Although erythropoietin (EPO) derivatives improve anemic status in most end-stage renal disease patients, some EPO-resistant patients remain. Asialo-type EPO is as effective as is native EPO in vitro, but in vivo, it is quickly trapped by the hepatic asialo receptors. Alkaline phosphatase (ALP) also binds to the asialo receptor for degradation.

We compared hematologic indices in 27 stable PD patients 1–3 months before and after the start of icodextrin solution. In selected patients, we also performed imaging with 99m-technetium–labeled galactosyl serum albumin (GSA) for asialo receptors. Resistance to EPO was defined as a hematocrit below 30% concurrent with EPO administration of more than 18,000 IU monthly.

In 19 patients without EPO resistance started on icodextrin, the average hematocrit level did not change (−1.2%), and the average ALP activity increased 36%. But in 8 patients with EPO resistance, the average hematocrit level increased by 12% (p = 0.03 as compared with baseline), and ALP activity increased by 79% (p = 0.02 as compared to non EPO resistant cases) after icodextrin introduction. In the patients with marked elevation of ALP activity, GSA scintigraphy showed inhibition of tracer binding. These results indicate that improvement in EPO-resistant anemia and greater ALP activity with icodextrin administration are mediated through blockade of the asialo receptors on hepatocytes.

Key words
Icodextrin, erythropoietin, asialo receptor, alkaline phosphatase

Introduction
Anemia is one of the key issues in the management of end-stage renal disease patients. The introduction of erythropoietin (EPO) derivatives dramatically improved not only anemia per se, but also prognosis and quality of life in these patients (1,2). However, a substantial number of EPO-resistant patients remain, and various causes of EPO resistance have been reported (3,4). Mammalian native EPO is metabolized into the asialo type by serum sialidase, and asialo-type EPO is more effective than is native EPO (sialo-type) in vitro; however, the asialo-type is much less effective in vivo because of its rapid disappearance from serum by binding to the asialo receptors on hepatocytes (5,6).

Icodextrin is an osmotic amylopectin molecule used in peritoneal dialysis (PD) solution; it known to be degraded into oligomaltoses by amylase activity in serum. The serum concentration of the end product, maltose, reaches the steady state at approximately 1 g/L when one bag of icodextrin solution is used daily (7). On the other hand, Blom et al. (8) reported that the alkaline phosphatase (ALP) protein can bind to asialo receptors and can then be internalized into lysosomes in hepatocytes for degradation. Gokal et al. speculated that the increase in ALP activity in patients using icodextrin is attributable to delay of the ALP protein’s degradation, because icodextrin metabolites block receptor binding (9). We hypothesized
that this blockade could be indirectly proved by imaging with 99m-technetium–labeled human galactosyl albumin (99mTc GSA).

Considering this background, we found that EPO-resistant anemia improved in patients using icodextrin solution. Moreover, those patients simultaneously showed a greater increase in ALP activity than did patients without EPO resistance. The mechanism of the improved anemia in EPO-resistant patients therefore seems to reflect blockade of asialo receptors and delayed breakdown of the ALP protein.

Patients and methods

We analyzed 27 stable patients on PD with icodextrin solution. We compared hematologic indices before and 1–3 months after the initiation of icodextrin solution. We performed liver imaging with 99mTc GSA for asialo receptors in 3 patients before and after the use of icodextrin. We defined EPO resistance as a hematocrit below 30% with concurrent administration of more than 18,000 IU EPO monthly. Statistical analyses used the paired or unpaired t-test, and we accepted p values of 0.05 or less as statistically significant.

Results

Table I shows the changes of hematocrit and ALP activity in patients with and without EPO-resistant anemia after icodextrin use. In 19 patients without EPO-resistant anemia, the average hematocrit level did not change significantly (–1.2%), and ALP activity increased only 36% from the baseline level. On the other hand, in 8 patients with EPO resistance, the average hematocrit increased 12% (p = 0.03 as compared with baseline, by paired t-test), and ALP activity rose by 79% (p = 0.02 as compared with that in patients without EPO resistance, by unpaired t-test). In the graphs for all 27 individual patients (Figure 1), we found no linear correlation between the percentage increase in hematocrit and ALP activity from baseline.

Figure 2 shows a representative liver imaging study by 99mTc GSA scintigraphy in a patient with marked elevation of ALP activity. The LHL 15 reading, which indicates tracer binding to hepatocytes, showed a normal value before the use of icodextrin; after icodextrin use, it showed moderately impaired uptake. In patients with a slight elevation of ALP activity, GSA scintigraphy showed no apparent change from the initial imaging performed before icodextrin use (Data not shown).

Discussion

In the present study, we show for the first time that icodextrin improves EPO-resistant anemia in PD patients. The possible mechanism seemed to be at least partly related to an elevation of serum ALP activity, because the increase of ALP activity in patients with EPO-resistant anemia was significantly higher than that in patients with a hematocrit of 30% or more, although a linear correlation between the improvement in hematocrit and the elevation of ALP activity was not achieved.

Since the early stages of erythropoietin development, glyco-moiety in the molecule has been regarded as essential for its in vivo activity, because a rapid disappearance of erythropoietin from serum was observed when the sialic acid at the end of intact molecule was removed by sialidase in serum (5,6). On

<table>
<thead>
<tr>
<th>Hematocrit (%)</th>
<th>ALP (U/L)</th>
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<tbody>
<tr>
<td>EPO-resistant</td>
<td>Not resistant</td>
</tr>
<tr>
<td>Before 25.7±3.2</td>
<td>34.1±3.7</td>
</tr>
<tr>
<td>After 28.7±4.5</td>
<td>33.7±4.5</td>
</tr>
<tr>
<td>Change (%) 12</td>
<td>–1.5</td>
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<tr>
<td>p Value 0.03</td>
<td>NS</td>
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</table>

EPO = erythropoietin; NS = nonsignificant.
Icodextrin Improves EPO-Resistance

On the other hand, as Blom et al. reported (8), ALP protein contains a galactose moiety at the end of its molecule, and blockade of the asialo receptor significantly increased ALP serum activity because of delayed degradation of the protein. Gokal et al. speculated that the increase of ALP activity in patients using icodextrin solution might involve the same mechanism as that for icodextrin metabolites (9). In proving this hypothesis (as shown by 99mTc GSA scintigraphy imaging of asialo receptors), we also demonstrated that only icodextrin users with increased ALP activity showed the inhibited receptor binding. The images suggest that the increased ALP activity is attributable to blockade of the hepatic asialo receptors by icodextrin metabolites, with a consequent delay in ALP breakdown.

Taking these findings together, we speculate that blockade of the asialo receptors by icodextrin metabolites also caused blockade of the degradation of asialo-form erythropoietin, with a consequent slight improvement in anemia. It might be argued that the observed elevation in hematocrit is attributable to plasma condensation in these patients because of increased ultrafiltration with icodextrin; however, this explanation is unlikely because other biochemical indices did not change (Data not shown).

Further studies are warranted to prove whether the serum level of erythropoietin increases with the use of icodextrin in resistant patients. We also need to clarify why patients with a hematocrit of 30% or more did not show a further increase in that value even though their ALP level was somewhat higher. And a last question to be investigated in the future is why some patients showed a marked increase in ALP activity, but some did not, even though all used icodextrin solution in the same way.

Conclusions

Icodextrin improved EPO-resistant anemia, and the mechanism seems to relate to blockade of the hepatic asialo receptors by icodextrin metabolites.

References

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