

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has been reported to be higher in HCV-infected patients who have biochemically and histologically active chronic hepatitis, suggesting that necroinflammation and its associated regenerative processes play a pivotal role in hepatic carcinogenesis.[8] Interferon (IFN) has been shown to eliminate HCV viremia and to reduce serum alanine aminotransferase (ALT).[9-11] However, IFN is not effective for all patients, and is sometimes not possible because of its high cost and side effects. Stronger Neo-Minophagen C® (SNMC), a preparation of glycyrrhizin, is a well-known Japanese medicine that is commonly administered to improve the serum ALT level of chronic hepatitis C patients, especially those resistant to IFN or who relapse after IFN treatment.[12]

SNMC is used for the treatment of allergic diseases and hepatitis in Japan. In 1977, intravenous injection with SNMC was permitted for patients with chronic hepatitis or liver cirrhosis, most of whom were infected with hepatitis viruses.[13] SNMC is reported to be effective for the reduction of elevated ALT levels in patients with chronic hepatitis B[14] and chronic hepatitis C.[15] Recently, van Rossum, TG and colleagues have done serial clinical studies on the pharmacokinetics, effectiveness, and adverse effects in European patients with chronic hepatitis C receiving SNMC.[16-19]

A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. The utilization of generic drugs in medical practice has been promoted in Japan for the purpose of minimizing drug costs ; however, the use of generic drugs has not increased as much as expected. Reasons for this may include concerns about the insufficiency of the information provided on generic drugs, especially about the clinical efficacy.

To determine the efficacy of SNMC (a preparation of glycyrrhizin) and generic drugs, we did a controlled, longitudinal study of Japanese patients with chronic hepatitis C treated with these drugs.

METHODS

Patients

A prospective, controlled study of Japanese patients with chronic hepatitis C was done from 2001 to 2002 in which the efficacy and safety of a single generic glycyrrhizin based drug was accurately compared with SNMC. In the present study, we analyzed the changes of ALT levels and HCV viremic level and the differences of the safety and glycyrrhizin concentration. All 82 patients enrolled in study (43 men and 39 women ; mean±SD age of 63.6±6.0 years ; age range 37-70 years ; serum mean±SD ALT levels at the start of SNMC treatment, 149.9±48.9 IU/L) were seen during routine visits to Kyushu University Hospital, Fukuoka, and Mitsutake Internal Medicine and Circulatory Disease Hospital, Iki Island, Nagasaki, Japan. All patients had serum ALT levels at least 2 times the upper limit of normal (ULN, 35 IU/L) for 12 weeks before SNMC treatment. The SNMC treatment was started for each patient with the aim of normalizing persistently high ALT to reduce the progression of liver disease. After receiving SNMC treatment for 6 months, patients were allocated to the treatment group of their choice : Group A, 46 patients receiving the switching treatment from SNMC to a generic drug, then returning to treatment with SNMC ; and, Group B, 36 patients receiving continuous SNMC treatment. The present study was not randomized, but controlled between the patients of the two hospitals. The Group A patients were followed at Mitsutake Internal Medicine and Circulatory Disease Hospital and the GroupB patients at Kyushu University Hospital. Patient characteristics at the start of the initial SNMC treatment are given in **Table 1**. About 70% of the patients were prior IFN treatment non-responders. No significant differences in characteristics were observed between Group A and B patients at baseline, including height and weight. All patients were positive for serum antibody to HCV and HCV RNA for over 6 months. No patients positive for serum hepatitis B virus surface antigen or antibody to human immunodeficiency virus or having other possible causes of hepatocellular injury, such as autoimmunity or drug-induced liver disease, were included. No patients had received antiviral or corticosteriod therapy within the 12 months prior to inclusion. Needle biopsy of the liver was done for each patient within 6 months before the start of treatment, and two pathologists examined the biopsy specimens independently without previous knowledge of the patients. Using the histological classification by Desmet, et al.[20] and the most widely used "histological activity index" (HAI) by Knodell, et al.,[21] minimal chronic hepatitis (CH) (a score from 1-3 that summed periportal necrosis, intralobular degeneration, and portal inflammation of HAI) was diagnosed in no Group

Table 1. Patient characteristics at baseline

Characteristics	Group A (N=46)	Group B (N=36)	P value
Male N (%)	24 (52.2)	19 (52.8)	NS
Mean body mass index (kg/m²)	23.1	22.9	NS
Mean age (yrs)	63.3	64.6	NS
Prior interferon N (%)	32 (69.6)	25 (69.4)	NS
HCV RNA (100 kIU/ml)	953±246	1156±289	NS
Genotype 1b N (%)	41 (89.1)	31 (86.1)	NS
Cirrhosis N (%)	12 (26.1)	10 (27.8)	NS
Mean ALT level (IU/L)	152.8	150.6	NS
ALT within 2 times ULN N (%)	0−	0−	NS

HCV, hepatitis C virus ; ALT, alanine aminotransferase ; ULN, upper limit of normal (35 IU/L) ; NS, not significant

Baseline is at the start of Stronger-Neo-Minophargen-C treatment.

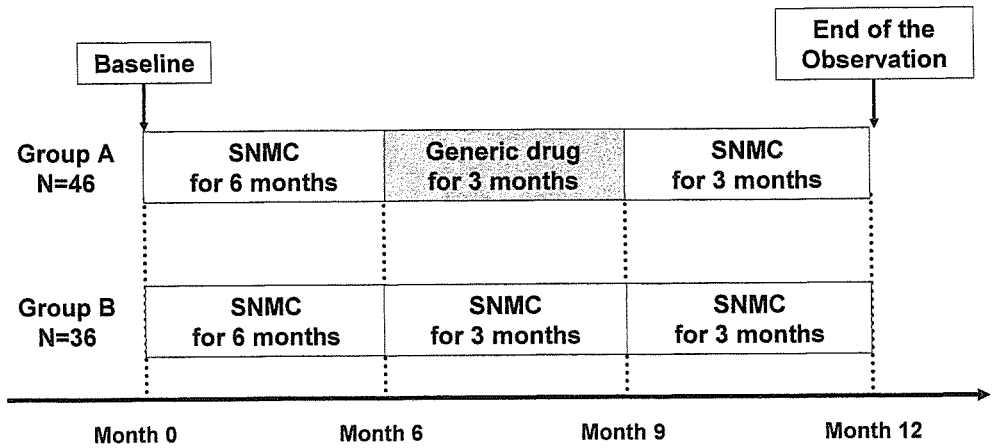


Figure 1. Intervention and study timeline of Group A and B patients. SNMC, Stronger Neo-Minophagen C. Baseline is at the start of SNMC treatment.

