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Side Effects and Pharmacokinetics of Nonionic Iodinated Contrast Medium in Hemodialized Patients

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透析患者における非イオン性ヨード造影剤の副作用と薬物動態

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22名の透析患者に対して，通常，腎機能正常者に行われるのと同様の方法で造影CT検査を施行し，副作用の頻度と種類，非イオン性ヨード造影剤の薬物動態について検討した．造影剤はIopamiron 370® 100mlを用いた．最長5日間の追跡中に，副作用として局所性蕁麻疹を1例(4.5%)みとめたのみで，非イオン性造影剤は透析患者に用いる際にも，注意深く使用する限り安全であると考えられた．造影剤注入後施行された2回の透析で，血中総ヨード量は著明に減少したが，特に初回透析による除去率が高かった(平均73%)．この除去率とダイアライザーの膜面積との間には統計学的に正の相関をみとめた．透析患者で著明に亢進しているvicarious excretionが，検索した2例で証明されたが，これは血中総ヨード濃度が高い場合のみ亢進発現され，そのほとんどは肝胆道系によるものであった．またvicarious excretionは造影剤注入後，比較的早期（数時間）に発現し，その後緩慢となる可能性が示唆された．

Summary

We conducted contrast CT scanning on 22 dialysis patients using the same method as usually applied to cases with normal renal function and studied the incidences and types of side effects and the pharmacological kinetics of non-ionic iodine contrast medium (Iopamiron 370®, 100 ml). During the follow-up period (five days at most), we found localized urtication as a side effect in only one case (4.5%). Therefore we speculate that non-ionic contrast medium is a safe agent in dialysis patients, as long as it is cautiously used. After contrast medium injection, we conducted dialysis twice, which definitely decreased total blood iodine content. The extraction ratio at first dialysis was particularly high (73% on average). We recognized a statistically positive correlation between this extraction ratio and dialyzer size. Although two cases studied proved the notable acceleration of vicarious excretion in dialysis patients, this acceleration appeared only with high total blood iodine content. This phenomenon was considered mainly due to

excretion from the hepatobiliary tract. Vicarious excretion appeared relatively soon after contrast medium injection (within a few hours), but showed a slower decreasing tendency.

Introduction

Recently, the survival period of chronic renal failure patients has improved with the progress of hemodialysis. For blood access evaluation[1] and detection of malignant tumors reported as of high incidence[2], occasions have increased for the use of iodine contrast medium in angiography and CT scanning for dialysis patients. Although there have been many reports on the side effects and pharmacological kinetics of contrast medium in cases with normal renal function, few researchers have reported on these aspects in patients with renal dysfunction, particularly dialysis patients[3,4]. A non-ionic contrast medium, probably having few side effects, has been on the market since 1986; unfortunately there are no detailed researches concerning its side effects and pharmacological kinetics using many cases of dialysis patients as subjects[5,6,7]. In the case of non-ionic contrast medium injection in hemodialized patients, we often hesitate to choose mode of injection, type and dose, although the low incidence of side effects is known. Injecting the same dose of iopamidol (Iopamiron 370®, 100 ml), a non-ionic contrast medium, as in cases of normal renal function, we conducted contrast CT scanning in a group of dialysis patients and investigated the types and incidences of side effects, intracorporeal pharmacological kinetics and safety of iopamidol; we report the results here.

Materials and Methods

The subjects were 22 dialysis patients injected with 100 ml Iopamiron 370® (iodine content 37 g,

