Pharmacokinetic Studies of Quinidine in Patients with Arrhythmias

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SUMMARY  The absorption and disposition of quinidine were measured in nine patients following single oral and intravenous dosing. A new specific chromatographic method was used to measure the drug in plasma and urine. After intravenous administration, the plasma half-life (t½) was 7.8 ± 0.7 h, the volume of distribution (Vd) was 3.0 ± 0.5 liters/kg, and the total body clearance was 4.8 ± 0.8 ml/min/kg. After oral administration, 87 ± 7% (mean ± SEM) was available to the systemic circulation. Quinidine was removed primarily by hepatic metabolism, with the renal clearance averaging only 1.0 ± 0.2 ml/min/kg. Mean quinidine concentrations were estimated in 42 patients on chronic therapy by averaging blood levels during a dosing interval. In patients without heart failure, these corresponded well to mean drug levels predicted from the pharmacokinetic parameters measured after a single intravenous dose, but in patients with heart failure, the values for mean quinidine concentrations were higher than predicted. This suggests that impaired elimination of the drug or a decreased volume of its distribution, or both, may develop in heart failure.

QUINIDINE has been used as an antiarrhythmic drug for many years. However, its toxicity including nausea, vomiting, diarrhea, and more serious problems of arrhythmias or sudden death has limited its usefulness in chronic therapy. Early studies provided little data about absorption, distribution, and elimination of quinidine and frequently the methods which were used for measuring quinidine failed to separate metabolites of the drug from the parent compound. Although plasma concentrations have been employed to monitor quinidine therapy for some time, it seemed likely that specific pharmacokinetic data might be of additional value in allowing a prediction of more rational dosing schedules. The value of such information has recently been shown for acute and chronic therapy with theophylline. Accordingly, we have studied a group of patients with cardiac disease and arrhythmias to determine standard pharmacokinetic parameters for quinidine. We have included observations of patients with heart failure to determine if this affects the fate of quinidine since conflicting data have been reported on this question. Because quinidine has been said to be eliminated primarily by nonrenal routes, we have included single dose studies of a patient with chronic renal insufficiency requiring dialysis and a patient with severe hepatocellular failure due to cirrhosis in order to confirm these concepts. Quinidine was measured by a new specific analytical technique which is rapid and sensitive and eliminates interference by metabolites of the drug.

Methods

Quinidine Measurement

The analytical technique which was used was high performance reverse phase liquid chromatography. A column, 100 X 0.25 cm, was packed with Phenyl/Corasil (Waters Associates, Milford, Mass.), a resin whose active phenyl group is attached to an inert glass bead coated with silica. The column was perfused at 3 ml/min with 0.05 M H3PO4 containing 0.5 M (NH4)2SO4 at 61°C. After injection of the sample, the concentration of methanol in the perfusate was linearly increased to 33% over a 2 min period by a solvent programmer. An Aminco Fluoro-Colorimeter was used to monitor the outflow of the column, using an excitation filter of 360 nm and an emission filter of 450 nm, and quinidine was quantified in samples by comparing peak heights on the chromatograph with those of a quinidine standard.

In patients taking quinidine, two peaks representing metabolites of the drug eluted from the column before quinidine (fig. 1). The standard curve obtained by measuring the peak heights was linear over the range of 0.1 to 7.0 μg/ml. Duplicate determinations had a precision of ± 5%. Standards and blood samples were also analyzed by the double extraction method of Cramer and Isaksson. Results of the two methods compared closely. Quinidine was analyzed by chromatography together with dihydroquinidine, a common contaminant of commercial preparations also possessing antiarrhythmic activity. Twenty plasma samples from patients not receiving quinidine were analyzed by chromatography; there were no fluorescent peaks which would have been confused with quinidine. In addition, most of the com-
monly used cardiovascular drugs were dissolved in appropriate solvents and injected onto the column. Only acetylsalicylic acid and furosemide produced significant peaks and neither had retention times similar to quinidine.

Plasma was separated from red cells immediately and stored at 4°C until analyzed. Samples were measured for quinidine within 24 hours or plasma was stored frozen and assayed within a week. Quinidine levels were unchanged by refrigeration or freezing.

