Sedation and Plasma Concentration of Clonidine Hydrochloride for Pre-anesthetic Medication in Pediatric Surgery

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Clonidine hydrochloride has been used for pre-anesthetic medication to provide a pre-operative sedation in pediatric surgery. The purpose of this study is to determine the plasma clonidine concentration, which gives satisfactory sedation in pediatric surgery. Sixteen pediatric patients (age: 1—11 years, weight: 9—33 kg) received either 2 or 4 μg/kg of clonidine lollipop before entering the operating room. Plasma clonidine concentrations were determined 120 min after administration of clonidine lollipop. Pre-operative sedation was evaluated by 5-point scoring systems at entering the operating room. The changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were also assessed before and after administration of clonidine lollipop. The patients with satisfactory sedation had higher plasma clonidine concentration than that of the patients with unsatisfactory sedation (0.45±0.16 ng/ml vs. 0.26±0.16 ng/ml, p<0.05). The clonidine concentrations in the satisfactory group ranged from 0.28 to 0.81 ng/ml. There was no significant difference in hemodynamic parameters (SBP, DBP and HR) before and after administration of clonidine lollipop in both satisfactory and unsatisfactory sedation groups. Plasma clonidine concentration of 0.3—0.8 ng/ml would be sufficient to produce satisfactory sedation without changes in hemodynamic parameters in pediatric surgery.

Key words plasma clonidine concentration; lollipop; pre-anesthetic sedation

Clonidine hydrochloride, an α₂-adrenoceptor agonist, is an anti-hypertensive drug owing to the effects on the central nervous and peripheral sympathetic nervous systems.1) Clonidine has been introduced currently as a pre-anesthetic medication because of its sedative and analgesic properties.2,3) In pediatric patients, as well as adults, pre-treatment of clonidine provides appropriate pre-operative sedation and prevents post-operative pain and vomiting.4—7)

We currently prepared clonidine lollipop, which pediatric patients were able to take easily, and applied them to pre-anesthetic medication.8) The use of clonidine lollipop in pre-operative sedation showed the sevoflurane dose sparing during the surgery.9) However, the effective plasma clonidine concentration for pre-operative sedation has not been available in pediatric surgery yet.

The purpose of the present study is to determine the plasma clonidine concentration, which provides satisfactory sedation, and to assess the efficacy and safety of clonidine lollipop in pediatric surgery. We investigated plasma clonidine concentration, sedation score and hemodynamic changes after administration of clonidine lollipop in pediatric patients.

SUBJECTS AND METHODS

Subjects We studied 16 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 guardians of each patient. Clonidine lollipops were administered 90 min before entering the operating room. Clonidine dose for each patient was assigned to 2 μg/kg (n=7) or 4 μg/kg (n=9), randomly (Table 1). The time for licking up clonidine lollipops required 5—10 min. Anesthesia was induced with 5% sevoflurane in 6 l/min oxygen for 10 min. Individual data for the patients were summarized in Table 1.

Preparation of Clonidine Lollipop Clonidine lollipops were prepared in our hospital according to the method previously described.8) Briefly, using clonidine hydrochloride (Wako Pure Chemical Industries, Osaka, Japan), sucrose and starch syrup, 2, 3, 4 and 5 g formulations of clonidine lollipops containing 10 μg/g of clonidine hydrochloride were prepared. Clonidine lollipop was stored at 25 °C until administration. Clonidine in the lollipop was stable at least 2 months under the room temperature.9)

Assessment of Sedation The level of sedation was assessed using a 5-point sedation scale (0=awake, combative, and crying; 1=awake but not crying; 2=eyes closed but responds to name call; 3=eyes closed but responds to minor stimulation; 4=does not respond to minor stimulation) as previously reported by Karl et al.11) with minor modification. Three physicians evaluated the levels of sedation, 90—120 min after administration of clonidine lollipop. Raw sedation scores were categorized as satisfactory (i.e., sedation score=2, 3, 4) and unsatisfactory (i.e., sedation score=0, 1).

