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Comparison of Losartan with ACE Inhibitors and Dihydropyridine Calcium Channel Antagonists

A Pilot Study of Prescription-Event Monitoring in Japan

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Abstract

Introduction: Two pilot studies for prescription-event monitoring in Japan (J-PEM) were launched in 1997 and 1998. Here we present data regarding adverse events that were reported in the second pilot J-PEM study where losartan was compared with ACE inhibitors and dihydropyridine calcium channel antagonists.
Study design: We conducted a cohort study with a concurrent control.
Methods/patient group: Study subjects prescribed losartan, an ACE inhibitor or a calcium channel antagonist were identified from prescriptions in hospital or community pharmacies. Events and other information were collected from doctors and pharmacists by mailed questionnaires. Events were coded and analysed using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Crude event rates were calculated and compared between patients treated with losartan and those receiving control drugs. When the difference was statistically significant, the event was further examined in several ways, including follow-up studies and by comparison with the data of the UK PEM study on losartan.
Results: Pharmacists were sent 4344 questionnaires and returned 3591 (83%), while doctors were sent 3517 questionnaires and returned 1380 (39%). In the doctors' data, the adverse event rate for losartan treatment was greater than that for ACE inhibitors and/or calcium channel antagonists for the following seven events: headache, palpitations, anaemia, insomnia, feeling abnormal, increased blood pressure and asthma. Most of these are known adverse drug reactions (ADRs) of losartan except for two events: increased blood pressure and asthma. In pharmacists' data, the event rate for losartan was significantly greater than that for control drugs for the following ten events: hot flushes, abnormal hepatic function, oedema, peripheral swelling, decreased blood pressure, increased blood pressure, rhinitis, contact dermatitis, dry skin and heat rash. The first five events were known ADRs of losartan but the other five were not. When the two sets of

data were combined, the rate of an additional event, increased blood creatinine phosphokinase, which is a known ADR of losartan, was significantly greater than that for the control drugs. The six events that were not documented as ADRs for losartan were not judged to be ADRs based on the results of follow-up studies and comparison with the UK PEM study on losartan. The crude rate of cough with losartan treatment was similar to that with calcium channel antagonists, but was significantly less than that with ACE inhibitors.

Conclusion: No novel safety problems were found in this observational cohort study on losartan. The rates of some known ADRs differed significantly between patients treated with losartan and those in the control groups.

Background

Prescription-event monitoring (PEM) uses an observational cohort design for postmarketing surveillance (PMS) and has been used to study the safety of selected newly licensed drugs in the UK since the early 1980s. Two pilot studies for PEM in Japan (J-PEM) were launched in 1997 and 1998 to examine the feasibility of observational studies similar to the UK PEM.

The drug, patient and prescribing doctor were identified using prescriptions in hospital/community pharmacies willing to participate in the study. Both patients prescribed a test drug and those prescribed control drug(s) were identified.

In the first J-PEM pilot study, conducted between 1997 and 1999, troglitazone was compared with other antidiabetic agents.[1-4] In this paper we report results of the second pilot study launched in 1998, where losartan was compared with ACE inhibitors and dihydropyridine calcium channel antagonists.

Some events were examined with particular interest. For example, dry cough associated with ACE inhibitors is a minor adverse drug reaction (ADR), but is nevertheless important because up to 39% of patients may experience this ADR, and it is often sufficiently annoying to cause the patient to discontinue treatment.[5] In a review of clinical trials, the incidence of cough with angiotensin II (AII)-receptor blockers was shown to be less than that with ACE inhibitors, but similar to that with placebo.[5] However, some anecdotal reports suggest that cough and bronchospasm may also occur with AII-receptor blockers.[6,7] Similarly, in the PEM study on losartan conducted in the UK, cough was frequently reported as a reason for stopping treatment, indicating that many doctors are concerned by a possible relationship between cough and AII-receptor blockers, despite the negative results obtained in many clinical trials.[8] In the UK PEM study on losartan, most cases of cough were thought to be due to 'carry-over' effects from previous ACE inhibitor therapy.[9]

Study Design

A J-PEM study of losartan was started as a cohort study with a concurrent control immediately after the drug was marketed in late August 1998 as the first AII-receptor blocker available in Japan.

Methods and Patient Group Studied

During the registration period between September 1998 and December 1999, pharmacists who dispensed the drug in a hospital or at a community pharmacy not affiliated with a hospital or clinic, registered patients who received the test drug (losartan) or one of the control drugs (ACE inhibitors and dihydropyridine calcium channel antagonists) for the first time after September 1998. When the pharmacist registered a control patient, possible subjects prescribed a control drug for the first time in that pharmacy were selected from records in the pharmacy. Prior to registering the individual control patient, the pharmacist asked the potential control patient whether he/she had ever used the control drug. Only when the pharmacist was certain that the control drug had not been prescribed previously, was the patient registered as a control.