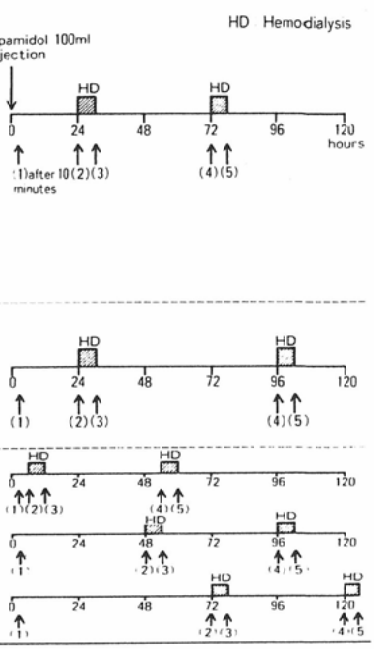
Table 1　Patient data

	Case	Age (yr)	Sex	Basal renal disease	Hemodialysis duration (yr)	Body weight (kg)	Urine volume (ml/day)	Dialyzer (Membrance surface area = m²)	
Group A	① S.A	77	M	DMN	2.5	35.1	0	Cuprophane	(0.8)
	② F.M	73	F	CGN	0.2	39.8	200	Cuprophane	(0.8)
	③ S.U	37	M	CGN	1	58.6	0	Cuprophane	(2.1)
	④ A.S	52	M	DMN	1	38.1	0	Cuprophane	(1.0)
	⑤ E.H	57	M	DMN	0.5	45.4	200	Cuprophane	(1.0)
	⑥ S.Mu	79	M	CGN	0.5	51.6	0	Cuprophane	(1.2)
	⑦ K.K	78	F	CGN	7	34.8	0	Cuprophane	(1.0)
	⑧ N.H	60	F	R-tbc	3.5	37.8	0	Cuprophane	(1.0)
	⑨ J.F	66	M	CGN	4	53.7	400	EVA	(1.8)
	⑩ M.F	54	F	DMN	1	58.6	0	Cuprophane	(1.5)
	⑪ H.Y	50	F	CGN	15	52.4	0	EVA	(1.8)
	⑫ S.Ma	58	M	CGN	4.5	50.5	0	PMMA	(1.6)
	⑬ K.N	64	M	CGN	16	49.7	0	Diacetate	(1.6)
Group B	⑭ M.M	72	M	CGN	1.5	40.3	0	Cuprophane	(1.0)
	⑮ T.U	46	M	CGN	1	44.4	0	Cuprophane	(1.5)
	⑯ S.Y	40	F	CGN	3	53.3	200	Cuprophane	(1.2)
	⑰ Se.A	39	M	CGN	17	47.3	0	Cuprophane	(2.1)
	⑱ A.N	62	M	CGN	4	51.1	0	Cuprophane	(1.5)
	⑲ T.I	62	M	PCK	1	39.2	200	Cuprophane	(1.0)
Group C	⑳ M.I	51	M	CGN	5	60.7	0	PMMA	(1.6)
	㉑ K.I	48	M	CGN	10	66.9	0	Cuprophane	(1.8)
	㉒ A.T	73	F	CGN	4	49.5	200	Cuprophane	(1.0)

CGN : Chronic glomerulonephritis　DMN : Diabetic nephropathy　PCK : Polycystic disease　R-tbc : Renal tuberculosis　PMMA : Polymethylmethacrylate　EVA : ethylenevinylalcohol

Table 2 Iodine concentration of plasma and schedule of blood sampling

	Case	Iodine concentration of plasma (mg/ml) (1) 10minutes after injection	(2) before first dialysis	(3) after first dialysis	(4) before second dialysis	(5) after second dialysis	Hemodialysis shift and time of blood sampling
Group A	①	6.70	2.04	0.57	0.60	0.61	
	②	5.30	2.42	0.56	0.62	0.43	
	③	4.80	2.13	0.23	0.39	0.05	
	④	2.45	1.83	0.75	0.76	0.33	
	⑤	3.17	1.17	0.43	0.35	0.32	
	⑥	6.75	1.18	0.55	0.50	0.21	
	⑦	7.00	2.87	0.73	0.65	0.20	
	⑧	5.28	2.34	0.51	0.63	0.18	
	⑨	3.02	1.39	0.43	0.31	0.10	
	⑩	2.86	1.06	0.24	0.17	0.04	
	⑪	5.13	1.58	0.55	0.58	0.19	
	⑫	3.12	2.37	0.49	0.55	0.12	
	⑬	3.43	1.84	0.49	0.54	0.17	
Group B	⑭	3.86	1.60	0.49	0.42	0.14	
	⑮	4.80	1.78	0.43	0.32	0.10	
	⑯	4.42	2.02	0.41	0.42	0.11	
	⑰	4.99	2.12	0.33	0.41	0.08	
	⑱	4.59	1.69	0.45	0.41	0.13	
	⑲	3.75	1.12	0.36	0.20	0.06	
Group C	⑳	3.75	1.22	0.42	0.43	0.18	
	㉑	8.48	1.87	0.40	0.43	0.09	
	㉒	3.54	1.46	0.47	0.52	0.19	