A and no Group B patients ; mild CH (a score of 4-8) in 12 Group A and 9 Group B patients ; moderate CH (a score of 9-12) in 11 Group A and 9 Group patients ; severe CH (a score of 13-18) in 11 Group A and 7 Group patients ; and, histologically proven liver cirrhosis (a staging (fibrosis) score of 4 on HAI) in 12 Group A and 10 Group B patients. No significant differences in histological findings were observed between Group A and B patients at baseline. Changes in serum ALT, HCV RNA, the potassium level, and the blood pressure of each patient were measured during the observation period. All patients gave written informed consent before the enrolment of this study. The study was approved by the ethics committee of each hospital. All procedures in the present study were done in accordance with the Helsinki Declaration of 1964 (1996 amended version).

Treatment protocol

Figure 1 shows the intervention and study timelines. The patients of both groups were initially given 60 mL SNMC (Stronger Neo-Minophagen C® , Minophagen Pharmaceutical Co., Ltd, Tokyo, Japan) intravenously three times per week for 6 months (from Month 0 to Month 6). At Month 6, the patients were allocated to the following treatment groups : Group A, 46 who received the switching treatment of the generic drug (Neophagen® , TAIHO Pharmaceutical Co., Ltd, Tokyo, Japan) from Month 6 to Month 9, and then returned for 3 more months of SNMC administration, from Month 9 to Month 12 ; and, Group B, 36 receiving continuous SNMC treatment for 6 months from Month 6 to Month 12. The weekly dosage of each patient was not changed during the observation period.

The package inserts of SNMC and the other generic drugs report that each drug containins 2 mg of

glycyrrhizin, 1 mg of cysteine, and 20 mg of glycine per mL of saline. Neophagen, has the best sales volume of the generic glycyrrhizin drugs sold in Japan.

Serum assay methods

Serum samples were drawn during the observation period and stored at −20°C. They were frozen and thawed only once before doing the qualitative analysis of HCV RNA.

HCV RNA was extracted from 50 μL of serum by Sep Gene RV (Sanko Junyaku, Tokyo, Japan). Complementary DNA was synthesized by the use of random primers and reverse transcriptase (Super Script II ; Life Technologies, Gaithersburg, MD, USA). HCV RNA was detected by 2-stage PCR with primers from the 5' non-coding region of the HCV genome[21] :
5'-CTGTGAGGAACTACTGTCTT-3' (sense) ;
5'-AACACTACTCGGCTAGCAGT-3' (antisense)
in the first stage ;
5'-TTCACGCAGAAAGCGTCTGT-3' (sense) ;
and,
5'-GTTGATCCAAGAAAGGACCC-3' (antisense)
in the second stage.

The HCV RNA genotype of each patient was determined by 2-stage PCR using universal and type-specific primers from the putative core region of the HCV genome by a modification of the method of Okamoto, et al.[22] and our previous report.[5] The genotype nomenclature was based on the system proposed by Simmonds, et al.[23]

Serum HCV RNA levels were determined by the second-generation Cobas Amplicor HCV Monitor assay (COBAS v2.0, Roche Diagnostics Systems, Meylan, France) (Amplicor monitor). The range of the linear relationship provided was 0.5×10^3 international unit per milliliter (kIU/mL) to 850 kIU/mL for Amplicor monitor.[24] Samples over 850 kIU/mL by Amplicor monitor were re-measured after 10 or 100 times dilution to determine accurate HCV RNA levels.

High-performance liquid chromatography

Seventeen generic SNMC drugs are approved for clinical use with patients in Japan. We analyzed the concentration of glycyrrhizin in SNMC and five of the generic drugs (Neophagen® and the other generic drug A (Glyphagen-C®), generic drug B (Hishipagen-C®), generic drug C (Kyominotin®), and generic drug D (Kebera-S®)) by a validated high-performance liquid chromatographic (HPLC) method. Neophagen and the generic drugs A to D were the top five sold in the Japanese market at the time of the study. The concentration of glycyrrhizin was determined by HPLC from 3 different lots of each drug. Five mL methanol was added to 10 μL aliquots of 20-times diluted saline from each drug. After mixing and centrifugation, the supernatant was decanted into another test tube with flushing nitrogen and evaporated at 50°C. After vortexing and centrifugation, 10 μL of the supernatant was injected into the HPLC system. The extract was separated on a Shimadzu-ODS (M) (Shimadzu, Kyoto, Japan) column with an acetonitrile/citrate buffer at a flow of 0.8 mL/min at the ambient temperature. Detection was ultraviolet absorption at 254 nm with the diode array detector by Shimadzu-C-R4A (Shimadzu).

Statistical Analysis

Continuous data were expressed as mean values± standard deviation (SD) of the mean. Statistical differences in the continuous data were determined by paired t-test, unpaired t-test, Kruskal-Wallis test, or Wilcoxon signed rank test, and categorical data were compared by chi-square test and Fisher's exact test.

A P value less than 0.05 was regarded as being statistically significant.