A pair of questionnaires, one for the pharmacist and one for the prescribing doctor, were mailed more than 6 months after the date that the first prescription of the study drug (losartan or a control drug) was issued to the individual patients. As described elsewhere,[1-4] questionnaires were issued for about two-thirds of patients registered in the study. Doctors and pharmacists were asked to report events that occurred after the patient was prescribed the drug, as well as other relevant information. Pharmacists were requested to give some details of the drugs, including those prescribed within 3 months before the test/control drug was prescribed. The following definition of an event given in each questionnaire to the doctor was exactly the same as that used in the UK PEM:[10] 'an event is any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration or improvement in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter in the patient's notes'.

As in the UK PEM, the doctor was not aware of which particular patient was selected until the doctor received the questionnaire. Therefore, the doctor reported events that were already in the patient's notes. Most events reported by doctors were considered to be significant health-related events as in the UK PEM. The definition of an event given in each questionnaire to the pharmacist was the same as that to the doctor except that 'any unexpected deterioration or improvement in a concurrent illness' was modified as 'any deterioration or improvement in a concurrent illness'. This modification was made because it was not practical to ask the pharmacist whether the deterioration or improvement was expected or unexpected.

When the event was the reason for stopping the study drug, or was likely to be an adverse reaction to any drug, the doctor/pharmacist were asked to describe this detail in the questionnaire. Both the doctor and pharmacist were also requested to answer whether or not the patient was still visiting the hospital, medical office or community pharmacy to which the reporter belonged. If the answer to this question was 'no', the reporter was asked to give the last date when the doctor or pharmacist saw the patient. In addition, the doctor or pharmacist was requested to answer whether or not the patient was still using the drug. If the patient was no longer visiting the hospital, medical office or community pharmacy, the reporter was asked whether or not the patient was using the drug on the last observation date. If the answer to either of the above two questions was 'no', the reporter was requested to give the last date when the patient used the drug. Throughout the entire study, patient ID codes, specifically created for the study, were employed to secure the confidentiality of the individual data, as detailed elsewhere.[1-4]

Events reported by pharmacists and doctors were coded using the lowest level terms (LLTs) from the Japanese translation of the Medical Dictionary for Regulatory Activities (MedDRA/J) terminology V3.3J (December 2000). When analysing the data, the LLT codes were converted to the corresponding PT (preferred term) codes.[11]

Statistical Analysis

Significant differences in baseline characteristics between patients who received losartan, an ACE inhibitor or a dihydropyridine calcium channel antagonist were determined using appropriate statistical methods, such as the chi-squared test and analysis of variance (ANOVA). When calculating the rate (incidence density), the observation period for an individual patient was defined as the duration between the first prescription date and the last observation date. The last observation date was defined as the date when the reporter returned the questionnaire if the reporter answered that the patient was still visiting the hospital, medical office or community pharmacy. Otherwise, the last observation date was defined as the last observation date specified by the reporter. The exposure period for an individual patient was defined as the duration between the first prescription date and the last date when the patient used the drug in the observation period. The last date when the patient

used the drug was the same as the last observation date if the patient was still using the drug on the last observation date. Otherwise the last date when the patient used the drug was the date specified by the doctor or pharmacist. Both the event rate (incidence density) in the observation period as well as the rate in the exposure period were calculated. However, the latter (the rate in the exposure period) was mainly used in the analysis. Since we had the event data reported by the doctors and those by the pharmacists, the crude event rates were calculated by three different methods and compared between the test drug and control groups using the likelihood ratio test, assuming an exponential distribution.[11] First, the crude event rate was calculated as the number of events reported by doctors while patients were taking the drug, divided by the corresponding period of patient-years. Second, the rate was calculated for events reported by pharmacists. Finally, the rate was calculated for events reported by a doctor and/or pharmacist. In addition to the crude event rates, the event rates adjusted for factors other than the exposure variable were estimated by Poisson regression analysis (GENMOD procedure SAS Release 6.12), as described previously.[12]

For several important events, including those with crude event rates that differed significantly between the treatment groups, we conducted follow-up studies by mailing an additional questionnaire for reporters to provide more detailed information.

Finally, we examined the data in the UK PEM study on losartan,[6] kindly offered by the Drug Safety Research Unit (DSRU), to elucidate the relationship between the drug treatment and some adverse events.

