CHANGES IN PLASMA CATECHOLAMINE CONCENTRATIONS FOLLOWING INFILTRATION WITH LARGE VOLUMES OF LOCAL ANAESTHETIC SOLUTION CONTAINING ADRENALINE

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Recent studies have demonstrated that there may be a considerable increase in the plasma concentration of adrenaline following the infiltration of tissues with solutions of local anaesthetic (plus adrenaline) which are used for the purpose of producing haemostasis during surgical procedures. In a study from this Department (Taylor, Achola and Smith, 1984) it was shown that, during ENT surgery, there was a 300% increase in plasma adrenaline concentration following the injection of 4 ml of 1:200 000 adrenaline (20 |ig) to the mucous membrane of the nasal septum.

This volume of adrenaline solution is modest in comparison with the volumes used for haemostasis during other forms of surgery, and during certain types of local anaesthetic blockade. During axillary brachial plexus blockade, it is customary to use volumes of the order of 30–40 ml and, during plastic surgery, it is routine for a volume of 20 ml of 0.5% lignocaine with adrenaline 1:200 000 to be used to aid haemostasis. If the absorption of adrenaline occurs at the same rate in both situations, brachial plexus infiltration might be expected to produce a 15-fold increase in plasma adrenaline concentrations.

The purpose of the present study was to measure the changes in plasma concentrations of adrenaline in response to its exogenous administration in two situations: (a) following infiltration of the nose with the volumes of lignocaine–adrenaline solution used routinely for rhinoplasty; and (b) following the performance of routine axillary brachial plexus blockade as undertaken by one of the authors.

SUMMARY

Plasma catecholamine concentrations have been measured in nine patients undergoing rhinoplasty following infiltration to the facial area of 21 ml of 0.5% lignocaine with adrenaline 1:200 000 and in seven patients undergoing brachial plexus blockade with 40 ml of 0.5% lignocaine, 0.25% bupivacaine and adrenaline 1:200 000. In the rhinoplasty group there was a 566% increase in plasma adrenaline concentration 2 min after cessation of infiltration, whilst in the brachial plexus group a 112% increase in the plasma concentration of adrenaline occurred at 10 min after completion of the block. There was no change in plasma noradrenaline concentration in either group. It is concluded that the so-called safe dose of adrenaline (1.0 |g kg⁻¹ during halothane anaesthesia) is meaningless unless the site of administration is specified.

PATIENTS AND METHODS

Rhinoplasty

Nine consecutive patients undergoing rhinoplasty on an individual surgical list gave consent for the removal of venous blood for the measurement of plasma catecholamine concentrations.

Each patient was premedicated with diazepam 10 mg orally and anaesthesia was induced with papaveretum 10 mg and thiopentone 3–4 mg kg⁻¹ i.v. The trachea was intubated following the

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administration of alcuronium 20 mg, and the lungs were ventilated artificially with 66% nitrous oxide in oxygen. A throat pack was inserted and a 14-gauge cannula was inserted to a vein in the antecubital fossa to permit sampling of venous blood. Following this routine anaesthetic sequence, a 10-min period was allowed to elapse to permit any sympathoadrenal response to intubation to wane. At this point, a control 10-ml sample of venous blood was withdrawn. In five patients, the nasal mucosa in each nostril was sprayed with 3% cocaine 1.5 ml. Five minutes later, the surgeon infiltrated the nose with anaesthetic solution in a fixed sequence: glabella, bridge of nose, floor of the nose, nasal bone towards the maxilla, and septum. During the infiltration, great care was exercised to ensure that injections were not administered intravascularly. A total volume of 21 ml of 0.5% lignocaine with adrenaline 1:200 000 was used. The point at which infiltration was completed was termed time zero and a 10-ml venous blood sample was withdrawn at that time. Subsequently, samples were withdrawn at 2, 5, 10 and 15 min after the completion of the infiltration. The operation was then commenced.

**Axillary brachial plexus block**

Seven patients scheduled for hand surgery for which axillary brachial plexus blockade was an appropriate mode of anaesthesia, gave informed consent for the removal of venous blood for the measurement of plasma catecholamine concentrations. Each patient was premedicated with diazepam 10 mg 1.5 h before the procedure. Axillary blockade was undertaken with a mixture of 20 ml of 1% lignocaine with adrenaline 1:200 000 and 20 ml of 0.5% bupivacaine with adrenaline 1:200 000. Thirty-four millilitre of this solution was injected to the axillary sheath and 6 ml injected subcutaneously as the needle was withdrawn. Venous blood samples (10 ml) were withdrawn at the following times: before the performance of the axillary blockade and at 2, 5, 10 and 15 min after termination of the injection. Venous blood samples were obtained from a cannula in the antecubital fossa of the arm contralateral to that which required blockade.