Acute Single Dose Studies

Studies were performed with nine patients in whom oral quinidine therapy was being considered. These patients ranged in age from 16-76 years and in weight from 42-74 kg. None of these patients had heart failure or impaired renal or hepatic function (table 1). None had hemodynamically significant arrhythmias at the time of study.

In order to clarify further the relative contribution of renal and hepatic insufficiency to elimination of quinidine, two additional patients were studied. The first had chronic renal insufficiency due to polycystic kidney disease and required dialysis three times per week. The second had prehepatic coma secondary to alcoholic liver disease as well as renal failure due to hepatorenal syndrome and required dialysis three times per week.

Quinidine gluconate was diluted in 5% dextrose in water and infused intravenously at a rate of 6.3 mg quinidine base per minute. A total dose of 2-6 mg/kg was administered. Blood was obtained from the contralateral arm through an indwelling catheter. Thereafter oral quinidine sulfate was given to these same nine patients when the plasma level from the intravenous dose had fallen to less than 0.3 μg/ml. The oral dose was administered with 250 ml H2O 2-3 hours after a normal breakfast. The total oral dose was 4-10 mg/kg. The patient with renal failure received intravenous quinidine on two occasions, once on a dialysis day and once on a day between dialyses, while the patient with liver disease received intravenous drug on one occasion.

Blood samples were collected in heparinized tubes immediately before infusion, and every 10 to 15 min for the first 90 min of the study. Subsequently, samples were obtained every hour for 4 to 6 hours and then every 2 to 4 hours for 1 to 2 days after beginning the study. Following oral administration, blood samples were collected every 30 min for the first 4 hours and then every 2 to 4 hours for 1 to 2 days.

Urine was collected for 24 hours following drug administration in most cases. In addition, separate 2-3 hour aliquots of urine were collected at a point which we anticipated would be on the exponential decay phase of the plasma concentration time curve. Quinidine urinary clearance was estimated from these aliquots. Creatinine clearance was calculated from the aliquots as well as the 24 hour sample.

Pharmacokinetic and Statistical Calculations

The half-time of rapid distribution, T½ (α), was calculated by fitting a line to initial data points derived by
Table 1. Clinical Characteristics of Patients Studied

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Wt (kg)</th>
<th>Diagnosis</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Total Bilirubin (mg/100 ml)</th>
<th>SGOT (IU/ml)</th>
<th>Alkaline Phosphatase (IU/ml)</th>
<th>Serum Albumin (g/100 ml)</th>
<th>Prothrombin time (pt/control) sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>GL/76/M</td>
<td>62.5</td>
<td>ASCVD</td>
<td>56.7</td>
<td>0.3</td>
<td>14</td>
<td>75</td>
<td>3.7</td>
<td>13/12</td>
</tr>
<tr>
<td>RA/21/F</td>
<td>50.0</td>
<td>Previous VF</td>
<td>95.0</td>
<td>0.2</td>
<td>13</td>
<td>—</td>
<td>4.9</td>
<td>12/12</td>
</tr>
<tr>
<td>LG/65/M</td>
<td>70.6</td>
<td>Tachycardia</td>
<td>90.3</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>13/13</td>
</tr>
<tr>
<td>RP/16/M</td>
<td>52.5</td>
<td>ASCVD</td>
<td>67.1</td>
<td>0.9</td>
<td>12</td>
<td>126</td>
<td>4.4</td>
<td>10.5/11</td>
</tr>
<tr>
<td>HL/61/F</td>
<td>41.7</td>
<td>PVCs</td>
<td>51.6</td>
<td>1.0</td>
<td>15</td>
<td>58</td>
<td>4.2</td>
<td>12/12.5</td>
</tr>
<tr>
<td>RM/20/M</td>
<td>68.0</td>
<td>PAT</td>
<td>89.8</td>
<td>1.3</td>
<td>15</td>
<td>29</td>
<td>4.5</td>
<td>11/10.5</td>
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<tr>
<td>HT/55/M</td>
<td>72.5</td>
<td>Atrial fib.</td>
<td>61.7</td>
<td>0.8</td>
<td>15</td>
<td>45</td>
<td>—</td>
<td>11/11</td>
</tr>
<tr>
<td>LW/56/F</td>
<td>65.0</td>
<td>Atrial fib.</td>
<td>60.5</td>
<td>0.6</td>
<td>24</td>
<td>61</td>
<td>5.0</td>
<td>12/12</td>
</tr>
<tr>
<td>HF/62/M</td>
<td>73.6</td>
<td>PVCs</td>
<td>69.6</td>
<td>0.7</td>
<td>21</td>
<td>49</td>
<td>4.8</td>
<td>11/13</td>
</tr>
<tr>
<td>RM/57/M</td>
<td>90.9</td>
<td>Polycystic kidney disease</td>
<td>0</td>
<td>0.8</td>
<td>18</td>
<td>300</td>
<td>—</td>
<td>12/10</td>
</tr>
<tr>
<td>AS/52/M</td>
<td>80.0</td>
<td>Laennec’s cirrhosis</td>
<td>0</td>
<td>27.5</td>
<td>31</td>
<td>460</td>
<td>2.5</td>
<td>14.5/10</td>
</tr>
</tbody>
</table>

