PLASMA CONCENTRATIONS OF CATECHOLAMINES FOLLOWING ADRENALINE INFILTRATION DURING GYNAECOLOGICAL SURGERY

J. M. LOW, J. T. HARVEY, G. M. COOPER AND W. J. PRENDIVILLE

SUMMARY

High pressure liquid chromatography with electrochemical detection has been used to measure plasma catecholamine concentrations in six gynaecological patients undergoing halothane anaesthesia for cervical cone biopsy. Mean catecholamine concentrations before infiltration were $1.01 \pm 0.23$ (SEM) nmol litre$^{-1}$ ($185 \pm 43$ pg ml$^{-1}$) for adrenaline, and $2.2 \pm 0.25$ nmol litre$^{-1}$ ($364 \pm 41$ pg ml$^{-1}$) for noradrenaline. Following infiltration with 0.5% bupivacaine 15 ml with adrenaline 1:200 000, plasma adrenaline concentrations increased to a mean peak concentration of $18.6 \pm 3.7$ nmol litre$^{-1}$ ($3.4 \pm 0.69$ ng litre$^{-1}$). The lack of sympathoneuronal response was confirmed by simultaneous measurements of plasma noradrenaline concentrations, which did not change significantly. The proportion of the injected adrenaline measured in the intravascular compartment was 21.8%. This failure to elicit a sympathomimetic response during infiltration is discussed in relation to the use of halothane anaesthesia and the concurrent injection of a local anaesthetic solution.

Despite meticulous anaesthetic technique and the use of deliberate hypotension, on occasions it is possible to achieve haemostasis only by the local application or infiltration of a vasoconstrictor, most commonly a solution of adrenaline. During cone biopsy of the cervix, the use of adrenaline overcomes the need for the Sturmdorf type of haemostatic epithelial sutures that are normally used. Avoiding this suture and consequent distortion of the cervical tissue allows a more comprehensive assessment of the cervix both cytologically and by colposcopy (Bielecki, 1964).

However, the ability of adrenaline to induce cardiac arrhythmia is well known and, although many authors have suggested safe doses of adrenaline, there has been little documentation of the actual plasma concentrations which result from the absorption of adrenaline used for infiltration. Clinical studies have been useful in defining the dose-response curves for injected adrenaline and the disturbances in ventricular rhythm which result, but the threshold for cardiac arrhythmias can only be defined in terms of the total dose of adrenaline given to the patient (Johnston, Eger and Wilson, 1976). Except in one study of the use of retrobulbar block with lignocaine and adrenaline during ophthalmic surgery (Donlon and Moss, 1979), none of the previous claims of safe doses of adrenaline have been supported by measurement of the plasma concentrations of the catecholamine. We have used the method of high pressure liquid chromatography to measure the plasma concentrations of the catecholamines in order to assess the degree of intravascular absorption of adrenaline following its infiltration in uterine cervical tissue.

PATIENTS AND METHODS

Six fit women undergoing surgery for cervical cone biopsy were studied. Informed consent was obtained for blood sampling. Papaveretum 15 mg and hyoscine 0.3 mg were given i.m. about 1 h before surgery. Anaesthesia was induced with thiopentone $3-4$ mg kg$^{-1}$ and maintained with nitrous oxide in oxygen, supplemented with 1.5% halothane, given by mask. The ECG was monitored (CM5 lead configuration), and arterial pressure measured automatically (Dinamap 845). Bupivacaine 0.5% 15 ml with adrenaline 1:200 000 (total dose 75 $\mu$g) was used to infiltrate the cervix. A cannula was inserted to a vein in an antecubital fossa and used exclusively for the sampling of blood: the cannula was flushed with heparinized saline between samples. Blood samples were taken at the following stages: immediately before infiltration; during the period of infiltration of adrenaline; at 1, 2, 3, 4, 5 and 10 min following the beginning of infiltration.

Blood was drawn into chilled lithium heparin
tubes to which had been added sodium metabisulphite 0.1 ml as an antioxidant. These samples were kept on ice and the plasma separated within 30 min, by centrifugation at 2000 rev min\(^{-1}\) for 15 min in a refrigerated (4 °C) centrifuge (Mistral 6L centrifuge: M.S.E. Ltd). The catecholamine assays were performed in duplicate on the day of collection.