Blood samples were centrifuged immediately and the plasma packed in ice temporarily before being frozen at −70 °C before analysis. Measurement of plasma catecholamine concentrations was undertaken using high pressure liquid chromatography. The methodology and accuracy of the technique as used in our laboratory have been described previously (Derbyshire et al., 1983).

**RESULTS**

**Rhinoplasty**

There were no significant differences in the plasma catecholamine data between the five patients who received cocaine before infiltration of the nose and the four patients in whom cocaine was not used. Thus, the data for all nine patients have been combined.

There were no significant changes in plasma noradrenaline concentration for the 15 min after completion of facial injections. However, plasma adrenaline concentration increased dramatically. By 2 min after completion of the injection, the mean plasma adrenaline concentration was 566% higher than the baseline pre-injection value. By 5 min after infiltration, the peak concentration of 4.1 pmol ml⁻¹ had declined to 2.4 pmol⁻¹, and over the subsequent 10 min there was a gradual decline to a value of 1.3 pmol ml⁻¹ (fig. 1).

No arrhythmias were detected during this
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Fig. 2. Plasma catecholamine concentrations (mean ± SEM; n = 7) following axillary brachial plexus block with 40 ml of 0.5% lignocaine, 0.25% bupivacaine and adrenaline 1:200000.

period, but a considerable tachycardia was evident: unfortunately, data were not collected to permit statistical evaluation of the results.

Axillary brachial plexus blockade

There were no significant changes in plasma noradrenaline concentration over the 15 min following completion of the brachial plexus block. Before instituting the block, the mean plasma adrenaline concentration was approximately 0.8 pmol ml⁻¹ and after completion of the block, there was a gradual increase to a peak of 1.8 pmol ml⁻¹; at 15 min, there was a small but statistically insignificant decline to 1.45 pmol ml⁻¹ (fig. 2).

Neither arrhythmias nor tachycardia occurred in any of these patients.

DISCUSSION

Following the infiltration of local anaesthetic-adrenaline solutions, there was an increase in the plasma concentrations of adrenaline of 112% at 10 min after institution of brachial plexus block, and of 566% 2 min after completion of infiltration around the nose. The doses of adrenaline injected in these two groups amounted to 200 µg and 105 µg, respectively, and the resulting blood concentrations suggest that the speed and extent of absorption was much more rapid following facial infiltration than following brachial plexus blockade.

There are several reasons for believing that these increases in plasma adrenaline concentration represented exogenously induced, rather than endogenous, changes. Stress responses to anaesthesia and surgery are accompanied normally by increases in concentration in both adrenaline and noradrenaline (Derbyshire and Smith, 1984). In the present study there were no significant changes in plasma noradrenaline concentration in either group. In the rhinoplasty group, infiltration was undertaken following induction of anaesthesia and tracheal intubation, a manœuvre which is well known to be associated with significant increases in catecholamines after the anaesthetic technique used here (Russell et al., 1981). However, in the absence of subsequent surgery, the pressor and catecholamine responses to tracheal intubation normally subside within 5–10 min (Derbyshire and Smith, 1984), and this period of time was allowed to elapse before the surgeon commenced infiltration of the nose.

The baseline concentrations of catecholamines in the present study were in the same range as those reported elsewhere from our laboratory in resting premedicated patients (Derbyshire et al., 1983). In the rhinoplasty group, the peak plasma concentration of adrenaline following infiltration of 4.1 pmol ml⁻¹ represents a value considerably higher than that reported to occur in response to tracheal intubation (1.2 pmol ml⁻¹ (Derbyshire et al., 1983)). Even cardiopulmonary bypass, which is known to be one of the most potent stimuli to the secretion of catecholamines during surgery (Derbyshire and Smith, 1984) was shown to produce values of only approximately 1.1 pmol ml⁻¹ during oxygen—fentanyl anaesthesia (Stanley et al., 1980) or halothane–nitrous oxide–oxygen anaesthesia (Hoar et al., 1981). Thus the value of 4.1 pmol ml⁻¹ is very high in relation to the perioperative period.