Abbreviations: SGOT = serum glutamylxaloacetic transaminase (normal values: 3-17 IU/ml); alkaline phosphatase (normal values: 50-200 IU/ml); ASCVD = arteriosclerotic cardiovascular disease; VF = ventricular fibrillation; MI = myocardial infarction; PVC = premature ventricular contraction; PAT = paroxysmal atrial tachycardia.

Subtracting the $\beta$ phase extrapolated to zero time from the actual data points. The half-time of elimination from plasma was calculated by fitting a line to all points 5 hours after beginning the infusion. Volume of distribution was calculated as the dose divided by the area under the intravenous plasma concentration time curve multiplied by the elimination rate constant. Total body clearance was calculated as the dose administered divided by the area under the intravenous plasma time curve. Absorption or fraction available to the systemic circulation after the first pass through the liver after oral dosing was calculated by dividing the area under the oral concentration time curve by that under the intravenous plasma concentration time curve. Renal clearance of quinidine was calculated by dividing the excretion rate of quinidine by the plasma concentration.

Statistical analysis of all data was performed by the two-tailed Student's $t$-test.

Chronic Quinidine Administration

Forty-two patients who were receiving quinidine sulfate (39) or quinidine gluconate (3) as therapy for arrhythmias were studied. All of these patients had received a constant dose of drug for at least three days before study. Twenty-one patients had heart failure as defined by presence of at least three of the following: paroxysmal nocturnal dyspnea, orthopnea, pedal edema, neck vein distention, basilar râles, $S_3$ gallop, Kerley B lines, or cardiomegaly on X-ray. Most patients had mild compensated heart failure at the time of study. Only three patients had laboratory evidence of mild abnormalities of liver function.

Blood samples were obtained from these patients at 2, 4, 6, and if necessary, 8 hours after a dose of drug. The average of the 3 or 4 samples taken was calculated in an attempt to estimate the mean plasma concentration of quinidine for the dosing interval studies. These mean values were then compared to those which were predicted to occur in the patient using data obtained from the acute studies. These predicted values were calculated as follows:

$$C_{sv} = \frac{Fa \times Dose}{V_d \times ke \times t^*}$$

where $Fa$ = fraction absorbed or the fraction available to the systemic circulation after first pass through the liver; $ke$ = the elimination rate constant ($\beta$) and $t^*$ = the dosing interval. Urine was collected for 24 hours and both creatinine clearance and quinidine excretion were measured on this sample.

Results

Acute Single Dose Studies

During intravenous infusion of quinidine plasma levels rose rapidly (fig. 2). The half-time of distribution $t_1/2$ ($\alpha$) was 12.4 ± 2.4 minutes. The half-life of elimination from plasma $t_1/2$ ($\beta$) was 7.8 ± 0.7 hours. The volume of distribution was 3.0 ± 0.5 L/kg. The total body clearance was 4.8 ± 0.8
FIGURE 3. A representative time concentration curve obtained by giving quinidine orally.

ml/min/kg and the renal clearance 1.0 ± 0.2 ml/min/kg. Total 24 hours urinary excretion of quinidine was 18.4 ± 2.3% of the administered dose.