Results

A total of 7452 patients were registered using prescriptions issued by 2026 doctors in 650 medical institutions (37 university hospitals, 230 other hospitals and 383 private medical offices) located in one of 47 prefectures in Japan. Between June 1999 and October 2000, questionnaires for a total of 4344 patients (2779 treated with losartan and 1565 with a control drug) were mailed to pharmacists who had registered patients. Questionnaires for a total of 3517 patients (2233 treated with losartan and 1284 with a control drug) were forwarded from the pharmacists to the prescribing doctors who participated in the study. Prior to February 2001, pharmacists in 587 pharmacies sent back 3591 questionnaires (83% of 4344) of which 98 were considered void, mostly because the drug was prescribed before September 1998. The remaining 3493 had useable information (2205 with losartan and 1288 with a control drug). 699 doctors in 331 medical institutions sent back 1380 forms (39% of 3517), of which 49 were considered void and 1331 had useable information (835 with losartan and 496 with a control drug).

Table I shows demographic data and baseline characteristics of the patient groups. Two-thirds of control patients were prescribed a dihydropyridine calcium channel antagonist, while the remaining one-third of patients were prescribed an ACE inhibitor. The distribution with respect to gender and age was roughly the same between the three drug groups, though the mean age of patients treated with losartan was slightly higher as compared with patients taking control drugs. The dosage of losartan was 50 mg/day for more than half of the patients and 25 mg/day for a quarter of the patients.

Hypertensive patients treated with losartan had: a longer duration of disease; a longer duration of treatment with any antihypertensive drug; received a greater number of antihypertensive drugs, other than the study drug (when the study drug was first prescribed); and had more concomitant diseases such as ischaemic heart disease and heart failure. Thus, patients prescribed losartan seem to have more advanced disease than those treated with a control drug. From the questionnaires returned from pharmacists, we could identify previous antihypertensive drug(s) used before the patient was prescribed the study drug as shown in table I. About 20% of patients prescribed losartan were previously treated with ACE inhibitors. Two patients prescribed losartan were previously treated

Table I. Demographic data and base-line characteristics

	Pharmacist-reported data			Doctor-reported data		
	test drug	control drug		test drug	control drug	
	losartan	ACE-I	calcium channel antagonist	losartan	ACE-I	calcium channel antagonist
Number of patients	2205	432	856	835	164	332
Demographic data [n (%)]						
Males	1008 (46)	214 (50)	399 (47)	387 (46)*[a]	90 (55)†##[a]	139 (42)
Females	1197 (54)	218 (50)	457 (53)	448 (54)	74 (45)	193 (58)
Age (years)	64 ± 12**[b]	62 ± 13††[c]	62 ± 12††[c]	64 ± 12**[b]	61 ± 14††[c]	63 ± 12
Daily dose [n (%)]						
25mg	568 (26)			221 (26)		
50mg	1347 (61)			461 (55)		
100mg	58 (3)			34 (4)		
Others, unknown	232 (11)			119 (14)		
Indication[d] [n (%)]						
Hypertension	1628 (74)**[e]	325 (75)††##[e]	667 (78)†[e]	767 (92)**[e]	144 (88)##[e]	320 (96)††[e]
Heart failure	6 (0.3)	3 (0.7)	0 (0)	21 (3)	2 (1)	0 (0)
Others	38 (2)	18 (4)	16 (2)	30 (4)	12 (7)	8 (2)
Unknown	533 (24)	86 (20)	173 (20)	17 (2)	6 (4)	4 (1)
Duration of disease and drug therapy (years)						
Duration of disease	3.9 ± 7.0**[b]	2.4 ± 6.0††[c]	1.6 ± 4.2††[c]	6.2 ± 8.0**[b]	4.5 ± 6.5†[c]	3.8 ± 6.4††[c]
	(n = 899)	(n = 212)	(n = 480)	(n = 686)	(n = 136)	(n = 275)
Duration of drug therapy	2.9 ± 5.7**[b]	1.1 ± 2.9††[c]	1.0 ± 3.1††[c]	4.7 ± 6.9**[b]	3.1 ± 5.8††[c]	2.8 ± 5.7††[c]
	(n = 1004)	(n = 241)	(n = 547)	(n = 689)	(n = 142)	(n = 285)
Number of other antihypertensives when test or control drug is administered [n (%)]						
0	868 (39)**[f]	220 (51)††##[g]	593 (69)††[g]	309 (37)**[f]	72 (44)†##[g]	220 (66)††[g]
1	825 (37)	137 (32)	174 (20)	289 (35)	57 (35)	71 (21)
2 or more	457 (21)	55 (13)	44 (5)	177 (21)	21 (13)	17 (5)
Unknown	55 (2)	20 (5)	45 (5)	60 (7)	14 (9)	24 (7)
Concomitant disease [n (%)][h]						
Ischaemic heart disease	165 (7)**[a]	27 (6)#[a]	30 (4)††[a]	105 (13)	18 (11)	34 (10)
Heart failure	61 (3)**[a]	9 (2)	8 (1)††[a]	95 (11)**[a]	15 (9)#[a]	13 (4)††[a]
Hyperlipidaemia	301 (14)	65 (15)	97 (11)	261 (31)	61 (37)	101 (30)
Diabetes mellitus	214 (10)*[a]	49 (11)##[a]	59 (7)†[a]	150 (18)	33 (20)	53 (16)
Cerebrovascular disease	113 (5)	22 (5)	33 (4)	78 (9)**[a]	16 (10)##[a]	13 (4)††[a]
Previous antihypertensive drugs [n (%)]						
Angiotensin II-receptor blocker	2 (0.1)	1 (0.2)	3 (0.4)	1 (0.1)	1 (0.6)	2 (0.6)
ACE-I	422 (19)	32 (7)	29 (3)	155 (19)	18 (11)	12 (4)
Calcium channel antagonist	137 (6)	18 (4)	74 (9)	48 (6)	4 (2)	35 (11)
Other drug(s)	128 (6)	14 (5)	23 (3)	48 (6)	8 (5)	10 (3)
No drug	1461 (66)	347 (80)	682 (80)	523 (63)	119 (73)	249 (75)
Unknown	55 (2)	20 (5)	45 (5)	60 (7)	14 (9)	24 (7)

