Dermal Anesthesia Using a Lidocaine Gel Patch for Pain of Human Growth Hormone (hGH) Self-injection and Relief of Anxiety

Noritaka Iwatani, Mihoko Kodama, Teruhisa Miike, Tatsuhiko Kano, Masahiro Nakano, Motohiro Mishima and Osami Tsuzuki

Department of Child Development (NI, MK, TM), Surgical Center (TK), Department of Pharmaceutical Service (MN), Medical School, Kumamoto University, Kumamoto and Daiichi College of Pharmaceutical Sciences (MM, OT), Fukuoka, Japan

Abstract We estimated the benefits of a transdermally applicable 10% lidocaine gel mixture with absorption promoter (glycyrrhetinic acid monohemiphthalate disodium: GA MHPh 2Na) for the self-injection of human growth hormone (hGH) to reduce injection distress in eight children with growth hormone deficiency (GHD). Pain rating scales upon both needle puncture and fluid injection of hGH were significantly lower with the lidocaine gel application than with the placebo. The use of the lidocaine gel application in hGH therapy can alleviate the pain of injection and accompanying anxiety, thus obtaining better compliance of children who need daily injections of hGH.

Key words: human growth hormone therapy, dermal anesthesia, lidocaine gel, injection compliance

Introduction

Injection is a painful and unpleasant procedure which causes considerable distress to many children (1). Especially for young children with GHD, it is difficult to comply with hGH therapy at home due to fear of injection. In the present report, we evaluate the efficacy of a 10% lidocaine gel in alleviating pain associated with hGH injections in children with GHD.

Subjects and Methods

Eight patients with GHD (3 boys) who were treated with hGH by self-injection or parent-injection participated in this study. Their mean (± SD) age was 7.5 (± 3.1) years (range 4-13 years). Informed consent was obtained from the patients and their parents. Approximately 100 µL of a 10% lidocaine gel mixture with 3% GA MHPh 2Na was applied to a 3 cm² gauze on a stretch-type bandage (like Band-Aid®), and patched on the skin of the upper hip for 30 minutes before subcutaneous hGH injection. The Table shows the composition of the lidocaine gel mixture. A disposable syringe with a 29-gauge needle
(Myjector, Terumo Corp., Tokyo, Japan) was used for every injection. The assessment of pain was made upon needle puncture and subsequently upon hGH fluid injection by the following verbal rating scale: no sensation (grade 0), sensation of touch only (grade 1), slight pain (grade 2), moderate to severe pain (grade 3). The effects of the gel on pain were compared to those of a placebo (stretch-type bandage only) in the same patients; the placebo was also supplied by parents without notification. Values were expressed as mean ± SD. Data comparing the effects of the lidocaine gel and the placebo were analyzed by the Chi-square test.

**Results**

A total of 136 injections (17.0 ± 3.2 injections per patient) with the lidocaine gel application, and 75 (9.4 ± 1.8 injections per patient) with the placebo bandage were analyzed.

The Fig. shows the rate of each pain grade upon needle puncture and upon subsequent fluid injection with the lidocaine gel and the placebo bandage for all patients.

Of the total number of needle punctures after lidocaine gel application, 79% were painless (grade 0 or 1) and the remaining 21% painful (grade 2 or 3). For the 75 punctures done with the placebo bandage, the figures were 9% painless and 91% painful. Statistically, the rate of painless punctures was significantly higher when the lidocaine gel was used ($\chi^2=105$, d.f.=3, P<0.0001).

As for the fluid injection subsequent to

- **Table** Composition of 10% lidocaine gel mixture with 3% w/w GA MHPH disodium

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine base</td>
<td>500 mg</td>
</tr>
<tr>
<td>Solvents</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>500 mg</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1500 mg</td>
</tr>
<tr>
<td>Absorption promoter</td>
<td></td>
</tr>
<tr>
<td>Glycyrrhetinic acid monohemisalate disodium</td>
<td>150 mg</td>
</tr>
<tr>
<td>Thickener</td>
<td></td>
</tr>
<tr>
<td>Hibi Wako 104</td>
<td>50 mg</td>
</tr>
<tr>
<td>Neutralizer</td>
<td></td>
</tr>
<tr>
<td>Diisopropanolamine</td>
<td>55 mg</td>
</tr>
</tbody>
</table>

*Add sterilized pure water to make 5.0g.

- **Fig.** Comparison of verbal rating scales for all injections, lidocaine-treated (n=136) versus placebo-treated (n=75) upon needle puncture (A) and hGH fluid injection (B). Chi-square analyses show a significantly greater incidence of painless injections (grades 0 and 1) for treatment with the lidocaine gel (A: $\chi^2=105$, d.f.=3, P<0.0001; B: $\chi^2=30$, d.f.=3, P<0.0001).
Dermal Anesthesia on hGH Injection

Needle puncture, out of 136 injections with the gel application, 73% were painless (grade 0 or 1), while 13% were painful (grade 2 or 3). For injections with the placebo bandage, there was no difference between the rate of painless (51%) and painful injections (49%). Compared with the placebo, the lidocaine gel application showed a significant pain-reducing effect ($\chi^2=30$, d.f.=3, $P<0.0001$). No serious side-effects were noted, and there were no cases of edema or blister. Skin redness occurred transiently in one patient following the gel application.

Discussion

Despite the development of finer, less painful needles, the daily injection of hGH can be a traumatic experience for many children. Fear of injection can cause loss of appetite and nightmares in young or sensitive children, especially at the initiation of hGH therapy. A painless injection would reduce the distress of such patients.

Transdermally applicable anesthetics such as eutectic mixture of local anesthetics (EMLA) are known to alleviate the pain of venepuncture or other needle insertions (2-6). We developed a 10% lidocaine gel mixture containing an absorption promoter, GA MHP 2Na, which was also effective (7-10) in reducing pain on needle puncture, with no significant difference from EMLA cream (11). In this study, we found that the application of this anesthetic to hGH injection was also beneficial for hGH therapy.

Pain rating scales upon hGH injection in GHD children were significantly lower with the lidocaine gel than with the placebo. Seventy-nine percent of all needle punctures with the lidocaine gel were rated pain-free. With the placebo bandage, however, the painless rate was only 9%. Regarding fluid injection, 77% of all injections with the lidocaine gel were pain free. With the placebo bandage, however, the figure was 51%. The analgesic effect of the lidocaine gel was obvious and was obtained within 30 minutes after the gel application. The necessary exposure time seems to be shorter in children than in adults (2), although analgesic effects in adults could also be obtained within 30 minutes by the pretreatment of skin stripping (9). Thus, children's skin may be more permeable to transdermally applied drugs.

Within two months of using the lidocaine gel, 6 out of 8 patients no longer required it. Its use reduced their anxiety and enabled them to become habituated to daily hGH treatment through experiencing painless injections. We conclude that the use of the 10% lidocaine gel benefits the induction of hGH therapy by alleviating the pain of injection and reducing anxiety due to fear of the needle, thus ensuring the compliance of children who need hGH by daily injection.

References

3. Juhlin L, Hägglund G, Evers H. Absorption of lidocaine and prilocaine after application of a eutectic mixture of local anesthetics (EMLA) on normal and