After oral administration plasma quinidine levels rose less rapidly than after intravenous administration, peaking at two hours (fig. 3); an initial rapid distribution phase was not seen. The plasma concentration decreased as an exponential function of time with a mean t½ of 11.0 ± 1.5 hours, longer than the half-life after intravenous administration (P < 0.05). Thus, half-life after oral administration is distorted by prolonged absorption of drug and data obtained from oral administration should be used only to estimate absorption. The amount of drug available to the circulation after oral administration was 87 ± 7% (table 2). This 87% then reflects both absorption and first pass effect.

Having determined in the above patients that renal clearance represented about 20% of the total clearance, we studied a patient with renal insufficiency requiring dialysis to see if distribution or elimination of quinidine was affected. Others12 have shown similar half-lives in patients with and without renal failure. Intravenous infusion of quinidine to our patient showed a t½ (b) of 12 hours, a volume distribution of 4.9 L/kg and a clearance of 4.8 ml/min/kg during dialysis; on a day between dialyses these values were 9.5 hours, 2.5 L/kg with a clearance of 3.0 ml/min/kg (fig. 4).

<table>
<thead>
<tr>
<th>Pt</th>
<th>Absorption (t1/2) (min)</th>
<th>t1/2 (b) (hours)</th>
<th>Vd (L/kg)</th>
<th>Clearance (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GL</td>
<td>86</td>
<td>15.0</td>
<td>11.8</td>
<td>15.5</td>
</tr>
<tr>
<td>RA</td>
<td>67</td>
<td>12.0</td>
<td>4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>LG</td>
<td>110</td>
<td>18.3</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>RP</td>
<td>120</td>
<td>-</td>
<td>7.4</td>
<td>14.8</td>
</tr>
<tr>
<td>HL</td>
<td>83</td>
<td>2.1</td>
<td>9.2</td>
<td>10.5</td>
</tr>
<tr>
<td>RM</td>
<td>100</td>
<td>2.5</td>
<td>6.0</td>
<td>16.0</td>
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<tr>
<td>HT</td>
<td>79</td>
<td>16.6</td>
<td>9.0</td>
<td>13.5</td>
</tr>
<tr>
<td>LW</td>
<td>71</td>
<td>10.0</td>
<td>8.2</td>
<td>8.5</td>
</tr>
<tr>
<td>HF</td>
<td>62</td>
<td>3.8</td>
<td>8.2</td>
<td>10.7</td>
</tr>
<tr>
<td>Mean</td>
<td>87</td>
<td>12.4</td>
<td>7.8</td>
<td>11.0</td>
</tr>
<tr>
<td>SEM</td>
<td>7</td>
<td>2.4</td>
<td>0.7</td>
<td>1.5</td>
</tr>
</tbody>
</table>

RM: Chronic renal failure:
- Dialysis: 22.0 12.0 4.9 4.8 0
- No Dialysis: 30.0 9.5 2.5 3.0 0

HL: Chronic hepatic failure:
- 38.0 53.0 9.7 2.1 0

Abbreviations: i.v. = intravenous; t1/2 (a) = half-time of distribution phase in plasma; t1/2 (b) = half-time of elimination phase in plasma; Vd = volume of distribution.

FIGURE 4. The time concentration curve in a patient with renal failure studied before (left) and during (right) dialysis. Quinidine was given intravenously for both studies.
Since these calculations were done as described in the Methods section, they excluded some of the initial dialysis data and included some late post-dialysis data. Therefore, we calculated kinetic parameters during the 6 hour dialysis period and a similar time period on the day between dialyses. During the actual dialysis period (2-8 hours after drug infusion), \( V_d \) calculated by extrapolation to \( t_a \) is 1.8 L/kg, the \( t_a \) is 3.8 hours, and the clearance 5.6 ml/min/kg. During the 2-8 hour time period on the day between dialyses, the \( V_d \) is 1.7 L/kg, the \( t_a \) 5.0 hours and the clearance 3.9 ml/min/kg. Thus, the increment in clearance during dialysis is similar using either method of calculation. In addition, we have found that blood obtained from the afferent and efferent limbs of the dialysis machine showed no difference in quinidine levels. On the other hand, quinidine metabolites accumulating in plasma were reduced by dialysis.