a Chi-squared test.
b Analysis of variance.
c T-test.
d One major indication per patient is classified into four categories.
e Fisher exact test.
f Kruskal-Wallis test.
g Wilcoxon rank sum test.
h The difference was tested for each concomitant disease.

ACE-I = ACE inhibitor; * $p < 0.05$ when compared among three groups with losartan and two control drugs; ** $p < 0.01$ when compared among three groups with losartan and two control drugs; † $p < 0.05$ when compared with losartan; †† $p < 0.01$ when compared with losartan; # $p < 0.05$ when compared between ACE-I and calcium channel antagonist; ## $p < 0.01$ when compared between ACE-I and calcium channel antagonist.

with candesartan which was marketed as the second available AII-receptor blocker in mid-1999 in Japan.

The doctors' subjective opinions concerning effectiveness differed between the three drug groups: the drug was said to be effective for 77.2% (645/835) of patients treated with losartan, 78.7% (129/164) with ACE inhibitors and 87.0% (289/332) with calcium channel antagonists ($p < 0.001$ chi-squared test).

Table II shows events, given as PTs, reported by a doctor or pharmacist as suspected reactions to the study drug and those as reasons for stopping the study drug. They included adverse reactions to losartan labelled in the package insert[13] (labelled ADRs), such as dizziness, headache, malaise and oedema. Cough was reported as an ADR or the reason for stopping drug treatment in 0.3% (6 of 2205) patients monitored by pharmacists and in 0.2% (2 of 835) patients monitored by doctors.

Table III shows the number of events with a crude rate for losartan that was significantly different from that for the two control drugs, compared either individually or with the data for the control groups pooled. In table III, the number of events coded while taking losartan or a control drug and the corresponding patient-years are presented. The information collected by pharmacists differed from that by doctors. Pharmacists reported mainly on events such as hot flushes and non-specific oedema, and sometimes on laboratory test results such as abnormal hepatic function.

In the doctors' data, the adverse event rate for losartan treatment was significantly different from

Table II. Events reported as suspected reactions, reported as a reason for stopping the drug. The number shown is the number of reports where the event was reported as a suspected reaction; the number in parentheses is the number of events where the event was reported as the reason for stopping the drug