**Biochemical measurements**

Plasma catecholamine concentrations were measured by a method modified after Causon, Carruthers and Rodnight (1981) and based on high pressure liquid chromatography. This technique has been shown to be as sensitive as the radioenzymatic and fluorimetric methods, and has the advantages of lower operating costs, rapid analysis of small sample batches, and the simultaneous quantification of noradrenaline and adrenaline in the same sample. Three main steps were involved.

First, the catecholamines were extracted from plasma by the method established by Lund (1950). They were then separated by an Altex Ultrasphere ODS column (25 cm x 0.46 cm i.d.) with a mobile phase flow rate of 1.0 ml min\(^{-1}\) produced by a Knauer 52:00 HPLC pump (Roth Scientific Company, 9–11 Alexandra Road, Farnborough). Finally, the passage of the catecholamines through the column was monitored by electrochemical detection (LCA15 detector, EDT Research Ltd, 14 Trading Estate Road, London NW10 7LU).

The lower limit of detection was 0.4 nmol litre\(^{-1}\) at a signal-to-noise ratio of 5:1. The coefficients of variation were 7.6% and 6.4% for noradrenaline and adrenaline, respectively, at 1.1 nmol litre\(^{-1}\). The linearity of detection ranged from the lower limit to 60 nmol (10 ng).

Plasma bupivacaine concentrations were measured in four of the six patients on all samples. The assay was based on a method described by Tucker (1970) and measurements were made on Perkin–Elmer Sigma 3B gas chromatograph.

**RESULTS**

The combined results of serial plasma catecholamine measurements are presented in figure 1. Mean values of the catecholamines before infiltration were 1.0 (±0.23 SEM) nmol litre\(^{-1}\) (185 pg ml\(^{-1}\)) for adrenaline and 2.2 (±0.25 SEM) nmol litre\(^{-1}\) (364 pg litre\(^{-1}\)) for noradrenaline. After infiltration, the mean peak adrenaline concentration was 18.6 (±3.7 SEM) nmol litre\(^{-1}\) (3.4 ng ml\(^{-1}\)) — an 18-fold increase from baseline. This peak was usually reached 2 min following the beginning of infiltration, although the peak occurred at 1 min in one patient and at 3 min in two others. The highest concentration of plasma adrenaline reached in an individual patient was 37.6 nmol litre\(^{-1}\) (6.9 ng ml\(^{-1}\)) and represented a 36-fold increase in adrenaline from that individual’s control values.

The mean weight of the patients was 52.6 kg and, therefore, the average dose of adrenaline injected was 1.36 μg kg\(^{-1}\). The mean blood volume, calculated on the basis of previous measurements of blood volume in white Caucasian females (79.5 ml kg\(^{-1}\)) was 4.48 litre. Therefore, the peak amount of adrenaline detected in the intravascular compartment was 16.3 μg, representing 21.8% of the injected dose.
Table I. Plasma bupivacaine concentrations. — = not detectable

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mean (µg ml⁻¹)</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>After infiltration</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>1.26</td>
<td>0.12</td>
</tr>
<tr>
<td>2</td>
<td>2.09</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>2.71</td>
<td>0.37</td>
</tr>
<tr>
<td>4</td>
<td>2.56</td>
<td>0.45</td>
</tr>
<tr>
<td>5</td>
<td>2.15</td>
<td>0.50</td>
</tr>
<tr>
<td>10</td>
<td>1.63</td>
<td>0.28</td>
</tr>
</tbody>
</table>

The plasma noradrenaline concentrations in the same samples did not alter significantly as assessed by Student's t-test paired against the control sample.

Plasma bupivacaine concentrations are presented in Table I. The peak concentration of bupivacaine (2.71 µg ml⁻¹) occurred at 3 min following infiltration. The amount of bupivacaine in the intravascular compartment may be derived as 12.1 mg, representing 16% of the total injected dose.

No changes in arterial pressure, heart rate or ECG configuration were noted throughout the study.

DISCUSSION

The absorption of adrenaline from uterine cervical tissue occurred very rapidly (in less than 3 min) and plasma concentrations of adrenaline of over 30 times baseline values were observed in one patient. The proportion of adrenaline detected in the intravascular compartment was 21.8% of that injected, which is considerably more than that measured by Donlon and Moss (1979) after retrobulbar blockade with local anaesthetic agents containing adrenaline 1:200 000. However, samples were measured only at 2 and 7 min following infiltration and may have missed the peak absorption, despite the use of a similar total dose of adrenaline (50–60 µg). Further, the degree of absorption of adrenaline is likely to be influenced by the vascularity of the tissue.