We next studied a patient with cirrhosis and hepatorenal syndrome in order to confirm the generally accepted hypothesis that hepatic metabolism is primarily responsible for elimination of quinidine. In that patient (fig. 5) the volume of distribution was increased to 778 L, three times that found in the first nine patients, and the half-life was markedly prolonged at 53 hours. The clearance of 2.1 ml/min/kg is in the low normal range. Thus, cirrhosis with ascites and hepatorenal syndrome profoundly alters both distribution and plasma half-life of quinidine.

Intravenous quinidine was well tolerated in all patients given drug at a rate of 6.3 mg/min. One patient complained of transient facial numbness, another of nasal stuffiness, and two others of drowsiness. Systolic blood pressure fell 5-15 mm Hg and heart rate rose by 5-20 beats/min. No treatment was necessary for any of these events.

**Chronic Dose Studies**

During chronic quinidine therapy, quinidine plasma levels fluctuated little about the mean value obtained by averaging the 3 or 4 samples taken (fig. 6). This fluctuation was similar with quinidine sulfate and quinidine gluconate (24% above, 22% below with quinidine sulfate; 16% above, 19% below with quinidine gluconate). Thus, quinidine sulfate given every 6 hours produces relatively constant quinidine concentrations in most patients.

In patients without heart failure, mean plasma quinidine levels fell appropriately about the levels predicted by the single dose data (fig. 7). The expected variation of mean plasma levels from patient to patient was confirmed. In this group of patients the average dose administered was 13.2 ± 1.0 mg/kg/day, resulting in an average plasma concentration of 1.7 ± 0.2 \( \mu \)g/ml. On the other hand, patients with heart failure had mean plasma concentrations of

![Plasma concentration curve](image)
quinidine higher than predicted by single dose data. Greater patient to patient variation was noted than in the group without heart failure. The average dose administered was 11.9 ± 0.7 mg/kg/day, resulting in an average plasma concentration of 2.8 ± 0.6 μg/ml, significantly higher than the mean concentration in patients without heart failure (P < 0.01).

Twenty-four hour urinary excretion of quinidine averaged 10.7 ± 0.9% of the daily dose in the chronic therapy studies. Heart failure did not influence the 24-hour urinary excretion of quinidine.

**Discussion**

The high performance liquid chromatographic method described has the advantages that it can be accomplished with as little as 3 μl of plasma and that it can be completed within 5 min of receiving the sample. Quinidine and dihydroquinidine, both of which are active compounds, are measured, but the metabolites are separated from the active parent compounds.

The single dose studies showed that quinidine is well absorbed after oral administration, that it disappears from the plasma with a half-life of 7.8 hours, and that clearance is primarily due to hepatic metabolism. The data we report are in agreement with those recently described by Ueda and associates.18 However, our τ₀ (α) was slightly longer (12.4 vs 7.19 min), and we saw a flattening of the terminal portion of the β phase of the plasma concentration time curve in only two patients. After oral administration the half-life was longer than that seen with intravenous administration, a finding we believe may be due to prolonged absorption after oral dosing.

Other investigators, using a method specific for quinidine, have shown that elimination of quinidine was similar in patients with renal failure and controls. However, these investigators studied only decay of plasma levels after oral dosing. Our studies show that renal failure *per se* has a negligible influence on quinidine kinetics. Dialysis removes quinidine metabolites well and is associated with an apparent increased clearance of quinidine. We have calculated clearance in two ways to study the effects of dialysis on this parameter. The first method using all points after 5 hours has two drawbacks. First, the 5 hour point occurs in the midst of dialysis. Thus, the initial dialysis period is excluded from the computation and the levels after 8 hours are at a time after dialysis has been completed. Second, because of difficulty with vascular access, only a limited number of plasma samples could be obtained after 5 hours and this permits a greater chance of error in the calculation of the kinetic data.