System organ class	Preferred term	Pharmacist-reported data			Doctor-reported data		
		losartan (n = 2205)	ACE-I (n = 432)	calcium channel antagonist (n = 856)	losartan (n = 835)	ACE-I (n = 164)	calcium channel antagonist (n = 332)
Nervous	Dizziness (excluding vertigo)	6 (13)	0 (0)	1 (0)	1 (2)	0 (0)	1 (0)
	Dizziness postural	0 (1)	0 (1)	0 (0)	1 (1)	0 (0)	0 (0)
	Headache NOS	2 (4)	0 (2)	4 (4)	3 (3)	0 (0)	2 (2)
	Insomnia NOS	0 (1)	1 (2)	0 (1)	0 (1)	0 (0)	0 (0)
Cardiac	Palpitation	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	1 (0)
	Tachycardia NOS	0 (1)	0 (0)	0 (1)	2 (0)	0 (0)	0 (0)
Vascular	Flushing	0 (0)	0 (0)	0 (2)	0 (1)	0 (0)	0 (0)
	Hot flushes NOS	0 (1)	0 (0)	3 (2)	1 (0)	0 (0)	1 (1)
Respiratory	Cough	6 (4)	22 (32)	0 (1)	0 (2)	6 (18)	0 (0)
Gastrointestinal	Abdominal pain upper	0 (2)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
	Nausea	0 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Sore throat NOS	1 (2)	3 (4)	0 (0)	0 (0)	1 (0)	0 (0)
Skin	Dermatitis NOS	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Eczema NOS	0 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Face oedema	1 (1)	0 (0)	0 (1)	1 (0)	0 (0)	0 (0)
Renal	Renal impairment NOS	0 (1)	0 (0)	0 (0)	0 (2)	0 (0)	0 (0)
General	Oedema NOS	0 (5)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)
	Malaise	1 (1)	0 (0)	0 (2)	0 (2)	0 (0)	0 (0)
	Thirst	1 (1)	0 (0)	0 (0)	0 (2)	0 (0)	0 (0)
Investigation	Blood pressure decreased	0 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Blood pressure increased	0 (3)	0 (1)	0 (1)	0 (1)	0 (0)	0 (2)

ACE-I = ACE inhibitor; **NOS** = not otherwise stated.

Table III. Preferred terms with a statistically significant difference in crude event rate between losartan and control drugs[a]

System organ class	Preferred term	Pharmacist-reported data				Doctor-reported data				Classification	
		losartan	control drugs	RR	p-value	losartan	control drugs	RR	p-value	losartan > control[b]	control > losartan[c]
Losartan *vs* ACE-I											
No. of patients		2186	428			816	163				
Patient-years		1729	280			652	120				
Nervous	Headache NOS	113	25	0.7	0.17	30	1	5.5*	0.03	D	
Cardiac	Palpitations	30	8	0.6	0.23	13	0	*	0.04	D	
Vascular	Hot flushes NOS	15	0	*	0.03	2	0		0.41	P	
Respiratory	Cough	111	87	0.2**	<0.001	18	28	0.1**	<0.001		DP
Gastrointestinal	Sore throat NOS	47	18	0.4**	0.004	9	3	0.6	0.40		P
	Vomiting NOS	13	6	0.4*	0.05	1	0		0.56		P
Hepatic	Hepatic function abnormal NOS	13	0	*	0.05	13	2	1.2	0.81	P	
Skin	Dermatitis contact	20	0	**	0.01	0	1	0	0.053	P	
	Dry skin	13	0	*	0.05	0	1	0	0.053	P	
General	Oedema NOS	33	0	**	0.002	0	0			P	
Investigation	Blood pressure decreased	13	0	*	0.05	1	1	0.2	0.26	P	
	Blood pressure increased	60	3	3.2*	0.02	14	0		0.03*	DP	
	Protein urine	7	6	0.2**	0.005	0	1	0	0.053		P
Losartan *vs* calcium channel antagonists											
No. of patients		2186	848			816	326				
Patient-years		1729	629			652	251				
Blood	Anaemia NOS	8	2	1.5	0.62	6	0	*	0.05	D	
Metabolic	Hyperlipidaemia NOS	30	20	0.5*	0.04	7	3	0.9	0.87		P
Nervous	Insomnia NEC	53	25	0.8	0.29	8	0	*	0.02	D	
	Headache NOS	113	66	0.6**	0.003	30	9	1.2	0.50		P
Ear	Tinnitus	6	7	0.3*	0.04	1	1	0.4	0.50		P
Vascular	Hot flushes NOS	15	14	0.4*	0.01	2	5	0.2*	0.02		DP
Respiratory	Rhinitis NOS	7	0	*	0.04	1	0	*	0.42	P	
	Rhinitis seasonal	18	14	0.5*	0.04	0	1	0	0.11		P
Gastrointestinal	Haemorrhoids	6	7	0.3*	0.04	1	1	0.4	0.51		P
General	Oedema NOS	33	4	3.0*	0.02	0	0			P	
Losartan *vs* all control drugs (ACE-I + calcium channel antagonists)											
No. of patients		2186	1276			816	489				
Patient-years		1729	909			652	370				
Metabolic	Hyperlipidaemia NOS	30	28	0.6*	0.03	7	4	1.0	0.99		P
Nervous	Headache NOS	113	91	0.7**	0.003	30	10	1.7	0.13		P
	Insomnia NEC	53	38	0.7	0.15	8	0	*	0.008	D	
Eye	Cataract NEC	2	5	0.2*	0.05	1	0	*	0.34		P
Cardiac	Palpitations	30	22	0.7	0.24	13	2	3.7*	0.05	D	
Respiratory	Asthma NOS	10	4	1.3	0.64	5	0	*	0.03	D	
	Cough	111	120	0.5**	<0.001	18	32	0.3**	<0.001		DP
	Rhinitis NOS	7	0	*	0.02	1	0		0.34	P	
Gastrointestinal	Diarrhoea NOS	48	25	1.0	0.97	5	9	0.3*	0.03		D
Skin	Heat rash	5	0	*	0.04	0	0			P	
General	Feeling abnormal	7	1	3.7	0.16	5	0	*	0.03	D	
	Oedema NOS	33	4	4.3**	<0.001	0	0			P	
	Peripheral swelling	6	0	*	0.02	1	0		0.34	P	
Investigation	Blood creatine phosphokinase increased	2	0		0.19	4	0		0.06	D+P	