We did not observe any change in arterial pressure during or after the period of infiltration. It was not considered reasonable to measure intra-arterial pressure directly, although this would have provided information on transient changes in arterial pressure.

The time-course and degree of the increase in plasma adrenaline concentration following infiltration highlight the mandatory use of the electrocardiograph during the period of infiltration, and for the first 10 min following injection. However, no disturbances of ventricular automaticity were observed, despite a 36-fold increase of plasma adrenaline concentration following infiltration, nor did we see any increase in heart rate. This may be regarded as surprising in view of the known ability (Raventos, 1956; Johnston, Eger and Wilson, 1976) of halothane to induce cardiac arrhythmias. However, the patients studied were all free from cardiac disease and the membrane-stabilizing effect of bupivacaine may have given some protection. Bupivacaine has been shown to be as effective as lignocaine in protecting the cardiac conduction system from adrenaline-induced arrhythmias under halothane anaesthesia (Chapin et al., 1980).

Increased plasma concentrations of noradrenaline reflect the spillover into the circulation of noradrenaline released from the sympathetic nerve terminals. Although the absolute concentrations of noradrenaline are influenced by changes in both release and uptake of noradrenaline (Esler, 1982) there are few circumstances in which the uptake of catecholamines will change suddenly during the course of a short anaesthetic or surgical procedure, the most likely being the use of pancuronium (Salt, Barnes and Conway, 1980; Cummings, Russell and Frewin, 1983). As this drug was not used in the present study, the absence of any significant change in the plasma concentration of noradrenaline reflects a constant level of sympathoadrenal activity during the procedure. Previous studies (Halter, Pflug and Porte, 1977; Nistrup Madsen et al., 1978; Cryer, 1980) have shown that sympathetic stimulation is reflected in corresponding increases in both adrenaline and noradrenaline. In view of the trivial degree of surgical stimulation during infiltration of the uterine cervix, it does not seem likely that the increase in plasma adrenaline concentration was caused by specific endogenous release of adrenaline from the adrenal medulla without concurrent release of noradrenaline. This possibility could have been excluded by studying a group of patients in whom the cervix was infiltrated with bupivacaine alone, or bupivacaine with felypressin.

Although most authors (Hall and Norris, 1958; Matteo, Katz and Papper, 1962; Forbes, 1966; Katz and Katz, 1966; Wallbank, 1970; Brock-Utne, 1972) who advocate the infiltration of adrenaline recommend dilute solutions and limitations of total dose, some have decried the use of adrenaline as an aid to haemostasis (Chang, Macartney and Graves, 1957; Johnstone and Nisbet, 1961; Varejes, 1963).
However, many anaesthetists have accepted the working guidelines proposed by Matteo, Katz and Papper (1962) that, under conditions of normocapnia and in the absence of thyrotoxicosis, the use of 10 ml of dilute (1:100,000) adrenaline over a period of 10 min is safe, and that this dose may be repeated three times within 1 h. These guidelines refer to the use of submucosal infiltration, and anaesthesia with halothane.

The presence of lignocaine will increase the threshold at which ventricular automaticity is effected (Johnston, Eger and Wilson, 1976). Although no lignocaine was used during submucosal infiltration (Matteo, Katz and Papper, 1962), the authors did use 4% lignocaine spray for topical anaesthesia to the larynx and it has been established that a considerable amount of lignocaine may be absorbed from the laryngeal mucosa (Scott et al., 1976). This may have contributed to the safety of the dose recommended by Matteo and colleagues (1962). Other authors who have suggested various safe doses for adrenaline have also included the use of lignocaine (Forbes, 1966; Wallbank, 1970; Johnston, Eger and Wilson, 1976; Donlon and Moss, 1979; Karl et al., 1983).

ACKNOWLEDGEMENTS

We should like to express our thanks to Miss G. M. Turner, Consultant Obstetrician, Bristol Maternity Hospital, for permission to study patients under her care. J. M. Low is in receipt of a Research Fellowship (No. 84) from the South Western Regional Health Authority Regional Research Committee.

