Haemodynamic effects of three doses of dihydroergotamine during spinal anaesthesia

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We performed a randomized study comparing the haemodynamic effects of three doses of the vasopressor dihydroergotamine (DHE) (5, 10 and 15 μg kg⁻¹) in 30 ASA 1 and 2 patients, aged 53–87 yr, undergoing spinal anaesthesia. Non-invasive systolic arterial pressure (SAP), heart rate and central venous pressure (CVP) were recorded continuously for 25 min. Intravenous fluids were withheld during this period. All three doses of DHE reversed the lowering effects of spinal anaesthesia on SAP and CVP (P<0.0001), and these effects were smooth in onset and sustained. Whereas the lowest (5 μg kg⁻¹) dose restored SAP and CVP to near prespinal values, the higher (10 and 15 μg kg⁻¹) doses resulted in above-baseline increases in SAP of 7% and in CVP of 2.7 cm H₂O (P<0.05). The haemodynamic profile of DHE makes it a useful agent for managing hypotension during spinal anaesthesia. A dose of 5–10 μg kg⁻¹ is recommended.

Keywords: anaesthetic techniques, regional; anaesthetic techniques, subarachnoid; anaesthesia, cardiovascular; complications, vasoconstriction; sympathetic nervous system, vasoconstrictor, dihydroergotamine

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Dihydroergotamine mesylate (DHE) (Dihydergot, Novartis, North Ryde, NSW, Australia) is a vasopressor that preferentially vasoconstricts the venous system. Its main clinical uses are in the treatment of migraine and orthostatic hypotension. It can also be used in doses of 0.5–1.0 mg to treat hypotension during spinal anaesthesia. However, its use as a vasopressor in managing spinal anaesthesia is not well accepted and there are major regional differences in its use and availability. There is little mention of the use of DHE as a vasopressor in the anaesthetic literature. Two groups have demonstrated its efficacy. Its main circulatory actions are to restore central blood volume and ventricular filling by constricting the venous capacitance vessels and, to a lesser extent, to maintain peripheral resistance by vasoconstricting dilated arteries.

Preliminary investigations in our department have shown that, during spinal anaesthesia, i.v. DHE has a smoother onset of action and a longer duration compared with other, more commonly used vasopressors. This therapeutic profile makes DHE an attractive drug for treating hypotension during spinal anaesthesia, because the peak and trough effects seen with other vasopressors are avoided. The objective of the present study was to define the haemodynamic profile of DHE during spinal anaesthesia and to determine a suitable i.v. dose.

Methods and results

Approval by the Clinical Research Ethics Committee of the Chinese University and written informed consent were obtained. Thirty ASA 1 or 2 (16:14) Chinese patients (28 males) with mean (range, or SD) age 71 (53–87) yr and weight 62 (11) kg, scheduled for elective urological or inguinal hernia repair surgery, were recruited. They were randomized to receive DHE 5, 10 or 15 μg kg⁻¹.

Patients were fasted overnight and premedicated with oral diazepam 5–10 mg. Haemodynamic monitoring consisted of non-invasive arterial pressure measurement at 1-min intervals, electrocardiogram, pulse oximetry and a 16-gauge central venous line in the right internal jugular vein attached to a pressure transducer. Data were measured with a Datex Engstrom AS/3 Compact Monitor (Datex-Ohmeda, Helsinki, Finland) and transferred to a laptop computer, where they were displayed and stored. After a 10-min stabilization period, baseline measurements were made. The patient was then turned to the lateral position and 3 ml of
0.5% heavy bupivacaine (Marcain Spinal 0.5% heavy; Astra, North Ryde, NSW, Australia) was injected intrathecally. The patient was then returned to the supine position and remained undisturbed for 25 min whilst data were collected. During this period no surgery was performed and i.v. fluids were withheld. Once the onset of spinal block had been confirmed by leg weakness, the preselected dose of DHE was administered i.v. with the investigator blind to the dose. The sensory level of the block to pin-prick was determined after 25 min.