a Events with at least five reports on one of two drugs (drug groups) compared are shown.

b Event rate in losartan is significantly greater than that in control drug(s).

c Event rate in control drug(s) is significantly greater than that in losartan.

ACE-I = ACE inhibitors; **D** = significant difference of the crude rates in doctors' data; **DP** = significant difference in both doctors' and pharmacists' data; **D+P** = significant difference found when doctors' data and pharmacists' data are combined; **NEC** = not elsewhere classified; **NOS** = not otherwise specified; **P** = significant difference in pharmacists' data; **RR** = relative risk; * $p < 0.05$ (likelihood ratio test); ** $p < 0.01$ (likelihood ratio test).

that for ACE inhibitors and/or calcium channel antagonists for ten events including the following seven where the rate for losartan was significantly greater than that for control drug(s): 'headache NOS' (not otherwise specified), 'palpitations', 'anaemia NOS', 'insomnia NEC' (not elsewhere classified), 'feeling abnormal', (the LLT 'floating feeling' was normally used for this PT) 'blood pressure increased' and 'asthma NOS'. These events were labelled ADRs except for the last two events, i.e. 'blood pressure increased' and 'asthma NOS'. In the pharmacists' data, the event rate for losartan was significantly different from that for the control drug(s) for 21 events. The rate for losartan for the following ten events was significantly greater than that for the control drug(s): 'hot flushes NOS', 'hepatic function abnormal', 'oedema NOS', 'peripheral swelling', 'blood pressure decreased', 'blood pressure increased', 'rhinitis', 'dermatitis contact', 'dry skin' and 'heat rash'. The first five events were labelled ADRs but the remaining five including all of the three skin events ('dermatitis contact', 'dry skin' and 'heat rash') were not documented ADRs. When the two sets of data were combined, the rate of an additional event, 'blood creatinine phosphokinase increased', which is a labelled ADR for losartan was significantly greater than that in the control drugs.

The six PTs, 'asthma NOS', 'blood pressure increased', 'rhinitis', 'dermatitis contact', 'dry skin' and 'heat rash' shown in table III were not labelled ADRs. No index case (certain or probable cases according to WHO causality assessment[14]) was found after re-examining the original questionnaires and follow-up studies for the patients with these six PTs. For example, of five cases with losartan who had 'asthma NOS' reported by doctors, two had cardiac failure, two of the remaining three had a history of asthma prior to losartan treatment and asthma in the last case improved while losartan therapy was continued.

To further examine those unlabelled adverse events, we compared our data with those of the UK PEM study on losartan.[8] Taking the difference between the MedDRA and the event dictionary used in the DSRU[15,16] into account, two events – 'dermatitis contact' and 'dry skin' – judged to be equivalent between the J-PEM and UK PEM studies. In the UK PEM study on losartan, the incidence densities (IDs) for these two events were 0.3 per 1000 patient-months or less, with no evidence suggesting that either is a signal (i.e. reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented[14]).

Selected Events of Interest

Abnormal Hepatic Function

In the follow-up study for 14 patients with 'hepatic function abnormal NOS' reported by pharmacists, laboratory values were tracked and reported for seven patients. Only one of these seven patients had serum ALT levels that exceeded three times the upper limit of normal (ULN) and the levels decreased when treatment with losartan was continued.

Skin Events

The rates of three skin events ('dermatitis contact', 'dry skin' and 'heat rash') for losartan were significantly higher than those for control drug(s) in the pharmacists' data (table III). Interestingly, these events were reported exclusively from pharmacists and no such event was reported for losartan from any doctor. Twenty reports on 'dermatitis contact' for losartan were reported from 20 different pharmacies. Similarly, 13 reports on 'dry skin' and five on 'heat rash' were reported from 13 and five different pharmacies, respectively.