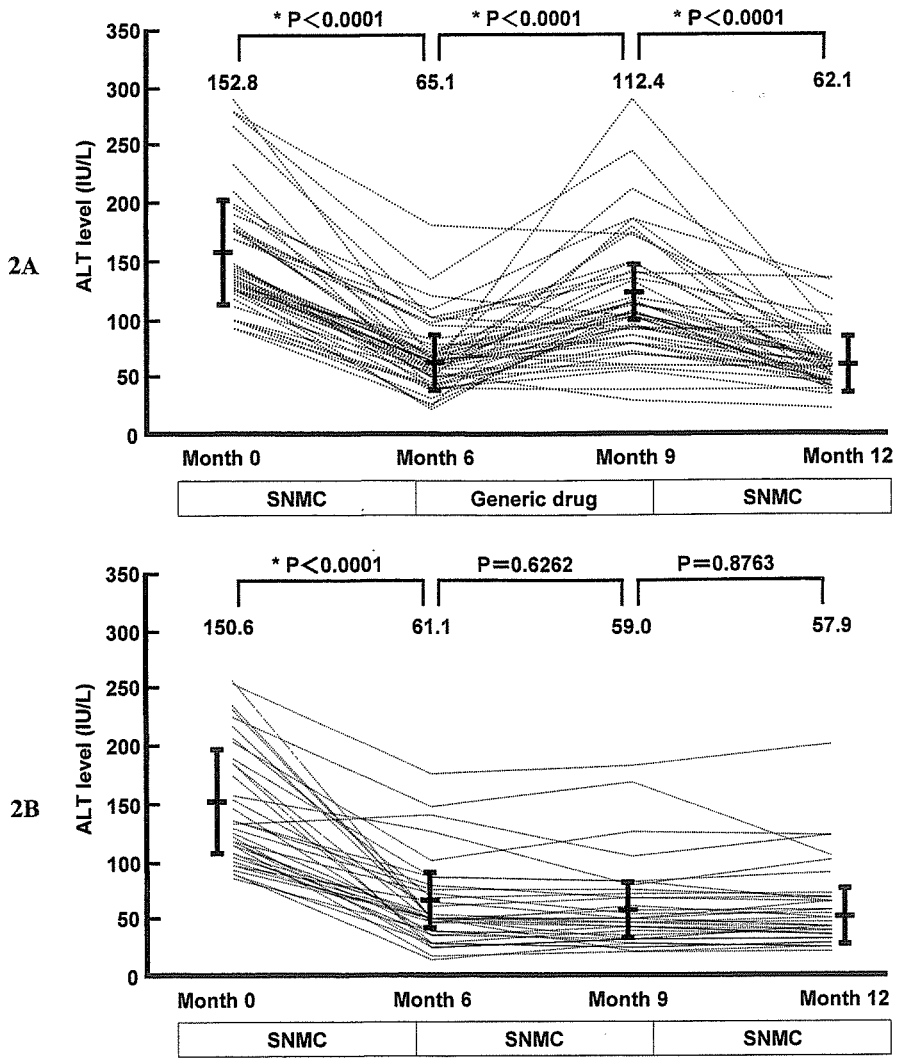
Conflict of Interest

We have no financial interests linked to this study.

RESULTS

Biochemical response to the initial SNMC treatment

After initial treatment with SNMC from Month 0 to Month 6, both Group A and Group B patients showed a significant decrease in mean ALT levels : Group A from 152.8±50.1 IU/L to 65.1±22.7 IU/L, and Group B from 150.6±49.2 IU/L to 61.1±30.7 IU/L (both $P < 0.0001$) (**Figures 2A and 2B**). The number of patients in both groups with an ALT level within 2 times ULN by SNMC, which indicated good response to SNMC, significantly increased during the period : Group A from 0% (0 of 46) to 73.9% (34 of 46), and Group B from 0% (0 of 46) to 75.0% (27 of 36) (both $P < 0.0001$). No significant difference in good response to SNMC was found between Groups A and B. Also, no



Figures 2A and 2B. Changes in serum alanine aminotransferase (ALT) levels in Groups A and B during the observation period. Figure 2A : Group A patients. Figure 2B : Group B patients. SNMC, Stronger Neo-Minophagen C.

significant difference between histological findings and response to SNMC was found either in Groups A or B.

Comparison of biochemical response of the switching and continuous treatment groups

From Month 6 to Month 9, Group A showed a significant increase in mean ALT levels (from 65.1±22.7 IU/L to 112.4±39.9 IU/L) ($P<0.0001$), whereas Group B showed no significant change (from 61.1±30.7 IU/L to 59.9±29.9 IU/L) ($P=0.6262$) (**Figures 2A and 2B**).

Figure 3 shows the rate of times increase of the serum ALT level of each patient from Month 6 to Month 9. In 46 Group A patients the following increases in ALT were observed : less than 1.25 times in 11 (23.9%) ; 1.25 times to 1.4 times in 9 (19.6%) ; 1.5 times to 1.9 times in 12 (26.1%) ; 2.0 times to less than 2.9 times in 7 (15.2%) ; and, 3.0 times or over in 7 (15.2%). For 36 Group B patients, the results were less than 1.25 times in 31 (86.1%) ; 1.25 times to less than 1.4 times in 4 (11.1%) ; 1.5 times to less than 1.9 times in 1 (2.8%) ; 2.0 times to less than 2.9 times in none ; and, 3.0 times or over in none.

A significant increase in mean ALT level was observed for the 34 Group A patients who had good response to the initial 6 months of SNMC treatment (from 41.9±9.9 IU/L to 110.0±48.8 IU/L) ($P<0.0001$). However, no significant increase was observed for the remaining 12 Group A patients without a good response (102.7±40.9 IU/L and 124.3±51.3 IU/L) ($P=0.0921$).

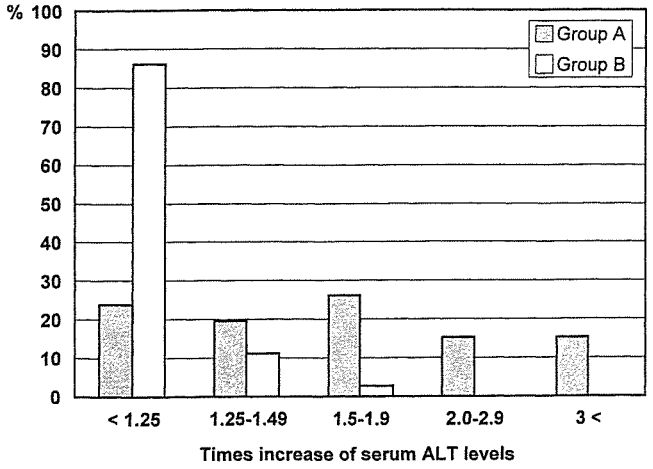


Figure 3. The rate of times increase of serum alanine aminotransferase (ALT) levels in Groups A and B from Month 6 to Month 9.

Table 2. Concentration of glycyrrhizin in SNMC and the five generic drugs, by the HPLC method

	Glycyrrhizin concentration	
	mg/ml**	Ratio to SNMC (%)
SNMC	2.00	—
Neophagen*	1.71	85.9
Generic drug A	1.88	94.4
Generic drug B	1.58	79.1
Generic drug C	1.65	82.7
Generic drug D	1.64	82.3

SNMC, stronger neo-minophagen C ; HPLC, high-performance liquid chromatographic

*was used in Group A patients of the present controlled study.

**shows the mean values from 3 different lots of each drug

The Group A patients returning to treatment with SNMC after switching to the generic drug showed a significant decrease in mean ALT level from Month 9 to Month 12 (from 112.4±39.9 IU/L to 62.1±23.0 IU/L) ($P<0.0001$) (**Figure 2A**). Continuous SNMC treatment of Group B patients resulted in no significant change of the mean ALT level during the same period (from 59.9±29.9 IU/L to 57.9±32.2 IU/L) ($P=0.8763$) (**Figure 2B**).

The above analysis was done in patients classified by histological findings and no significant difference between histological findings and treatment response was found either in Groups A or B.

Comparison of Virological response to switching and continuous treatment

The mean HCV RNA levels at Months 0, 6, and 9 were 953±246 kIU/mL, 1163±222 kIU/mL, and 1052±210 kIU/mL in Group A, and 1156±289 kIU/mL, 1313±249 kIU/mL, and 1284±328 kIU/mL in Group B. No significant differences in serum mean HCV RNA levels during the period were observed in either Group A or B patients. No patients had viremic clearance during the treatment.

