Oral mucosal blood flow, plasma epinephrine and haemodynamic responses after injection of lidocaine with epinephrine during midazolam sedation and isoflurane anaesthesia

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We have investigated the relationship between oral mucosal blood flow and plasma epinephrine concentration, and the effects of conscious sedation vs general anaesthesia on haemodynamic responses after submucosal epinephrine injection in 14 subjects. The same seven patients were studied both as controls and after sedation. For sedation, midazolam i.v. was used. Another seven patients underwent orthognathic surgery with isoflurane anaesthesia. All subjects received a submucosal injection of epinephrine 0.8 µg kg⁻¹, given as 2% lidocaine hydrochloride with epinephrine 12.5 µg ml⁻¹. Baseline mucosal blood flow and peak increase in plasma epinephrine concentration in the general anaesthesia and sedation groups were approximately 2.0 and 1.5 times, respectively, higher than those in the control group. Mean plasma epinephrine concentration reached a maximum 3 min after administration of epinephrine in all groups. Overall, there was a significant correlation (r=0.65) between baseline mucosal blood flow and the maximum increase in plasma epinephrine concentration. There were no differences in haemodynamic changes except for heart rate, between the three groups. These results suggest that plasma epinephrine concentration after submucosal injection depends on the initial mucosal blood flow in the injected area. Haemodynamic changes, except heart rate, in the sedation and general anaesthesia groups were similar despite different changes in maximum plasma epinephrine concentration.

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Local anaesthetic solutions containing epinephrine are used commonly with or without conscious sedation for dentistry and oral surgery. Epinephrine deepens and prolongs the local anaesthetic effect and improves haemostasis in the operative field. Local anaesthetics with epinephrine may also produce pre-emptive analgesia in patients undergoing oral surgery with general anaesthesia. Although potentiation of the local anaesthetic effect is important for dental treatment, care must be taken in the administration of epinephrine to patients with cardiovascular disease because adverse haemodynamic responses are possible.

In general, peripheral blood flow varies in response to haemodynamic changes caused by general anaesthesia and conscious sedation. Mucosal blood flow, which may also be influenced by such haemodynamic changes, affects, in turn, the absorption of submucosally administered drugs, including epinephrine. Therefore, we hypothesized that the plasma concentration of submucosally administered epinephrine may depend on the patient’s condition (unsedated, sedated or anaesthetized) because of differences in mucosal blood flow, and that haemodynamic responses to the absorbed epinephrine may be modified by inhaled anaesthetics or i.v. sedatives.

The purpose of this study was two-fold: first, to observe the relationship between oral mucosal blood flow and plasma epinephrine; and second, to ascertain the effects of conscious sedation and general anaesthesia on haemodynamic responses after submucosal injection of epinephrine.

Patients and methods

We studied 14 male subjects: seven subjects were allocated to be studied both as controls and after sedation. In the control study, subjects did not receive i.v. sedation or general anaesthesia. In the sedation study, the same subjects were sedated with midazolam i.v. Two weeks were allowed...
to elapse between the two investigations; the order of treatment was randomized. In the general anaesthesia group, seven ASA I subjects underwent orthognathic surgery with isoflurane, nitrous oxide and oxygen anaesthesia. The study was approved by the Ethics Committee of Tokyo Dental College, and written informed consent was obtained from all subjects.

With each subject in the supine position, a forearm vein and radial artery were cannulated using 20-gauge and 22-gauge indwelling catheters, respectively, for infusion of fluid, arterial pressure monitoring and blood sampling. After an infusion of lactated Ringer’s solution 10 ml kg⁻¹ h⁻¹ was started and haemodynamic state was allowed to stabilize for 20 min, a pre-baseline evaluation of mucosal blood flow was performed. Mucosal blood flow was measured using a laser flowmeter (ALF 21; Advance, Tokyo, Japan). The flow probe (NS-probe) was applied on the oral mucosa close to the root of the left upper second incisor. The probe was fixed in place with dental resin compound applied to the adjacent teeth. Haemodynamic variables were measured and arterial blood sampling for measurement of plasma concentrations of epinephrine was performed. After the pre-baseline measurements, subjects in the sedation group received midazolam 0.07 mg kg⁻¹ i.v. (Dormicum; Roche, Tokyo, Japan) over 2 min. In the general anaesthesia group, anaesthesia was induced with thiopental 4 mg kg⁻¹ (Ravonal; Tanabe, Osaka, Japan). Nasotracheal intubation was facilitated with vecuronium 0.08 mg kg⁻¹ (Musculax; Organon, Tokyo, Japan). Anaesthesia was maintained with 0.9% isoflurane and nitrous oxide 3 litre min⁻¹ in oxygen 2 litre min⁻¹. Subjects underwent mechanical ventilation, and end-tidal carbon dioxide tension (PℓCO₂) was maintained at 4.7–5.3 kPa. End-tidal isoflurane concentration and PℓCO₂ were monitored continuously with an anaesthetic gas monitor (Capnomac; Datex, Helsinki, Finland). Baseline measurements, including mucosal blood flow, arterial blood sampling for measurement of plasma concentrations of epinephrine and haemodynamic variables were performed 15 min after the pre-baseline measurements in the control group, 5 min after completion of midazolam injection in the sedation group and 15 min after the start of inhalation anaesthesia in the general anaesthesia group, respectively, when haemodynamic stability was present. Mucosal blood flow was expressed as a percentage of pre-baseline values.