molecular weight 777) for contrast CT scanning (Table 1). We administered 50 ml Iopamiron 370® in a bolus via a 19 G buttefly needle inserted in the dorsum manus and another 50 ml by instillation. Before Iopamiron 370® administration, we explained to the patients the possible types of side effects, based on the classification by Ansell[8]. The patients were asked to observe themselves and inform us as to their side effects during and after the injection period (five days at most).

We investigated the types and incidences of side effects. Blood samples were collected five times: 10 minutes after injection, before and after first dialysis (4~72 hours after injection), before and after second dialysis (52~120 hours after injection). We measured the blood contrast medium concentration as total iodine content. Based on this result, we assessed the ratio of contrast medium extraction by dialysis, using an ICP luminous spectroanalyzer SPS 1200 Type A® (Seiko Electronics) for measurement. We conducted four-hour bicarbonate dialysis by double needle operation using 200 ml/min bloodstream and 500 ml/min dialysate. Because the subjects consisted of randomly selected patients, the period between the first dialysis and the second differed depending on the condition of the patient. Changes in dialysis and protocol for blood-collecting in each patient are shown in Table 2. Types and sizes of dialyzers for each patient are described in Table 1. We investigated the relationship between extraction ratio {extraction ratio=(predialytic level − postdialytic level)/predialytic level} and type and size of dialyzer in the first dialysis. We examined the acceleration of vicarious non-renal excretion in the two patients who underwent a second abdominal scout CT scan between 24 hours after contrast medium administration and first dialysis.

Results

The types and incidences of side effects caused by iopamidol, according to the classification by Ansell,

Table 3　Various kinds and incidence of side effects in patient receiving iopamidol. (Citation from Ansell[8])

Severity of side effects	Kinds of side effects	Patients reporting side effects
1. Mild	nausea, vomiting (mild), heat sensation, limited urticaria pale face, sweating, itching	3cases (13.6%) Case ②, Case ⑧ heat sensation of arm with injection of Iopamidol. Case ⑫—limited urticaria (4.5%)
2. Moderate	faintness, vomiting (severe), extensive urticaria, facial edema glottic edema, dyspnea, bronchospasm, chest pain, abdominal pain, severe headache	0
3. Severe	loss of consciousness, cardiac arrest, shock, symptomatic cardiac arrhythmia, pulmonary edema.	0
4. Death		0

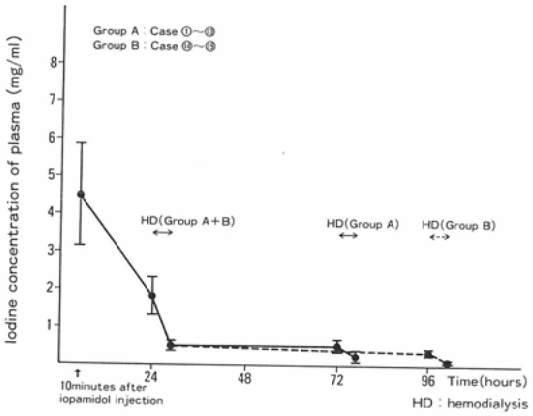


Fig. 1　Elimination of iopamidol by hemodialysis (Group A and B)