Cough

As in the UK PEM study on losartan, 'cough' was frequently reported for patients treated with losartan in this J-PEM study. In the doctors' data, the rate of 'cough' with losartan was 27.6/1000 patient-years similar to that with calcium channel antagonists (15.9/1000 patient-years) but significantly less than that with ACE-inhibitors (233/1000 patient-years). In the pharmacists' data, the rate of 'cough' with losartan was 52.5/1000 patient-years similar to that with calcium channel

antagonists (64.2/1000 patient-years) but significantly less than that with ACE inhibitors (311/1000 patient-years) [see table III for the number of cough and patient-years]. The finding was essentially the same even when the rate was adjusted for age, gender, heart failure, respiratory tract infection and asthma/chronic bronchitis. As shown in table III, 111 of 2186 patients prescribed losartan were reported to have a cough by pharmacists and 18 of 816 patients prescribed losartan were reported to have a cough by doctors. After making allowance for 756 patients where the information was available from both the pharmacist and doctor, it was found that a total of 125 of 2246 patients prescribed losartan were reported to have a cough either by a pharmacist or a doctor. The information on whether the patient was previously treated by any antihypertensive drug(s) was available for all but 96 of those 2246 patients prescribed losartan. Excluding 96 patients without the information on the previous drug, in 31 (25%) of 125 patients with a cough and in 392 (19%) of 2025 patients without a cough, the patient prescribed losartan was previously treated by ACE inhibitors ($p > 0.05$, Fisher's exact test). A total of six patients were reported to have discontinued losartan due to a cough (table II) and five of those six prescribed losartan were previously treated by ACE inhibitors.

Discussion

As shown in table III, the rates of some known ADRs to losartan were significantly higher in patients treated with losartan as compared individually with one of the two control drugs (ACE inhibitors and dihydropyridine calcium channel antagonists) or as pooled data. They included those shown in the doctors' data, 'headache NOS', 'palpitations', 'anaemia NOS', 'insomnia NEC' and 'feeling abnormal'. The known ADRs shown in the pharmacists' data were 'hot flushes NOS', 'hepatic function abnormal', 'oedema NOS', 'peripheral swelling' and 'blood pressure decreased'. One such ADR revealed when both the doctors' and pharmacists' data were combined was 'blood creatinine phosphokinase increased'.

As shown in table III, statistically significant differences in the rates of some known ADRs to losartan were observed only between patients treated with losartan and those in one of the two control groups. It may therefore be advantageous to routinely employ control groups using at least two drug classes, such as ACE inhibitors and dihydropyridine calcium channel antagonists.

The idea of concurrent control is not unique to J-PEM. When designing PEM in the UK, Inman wrote as follows:[17] 'Each 'test' drug will be matched with a 'control drug', the test drug being one that has recently been granted a product license and the control drug will usually be a chemically or pharmacologically similar drug already marketed for the same indication. An unknown proportion of the patients receiving the control drug will have been taking it for some time, though this will not be apparent from the prescription. Others will be 'new' patients who have recently started treatment. The first task will be to process prescriptions for the control drug in such a way that contemporary treatments may be selected for comparison with the new product'.

Though the original idea of identifying the 'contemporary treatments' (concurrent controls) was abandoned for a number of reasons in the UK PEM,[13] the reasons behind the choice of control cohorts in J-PEM are exactly the same as in this original design of the UK PEM.

Our results indicate that some known ADRs might be illuminated as events where the event rates are significantly higher than those for the control drug(s). Though unknown ADRs were not detected in this study, the use of the cohort design with concurrent control might work as a tool for signal generation. There were a number of instances where the test drug gave a significantly higher rate of non-ADR events (i.e. false positives) than for the control drug(s). However, it is relatively easy to distinguish a false signal from a true one using various means such as follow-up studies and the comparison between J-PEM data and the UK PEM data.

Our findings indicate that the rate of cough with losartan is similar to that with dihydropyridine calcium channel antagonists. In the UK PEM on losartan, cough was reported for as many as 1418 out of 14 522 patients and the main reason for this observation was thought to be 'carry-over' effects because of the following two reasons. First, when reports of a cough between days 1 and 7 were excluded, rates of cough were significantly higher for the ACE inhibitors when compared with losartan. Second, 91% of 101 patients who had discontinued losartan due to cough had previously been treated with ACE inhibitors.[9] In this J-PEM study, similar to the UK PEM, five (83%) of six patients who had discontinued losartan due to a cough had previously been treated with ACE inhibitors. Nevertheless, in this J-PEM study on losartan, we could not find strong evidence suggesting that cough was reported due to 'carry-over' effects. This is because 31 (25%) of 125 patients with a cough and 392 (19%) of 2025 patients without a cough that were prescribed losartan were previously treated with ACE inhibitors and the difference was not significant. This indicates that for most patients prescribed losartan who had a cough, cough could not be attributed to 'carry over' effects except for a small fraction of patients who discontinued losartan due to a cough.

