Assessment of Clonidine Orally Disintegrating Tablet for Pre-anesthetic Medication in Pediatric Surgery

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The purpose of this study is to assess orally-disintegrating (OD) tablet of clonidine hydrochloride (CL) for a pre-operative sedation in pediatric surgery. Sedation score and plasma CL concentration of OD formulation was compared with original preparation, CL lollipop, in pediatric patients. Fourteen patients (age: 3.9±2.3 years, weight: 16.9±5.0 kg) for OD group and 9 patients (age: 4.4±3.1 years, weight: 17.2±7.0 kg) for lollipop group received 4 μg/kg of CL preparation. Pre-operative sedation was evaluated by 5-point scoring systems at entering the operating room. Plasma CL concentrations were determined 120 min after administration of CL preparation. The changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were also assessed before and after administration of CL preparation. Every patients in OD group had satisfactory sedation (sedation score: 2 and 3), whereas, 3 (33%) in lollipop group had unsatisfactory sedation (sedation score: 0 and 1). Plasma CL concentration in OD group was significantly higher than those in lollipop group (0.75±0.15 vs. 0.42±0.21 ng/ml, p<0.01). There was no significant difference in hemodynamic parameters (SBP, DBP and HR) between before and after administration of CL preparation in both OD and lollipop group. We conclude that OD is superior preparation of CL for pre-operative sedation in pediatric surgery.

Key words plasma clonidine concentration; orally-disintegrating tablet; pediatric surgery; pre-anesthetic sedation

Clonidine hydrochloride (CL), an α2-adrenoceptor agonist, is currently used for pre-anesthetic medication owing to its sedative and analgesic properties.1—3) These unique properties provide pre-operative sedation and preventing post-operative pain and vomiting in pediatric patients, as well as adults.4—7) One drawback for this medicine applying to pediatric patients is difficulty in taking. To overcome this problem, several formulations including lollipop have been developed so far.8—10)

We previously evaluated efficacy and safety of lollipop preparation in pediatric patients and found individual variation of sedative effects owing to variable blood CL concentrations, which were due to the difference in taking lollipop in individual patient.9) The patients especially aged 1—3 years old seemed to be difficult to lick the CL-lollipop completely, so they could not take it up to the prescribed dose. We, therefore, developed orally-disintegrating (OD) tablets as an alternative preparation of CL to resolve the problem.11) In this study, we evaluated the newly developed OD preparation by comparing with lollipop preparation in sedation score, blood CL concentration and hemodynamic changes in pediatric surgery.

SUBJECTS AND METHODS

Subjects We studied 23 pediatric patients, American Society of Anesthesiologists’ (ASA) physical status I, ranging in age from 1 to 11 years. General anesthesia for elective surgery was performed for each patient. The study protocol was approved by our Clinical Investigation Committee, and informed consent was obtained from the parents or their guardians. CL-preparation, OD or lollipop (4 μg/kg), was administered 90 min before entering the operating room. Anesthesia was induced with 5% sevoflurane in 6 l/min oxygen for 10 min. Patient characteristics were summarized in Table 1. There was no difference in patient’s backgrounds between OD and lollipop group.

Preparation of CL Preparations CL-OD and -lollipop were prepared in our hospital according to the method previously described.8,9,11) CL was obtained from Wako Pure Chemical Industries (Osaka, Japan). CL-OD was prepared by the method of drying an aqueous CL suspension.11) Briefly, using CL and powdered lactose (Yoshida Pharmaceutical, Tokyo, Japan), composition ratio of CL suspension was 2:1 (powdered lactose: 0.048% or 0.072% CL-solution). Four milliliters of CL solution and 8 g powdered lactose was mixed for 60 s. Two hundred fifty milligrams of CL-suspension was put into the mold, and dried inside of refrigerator at 4°C and at 72% humidity for 4 d. Dried formulation (0.167

Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>OD tablet</th>
<th>Lollipop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (male/female)</td>
<td>14 (9/5)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>3.9±2.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>16.9±5.0</td>
</tr>
<tr>
<td>Clonidine dose (μg/kg)</td>
<td>3.8±0.3</td>
</tr>
<tr>
<td>Sedation score*</td>
<td></td>
</tr>
<tr>
<td>Satisfactory (score=2/3)</td>
<td>14 (13/1)</td>
</tr>
<tr>
<td>Unsatisfactory (score=0/1)</td>
<td>0</td>
</tr>
<tr>
<td>Hemodynamic parameters</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>101±11</td>
</tr>
<tr>
<td>90 min after administration</td>
<td>104±10</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>59±11</td>
</tr>
<tr>
<td>90 min after administration</td>
<td>58±8</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>99±15</td>
</tr>
<tr>
<td>90 min after administration</td>
<td>90±17</td>
</tr>
</tbody>
</table>

Values are expressed as the mean±S.D. Significant difference was observed between the groups; *p<0.05.