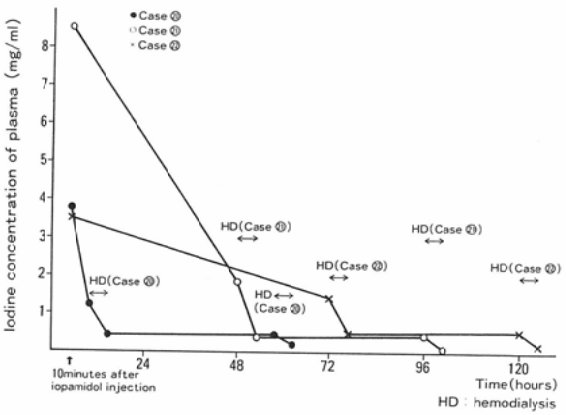


Fig. 2　Elinination of iopamidol by hemodialysis (Group C)

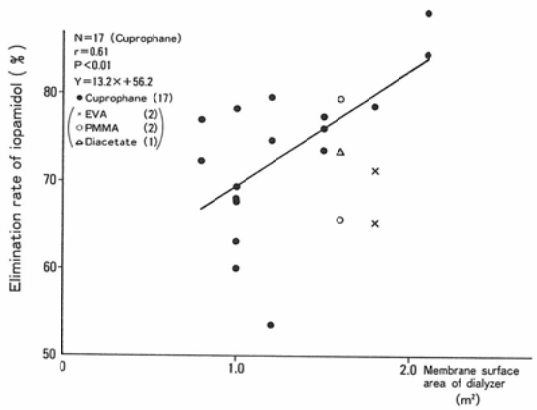


Fig. 3　Correlation between membrane surface area of dialyzer and elimination rate of iopamidol (at first hemodialysis)

are described in Table 3. Among the 22 cases, three (13.6%) showed side effects. Although two (cases 2 and 8) complained of a slightly heat sensation in their injected arms at contrast medium injection, the feeling disappeared at the termination of bolus injection. Only case 12 required anti-histaminic intravenous injection. The incidence of mild side effects as systemic symptoms was 4.5% (1/22). We recognized no side effects more serious than those of moderate level. After contrast medium injection, we collected blood samples five times; the total blood iodine content is shown in Table 2. Group A (cases 1~13) consisted of patients whose first and second dialyses were conducted 14 and 72 hours, respectively, after contrast medium injection. Group B (cases 14~19) consisted of those whose dialyses were conducted 24 and 96 hours, respectively, after injection. The time courses of the total blood iodine contents in groups A and B are shown in Fig. 1. Because the dialytic shifts in cases 20, 21 and 22 were markedly different from the others, we regarded them as group C, whose relation between time course and total blood iodine content is separately given in Fig. 2. The total blood iodine contents in group A, B and C were less than 1 mg/ml after first dialysis and less than 0.5 mg/ml after the second, which reflects indicate the definite decrease among all cases. The graph clearly indicates that the extraction ratio in the first dialysis (53.4~89.2%, 73% on average) was satisfactory, showing higher levels than in the second dialysis. We noted a positive

