Prediction of iopromide reduction rates during haemodialysis using an *in vitro* dialysis system

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Abstract

**Background.** In clinical studies, it has been difficult to evaluate the influence of haemodialysis (HD) parameters on HD clearance (CL\(_{HD}\)) and reduction rate (RR) of non-ionic contrast medium during HD sessions. We therefore predicted clinical values of CL\(_{HD}\) and RR of iopromide, a non-ionic contrast medium, from findings obtained from *in vitro* experiments, and confirmed that these predictive values were comparable with the actual values in clinical cases.

**Methods.** We developed a correlation equation for predicting CL\(_{HD}\) on the basis of *in vitro* HD experiments by varying blood flow rates between 100 and 200 ml/min with a cuprammonium rayon dialyser (AM-SD-10H). Total body clearance of iopromide (CL\(_{PT}\)) was estimated by the Cockroft–Gault equation. The volume of distribution (V\(_d\)) was obtained from the reported value. By using the HD and three pharmacokinetic parameters (CL\(_{HD}\), CL\(_{PT}\) and V\(_d\)), we predicted CL\(_{HD}\) and RR for seven patients undergoing HD after the administration of iopromide.

**Results.** In the *in vitro* study, the mean values (±SD) of iopromide clearance at blood flow rates of 100 and 200 ml/min were 45.35 (2.54), 53.88 (6.46) and 57.61 (4.72) ml/min, respectively. There were highly significant correlations between clearance and blood flow rate (r = 0.975). Although the predicted CL\(_{HD}\) showed a tendency towards underestimation, a good correlation was found. Predicted RR values were similar to observed values except for one case.

**Conclusion.** The *in vitro* model used in the present study provides pertinent information about CL\(_{HD}\) and is helpful for predicting RR during HD in individual patients undergoing HD.

**Keywords:** drug removal; haemodialysis; iopromide; pharmacokinetics; radiocontrast media

Introduction

Because the kidneys and liver are the main organs involved in drug elimination, drugs that are eliminated mainly by the kidneys will accumulate to toxic levels during renal failure. Patients with advanced or end-stage renal failure require some form of renal replacement therapy such as haemodialysis (HD). For patients on HD therapy, the apparatus provides one of the major routes for drug elimination. In this setting, the rate of administered drug removal by HD must be considered in order to obtain the desired level of medication. However, it is difficult to obtain information on the dialysability of drugs from clinical investigations.

Contrast media-induced nephropathy has become an important cause of iatrogenic acute renal impairment [1]. Although acute nephropathy can be induced during the use of non-ionic contrast media, such as iohexol and iopromide, the frequency of these events is probably lower than with ionic contrast media [1]. Because HD effectively removes contrast media [2–5], prophylactic HD, after the administration of contrast media, has been performed to prevent contrast media-induced nephropathy in patients with mild to moderate renal failure. However, one study reported that HD did not decrease the incidence of contrast media-induced nephropathy [6]. Nevertheless, others have proposed that ≥2 h of HD immediately after angiography may be beneficial in patients
with moderate renal failure and additional risk factors in order to prevent contrast media-induced nephropathy [7].

The studies described above indicate that the efficacy of HD for contrast media-induced nephropathy is controversial. Although some have shown that contrast media can be removed efficiently by HD, few studies have examined the quantity of contrast media elimination by HD that is necessary to prevent contrast media-induced nephropathy. Furthermore, the influence of HD parameters, such as blood flow rate and ultrafiltration rate, on the clearance of contrast media has not been evaluated adequately because these parameters differ from patient to patient in the clinical setting.

To address these issues, we examined the dialysability of iopromide, a non-ionic contrast agent, during HD using an *in vitro* dialysis system with various dialysis parameters. From these results, we predicted the clearance and the elimination rate of iopromide during HD in the clinical setting. We also confirmed that these predictive values were comparable with actual clinical values.

**Subjects and methods**

In *vitro* study

Iopromide (Proscope® 370 containing 370 mg/ml), a non-ionic iodinate contrast medium, was kindly provided by Tanabe Seiyaku Co., Ltd (Tokyo, Japan). We used an AM-SD-10H dialyser (surface area 1.0 m², Asahi Medical Co., Ltd, Tokyo, Japan), which is made of cuprammonium rayon and classified as a low-flux dialyser.

Fresh bovine blood was obtained in the morning of the experimental days from Tokyo Shibaura Zoki Co. (Tokyo, Japan). At the time of blood collection, 200 ml of blood preservation solution (ACD-A Solution, Terumo Co., Ltd, Tokyo, Japan) was added to 11 of bovine blood to prevent coagulation, and the blood was used in the experiments ~2 h later. After arrival at the laboratory, the blood was filtered through double gauze. Haematocrit was adjusted to a standard value of 30.0±3.0% by the addition of physiological saline.