Comparison of adverse reactions to switching and continuous treatment

The expected adverse effects of glycyrrhizin preparation administration include pseudo-aldosteronism with hypokalemia, sodium retention, elevated blood pressure, and retention of body fluids. No Group A or B patients had any symptoms of pseudo-aldosteronism. The mean serum potassium levels at Months 0, 6, and 9 did not significantly decrease in Group A or B patients : Group A, 4.3±0.4 mMol/L, 4.1±0.4 mMol/L and 4.2±0.3 mMol/L ; Group B, 4.0±0.4 mMol/L, 4.0±0.3 mMol/L, and 4.2±0.3 mMol/L. The mean systolic blood pressure at Months 0, 6, and 9 did not significantly rise in Group A or B patients : Group A, 129.1±19.9 mmHg, 130.3±23.3 mmHg, 132.1±18.7 mmHg ; Group B, 131.1±15.7 mmHg, 134.1±19.2 mmHg, and 132.1±13.9 mmHg.

Concentration of glycyrrhizin in SNMC and the five other generic drugs by HPLC

Table 2 shows the average concentration of glycyrrhizin in 3 different lot numbers of each drug, determined by HPLC. The average concentration of glycyrrhizin in Neophagen and generic drugs A to D was lower than that in SNMC, with a range in the ratio to SNMC of from 79.1 to 94.4%. No significant difference was found in the concentration of glycyrrhizin among different lot numbers of each drug.

DISCUSSION

To our knowledge, no study comparing the clinical efficacy of SNMC, the original preparation of glycyrrhizin, with any other generic drugs has been published. Although the study was not randomized or blinded, we were able to document differences in efficacy between SNMC and the generic drugs in a longitudinally controlled study of chronic hepatitis C patients.

The effect on ALT of the 6-month SNMC treatment was significantly more often lost in the patients that switched to the generic drug than in those receiving continuous treatment, especially among patients with an initially good response. These findings suggest that a blind, randomized, control trial of the effectiveness of SNMC and its generic drugs is needed.

SNMC, the most popular glycyrrhizin based drug in Japan, is derived from the roots of the plant *Glycyrrhiza glabra* (licorice). Glycyrrhizin has been used for the treatment of chronic hepatitis for more than 20 years in Japan.[13] The exact mechanism by which glycyrrhizin reduces the progression of liver disease without clearing the virus is unknown. A few in vitro and animal studies suggest that glycyrrhizin or its metabolite glycyrrhetinic acid inhibits lipid peroxidation, thereby protecting the hepatocytes.[22]

It was reported that up to half of patients with chronic HCV infection treated with SNMC either had an improved or normal ALT level, depending on the frequency of SNMC administration.[23] The effect on ALT was also lost after cessation of SNMC treatment, suggesting a rebound phenomenon. The present study found SNMC to have a 5.6% to 20.9% higher concentration of glycyrrhizin than the generic drugs, even though the package inserts stated that each drug contained 2 mg of glycyrrhizin per mL in saline. The Japanese Pharmacopoeia states that any glycyrrhizin drug must be a derivative of licorice and contain at least 2.5% glycyrrhizin. Glycyrrhizin based drugs cannot be synthesized, but must be a naturally occurring compound. Therefore, the drug purity depends on the purification process : the method of licorice extraction, the temperature, time, solvent, and medium used for purification, and the purifying method, HPCL or absorption. It is possible that the processes used resulted in the observed differences in glycyrrhizin concentration in the SNMC and the generic drugs tested in this study. Whatever the reason for these differences, however, our findings suggest that these differences in concentration lead to differences in efficacy in reducing the ALT level of the patients switching to generic drug.

The efficacy of glycyrrhizin for liver disease has been well documented in Japan. Although SNMC decreases the ALT level in chronic hepatitis C patients, SNMC does not have any significant effect on viral clearance.[24] We also documented no significant effect on the HCV RNA level by either SNMC or the generic drugs. However, SNMC is used extensively for chronic hepatitis C, in particular for patients who did not respond to IFN treatment. SNMC has been reported to reduce the cumulative risk of HCC by more than half, from 25% to 12% at 15 years.[15] Glycyrrhizin acts in a cytoprotective manner, possibly by its ability to inhibit tumor necrosis factor α-mediated apoptosis[25] and/or by inhibition of anti-Fas antibody-induced hepatitis.[26]

It is also very important to consider cost-effectiveness analysis of the generic drugs. The utilization of low price generic drugs has been promoted to minimize the cost of drugs in Japan. The difference in price of a single ampoule of SNMC and the generic drugs is under one U. S. dollar. However, because nearly 100 million ampoules of SNMC are used each year in Japan for the treatment of chronic hepatitis, even a slight difference in price of one ampoule leads to a significant difference in total drug cost. Nevertheless, the lower clinical efficacy of the generic drugs does not warrant their use, even though there may be a substantial cost savings.

Although we already reported a part of the present study in a Japanese journal,[27] the present study includes additional data about the influence on HCV RNA levels by intravenous glycyrrhizin and the concentrations of glycyrrhizin among different glycyrrhizin products.

In concluding, one potential limitation of the present study should be noted : There may be study bias, because we divided our patients into two groups, SNMC and generic drug treatment groups, according to treatment hospitals. Nevertheless, the two groups of patients had no significant difference in baseline data. Therefore, we believe that our findings offer physicians important information on the efficacy of SNMC and similarly used generic drugs. In conclusion, SNMC and the generic drugs differed in their ability to reduce ALT in patients with chronic hepatitis C.

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Factor XII gene (F12) –4C/C polymorphism in combination with low protein S activity is associated with deep vein thrombosis

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Dear Sir,

Blood coagulation is thought to be triggered by plasma proteinase factor VIIa (FVIIa) that binds to membrane protein tissue factor (TF). In contrast, coagulation factor XII (FXII, Hageman factor) is not believed to play an important role in coagulation, as deficiencies in FXII do not cause bleeding in humans. Therefore, FXII was long considered unimportant for clotting *in vivo*.

Recently, Renne et al. showed that FXII-deficient mice have no tendency to bleed; however, these mice were protected against thrombosis in response to vessel injury, with inhibition of FXII protecting mice from ischemic brain injury (1, 2). That study demonstrated that FXII works as an inducer of pathologic fibrin formation but is not necessary for hemostasis, suggesting that high levels of FXII may be a risk factor for thrombosis. We previously demonstrated that a C>T polymorphism four nucleotides upstream of the start codon of the FXII gene (-4C>T, originally referred to as a 46C>T polymorphism) has been linked with low FXII levels (3). Bertina et al. observed a slight protective effect of the –4T allele against deep vein thrombosis (DVT) in a Leiden factor thrombophilia study (4). This observation agrees with results of the FXII-deficient-mouse thrombosis model. It is therefore worth reevaluating the role of factor XII in thrombosis.