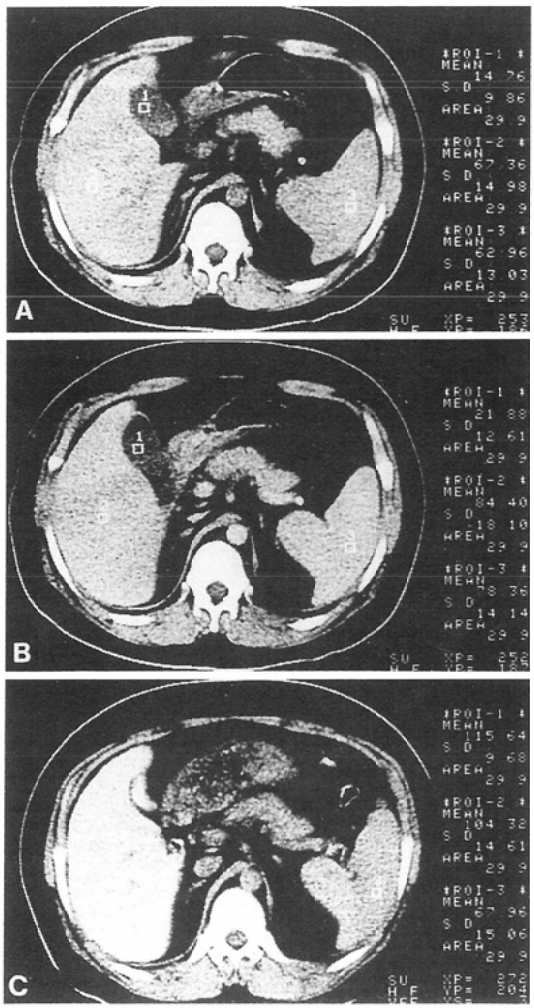


Fig. 4 CT of abdominal splanchnic system before and after iopamidol injection in case ③
(A) plain CT. (B) conventional enhanced CT. (C) shows the CT 24 hours after (B) demonstrating marked high density of the gall bladder and liver compared with spleen.

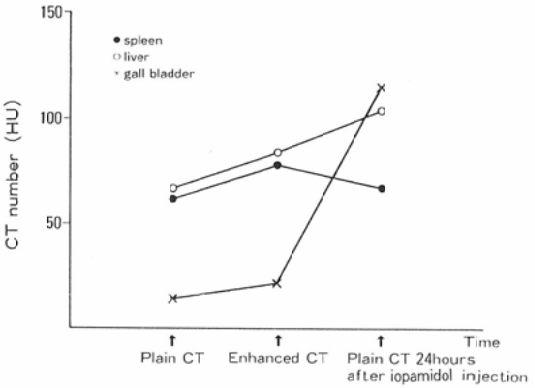


Fig. 5 Change of CT number of liver, gall bladder and spleen in case ③ after iopamidol injection.

correlation between these extraction ratios and dialyzer size (Fig. 3). The dialyzer used in the present study was a cuprophan filter, the most common filter in recent clinical use. Because the number of cases treated with highly efficient membranes (such as PMMA (polymethylmethacrylate) and EVA (ethylenevinyl-alcohol) filters) was limited, it was difficult to elucidate the differences depending on filter type. For reference, data on other filters are shown in Fig. 3. Although groups A, B and C showed symptoms such as anuria, their total blood iodine contents decreased to less than half (2.5~8.5 mg/ml → 1.1~2.4 mg/ml) during the period between 10 minutes after contrast medium injection and first dialysis (4~72 hours) (Figs. 1 and 2). We recognized no statistical correlations between this decrease and the time course before first dialysis or residual renal function (urine volume). To judge the acceleration of vicarious non-renal excretion of contrast medium, we conducted abdominal scout CT scanning in two cases (cases 3 and 17) 24 hours after injection. The concentrations of contrast medium in liver and gall bladder 24 hours after injection were definitely higher than those right before and after. We confirmed the notable excretion of contrast medium, especially into the gall bladder. Fig. 4 illustrates the case 3 CT scan images of liver, gall bladder and spleen immediately before and after injection and 24 hours after. The changes in concentrations of contrast medium in these organs are shown in the graph in Fig. 5. Although the changes in concentrations in the spleen in dialysis patients immediately before and after the injections are approximately the same on the graphs as those of the cases with normal renal function, concentrations in the liver and gall bladder increased even 24 hours after injection. This increasing tendency was markedly observed in the gall bladder. The total blood iodine content between first and second dialyses showed scarcely any change.

