Lidocaine for the Alleviation of Pain Associated With Subcutaneous Erythropoietin Injection

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Predialysis patients and those on peritoneal dialysis receive recombinant human erythropoietin (rHuEPO) by sc injection (1,2). Experience has shown that the sc injection of rHuEPO is quite painful and especially in children may become a matter concerning the patient's compliance with the medicine (3–6). The manufacturer of ceftriaxone (Roche Laboratories, Nutley, NJ) modified the pain associated with the intramuscular preparation of this antimicrobial agent by adding lidocaine to its diluent (7,8). We hypothesized that the addition of lidocaine to sc-injected rHuEPO may have a similar beneficial effect. In a recent study on % nephrectomized rats, we found that the addition of lidocaine to rHuEPO did not interfere with the erythropoietic properties of the latter when given sc three times a week for 2 wk (9). In this study, we investigated the effect of the addition of lidocaine to rHuEPO on pain perception and hematocrit in children on chronic peritoneal dialysis.

MATERIALS AND METHODS

Entry criteria to the study included age 5 to 20 yr, stable dialysis prescription, no peritonitis, fixed rHuEPO dose, stable hematocrit (Hct) and a transferrin saturation value >12% in the preceding 2 months, and no known allergies to lidocaine. Families and patients signed an informed consent form approved by our institution review board.

Patients were randomized to receive first either a combination of rHuEPO/saline or a combination of rHuEPO/lidocaine for 8 wk with crossover to the other combination for another 8-wk period. Patients, families, and caregivers were masked to the combination given; it was known only to the assigned pharmacist who randomized and dispensed the medications. Parents, and when applicable also patients, were instructed and trained on how to mix the additive (lidocaine or saline) to rHuEPO before each injection. Patients were kept on the prestudy rHuEPO dose, which was mixed with 0.2 mL of either 2% lidocaine or normal saline. The total volume injected was restricted to 1.0 mL. The first injection of each combination was administered in the dialysis unit and afterwards once a week at home. The site of injection was rotated in all four extremities. All patients were maintained on oral iron supplementation. Blood Hct was checked every 2 wk, and iron status was checked once every 4 wk. Treatment was held for a week if Hct exceeded 36%.

Patients were trained to complete the visual analogue pain scale (3,5,8). At the end of all studies, the code was broken and scales were scored from 0 (no pain) to 10 (maximum pain). Pain scores were analyzed by the nonparametric procedure, N PAR1WAY, unpaired t test, and χ² test. Data are presented as mean ± SD.

RESULTS

Six children were studied (Table 1). All of them completed the study uneventfully. Their weekly rHuEPO dose ranged between 60 and 95 U/kg. No side effects to the two combination therapies were reported. In two children, the rHuEPO/saline mixture was given first, and in the other four children, rHuEPO/lidocaine was given first.

Hct values at the beginning and end of the rHuEPO/saline mixture were 30.5 ± 5.7 and 28.5 ± 5.9%, respectively, and at the beginning and end of the rHuEPO/lidocaine mixture were 31.2 ± 5.9 and 30.7 ± 4.3%, respectively (nonsignificant for either combination). The transferrin saturation was ≥16% in all patients throughout the study. In three patients combined, treatment was held because the Hct was more than 36%, five times during rHuEPO/saline and four times during rHuEPO/lidocaine treatment.

For the whole group, the pain perception associated with rHuEPO/saline of 4.03 ± 3.09 (median, 4.0) decreased significantly with the rHuEPO/lidocaine mixture to 1.68 ± 2.73 (median, 0.6) (P = 0.0001). Of the rHuEPO/lidocaine injections, 44.2% were associated with no pain compared with 15.9% with rHuEPO/saline mixture (P < 0.01). Patients 1 to 4 (Table 1) greatly benefited from the rHuEPO/lidocaine combination; the pain perception of Patient 5 was very erratic with both combinations, whereas Patient 6 experienced very little pain with either combination.

DISCUSSION

The subcutaneous injection of rHuEPO enables the treatment of predialysis patients (10,11) and those on peritoneal dialysis (1,2) without iv access. Moreover, on the basis of the pharmacokinetic properties of the medicine when injected sc, the drug is slowly released into the circulation (12,13). Consequently, compared with iv administration, it requires lower doses and less frequent administrations, resulting in cost containment (10,11,14,15). Thus, some authors have recom-
mended that patients on hemodialysis also receive rHuEPO sc (11,14).

The local pain associated with sc injection has been described as burning, itching, or stinging (3,5,15) and it lasts 10 to 15 min in adults (5). It is thought to be caused by the citrate component of the buffered solution (5). In some cases, the pain has resulted in patients' refusal of the sc administration of the drug (4,15). In children, it was reported to be painful and frightening and to considerably increase the burden placed on parents, creating a stressful environment at home (6).

In this study, we found that, for the whole group investigated, the addition of lidocaine to sc rHuEPO significantly alleviated/attenuated the pain associated with the injection compared with the rHuEPO/saline combination. Previous studies have shown that the sc injection of saline alone does not cause pain (3,5). This was also our experience in one of the patients in whom we compared the pain perception with rHuEPO alone with that of the rHuEPO/saline combination (data not shown). As found in our earlier study on uremic rats (9), the addition of lidocaine did not interfere with the erythropoietic action of rHuEPO.

Thus, until a better solution to pain associated with sc injection is found, it seems that a selected group of patients may benefit from the addition of lidocaine. However, further studies are indicated to investigate the long-term safety and efficiency of this practice.

ACKNOWLEDGMENT

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REFERENCES

2. Hood VL, Ingraham A: Erythropoietin for chronic ambula-

TABLE 1. Clinical and hematologic data on six children with ESRD studied with rHuEPO/lidocaine

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex/Race</th>
<th>Primary Diagnosis</th>
<th>Time on Dialysis (months)</th>
<th>rHuEPO/ Saline</th>
<th>rHuEPO/ Lidocaine</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Start</td>
<td>End</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>F/W</td>
<td>Juvenile nephronophthisis</td>
<td>9</td>
<td>28.5</td>
<td>30.5</td>
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<tr>
<td>2</td>
<td>10</td>
<td>M/W</td>
<td>Interstitial nephritis</td>
<td>24</td>
<td>38.7</td>
<td>33.4</td>
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<tr>
<td>3</td>
<td>12</td>
<td>M/W</td>
<td>Alport syndrome</td>
<td>14</td>
<td>24.3</td>
<td>26.1</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>F/W</td>
<td>Focal segmental glomerulosclerosis</td>
<td>6</td>
<td>29.7</td>
<td>25.5</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>F/B</td>
<td>Interstitial nephritis</td>
<td>10</td>
<td>25.7</td>
<td>27.7</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>M/B</td>
<td>Posterior urethral valves</td>
<td>68</td>
<td>36.0</td>
<td>27.8</td>
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