REFERENCES


CONCENTRATIONS PLASMATIQUES DE CATECHOLAMINES APRÈS INFILTRATION ADRENALINÉE AU COURS DE LA CHIRURGIE GYNECOLOGIQUE

RESUME

Une chromatographie liquide à haute pression avec détection électrochimique a été utilisée pour mesurer les concentrations plasmaticques de catécholamines chez six patientes anesthésiées à l’halothane, pour une conisation du col de l’utérus. Les concentrations moyennes de catécholamines avant l’infiltration étaient
CATECHOLAMINE CONCENTRATIONS: INFILTRATION OF ADRENALINE

1.01 ± 0.23 (SEM) nmol litre⁻¹ (185 ± 43 pg ml⁻¹) for the adrenaline and 2.2 ± 0.25 nmol litre⁻¹ (364 ± 41 pg ml⁻¹) for the noradrenaline. After infiltration with 15 ml of a solution of 0.5% bupivacaine adrenaline (1:200000), the concentrations plasmatic of adrenaline augmented for attainment a peak whose mean value was 18.6 ± 3.7 nmol litre⁻¹ (3.4 ± 0.69 ng litre⁻¹). The absence of response of the sympathetic system was confirmed by measures simultaneous of concentrations plasmatic of noradrenaline which were not significantly modified. The proportion of adrenaline injected, retrieved in the intravascular compartment, was 21.8%. The absorption intravascular of the adrenaline exogenous is discussed in relation with the use of halothane for anesthesia and the simultaneous injection of local anesthetics.

PLASMAKONZENTRATIONEN VON KATECHOLAMINEN NACH ADRENALININFILTRATION WAHREN GYNÄKOLOGISCHER OPERATIONEN

ZUSAMMENFASSUNG

Bei sechs gynäkologischen Patientinnen wurde während Halothannarkose für Zervixkonus-Biopsie die Plasmakatecholaminkonzentration über Hochdruckliquiddioxid-Chromatographie mit elektrochemischer Detektion gemessen. Vor der Infiltration lagen die mittleren Konzentrationen von Adrenalin bei 1,01 ± 0.23 (SEM) nmol litre⁻¹ (185 ± 43 pg ml⁻¹), von Noradrenalin bei 2,2 ± 0,25 nmol litre⁻¹ (364 ± 41 pg ml⁻¹). Nach Infiltration mit 15 ml 0,5% igem Bupivacain mit Adrenalin 1:200000 stieg die Adrenalkonzentration auf einen mittleren Konzentrationsgipfel von 18,6 ± 3,7 nmol litre⁻¹ (3,4 ± 0,69 ng litre⁻¹). Das Fehlen einer sympathoneuronalen Reaktion wurde durch gleichzeitige Messungen des Noradrenalinspiegels bestätigt, der sich nicht signifikant änderte. Der Anteil des injizierten Adrenalins, der im intravaskulären Kompartment gemessen wurde, betrug 21,8%. Die Bedeutung der intravaskulären Aufnahme exogener Adrenalins wird hinsichtlich der Anwendung von Halothan und der gleichzeitigen Injektion von Lokalanästhetika diskutiert.

CONCENTRACIONES DE CATECOLAMINAS EN EL PLASMA A RAIZ DE LA INFILTRACION DE ADRENALINA DURANTE CIRUGIA GINECOLOGICA

SUMARIO

Se usó cromatografía por líquido bajo alta presión con detección electroquímica para medir las concentraciones de catecolaminas en el plasma en seis pacientes ginecológicas puestas bajo anestesia por halotano en vista de una biopsia del cono cervical. Antes de la infiltración, las concentraciones medias de catecolaminas eran de 1,01 ± 0,23 (SEM) nmol litro⁻¹ (185 ± 43 pg ml⁻¹) para la adrenalina y de 2,2 ± 0,25 nmol litro⁻¹ (364 ± 41 pg ml⁻¹) para la noradrenalina. Después de la infiltración con 15 ml de bupivacaina al 0,5% con 1:200 000 de adrenalina, las concentraciones de adrenalina en el plasma aumentaron hasta una concentración media tope de 18,6 ± 3,7 nmol litro⁻¹ (3,4 ± 0,69 ng litro⁻¹). Se confirmó la ausencia de respuesta simpatorneural mediante las mediciones simultáneas de las concentraciones de noradrenalina en el plasma que no cambiaron de manera significativa. La proporción de adrenalina inyectada medida en el compartimiento intravascular era de 21,8%. Se discute del significado de la absorción intravascular de la adrenalina exógena en relación con el uso de la anestesia por halotano y la inyección concurrente de una solución anestésica local.