The effect of the –4C>T polymorphism in the factor XII gene (F12) on thrombosis risk was reevaluated in a case control study using previously analyzed DVT patients (5).

This study included 81 Japanese patients (38 males and 43 females) with DVT (aged 10 to 76 years, mean 45.3, SD 16.0) and 151 healthy control subjects (61 males and 90 females, aged 21 to 61 years, mean 36.2, SD 13.0). This clinical study has been formally approved by the Institutional Review Board of the Graduate School of Medical Sciences, Kyushu University. Anticoagulant activity of protein S (PS) was determined using the Staclot protein S kit (Diagnostica Stago, Asnières, France).

Isolation of genomic DNA and detection of FXII –4C>T genotype were generated as described previously (3, 5).

Association between factor XII genotype and DVT was assessed in terms of odds ratio (OR), with adjustment for sex and age, and statistical significance determined by 95% CI. Adjusted OR and 95% CI were calculated using unconditional logistic regression analysis. All statistical calculations were performed using Stata Statistical Software Release 8.0 (Stata Corporation, USA).

Frequency of the –4C allele was 0.301 in control and 0.364 in DVT patients. There was an allele-specific dose-dependent ef-

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Table 1: Factor XII –4c/t polymorphism risk association for deep vein thrombosis.

FXII genotype	Patients n (%)	Controls n (%)	Adjusted OR*	95% CI
–4T/T	35 (43.2%)	72 (47.7%)	1.00	1.00 (reference)
–4C/T	33 (40.7%)	67 (44.4%)	1.05	0.57–1.93
–4C/C	13 (16.1%)	12 (7.9%)	2.69	1.06–6.82
FXII genotype	**Low PS DVT (<60%)**		**High PS DVT (≥60%)**	
	n†	**OR* (95% C.I.)**	**n†**	**OR* (95% C.I.)**
–4T/T	10/72	1.00 (reference)	8/72	1.00 (reference)
–4C/T	7/67	0.79 (0.28–2.20)	14/67	2.50 (0.90–6.90)
–4C/C	7/12	4.54 (1.42–14.56)	2/12	2.65 (0.44–16.04)

*Adjusted for sex and age; †Number of cases/controls.

fect of –4T allele on plasma FXII activity and antigen levels. There was no overall difference in FXII activity and antigen levels between controls and DVT patients. For each genotype (C/C, C/T, T/T), however, FXII activity and antigen levels were generally lower in DVT patients than controls (data not shown).

Table 1 shows frequency of the –4C/T genotypes in DVT patients and controls. Age and sex adjusted OR was calculated as an estimate of relative risk. Homozygous carriers of –4C had an increased risk of venous thrombosis (OR –4C/C-carriers 2.69, 95% CI 1.06–6.82) (Table 1, top). A total of five studies, including data from this study, have addressed the association between FXII –4C/C polymorphism and risk of DVT (4, 6–8). The combined OR (random effect model) for –4C/C versus –4T/T genotype is estimated to be 1.051 (95% CI 0.69–1.61 p = 0.089), suggesting that FXII –4C/C polymorphism in itself is neutral and is not an independent risk factor for DVT.

We previously reported that frequency (19/85 = 0.22) of PS mutation was very high in Japanese DVT patients (5). Therefore, association with the –4C/T polymorphism was examined in combination with PS activity. Patients with no warfarin intake were selected for this study. Low PS activity (<60%) in combination with –4C/C polymorphism was related to an increased risk of DVT compared to high protein S activity alone (≥60%). Adjusted OR for low PS activity and homozygous carriers of –4C was 4.54 (95% CI 1.42–14.56) (Table 1, bottom). The –4C/C polymorphism in the factor XII gene (*F12*) in combination with low PS activity is associated with DVT. *F12* –4C/C polymorphism, indicating a high level of FXII, might be an accelerated risk factor for DVT. Future studies of *F12* –4C/C polymorphism in combination with other established risk factors, such as PS deficiency or factor V Leiden, will provide a better understanding of the role factor XII in thrombosis.

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Classification of patients with antiphospholipid syndrome into risk categories: An evolving process

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Dear Sir,

Antiphospholipid Syndrome (APS) was formerly defined as the association between clinical events (venous/arterial thromboembolism or pregnancy morbidity) and the positivity of at least one laboratory test detecting antiphospholipid antibodies, namely lupus anticoagulant (LAC) and anti-cardiolipin (aCL) antibodies (1). Although this definition is still valid, a new laboratory criterion [anti-β2-glycoprotein I (aβ2GPI) antibodies] was introduced in the recently published consensus conference (2). This raised the possibility of multiple-test positivity with consequent interpretation. Participants in the Sydney consensus conference decided that the presence of more than one of the three laboratory tests in any combination should be considered a strong indicator of definite APS, and these patients are allocated in classification category I. Conversely, patients with a single laboratory criterion are classified in category IIa, IIb and IIc according to the sole positivity of LAC, aCL and aβ2GPI, respectively. From now on, all three laboratory tests must be performed, and clinicians should analyze and interpret the antiphospholipid-antibody profiles of their patients.

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17. 高齢者の内分泌疾患の特徴

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はじめに

高齢者の内分泌疾患の特徴として，臨床症状が無症候となりやすく，あっても非定型的となる傾向がある．ぼけ，意識障害などの精神・神経症状が出やすい．また，高齢者では正常値や，生理的，薬理的刺激に対するホルモンの分泌反応が異なることがある．

加齢による内分泌系の変動

加齢によりホルモン分泌は低下する群（エストロゲン，テストステロン，副腎アンドロゲン），不変群（インスリン，甲状腺ホルモン，副腎皮質刺激ホルモン，コルチゾールなど生命維持に不可欠のもの），上昇する群（性腺刺激ホルモン）に大別される（**図1**）[1]．

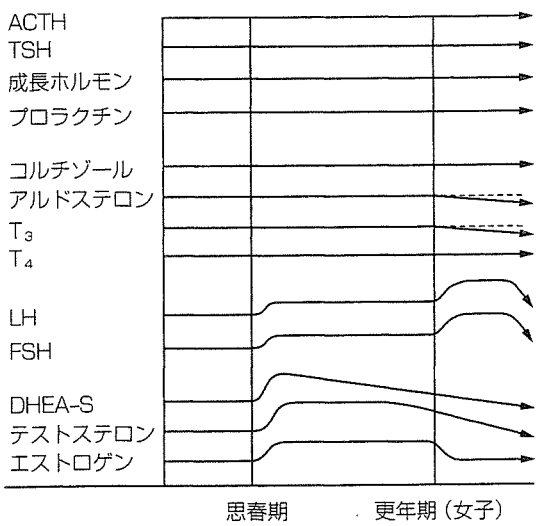

図1　各種ホルモンの血中濃度の加齢に伴う変動[1]