After baseline data were collected, each subject received a submucosal injection of 2% lidocaine solution containing epinephrine 12.5 µg ml⁻¹ (Xylocaine with Epinephrine; Astra, Osaka, Japan). A total dose of epinephrine 0.8 µg kg⁻¹ was injected using a device (New Cartri-Ace; Dentronics, Tokyo, Japan) that allowed a constant speed of injection. Initially, 0.5 ml of solution was administered near the mucosal blood flow probe in 20 s; the rest was injected into the non-inflamed left maxillary alveolar mucosa in the molar region. Mucosal blood flow and haemodynamic variables were measured and arterial blood for measurement of plasma concentrations of epinephrine was sampled at 1, 3, 5, 10 and 15 min after completion of administration of epinephrine. In addition, mucosal blood flow was also measured at 0.5, 1, 1.5 and 2 min after the beginning of administration of epinephrine. In the general anaesthesia group, the operation started after these observations had been completed.

Mucosal blood flow, arterial pressure (systolic arterial pressure (SAP); diastolic arterial pressure (DAP); mean arterial pressure (MAP)) and heart rate (HR) were recorded continuously. Cardiac index (CI) and stroke volume index (SVI) were measured using impedance cardiography (NCCOM3-R7; CDIC, Irvine, CA, USA). These data were stored continuously on computer. Total peripheral resistance index (TPRI) was calculated using a conventional equation:

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TPRI = \frac{MAP}{CI} \times 1.332 \, \text{dyn s cm}^{-5} \, \text{m}^2
\]

For measurement of plasma epinephrine concentrations, arterial blood (4 ml) was obtained via the indwelling radial catheter and the plasma separated in a refrigerated centrifuge (4°C, 3000 rpm, 10 min). Plasma concentrations were measured using high-performance liquid chromatography with electrochemical detection (LC-4C; BAS, Tokyo, Japan).

All data are expressed as mean (sd). Patient characteristics were compared using the Student’s t test. Inter-group comparisons were made with one-way analysis of variance followed by the Student–Newman–Keuls test for multiple comparisons. Intra-group comparisons were made using one-way analysis of variance for repeated measurements followed by Dunnett’s test for multiple comparisons. Regression analysis was performed using the least squares method. \( P<0.05 \) indicated statistical significance.

**Results**

There were no significant differences between the two groups in age, weight or height, or in duration of administration of epinephrine between the three groups (Table 1). The reading of a laser flowmeter at pre-baseline in each group served as the control (100%, Fig. 1). These control readings were similar. In contrast, baseline mucosal blood flow was significantly higher in the general anaesthesia and sedation groups. Mucosal blood flow decreased immediately after administration of epinephrine, reaching a nadir in 30–90 s in all groups. Mucosal blood flow remained markedly depressed throughout the remainder of the study.

Baseline concentrations of plasma epinephrine were similar in the three groups (control group 65 (27) pg ml⁻¹; sedation group 45 (19) pg ml⁻¹; general anaesthesia group 62 (13) pg ml⁻¹). Mean plasma concentrations increased significantly after administration and reached a maximum in 3 min in all groups (Fig. 2). The greatest increase in plasma epinephrine (ΔEpi) was observed in the general anaesthesia group (control group 285 (19) pg ml⁻¹; sedation group 433 (56) pg ml⁻¹; general anaesthesia group 549 (37) pg ml⁻¹). ΔEpi at 3 min after completion of epinephrine injection in the general anaesthesia group was twice as great as that in the control group. Plasma epinephrine...
Table 1 Patient data (mean (SD or range)). There was no significant difference between the control and sedation group, and the general anaesthesia group.