J-PEM has several problems to be solved in the future. For instance, it is still not clear how to use pharmacists' data in addition to the doctors' data. As shown in table III, the significant difference in the rates between losartan and control drug(s) for five known ADRs were found only in pharmacists' data. In addition, the rate of losartan for one additional known ADR 'blood creatinine phosphokinase increased' became significantly greater than that in the control drugs when the pharmacists' and doctors' data were combined. Therefore, it seems valuable to use pharmacists' data in addition to the doctors' data. However, it might be of concern that a false positive signal was obtained in the pharmacists' data somewhat more often than in the doctors' data. This was particularly true for three skin events. Similarly, the reason why 'oedema NOS' and 'peripheral swelling' were reported mainly from pharmacists needs to be determined.

Most of those events were reported from different pharmacies. Therefore, it could not be justified to ascribe the reports on those events in the pharmacists' data to the reporting behaviours of a few specific pharmacists. In the current J-PEM pilot study, the pharmacists knew which patients were likely to be monitored when they registered the patients before they received the questionnaire for the individual patients. Though pharmacists were, when participating in J-PEM, instructed to collect the information in the daily practice in their pharmacies, some of them seemed inclined to obtain information on every event including trivial ones from the possible subjects. This may explain why some minor events were exclusively reported from pharmacists. However, this does not explain why these events are exclusively reported for patients prescribed losartan. Therefore, we cannot rule out the possibility that some of the events exclusively reported from pharmacists in this J-PEM study may be associated with the effect of losartan in the future.

Though several problems with J-PEM remain to be solved, J-PEM is useful in generating data that help increase the safety information on the newly marketed drugs in Japan. Based upon two pilot studies, we are now launching a permanent system of J-PEM and the results of these studies will be reported elsewhere.

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References

1. Kubota K. A design for prescription-event monitoring in Japan (J-PEM). Pharmacoepidemiol Drug Saf 1999; 8: 447-56

2. Kubota K, Kawabe E, Hinotsu S, et al. Pilot study of prescription-event monitoring in Japan comparing troglitazone with alternative oral hypoglycaemics. Eur J Clin Pharmacol 2001; 56: 831-8
3. Tanaka K, Morita Y, Kawabe E, et al. Drug use investigation (DUI) and prescription-event monitoring in Japan (J-PEM). Pharmacoepidemiol Drug Saf 2001; 10: 653-8
4. Kubota K. Prescription-event monitoring in Japan (J-PEM). Drug Saf 2002; 25 (6): 441-4
5. Pylypchuc GB. ACE-inhibitor-versus angiotensin II blocker-induced cough and angioedema. Ann Pharmacother 1998; 32: 1060-6
6. Conigliaro RL, Gleason PP. Losartan-induced cough after lisinopril therapy. Am J Health Syst Pharm 1999; 56: 914-5
7. Dicpinigaitis PV, Thomas SA, Sherman MB, et al. Losartan-induced bronchospasm. J Allergy Clin Immunol 1996; 98: 1128-30
8. Mann RD, Mackay F, Pearce G, et al. Losartan: a study of pharmacovigilance data on 14522 patients. J Hum Hypertens 1999; 13: 551-7
9. Makay FJ, Pearce GL, Mann RD. Cough and angiotensin II receptor antagonists: cause or confounding? Br J Clin Pharmacol 1999; 47: 111-4
10. Mann RD. Prescription-even monitoring. In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. New York (NY): John Wiley & Sons, 2000: 231-46
11. Yokotsuka M, Aoyama M, Kubota K. The use of medical dictionary for regulatory activities terminology (MedDRA) in prescription-event monitoring in Japan (J-PEM). Int J Med Inf 2000; 57: 139-53
12. Kalbfleish JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley, 1980
13. Nu-lotan package insert [Japanese]. Ban-yu Pharmaceutical Co., Ltd., Tokyo, Japan. Feb 2001
14. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255-9
15. Kubota K, Inman WHW. Terminology in prescription-event monitoring. Eur J Clin Pharmacol 1994; 46: 497-500
16. Inman WHW. Postmarketing surveillance of adverse drug reactions in general practice. II: prescription-event monitoring at the University of Southampton. BMJ 1981; 282: 1216-7
17. Inman WHW, Rawson NSB, Wilton LV. Prescription-event monitoring. In: Inman WHW, editor. Monitoring for drug safety. 2nd ed. Lancaster: MTP Press, 1985: 213-35

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