1 視床下部-成長ホルモン-IGF-1系，プロラクチン

GHは10歳代にピークがあり，加齢と共に低下し，GRHに対するGHの反応も低下する．IGF-1（ソマトメジンC）も加齢に伴い低下する．プロラクチンの基礎分泌値は男女とも加齢と共に軽度上昇する．

2 視床下部-下垂体-甲状腺系

T_4，遊離T_4，TSHは加齢によってほとんど変化しない．一方末梢におけるT_4からT_3への変換が低下するため，血中T_3は遊離T_3と共に加齢により低下する．また，非活性のrT_3が増加する．高齢者ではしばしば他の全身性疾患の合併によりT_3が低下（low T_3症候群）するが，原発性甲状腺機能低下症と異なりTSHは上昇せず，ホルモン補充を必要としない．

3 視床下部-下垂体-副腎皮質系

下垂体よりのACTH分泌の日内変動は加齢による影響はほとんどない．コルチゾールの代謝速度は加齢と共に遅延するが，その基礎値および日内変動は，加齢によってあまり変化を受けない．またACTHやインスリン低血糖刺激に対する反応，デキサメサゾンによる分泌抑制にも加齢変化は認めない．一方，アルドステロンの分泌は，血中レニン活性と共に加齢により低下し，食塩制限や立位負荷などの刺激に対するレニンおよびアルドステロンの分泌反応も著明に低下する．また，副腎アンドロゲン（DHEA，DHEA-S）の血中濃度は，20歳代をピークに加齢と共に直線的に低下し，老化のよい指標となる．

4 視床下部-下垂体-性腺系

テストステロンは20歳代でピークとなり加齢と共に減少し，70歳代で20歳代の30％程度と

なる．インヒビンの血中濃度も加齢と共に減少する．これに伴い，50歳代以降，黄体刺激ホルモン（LH）およびFSHの血中濃度は高値となり，LH-RHに対し高反応となる．一方，男性におけるエストロゲン値に加齢変化は認めない．女性では閉経を契機に血中エストロゲン値は劇的に低下する．エストラジオール（E2）およびエストリオール（E3）値は，それぞれ成人の10％および30％程度に低下する．これに伴い，血中LHおよびFSH値は著明に高値となる．60歳以降は，閉経前と比較し高値ではあるものの，LHおよびFSH値は低下傾向となる．

5 抗利尿ホルモン，カルシウム代謝調節ホルモン他

ADHの基礎値は加齢による変化を認めないが，各種刺激に対する分泌反応は増大する．高齢者ではCa吸収能が低下しており，これには1,25-$(OH)_2$ビタミンDの血中濃度およびその反応性の低下の関与が考えられている．PTHは，一般に加齢と共に高値となる．一方カルシトニンは基礎値，Ca注入に対する反応性とも加齢と共に低下し，標的器官の応答性も低下する．これらの変化は骨粗鬆症に促進的に働くとされる．血中ノルエピネフリンは加齢と共に上昇する．心房性ナトリウム利尿ペプチドの血中濃度は加齢と共に高値となり，容量負荷に対する分泌反応も増加する．レプチンは加齢と共に低下する．血中メラトニン濃度も加齢により低下する．

高齢者の各内分泌疾患の特徴

1 下垂体疾患

① 下垂体機能低下症と下垂体腫瘍

下垂体機能低下症は種々の病因で起こるが，成人の場合，頻度の高いものは下垂体腺腫で，とくに高齢者ではホルモンの産生能のない非機能性腺腫が多く，大きく発育して視力障害をきたすまで患者が無自覚のことが多い．汎下垂体機能低下症が高齢者では，動脈硬化や糖尿病性血管合併症で下垂体前葉の梗塞により発症することがある．汎下垂体機能低下症の症状はいわゆる老化現象と類似しているため見過ごされやすい．

② 先端巨大症

長期経過観察した高齢者の先端巨大症の合併症は糖尿病，高血圧，高脂血症が多く，成人病として治療されている症例が存在する．一方，悪性腫瘍の合併例も多く，とくに大腸ポリープ，大腸癌の合併が高く，50歳以上で10年以上の罹病期間を持つ例は大腸の検査が必須である．

③ クッシング病

1997年度の全国調査におけるクッシング症候群の主要症状を**表1**に示す[2]．下垂体性，副腎性で症状の出現頻度に差は認められなかったが，65歳以上の高齢者では満月様顔貌，中心性肥満，水牛様脂肪沈着，進展性皮膚線条，にきび，多毛の出現頻度が低く，筋力低下，浮腫，糖尿病，骨粗鬆症は逆に出現率が高かった．すなわち，高齢者のクッシング症候群では特徴的な症候を欠く傾向が認められた．このように高齢者では，特徴的な症候が乏しいこと，罹病期間の長い例が多く，筋萎縮，皮膚萎縮が進み，高血圧，糖尿病，感染症の合併が多いことからクッシング症候群がmask

表1　Cushing症候群の症候の出現率（%）

	全症例	年齢	
		64歳以下	65歳以上
満月様顔貌	84.3	82.4	70.7
高血圧	83.9	83.3	88.4
中心性肥満	81.2	82.3	71.8
buffalo hump	63.2	64.7	50.0
月経異常	59.8	−	−
伸展性皮膚線条	52.7	56.3	21.1
皮下溢血	45.6	45.1	48.6
筋力低下	48.6	46.3	66.7
ざ瘡（にきび）	45.2	48.2	18.9
多毛	41.8	45.2	13.9
浮腫	50.4	48.7	62.5
糖尿病	46.7	43.4	70.5
骨粗鬆症	48.4	45.1	74.2
精神障害	17.6	17.3	21.1
色素沈着	19.9	19.5	23.5

されることがある．また，老年者クッシング症候群では，低K血症，低蛋白血症の程度が強い[3]．

2 甲状腺疾患

① 甲状腺機能亢進症

高齢者においてはしばしば無気力，無表情，非活動的となり，apathetic hyperthyroidismと呼ばれる．さらに，甲状腺腫や眼球突出を欠き，心血管系，呼吸器系，消化器系などの1つの器官の症状が前面に出てこれら器官特有の疾患と間違えられることもあり，masked hyperthyroidismと呼ばれる．体重減少が著しいことが多く，多食より，むしろ食欲不振となることがある．また，心房細動の合併が多い．検査所見では，T_4，T_3は軽度の上昇に留まることも多く，とくにT_3は前述のごとく高齢者で低値をとりやすい．^{123}I摂取率も，高齢者では1/3程度の患者で正常となる．高齢者では，甲状腺腫があまり大きくない症例も多く，抗甲状腺剤に対する反応も良好なことが多い．