To prevent coagulation, heparin calcium (Caprocin®, Nihon Shering K.K., Osaka, Japan) was used in the haemolysis circuit, and Kindaly Solution AF-2 (Fuso Pharmaceutical Industries, Ltd, Osaka, Japan) was used in the dialysate. We also used disposable blood tubing NK-Y820P (Nikkiso Co., Ltd, Tokyo, Japan) for the HD circuit, and DBB-22B (NIKKISO Co., Ltd., Tokyo, Japan) as the HD machine.

In *vitro* haemodialysis experiments

Our *in vitro* HD model is shown in Figure 1. The circuit and dialyser were primed with physiological saline and then placed in the HD machine. Heparin calcium at 5000 U was added to 2 l of prepared blood and placed in the beaker. Proscope® 370 was added to blood at a final concentration of 10 mg/ml. Following the addition and mixing of the drug, the blood was gently stirred by a stirrer and kept in a thermostat bath at 37°C during the experiments.

The HD session lasted 2 h. The blood flow rate was varied between 100 and 200 ml/min. The flow rate of dialysate and the ultrafiltration rate were set at 500 and 0 ml/min, respectively. To prevent blood coagulation during the experiment, a single dose of 2000 U of heparin calcium was injected into the circuit (arterial side), and heparin calcium was then infused at 2000 U/h.

Single blood samples were obtained from single beakers just before the beginning of dialysis (0 min). In the HD experiments, blood samples were simultaneously collected from the arterial and venous sides of the circuit at 5, 10, 15,
20, 30, 45, 60, 90 and 120 min after initiation of HD. These samples were centrifuged, and the isolated plasma specimens were stored at −30°C until measurement.

The drug concentration in plasma was measured using high-performance liquid chromatography (HPLC) at our laboratory. The HPLC assay and sample clean-up procedures were developed and modified on the basis of previously described methods [8,9]. The lower limit of detection of iopromide was 0.1 mg/ml.

The reduction rate (RR) and clearance during HD (CLHD) were calculated from the following equations:

\[
RR\% = \frac{[(C_0 - C_t)/C_0] \times 100}{100} \quad (1)
\]

where \(C_0\) is the plasma drug concentration at the initiation of dialysis, \(C_t\) is the plasma drug concentration at each sampling time (A side), and

\[
CL_{HD} (\text{ml/min}) = [(C_{an} - C_v)/C_a] \times Q_b(1 - Hct) \quad (2)
\]

where \(C_a\) is the plasma drug concentration at the arterial side of the dialyser (mg/ml), \(C_v\) is the plasma drug concentration at the venous side of the dialyser (mg/ml), \(Q_b\) is the blood flow rate (ml/min) and Hct is whole blood haematocrit (%).

**Clinical study**

Seven patients [three females and four males, mean age 75 years (56–89 years), mean weight 59 kg (44–74 kg)] with chronic stable renal failure undergoing angiography with iopromide administration, including both diagnostic and therapeutic procedures, were studied at Shin-Tokyo Hospital. Patients were enrolled between October 2001 and June 2003. Informed consent was obtained from all patients, and the study protocol was approved by the hospital Institutional Review Board.

At Shin-Tokyo Hospital, patients with known chronic stable renal failure (serum creatinine level >1.7 mg/dl as measured by the creatininase–sarcosine oxidase–peroxidase method using an autoanalyser) usually underwent HD after contrast medium administration. Patients underwent HD as soon as technically possible after angiography.

One venous blood sample was obtained just before HD, and samples were then collected from the arterial and venous sides of the HD circuit at 30, 60, 120 and 180 min after HD onset. These samples were centrifuged and the plasma isolates were stored at −30°C until measurement. The iopromide concentration in plasma was measured by the HPLC method used for the *in vitro* study.

The RR and CL_{HD} were calculated using equations 1 and 2. Iopromide (mol. wt 791 Da) as well as iohexol (mol. wt 821 Da) are eliminated exclusively by glomerular filtration in an unchanged form without tubular reabsorption, and protein binding is practically zero [10]. Iopromide is therefore an effective marker of the glomerular filtration rate for patients with normal renal function or even with different degrees of renal insufficiency [11].

We predicted the CL_{HD} of iopromide in the clinical setting by the following equation:

\[
CL_{HD} = CL_{vitr} + F \quad (3)
\]

where \(CL_{HD}\) is the HD clearance of iopromide (ml/min), \(CL_{vitr}\) is the HD clearance of iopromide obtained from the *in vitro* study without ultrafiltration (ml/min) and \(F\) is the ultrafiltration rate (ml/min). Because of the negligible protein binding of contrast media [10], we assumed that clearance would increase in parallel with the ultrafiltration rate.