The second method of calculation, using points 2–8 hours after infusion, including the entire dialysis period and a corresponding period on the nondialysis day also is imprecise for two reasons. First, that time period includes some of the initial distribution phase, and second, V_d is calculated by extrapolation to t₀ and not by area under the curve. By both methods, however, dialysis seems to increase clearance. Since dialysis flow rate was only 1 ml/min/kg, dialysis itself could increase clearance only by this amount even if 100% of both bound and unbound quinidine was removed by the
procedure. Since we showed no A-V difference at any time, we feel that the changes in clearance are not due to the dialysis procedure. It is possible, however, that dialysis decreased protein binding of quinidine, thereby increasing the estimated $V_d$ and the calculated clearance. A decreased protein binding would also make more free drug available for removal by the liver. It is also conceivable that dialysis increases hepatic drug clearance by improved hemodynamics in a fluid overloaded patient.

In severe hepatic failure, when due to cirrhosis and accompanied by ascites, the volume of distribution of quinidine is greatly increased and the elimination of drug from plasma drastically slowed. Klotz and associates showed a more than two-fold prolongation of half-life, a 50% increase in the steady state volume of distribution and a 50% decrease in total clearance of diazepam in three patients with cirrhosis. These authors attributed part of the increase in $V_d$ to decreased protein binding in cirrhotics. Our patient had more advanced liver disease and showed more striking alterations in drug distribution and plasma half-life than the patients they evaluated. However, clearance in our patient remained in the low normal range. Decreased plasma protein binding of quinidine probably accounts for some of the increase in the volume of distribution and thus serves to increase spuriously the calculated clearance, but we cannot assess this parameter critically since protein binding was not measured in this study. Thus, we have demonstrated marked changes in $V_d$ and half-life in this patient, but we have not conclusively shown that the ability of the liver to metabolize drug is greatly reduced.

Our chronic dose studies confirmed the validity of the pharmacokinetic data in predicting the mean plasma levels which one would expect to achieve in patients without heart failure or impaired liver function. However, distinctly higher plasma quinidine levels were observed in patients with heart failure. Some studies have found higher quinidine levels in patients with heart failure after a single dose of drug, but these observations can be questioned because the non-specific method of Brodie and Udenfriend was used for quinidine determinations and this method measures metabolites as well as unchanged quinidine. Using a more specific extraction method for assaying quinidine, higher levels have been found in heart failure after three oral doses, but the study design makes it difficult to interpret these observations. Kessler and associates using a specific extraction method found that quinidine half-life was similar in patients with and without heart failure. In addition, comparable steady state quinidine levels were found in the two groups of patients after chronic therapy. However, the blood levels were not related to weight-adjusted daily dose of quinidine and it is questionable whether the differences we have observed would be apparent in the absence of such a consideration. In order to explain our findings of elevated plasma levels in heart failure in light of Kessler's findings of normal half-life in those patients, one must postulate that the volume of distribution is reduced in heart failure. It has been shown that the volume of distribution for lidocaine is smaller in heart failure, and this fact plus impaired elimination lead to higher lidocaine levels in such patients.

Although there is some variability in the kinetics of absorption, distribution and elimination of quinidine, even in the absence of heart failure, one can use the data derived from our studies to make predictions regarding dosing schedules for acute and chronic quinidine therapy. In order to achieve therapeutic plasma quinidine levels of 2.3-5.0 $\mu$g/ml in the chronic situation, patients without heart failure should receive at least 14 mg/kg/day in four divided doses. This would be equivalent to administering approximately 300 mg quinidine sulfate every 6 hours to a 70 kg man. Patients with mild heart failure may receive a similar dose as initial therapy, whereas patients with more severe heart failure should probably receive a reduced dose. However, despite the validity of these recommendations for the average patient, plasma quinidine levels should be obtained in all patients, and particularly in those with heart failure, after 6-8 doses of drug, in order to assure that therapeutic but not potentially toxic plasma quinidine levels have been attained.

References

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doi: 10.1161/01.CIR.55.1.1/b
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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