② 甲状腺機能低下症

本症はその典型的症状がしばしば老化現象として軽視され，見逃されることが多い．高コレステロール血症，貧血，頑固な便秘，痴呆症状の裏に本症が潜む可能性を念頭に置くべきである．また，明らかな甲状腺機能低下症状を示さなくとも，TSHが上昇してくる症例が加齢に伴って増加し，潜在的甲状腺機能低下症（subclinical hypothyroidism）と呼ばれる．

3 副腎疾患

① Cushing症候群

各副腎皮質疾患における65歳以上の老年者の割合は1997年度の全国調査[2,4]ではクッシング症候群（広義），原発性アルドステロン症，アジソン（Addison）病，褐色細胞腫，各々，10.6％，14.0％，49.5％，23.4％であり，アジソン病で高齢者の割合が高かった．稀な疾患ではあるが高齢者では両側性に多発性に結節形成が認められるACTH非依存性両側副腎皮質大結節性過形成（AIMAH）を認めることがある．

②続発性選択的低アルドステロン症

高齢者では後天的なレニン分泌不全のため，続発的にアルドステロン分泌が低下する続発性選択的低アルドステロン症がみられる．とくに糖尿病を基礎疾患として発症することが多い．その症状は易疲労感，脱力感，食欲不振など老年者に多くみられる非特異的症状が主で，見逃されやすい疾患であり，高K血症を示す高齢者では本症の存在を念頭に置く必要がある．

③インシデンタローマ，副腎性プレクリニカルクッシング症候群

最近，画像検査の進歩によりインシデンタローマとして発見される機会の多くなった非機能性副腎腫瘍では老年者の占める割合が多い．褐色細胞腫は高齢者ではインシデンタローマとして発見されることが多い．インシデンタローマは非機能性副腎腺腫が大部分を占めるが，悪性腫瘍が5～10％，ホルモン分泌腫瘍が5～7％存在することは注意すべき点と考えられる[3]．

④ミネラロコルチコイド反応性低Na血症（mineralocorticoid-responsive hyponatremia of the elderly : MRHE）[5]

高齢者に特異的にみられる低Na血症で，ミネラロコルチコイドで改善されるという特徴がある．血中Kは正常である．本症は加齢により，腎におけるNa保持能が低下するため，尿中へのNa排泄が増加し，循環血漿量が軽度低下するが，レニン・アルドステロン系が加齢のため充分に活性化されない．そのため，不足したNaが補償されない．高齢者では，加齢による尿の濃縮力の減退や血管の圧受容器機能の減退に対してAVPの分泌が代償的に亢進する．これに加えて，本症では，軽度の循環血漿量の低下がさらにAVPの分泌を助長する．その結果，低Na血症をきたす．血中AVPは血漿浸透圧に比し，高値であり，一見，SIADHの診断基準と合致するため，SIADHと診断される危険性がある．SIADHでは水制限により，病態は改善するが，MRHEでは悪化し，水制限を継続すると致命的となりうる．MRHE

ではミネラロコルチコイドの投与により低Na血症が改善できる．高齢者の頭部外傷後にMRHEが発症することが報告されている．SIADHと診断されても，水制限で改善されず，高齢者で初診時，軽度の脱水が疑われた場合は本症の存在を念頭に置く必要がある．

おわりに

高齢者の内分泌疾患の理解に必要な加齢による内分泌系の生理的変化と各疾患の高齢者における特徴を概説した．

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トピックス

I. 内分泌性高血圧症の分類と疫学
2. 内分泌性高血圧症の疫学：本邦における全国疫学調査

高柳　涼一

要　旨

内分泌性高血圧症は下垂体性のCushing病と副腎ホルモン産生異常による副腎性高血圧症が主なものである．本邦においては以前より厚生省特定疾患調査研究班による副腎ホルモン産生異常症の全国的な疫学調査が行われてきた．この中で1997年の名和田班[1]による全国的な疫学調査結果は従来の調査とほぼ同様であったが，初めて統計的に信頼できる全国推定患者数を算出したことが注目すべき成果であった．従来，これらの内分泌性高血圧症は全高血圧症の1%以下であるとされていたが，最近，正カリウム性の原発性アルドステロン症の患者は予想以上に多く，高血圧患者の約6%に達するという報告があり，注目を集めている．〔日内会誌　95：622～628，2006〕

Key words：二次性高血圧，疫学調査，内分泌性高血圧，原発性アルドステロン症，Cushing症候群，preclinical Cushing症候群，褐色細胞腫

はじめに

内分泌性高血圧症は下垂体からのACTH (adrenocorticotropic hormone) 過剰分泌によるCushing病と副腎腫瘍からの自律的ホルモン過剰分泌による副腎性高血圧症が主なものである．内分泌性高血圧症は外科的治療または薬物治療にて完治が期待できるものであり，迅速かつ的確な診断が必要である．従来，内分泌性高血圧症の頻度は全高血圧症の1%以下とされてきたが，最近，正カリウム性の原発性アルドステロン症の患者が予想以上に多く，高血圧患者の約6%に達するという報告があいついでなされ，内分泌性高血圧症の見直しの気運が高まっている．本稿では，1997年の厚生省特定疾患「副腎ホルモン産生異常症」調査研究班による全国疫学調査結果[1]を基に，副腎性高血圧を来たす各疾患の疫学および臨床統計について概説する．

たかやなぎ　りょういち：九州大学大学院医学研究院病態制御内科学

1. 副腎ホルモン産生異常症の全国疫学調査

本邦における厚生省特定疾患としての副腎ホルモン産生異常症の全国疫学調査には，1975年に厚生省特定疾患「副腎ホルモン産生異常症」調査研究班としてスタートし，本邦における実態調査と臨床病態の解明に向けて研究が行われてきた．井林(1972～76年)[2]，(1972～76年)[3]，竹田(1982～86年)[4]，名和田(1977年)[5]らを班長とする調査研究班による全国疫学調査が報告されている．1997年の名和田班によるアンケート調査では，全国の4,060の診療科に対して，1997年1月から同年12月までの患者数を調査し（1次調査），各疾患患者の存在が示された診療科に対して各患者の詳しい情報を依頼し情報を得た