Blood Clonidine Analysis Blood samples for determination of plasma clonidine were taken 120 min after administration of clonidine lollipop. The plasma was frozen (−20 °C) until analysis. Plasma clonidine concentrations were determined by radioimmunoassay (Nippon Boehringer Ingelheim Co., Ltd., Hyogo, Japan) previously reported.12) Assay performance was assessed 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 and the values were expressed as the mean. The quantitation limit for this assay was 0.025 ng/ml with coefficient of variations less than 8%.

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Hemodynamic Measurements  Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded before (baseline) and 90 min after administration of clonidine lollipop. The bradycardia and hypotension as the adverse events of clonidine 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 clonidine concentration between the satisfactory and unsatisfactory sedation groups was analyzed by unpaired Student’s t-test. Mann–Whitney U-test was used to compare the data between the two sedation groups and the variables from baseline values. The p value less than 0.05 was considered to be significant statistically.

RESULTS  

Satisfactory sedation was achieved in 10 patients. The other patients (6 cases) showed unsatisfactory sedation (Table 1). The cases, 7, 15 and 16, aged 1—3 years old were hard to lick the clonidine lollipop completely. As shown in Fig. 1, plasma clonidine concentration in the satisfactory sedation group was significantly higher than that of the unsatisfactory group (0.45±0.16 ng/ml vs. 0.26±0.16 ng/ml, p<0.05).

The clonidine concentrations in the satisfactory group ranged from 0.28 to 0.81 ng/ml. Plasma clonidine concentrations for 2 µg/kg group (n=6) tended to be lower than those for 4 µg/kg group (n=7) (0.36±0.05 vs. 0.50±0.16 ng/ml, p=0.068), though the difference was not statistically significant. Clear relationship between the clonidine dose and the sedation score was not observed (data not shown).

There were no significant differences in hemodynamic parameters (SBP, DBP and HR) between the satisfactory and unsatisfactory sedation groups (Table 2). Also, changes in the three hemodynamic parameters did not differ before and after administration of clonidine lollipop (Table 2). No clinically significant bradycardia and/or hypotension was observed.

DISCUSSION  

We found the correlation between pre-operative sedation and plasma clonidine concentrations. Therapeutic range of plasma clonidine for sedation was estimated as 0.3—0.8 ng/ml in pediatric surgery. This is supported by the data previously reported by Ivani et al. They investigated plasma clonidine concentrations following the epidural administration, and found that post-operative sedation was not enough in the patients with plasma clonidine concentration below 0.3 ng/ml.

In the present study, three patients aged 1—3 years old could not take the lollipop completely (Table 1). Their plasma clonidine concentrations were lower than 0.3 ng/ml, resulting in unsatisfactory sedation. Clonidine lollipop may not be suitable formulation for the patients aged 1—3 years old. Alternative preparation such as orally disintegrating tablets may resolve the problem in these patients.

Lowenthal et al. reported that plasma clonidine increased rapidly and achieved a peak 90 min after oral administration and then, eliminated from the plasma with the half-life of over 10 h. These findings suggest that plasma clonidine...
concentrations 90—120 min after administration of clonidine lollipop was retained the maximum concentration (\(C_{\text{max}}\)). Our preliminary study conducted in one pediatric patient suggested that time for \(C_{\text{max}}\) of clonidine for lollipop preparation was shorter than at least 120 min (data not shown). This observation supports the idea that the concentration at 120 min after the administration is almost equal to \(C_{\text{max}}\). Furthermore, the maximal sedative effects have known to be observed at 105—120 min after clonidine administration in pediatric surgery.\(^4\) Therefore, the plasma clonidine concentration at 120 min was considered to be appropriate for assessing sedative effects and adverse events such as hemodynamic changes.

We did not observe significant hemodynamic changes before and after administration of clonidine lollipop in both satisfactory and unsatisfactory sedation groups. Similar observations have been reported by Mikawa et al.\(^6\) They found no change in SBP, DBP and HR between baseline and post-operation in both clonidine (2 or 4 \(\mu\)g/kg) and placebo administration.\(^6\) The sedation and hemodynamics of clonidine lollipop may be independent events in terms of different therapeutic ranges. Neither peri-operative hypotension nor bradycardia was observed in the present study.

In conclusion, plasma clonidine concentration of 0.3—0.8 ng/ml would be sufficient to produce a satisfactory sedation in pediatric surgery. Clonidine lollipops can be used safely for pre-operative sedation in the patients aged 4—11 years.

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