The RR of contrast media by HD is represented by equation 1. Moreover, \(C_t\) is expressed as:

\[
C_t = C_0 \times \exp(-k_{HD} \times t) \quad (4)
\]

\[
k_{HD} = (CL_{HD} + CL_{PT})/V_d \quad (5)
\]

where \(k_{HD}\) is the elimination rate constant during HD, \(t\) is the duration of HD, \(CL_{PT}\) is the total body clearance of the patient, and \(V_d\) is the distribution volume of the contrast medium.

Substitution of equations 4 and 5 into equation 1 results in:

\[
RR(%) = \left\{1 - \exp\left[(CL_{HD} + CL_{PT})/V_d \times t\right]\right\} \times 100 \quad (6)
\]

Creatinine clearance estimated by the Cockroft-Gault equation [12] was assigned to \(CL_{PT}\). Values of \(V_d\) and \(CL_{HD}\) were then obtained from the reported value of 0.191/kg [10] and from equation 3, respectively.

**Results**

**In vitro study**

The plasma iopromide concentration decreased rapidly during HD for each blood flow rate (Figure 2), and at 150 and 200 ml/min it was below the lower detection limit (0.1 mg/ml) after 120 min of HD. Most of the iopromide had been eliminated by the end of HD following any of the blood flow conditions (Table 1).

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**Fig. 2.** Time course of iopromide concentration in plasma during *in vitro* haemodialysis. Haemodialysis was performed at blood flow rates of 100, 150 and 200 ml/min. Values represent the mean ± SD, \(n = 2\).
When blood flow rates were set at 100, 150 and 200 ml/min, plasma flow rates were 70, 105 and 140 ml/min, respectively, because the haematocrit had been adjusted to 30% for these experiments. The mean values (±SD) of iopromide clearance at these plasma flow rates were 45.35 (2.54), 53.88 (6.46) and 57.61 (4.72) ml/min, respectively. There were highly significant correlations between clearance and plasma flow rate (regression equation, \( y = 0.18x + 33.89 \); correlation coefficient, \( r = 0.975 \)). Therefore, clearance of iopromide (\( \text{CL}_{\text{vitr}} \)) was calculated by the following regression equation:

\[
\text{CL}_{\text{vitr}} = 0.18 \times Q_b (1 - \text{Hct}) + 33.89
\]

Clinical study

Characteristics of patients. Seven patients were enrolled in this study. The patients underwent coronary (\( n = 5 \)) or cerebral (\( n = 2 \)) angiography. The mean serum creatinine level, haematocrit and mean dose of iopromide (±SD, range) were 2.1 (0.53, 1.7–3.1) mg/dl, 31.7 (3.98, 23.9–36.5)% and 121 (46, 35–180) ml, respectively. Dialysis by the low-flux dialyser (cuprammonium rayon, AM-SD-10H) was started between 23 and 62 min (median, 46 min) after administration of the last bolus of contrast agent. The duration of HD ranged from 60 to 180 min.

Prediction of clearance of iopromide. We predicted the \( \text{CL}_{\text{HD}} \) of iopromide from equations 3 and 7 in seven HD cases using the AM-SD-10H. The blood flow rate was set at 100 (\( n = 4 \)) or 120 ml/min (\( n = 3 \)), and the dialysate flow rate was 500 ml/min. The ultrafiltration rate was set at 0 (\( n = 4 \)), 2.5 (\( n = 2 \)) and 5 ml/min (\( n = 1 \)). Although the predicted values showed a tendency for underestimation, a comparably good correlation was found (Figure 3).

Precision of reduction rate of iopromide. We predicted the RR of iopromide during HD from equation 6. \( V_d \) was estimated from the product of body weight \( \times 0.19 \). The predicted values were similar to the observed values, except for one case (Figure 4).

Discussion

During HD, drug pharmacokinetics are generally described by the elimination phase. In the present study, to predict the RR of iopromide after \( t \) min from the start of HD, we obtained several pharmacokinetic parameters including distribution volume (\( V_d \)), total body clearance of the patient (\( \text{CL}_{\text{PT}} \)) and HD clearance (\( \text{CL}_{\text{HD}} \)) (equation 6). We then multiplied the RR by the drug concentration just before HD to predict drug concentration after HD. Although it is relatively easy to obtain values of \( V_d \) and \( \text{CL}_{\text{PT}} \), there is little adequate information on \( \text{CL}_{\text{HD}} \) because of differences in HD parameters, such as dialyser type, blood flow rate and ultrafiltration rate. For these reasons, we studied
the dialysability of contrast media using an \textit{in vitro} HD system in order to obtain CL\textsubscript{HD}. We used results from our \textit{in vitro} study to predict drug clearance and RR during dialysis in the clinical setting. These predicted values were then confirmed by comparison with actual clinical values.