(2次調査). 1次調査によるアンケートの回収率は63.7%で，2次調査による回収率は53.0%であった．従来の「副腎ホルモン産生異常症」調査研究班においては，対象病院を特定したため真の疫学調査と言い難い面もあったが，当調査においては，一定規模以上の病院は全てを，小規模の病院は無作為に抽出することで，精度の高い疫学調査となった．また当調査において，初めて統計的に信頼できる全国推定患者が算出された．各疾患の疫学調査では，Addison病で結核性が減少し，特発性が増加した点以外は，従来とほぼかわらなかった．また，下垂体性Cushing病はCushing症候群として調査に含まれている．以下，各疾患の調査結果について概説する．

1）原発性アルドステロン症

原発性アルドステロン症は，副腎腺腫あるいは稀ではあるが副腎過形成により，副腎皮質からのアルドステロンの分泌が増加し，腎臓でのナトリウム再吸収の促進により循環血液量の増加を来たし，高血圧症と低レニン血症をきたす疾患である．副腎性高血圧症をきたす疾患では最も頻度の多い疾患で，全高血圧症例の約0.05%を占めると言われている．1997年の厚生省特定疾患調査研究班（名和田班）[1]における全国推定患者数は，1,450名(95% 信頼区間：1,250〜1,650名)(表1)で副腎ホルモン産生異常症の中で最も多く，男女比1：1.5であった．年齢分布は1峰性の分布を示し，ピークは男女とも50歳前後にあった．患者の平均年齢は男53.4歳，女52.2歳，推定発症平均年齢は男43.6歳，女42.1歳であった．後述するが，最近正K性のアルドステロン症の割合が全体の50% 近くあるという報告があり，今後，原発性アルドステロン症の頻度は見直しが必要である．1997年の全国調査における病型分類とその頻度は，1)アルドステロン産生腺腫(aldosterone-producing adenoma：APA) 84.4%（367/435），2）両側性副腎過形成（特発性アルドステロン症(idiopathic hyperaldosteronism：IHA))8.3%(36/435)，3)片側性副腎過形成（原発性副腎過形成（primary adrenal hyperplasia：PAH))1.6%（7/435），4）グルココルチコイド奏効性アルドステロン症(glucocorticoid-remediable aldosteronism：GRA)0.2%(1/435)，5）その他：5.5%（24/435）であった．

主要検査の陽性率は，1)低K血症：87.3%(365症例中)，2)高アルドステロン血症：94.4%(387症例中)，3)低レニン血症：86.1%(348症例中)，4)レニン刺激試験に低反応：77.9%(176症例中)であった．局在診断は，エコー，CT(computed tomography)，MRI(magnetic resonance imaging)，I^{131}-アドステロール副腎シンチによってなされるが，APAの微小腺腫例や，IHAの診断においては，局在診断が困難な場合が多い．全体の57.8% で選択性副腎静脈サンプリングが施行されており，診断の有用性は腺腫例で64.4〜71.4%と集計され，局在診断における有用性が示された．副腎静脈，特に右副腎静脈が細く，サンプリングが放射線科医の技量に依存してしまうため，その差をなくすことや，副腎静脈の選択性を評価するために用いる副腎静脈コルチゾール値/下大静脈コルチゾール値やACTH負荷時のサンプリング値の統一化，などが今後の課題である．

APAでは，腫瘍の摘出が第一選択であるが，手術不可能例においては，スピロノラクトンによる薬物療法を行う．IHAでは外科的治療の有用性は確立しておらず，スピロノラクトンによる薬物療法が第一選択となる．APAの85.2% が腫瘍摘出を受け，IHAの88.9% が薬物療法の適用となった（表2）．全アルドステロン症患者の高血圧症は，手術療法にて88.5%(293/331)，薬物療法にて74.1（63/85）%の頻度で改善を認めた（表2）．転帰では，死亡例は認めず（表3），比較的予後は良好で，適切な治療が行われれば治療効果は高いことが示されたが，近年アルドステロンが血管炎を基盤とした直接的臓器障害作用を持つことが明らかとなっており，迅速で的確な診断が必要である．最近の話題として，1994

表 1. 主要な副腎ホルモン産生異常症の全国推定患者

疾患	患者数			全国推定患者数 [95% 信頼区間]	2 次調査での悪性症例数
	男	女	計		
原発性アルドステロン症	331 (1 : 1.5)	494	825	1450 [1250-1650]	1/435 (0.2%)
Cushing 症候群	151 (1 : 3.9)	586	737	1250 [1100-1400]	5/417 (1.2%)
副腎性 preclinical Cushing 症候群	61 (1 : 1.7)	102	163	290 [230-350]	0/78 (0%)
褐色細胞腫	270 (1 : 0.93)	252	522	1030 [860-1200]	30/279 (10.8%)

1) より引用

表 2. 原発性アルドステロン症における腫瘍摘出術と薬物療法の効果

	高血圧症			低 K 血症		
	改善	不変	不明 (%)	改善	不変	不明 (%)
原発性アルドステロン症全例						
腫瘍摘出 76.1% (331/435)	88.5	8.8	2.7	87.6	6.3	6.1
薬物療法 19.5% (85/435)	74.1	18.8	7.1	76.5	18.8	4.7
片側性副腎腺腫						
腫瘍摘出 85.2% (305/358)	88.9	8.1	3.0	87.5	6.6	5.9
薬物療法 12.3% (44/358)	65.9	27.3	6.8	75.0	15.9	9.1
特発性アルドステロン症						
腫瘍摘出 8.3% (3/36)	100	0	0	100	0	0
薬物療法 88.9% (32/36)	81.3	9.4	9.4	81.3	18.7	0

腫瘍摘出例は薬物療法併用を含む

1) より引用

表 3. 原発性アルドステロン症，Cushing 症候群，preclinical Cushing 症候群，褐色細胞腫の転帰

	症例数 (人)	治癒 (%)	改善 (%)	不変 (%)	悪化 (%)	死亡 (%)	不明
原発性アルドステロン症	435	37.5	50.3	8.3	0.5	0	3.4
Cushing 症候群	417	37.9	49.2	7.9	0.2	2.6	2.2
preclinical Cushing 症候群	78	28.2	23.1	44.9	1.3	0	2.6
褐色細胞腫	279	55.6	25.8	10.8	2.9	1.8	3.1

1) より引用

年にGordonら[5]によって，199 名の高血圧症患者に対して，立位での血漿アルドステロン濃度/血漿レニン活性比40をカットオフ値としてスクリーニングし，フルドロコルチゾン抑制試験を行った結果，8.5% が原発性アルドステロン症患者であり，その半数において血清K濃度が正常であり，その 1/3 以上の症例で血漿アルドステロン濃度が正常であったと報告している．Plouinら[6]が，7 つの報告をまとめた結果，5,851 例の高血圧患者のうち 364 例（6.6%）が原発性アルドステロ