Haemodynamic data were later converted to baseline and 1-min interval data using Microsoft Excel (Windows 95). This program was used to determine the greatest recorded effect of spinal anaesthesia before DHE administration and the average effect of DHE recorded between 5 and 25 min after spinal injection. The percentage change or the numerical difference in central venous pressure (CVP) with respect to the baseline for each 1-min interval was also calculated, and was used to determine the magnitude of the effect of each dose of DHE over 5 to 25 min. Statistical analysis was performed using Statview 4.5 (SAS Institute, Cary, NC, USA). Data were compared using analysis of variance (ANOVA), the Kruskal–Wallis test or the χ² test as appropriate. Continuous (1-min) haemodynamic data were analysed by ANOVA for repeated measures, with Bonferroni/Dunn adjustment for post hoc comparisons. P<0.05 was considered as significant.

Groups were similar with respect to patient characteristics, sensory block and baseline haemodynamic data (Table 1), with the exception of the lowest dose (5 µg kg⁻¹) group, in which the heart rate was higher (P=0.03). Sensory blockade reached thoracic dermatome 6 (2–10).

The response to DHE is shown in Table 1. In no patient did SAP fall below 25% of baseline. The greatest recorded decrease after spinal injection (mean (SD)) in SAP was 8 (9)%, that in CVP was 1.1 (1.1) cm H₂O and the increase in heart rate was 11 (8)%. Intravenous DHE reversed the initial depressant effects of spinal anaesthesia. SAP increased with respect to baseline values after the 10 and 15 µg kg⁻¹ doses (P<0.0001) but remained below baseline values after the 5 µg kg⁻¹ dose (P<0.02). Similar changes were found in mean and diastolic arterial pressures. CVP increased above baseline values after all three doses (P<0.0001), the increases after the 10 and 15 µg kg⁻¹ doses being greater than after the 5 µg kg⁻¹ dose (P<0.02). Heart rate increased after spinal anaesthesia and then decreased after DHE in all three groups (P<0.0005).

**Comment**

This study shows the haemodynamic effects of i.v. DHE, unmodified by i.v. fluid administration, in healthy middle-aged and elderly patients receiving spinal anaesthesia. DHE was effective in reversing the main haemodynamic effects of spinal anaesthesia because it increased blood pressure and restored CVP and thus ventricular filling. Its effects lasted at least 25 min. A dose of 5–10 µg kg⁻¹, or 0.3–0.6 mg for our average 60-kg adult, was sufficient to restore spinal-induced decreases in blood pressure and CVP within 3 min of administration.

DHE administration has few side-effects. Excessive doses can cause nausea, vomiting and vasospasm, which could be troublesome in patients with ischaemic heart disease. However, this was a greater problem with ergotamine, the predecessor of DHE.

A number of authors have studied the pharmacokinetics and circulatory effects of DHE during central neural block. Stanton-Hick and colleagues, in a number of eloquent studies using whole-body scintigraphy with technetium 99m-labelled erythrocytes, showed that epidural anaesthesia caused a redistribution of blood to denervated capacitance vessels in skeletal muscle and skin at the expense of ventricular filling, which compromised cardiac output. DHE preferentially constricted these capacitance vessels, replenishing the central circulation and thus ventricular filling. The significance of this replenishment

**Table 1** Mean (SD) values (averaged between 5 and 25 min) of systolic arterial pressure (SAP), heart rate and central venous pressure (CVP) for each dose of DHE at baseline, after spinal anaesthesia (greatest recorded effect) and after DHE administration.