<table>
<thead>
<tr>
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<th>Control and sedation group</th>
<th>General anaesthesia group</th>
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<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>23.9 (19–28)</td>
<td>23.4 (18–70)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.3 (12.7)</td>
<td>169.6 (11.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.1 (16.6)</td>
<td>64.2 (13.6)</td>
</tr>
<tr>
<td>Duration of epinephrine injection (s)</td>
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<td>244</td>
</tr>
<tr>
<td>Total epinephrine (µg)</td>
<td>52.1 (19.6)</td>
<td>51.4 (14.8)</td>
</tr>
<tr>
<td>Total lidocaine (mg)</td>
<td>83.4 (24.3)</td>
<td>82.2 (22.5)</td>
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Fig 1 Changes in mucosal blood flow (MBF) as a function of pre-baseline values in the control, sedated and general anaesthesia (GA) groups. Mucosal blood flow was measured immediately before (Pre-B) and at baseline (B) and at 0.5, 1, 1.5 and 2 min after the beginning of administration of epinephrine and also 1, 3, 5, 10 and 15 min after completion of epinephrine injection. All values after epinephrine injection were significantly depressed compared with pre-baseline and baseline controls. Data are mean (SD). *P<0.05, significant difference between groups at baseline.

Fig 2 Changes in plasma epinephrine concentration (ΔEpinephrine) from baseline in the control, sedated and general anaesthesia (GA) groups. Plasma epinephrine reached a maximum in 3 min after epinephrine administration in all groups. All measurements after baseline were statistically significant. Data are mean (SD). *P<0.05, significant difference between groups at 3 and 5 min.

were less than in the other two groups, SAP, DAP and MAP did not change throughout the study within groups. HR increased after completion of epinephrine injection in the sedation and control groups, whereas it remained unchanged in the general anaesthesia group in spite of the greater increase in plasma epinephrine concentration in that group. Significant increases in CI and SVI and decreases in TPRI were observed in all groups. All groups showed similar changes in CI and TPRI in spite of different maximum plasma concentrations of epinephrine. The general anaesthesia group, however, had the greatest increase in SVI. (Fig. 4).

Discussion

Blood concentrations of regionally administered drugs are influenced by three factors: absorption, biotransformation and excretion. The rate of absorption is dependent on the dose and concentration of the administered drug. The microcirculation in the drug-injected site also affects the absorption of regionally administered drugs. Increased blood flow enhances systemic uptake, whereas decreased blood flow caused by vasoconstrictors impedes it. The absorption of epinephrine in this study was complicated by several
Mucosal blood flow and epinephrine

The injection dose of local anaesthetic solution for routine dental treatment is less than 4 ml, or two 1.8-ml anaesthetic cartridges. As a solution of 2% lidocaine with epinephrine 10–12.5 µg ml is the most popular anaesthetic for dental use in the world, up to 45 µg of epinephrine is the usual dose administered. Small doses of epinephrine, as used in this study, may increase HR and SAP and lead to an increase in myocardial oxygen consumption, as suggested by a greater rate–pressure product for dental patients with cardiovascular disease.1 Whether the use of epinephrine in these patients may be appropriate needs further discussion.

Conscious sedation is usually administered for the systemic management of dental patients with cardiovascular disease.2-4 The increase in HR after epinephrine injection was greater in the sedation group than in the control group. The higher plasma concentrations of epinephrine in the sedation group than in the control group may explain this difference. I.v. midazolam allowed subjects freedom from anxiety, which is usually followed by cardiovascular stimulation. The approximate 20% increase in SVI and HR, however, is probably of little significance in patients with mild ischemic heart disease. Therefore, the importance of conscious sedation for these patients should not be denied.

The reason why HR in the general anaesthesia group did not increase is unclear. Further investigations in this area are needed.

In summary, plasma concentrations of epinephrine were greater in the sedation and general anaesthesia groups than in the control group after the same dose of epinephrine was injected during administration of local anaesthesia. Mucosal blood flow was increased in the sedation and general anaesthesia groups before injection of epinephrine. Baseline mucosal blood flow and the maximum Δepi showed a strong correlation. These results suggest that Δepi after submucosal injection of a local anaesthetic solution containing epinephrine depends on mucosal blood flow in the injected area. Dionne, Goldstein and Wirdzek9 studied the time course of plasma epinephrine concentrations after submucosal epinephrine injection with or without diazepam sedation. They found that the same dose of epinephrine (54 µg) produced different maximum epinephrine concentrations in the sedated group (302 (142) pg ml\(^{-1}\)) than in the unsedated group (106 (70) pg ml\(^{-1}\)). The disparity may be attributable to differences in mucosal blood flow.

The second goal of our study was to identify differences in the cardiovascular effects of epinephrine between the three groups. The most distinctive effects of epinephrine on the haemodynamics in the control group were attributable to the β-receptor stimulating action of the drug, as documented in other reports.9-13 No differences in haemodynamic variables were observed between the three groups, except for HR.

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