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g) of CL-OD containing 40 μg or 60 μg was stored at 25 °C until use. CL-lollipop containing 10 μg/g of CL was prepared by using CL, sucrose and starch syrup to make 2, 3, 4 and 5 g formulations.8,9) CL-lollipop was stored at 25 °C until use. CL in the lollipop was stable at least 2 months under the room temperature.8)

Assessment of Sedation Sedation for each patient was assessed using a 5-point scale (0 = afraid, combative, and crying; 1 = awake but not crying; 2 = eyes closed but responds to name call; 3 = eyes closed but respond to minor stimulation; 4 = dose not respond to minor stimulation).12,13) The scores were evaluated by three blinded observers 90—120 min after administration of CL-preparation, OD or lollipop. Sedation scores were categorized as satisfactory (i.e., sedation score = 2, 3, 4) and unsatisfactory (i.e., sedation score = 0, 1).

Blood CL Analysis Blood samples for determination of plasma CL were taken 120 min after administration of CL-preparation. The plasma samples were stored at −20 °C until analysis. Plasma CL concentrations were determined by radioimmunoassay (Nippon Boehringer Ingerheim Co. Ltd., Hyogo, Japan) previously reported.14) Assay was performed on the basis of a 6-point calibration curve (0.025, 0.05, 0.1, 0.25, 0.5, 1 ng/ml). Each sample was analyzed in triplicate. The quantification limit for this assay was 0.025 ng/ml with coefficient of variations less than 8%.

Hemodynamic Measurements Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded before (baseline) and 90 min after administration of CL-preparations, OD and lollipop. The bradycardia and hypotension as the adverse events of CL were assessed by HR < 60 beats/min and SBP < 70 mmHg. The occurrence of these events for each patient was monitored throughout the study.

Data Analysis Values were expressed as the mean ± S.D. The difference in the plasma CL concentration between the two groups was analyzed by unpaired Student’s t-test. Mann–Whitney U-test was used to compare the data between the two groups and the variables from baseline values. The p value less than 0.05 was considered to be significant statistically.

RESULTS AND DISCUSSION

Every patients in OD group had satisfactory sedation (sedation score: 2 and 3), whereas 3 (33%) of 9 patients in lollipop group had unsatisfactory sedation (sedation score: 0 and 1) (Table 1). Plasma CL concentration in OD group was significantly higher than those in lollipop group (0.75 ± 0.15 vs. 0.42 ± 0.21 ng/ml, p < 0.01) (Fig. 1). Three patients showing unsatisfactory sedation had a low CL blood concentration (Fig. 1).

There was no significant difference in hemodynamic parameters (SBP, DBP and HR) between before and after administration of CL-preparation in both OD and lollipop group (Table 1). No clinically significant bradycardia or/and hypotension was observed.

These results demonstrated that OD formulation was superior to lollipop preparation in taking and efficacy of CL for pre-operative sedation in pediatric surgery. Higher blood concentration of CL in OD group was achieved by improving in easy to take, resulting in satisfactory sedation. On the other hand, lollipop preparation, which is not always taken completely in several pediatric patients, provided lower blood concentration of CL with large individual variation. Safety assessed by hemodynamic parameters and occurrence of adverse events was same in both two preparations.

OD preparation is especially serviceable for the patients aged 1—3 years old, some of whom cannot take up the lollipop preparation. In our previous study, 20% of pediatric patients had such occasion.15) Since licking lollipop seems to be hard and take a time around 10 min, lollipop is not always suitable for pediatric patients.

Our previously report16) and Ivani et al.14) revealed that plasma CL concentration for optimal pre-operative sedation was 0.3—1.0 ng/ml, which were determined 90—120 min after the administration. This concentration corresponding with the maximum CL concentration is maintained similar levels during the short surgical operation, because the time for the maximum concentration of CL has been reported to be 90 min after dose and the elimination half life of CL, over 10 h.15,16) The maximal sedative effect is also observed at 105—120 min after CL administration.4) We, therefore, determined the plasma CL concentration 120 min after CL administration to assess the efficacy and safety with minimum blood collection.

All patients in OD group showed above 0.3 ng/ml of plasma CL concentration with the coefficients of variation (CV) less than 30%. No one exceeded 1.0 ng/ml. On the other hand, 3 patients in lollipop group provided below 0.3 ng/ml. Thus, OD preparation is superior to lollipop preparation in pharmacokinetics of CL in terms of keeping target plasma concentration of 0.3—1.0 ng/ml with smaller individual variation (Fig. 1).

No significant change in hemodynamic changes (SBP, DBP and HR) was observed before and after administration of CL (4 μg/kg) in both OD and lollipop groups. This is supported by our and Mikawa’s reports that 2—4 μg/kg of CL did not provided any change in SBP, DBP and HR.6,9) Neither perioperative hypotension nor bradycardia was seen in the present study. We confirmed that CL-OD was also safety preparation as well as CL lollipop even though blood CL concentration was higher than that of CL lollipop. We conclude that CL-OD preparation is alternative formulation for pre-operative CL sedation in pediatric surgery.

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REFERENCES