<table>
<thead>
<tr>
<th>Dose of DHE (µg kg⁻¹)</th>
<th>5 (n=10)</th>
<th>10 (n=10)</th>
<th>15 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>142 (25)</td>
<td>147 (19)</td>
<td>138 (19)</td>
</tr>
<tr>
<td>After spinal</td>
<td>135 (28)</td>
<td>136 (16)</td>
<td>123 (22)</td>
</tr>
<tr>
<td>After DHE</td>
<td>138 (28)</td>
<td>157 (19)</td>
<td>147 (28)</td>
</tr>
<tr>
<td><strong>Heart rate (beats min⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80 (11)</td>
<td>64 (10)</td>
<td>66 (12)</td>
</tr>
<tr>
<td>After spinal</td>
<td>92 (13)</td>
<td>73 (14)</td>
<td>69 (14)</td>
</tr>
<tr>
<td>After DHE</td>
<td>83 (19)</td>
<td>60 (10)</td>
<td>59 (8)</td>
</tr>
<tr>
<td><strong>CVP (cm H₂O)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.7 (2.6)</td>
<td>5.3 (1.9)</td>
<td>5.5 (2.4)</td>
</tr>
<tr>
<td>After spinal</td>
<td>3.5 (2.1)</td>
<td>3.9 (2.0)</td>
<td>4.8 (2.5)</td>
</tr>
<tr>
<td>After DHE</td>
<td>5.0 (3.5)</td>
<td>8.1 (3.1)</td>
<td>8.1 (3.4)</td>
</tr>
</tbody>
</table>
of the central circulation was first demonstrated by Pugh and Wyndham in 1950, when they tilted the patient’s head up during spinal anaesthesia and caused a reduction in ventricular filling and cardiac output, which resulted in severe hypotension.\(^\text{12}\) Therefore, it would seem desirable to maintain an adequate circulating volume during spinal anaesthesia, and i.v. DHE seems a particularly good drug for ensuring that this happens. Compared with data collected previously by our group during spinal anaesthesia with other vasopressors,\(^\text{7 8}\) DHE had a slower onset of effect and longer duration of action, and this seems to be an important feature of using DHE that merits further investigation.

Previously, in a similar group of patients receiving spinal anaesthesia, we found that 60% developed hypotension requiring treatment.\(^\text{13}\) In the present study, all three doses of DHE were highly effective in preventing severe hypotension and the CVP was maintained above baseline. To restore SAP to baseline values, a dose of 5–10 μg kg\(^{-1}\) was needed. Our results showed very little difference in effect between the higher 10 and 15 μg kg\(^{-1}\) doses, suggesting that DHE has an upper limit to its circulatory effects, its maximal effects being an increase in blood pressure of 5–10% and an increase in CVP of 3 cm H\(_2\)O.

However, it should be noted that we studied healthy adult patients. Whether our findings are equally applicable to elderly and infirm patients, such as those with traumatic hip fracture and who frequently require spinal anaesthesia but are at much greater risk of developing hypotension, is questionable. In such patients, large increases in ventricular filling induced by DHE could precipitate acute pulmonary oedema and DHE may not have the potency to overcome the large decreases in peripheral vascular resistance that frequently occur in this more frail group of patients.\(^\text{13}\)

Despite the positive findings of our study, DHE has not gained wide acceptance as a vasopressor for use in spinal anaesthesia. This is difficult to explain. DHE has no serious side-effect that would discourage its use. However, the market for vasopressors has been dominated for many years by ephedrine because of its extensive use in obstetric anaesthesia,\(^\text{14}\) and this has left little freedom for other potentially useful drugs to emerge. Also, pharmaceutical companies have tended not to promote the sales of vasopressors because their clinical use is small compared with other products, such as muscle relaxants and opioids. However, despite its well-established use, ephedrine has recently been shown to be ineffective in treating hypotension during spinal anaesthesia in both elderly and obstetric patients,\(^\text{14 15}\) which has led to renewed interest in alternative vasopressors. Recent improvements in anaesthetic monitoring systems have made it easier to study in detail their cardiovascular effects.\(^\text{7 8}\)

In conclusion, DHE has many features to recommend its use as a vasopressor in the treatment and prevention of hypotension during spinal anaesthesia. In particular, its action has a smooth onset and a clinically useful duration. It restores CVP, which should protect against sudden cardiovascular collapse. It can be given conveniently as a single i.v. injection, and we recommend using a dose between 5 and 10 μg kg\(^{-1}\).

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