Iopromide and iohexol are non-ionic low osmolar contrast agents. Iopromide is eliminated exclusively by glomerular filtration in an unchanged form without tubular reabsorption, and its protein binding is practically zero [10]. It therefore provides an effective marker for the glomerular filtration rate in patients with normal renal function or even with different degrees of renal insufficiency [11]. We estimated the CL\textsubscript{PT} of iopromide by using the Cockcroft–Gault formula [12], which is widely used in clinical situations.

A few previous studies have reported HD clearances of iopromide by low-flux dialysers. Matzkies \textit{et al.} [2] found that iopromide clearance was 109 ml/min when blood flow was set at 250 ml/min with a 1.3 m\textsuperscript{2} haemophan dialyser. They also reported clearances of 87 and 121 ml/min when the blood flow was set at 200 ml/min with 1.3 and 1.8 m\textsuperscript{2} haemophan dialysers, respectively [3]. Moreover, they showed that cuprophan membranes produced significantly reduced clearance values (102–106 ml/min) compared with polysulphone membranes (154–158 ml/min; \(P < 0.001\)) [4]. However, these clearances were calculated from plasma concentrations obtained from the arterial and venous blood lines and from the blood flow rate, rather than from the plasma flow rate. These differences make it difficult to compare these values with our results. On the other hand, Schindler \textit{et al.} [5] reported that the clearance of iopromide, calculated from the plasma flow rate, was 82 ml/min when the blood flow rate was 200 ml/min with a 1.6 m\textsuperscript{2} haemophan dialyser. Compared with our results, these findings indicate that the CL\textsubscript{HD} of iopromide per membrane area is almost equal with cuprammonium rayon and haemophan dialysers.

While performing a similar \textit{in vitro} dialysis study using normal saline to characterize vancomycin removal, Hudson \textit{et al.} [13] found that there were no differences between the \textit{in vitro} and \textit{in vivo} vancomycin dialysis clearance values at a high blood flow rate (450 ml/min) [13]. However, this study did not examine how changes in blood flow rate or ultrafiltration rate or how protein binding to vancomycin affected clearance values, indicating the necessity of studying there parameter effects on clearance. Our present study showed that the CL\textsubscript{HD} of iopromide was correlated with blood flow rate. However, whether this correlation persists at higher blood flow rates (>200 ml/min) and with other drugs is uncertain.

The use of contrast media, decreased renal perfusion, certain medications and surgery are the common causes of hospital-acquired renal insufficiency [14]. To prevent contrast media-induced nephropathy, only hydration has been uniformly accepted for use in clinical practice [15]. In the present study, all patients administered prophylactic temporary HD were also given hydration, and none developed contrast media-induced nephropathy defined as a maximum increase in serum creatinine level >1.5 mg/dl or >50% above baseline value [6,16]. In addition, adverse effects related to HD did not occur. However, the small number of participants in our study make it difficult to draw definite conclusions. Further studies with larger patient populations with serum creatinine values >3 mg/dl will be needed to determine whether HD after contrast media administration is effective for preventing contrast media-induced nephropathy. Ideally, such studies will make it possible to determine the applicability and dosage of prophylactic HD based on patient characteristics and on the dosage of the contrast media.

There were several limitations in the present study. First, our study population was small and a low-flux membrane dialyser was used for all participants. Although HD with high-flux membranes may remove iopromide more effectively, the present study showed that iopromide, a middle molecular weight substance, was removed adequately by HD with a low-flux membrane. Further studies will be necessary to evaluate the permeability of iopromide using high-flux membranes. Secondly, because the interval between the last iopromide injection of iopromide and the starting time of HD was relatively short (23–62 min), the plasma concentration of iopromide may not have corresponded to a postulated ‘steady state’ between the two compartments. For example, a patient having an interval of 23 min showed a reduction rate of iopromide (55.2%) which was greater than the predicted value (29.5%). In this patient, the distribution volume may have been <0.191/kg. However, this result may indicate that short intervals produce efficient elimination of iopromide even when low-flux membrane dialysers are used.

In conclusion, the present study shows that the RR of iopromide after \(t\) min from the start of HD can be predicted by the pharmacokinetic parameters of the \(V_d\), CL\textsubscript{PT} and CL\textsubscript{HD}. Although it is difficult to obtain precise information about HD clearance because HD parameters differ from patient to patient in the clinical setting, the present \textit{in vitro} model may be helpful in predicting iopromide clearance and RR during the HD in individual patients. Additional studies will be needed to evaluate whether the present \textit{in vitro} dialysis findings are applicable to other drugs and dialysis procedures.

\textit{Conflict of interest statement}. None declared.

\textbf{References}


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