Discussion

In principle, renal failure patients require dialytic treatment, but physicians hesitate to use iodine contrast medium for dialysis patients, for fear of causing side effects. At our institute, over the past four years, we have applied contrast CT scanning to approximately 300 cases of dialysis patients, including 100 ionic contrast medium-injected cases; for the past two years, we have injected iopamidol to all the 200 other cases. Although we have administered both ionic and non-ionic contrast media to dialysis patients with some anxiety, in fact we found no notable differences between the dialysis patients and those with normal renal function, as regards the incidence of side effects. In the present study, we assessed in detail the incidence of side effects in dialysis patients and discuss whether to be more sensitive to side effects in the use of non-ionic contrast media. Generally, non-ionic contrast media are reported as having a distinctly lower incidence of side effects than ionic contrast media[9,10,11]. According to a report based on a large-scale investigation using 120,000 subjects with normal renal function, the incidences of side effects were 4.2% with non-ionic contrast medium and 13.5% with ionic contrast medium[9]. There were no significant differences between incidences in the present study, using non-ionic contrast medium (4.5%), and those in the aforementioned study of subjects with normal renal function (4.2%). The only case showing any side effect was case 12, with symptoms of localized urtication. We recognized no side effects more serious than moderate level according to the classification by Ansell. There are several reports concerning immediate general side effects[12,13] and recently noted delayed side effects[11], which are induced by non-ionic contrast media in the cases of normal renal function. In view of these reports, physicians should exercise as much caution as possible in using non-ionic contrast medium.

Such careful attention will obviate unreasonable anxiety about the side effects in dialysis patients. The amount of iopamidol used for each patient was 100 ml in the present experiment. We injected iopamidol to the patient (case 7) at a rate of up to 2.87 ml/kg (body weight). Although we observed no relationship between iopamidol injection amount per unit body weight and side effects, in dialysis patients

physicians are advised to follow the clinical performance safety guidelines for those with normal renal function, as determined by Nakata et al. (2 ml/kg)[14]. It is sometimes difficult to conduct the examinations on dialysis patients right before dialyses because of the time limitation. The time between 10 minutes after contrast medium injection and first dialysis ranged widely in the present experiment, from four to 72 hours. There were no correlations between the difference in these periods and the incidence of side effects. According to some reports, with the increase in iodine contrast medium dwelling time, central nervous system side effects frequently occurred[5] and tended to be prolonged[4]. Consequently the first dialysis after examination with high contrast medium extraction ratio (73% on average) should be conducted as soon as possible. Before dialysis, we observed the decrease in injected contrast medium blood concentration to less than half. As do Hansson[15] and Becker[16], we speculate that this decrease was induced by the acceleration of vicarious excretion in the hepatobiliary system, sweat and saliva. We confirmed this in cases 3 and 17. Although we conducted CT scanning not only for the liver and gall bladder but also for the parotid gland in these two cases, 24 hours after the contrast medium injection, no significant increase in concentration was observed. Therefore we presume that vicarious excretion chiefly occurred in the hepatobiliary system. The vicarious excretion level was considered accelerated in dialysis patients, judging from the fact that the normal level is less than 1%. On the other hand, some researchers point out that this acceleration was hardly observed in all cases[17]. There were dispersions in the data which could have resulted from the fact that data were obtained solely via scout roentgenograms. In all the cases, vicarious excretion acceleration would have been observed if our experimental method and CT scanning of sufficient contrast had been used. Because the degree of vicarious excretion had no correlation with the differences in time before first dialysis (4~72 hours), there is a possibility that this acceleration appears during the relatively early period, within a few hours, and slows down subsequently. This is no better than a presumption because we have to conduct unpractical examinations, repeated CT scanning after contrast medium injection, in order to prove it. Furthermore, we speculate that the acceleration of vicarious excretion appeared only in cases of high blood concentration of contrast medium, because total blood iodine content, which decreased before the first dialysis, showed few changes during the period between the first and second dialyses. In the present study, we recognize a positive correlation between contrast medium extraction ratio and dialyzer size. We missed the opportunity to refer to the significance of highly efficient dialyzers such as PMMA and EVA filters. The incidence of side effects induced by non-ionic contrast medium became lower than that induced by ordinary ionic contrast medium. The molecular weight of non-ionic contrast medium, however, is more than that of ionic (approximately 800 non-ionic contrast medium, 610~630 ionic contrast medium). Considering the dialytic effects, it might be important to assess the extraction ratios of highly efficient dialyzers.

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