There have been relatively few other studies of the plasma catecholamine concentrations produced following exogenous administration. Tolas,
Pflug and Halter (1982) measured catecholamine concentrations in anaesthetized subjects following the administration of adrenaline 18 μg during dental nerve blockade and found a maximum value of 1.26 pmol ml\(^{-1}\) at 3 min following injection. In a separate study, Taylor, Achola and Smith (1984) examined plasma concentrations of adrenaline following infiltration of the nasal mucosa with adrenaline 20 μg during anaesthesia. A peak plasma concentration of adrenaline of approximately 1.6 pmol ml\(^{-1}\) was obtained 2 min after infiltration. This study, in combination with the present study, which has also demonstrated a peak value occurring at approximately 2 min after infiltration around the nose, reinforces the view that the absorption of adrenaline from the facial area is rapid.

In another study involving the facial area, Donlon and Moss (1979) found that the plasma concentration of adrenaline increased from 0.6 to 2.4 pmol ml\(^{-1}\) following retrobulbar block with adrenaline 50–60 μg.

In the present study, the administration of cocaine in five patients before infiltration of the nasal mucosa was found not to attenuate the pattern of change in plasma concentration following nasal and facial infiltration and, therefore, the data have been combined for all nine patients. Although the number of patients studied was relatively small, these data do not support the commonly held view that the prior administration of cocaine reduces the rate of uptake of adrenaline administered subsequently.

The injected dose of adrenaline used in patients undergoing rhinoplasty amounted to almost 1.5 μg kg\(^{-1}\), which is close to the value of 1 μg kg\(^{-1}\) recommended by Johnston, Eger and Wilson (1976) as safe during halothane anaesthesia. However, plasma concentrations of adrenaline were not measured by these authors and, unfortunately, there are no data available on the arrhythmogenic threshold for plasma concentrations of catecholamines in man. However, in the dog, it has been reported that the threshold is a plasma concentration of 230 pmol ml\(^{-1}\), produced by an i.v. infusion rate of 2.18 μg kg\(^{-1}\) min\(^{-1}\) (Sumikawa, Ishizaka and Suzaki, 1983). Recently, it was confirmed that the dose threshold for ventricular arrhythmias in dogs anaesthetized with 1.2 MAC of halothane was 2.2 μg kg\(^{-1}\) min\(^{-1}\) administered by i.v. infusion (Maze and Smith, 1983). Clearly, these doses are not relevant to the performance of clinical local anaesthesia, since they relate to the i.v. administration of adrenaline. Although the arrhythmogenic plasma concentration for adrenaline was reported in the dog as 50 times higher than the peak value noted in the present study, it has been suggested that there is a marked species difference (Sumikawa, Ishizaka and Suzaki, 1983).

It has been suggested recently that the arrhythmogenic threshold in children may be higher than that for adults. In a clinical study of paediatric patients, Karl and colleagues (1983) measured heart rate in children in whom adrenaline was administered in a dose of 0.4–15.7 μg kg\(^{-1}\) for surgical haemostasis. Unfortunately, the plasma concentration of adrenaline was not measured, but on the evidence of the changes in heart rate, it was suggested that adrenaline 10 μg kg\(^{-1}\) was safe with normo- or hypo-capnia during halothane anaesthesia since no ventricular arrhythmias were observed.

Although no serious arrhythmias were detected in the present study, a considerable tachycardia was apparent in the patients undergoing rhinoplasty. The finding of a peak plasma adrenaline concentration of 4.1 pmol ml\(^{-1}\) following an injection of 105 μg of adrenaline in rhinoplasty, as opposed to 1.4 pmol ml\(^{-1}\) following an injection of 200 μg in association with brachial plexus blockade, suggests that considerable caution should be exercised in the interpretation of the so-called “safe” doses of adrenaline, which are usually quoted in terms of μg kg\(^{-1}\) dose injected. The results of the present study confirm the view that the site of administration is as important as the dose of adrenaline injected. We would suggest that, in the absence of measurement of plasma catecholamine concentrations, it is difficult to be precise regarding an acceptable dose of adrenaline for a specific site of administration. Furthermore, based on the finding that the plasma adrenaline concentration may increase some 300% in response to tracheal intubation (Derbyshire and Smith, 1984) during conventional anaesthesia (accompanied by a marked pressor response) we would suggest that a plasma adrenaline concentration of 1.5–2.0 pmol ml\(^{-1}\) is possibly acceptable. A value approaching 4.0 pmol ml\(^{-1}\) as noted in the present study is probably unacceptable, despite the fact that the injected dose of 1.4 μg kg\(^{-1}\) is ostensibly reasonable. As a result of this study, the volume of adrenaline solution used by one of the authors for rhinoplasty has been reduced to 10 ml of 1:200000.

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