EFFECTS OF ALFENTANIL AND FENTANYL ON INDUCTION OF ANAESTHESIA IN PATIENTS WITH SEVERE PREGNANCY-INDUCED HYPERTENSION

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SUMMARY

Forty patients with severe pregnancy-induced hypertension presenting for Caesarean section under general anaesthesia were allocated randomly to receive either fentanyl 2.5 μg kg⁻¹ or alfentanil 10 μg kg⁻¹ as part of the anaesthetic induction sequence. In all patients, the cardiovascular response to trachea/intubation was measured. Both drugs attenuated the response equally but did not abolish it in all patients. Alfentanil 10 μg kg⁻¹ is a suitable alternative to fentanyl 2.5 μg kg⁻¹ for patients with pregnancy-induced hypertension.

KEY WORDS


Although there has been a steady decrease in hypertension as a cause of maternal mortality in England and Wales, the number of cerebrovascular deaths in the latest triennium, 1982–84, was the greatest since the reports began [1]. The latest Report on Confidential Enquiries into Maternal Deaths in England and Wales emphasized the high incidence (72%) of substandard care in hypertensive patients and recommended that, as pre-eclampsia of life threatening severity is now rare, regional teams with special expertise should be formed to provide advice or assume management [1, 2]. The problem of pregnancy-induced hypertension (PIH) appears to be increasing in the developing world [3] and in our own institution PIH is the greatest cause of maternal death in a society in which maternal mortality rates are 10 times higher than in the developed world [4]. In our population, patients presenting with either PIH or pregnancy-aggravated hypertension (PAH) represent 5–12% of all deliveries, 50% of which require delivery by Caesarean section [5].

As cerebrovascular accident is the commonest cause of death in PIH, attention should be directed towards an anaesthetic technique that provides haemodynamic stability throughout the surgical procedure and, unless contraindicated, extradural analgesia is probably the preferred technique [6]. However, under circumstances in which the mother has suffered a convulsion ( eclampsia) or there are problems with maternal coagulation or fetal distress, general anaesthesia may be necessary [7]. If general anaesthesia is used for patients with PIH or PAH, haemodynamic stability must be provided, particularly during the period of tracheal intubation when patients are at greatest risk [8]. Several methods have been advocated to obtund the pressor response to intubation, including administration of opioids before induction of anaesthesia. The ultra short-acting opioid alfentanil has been shown to obtund the pressor response to tracheal intubation in the normal pregnant patient [9], but to our knowledge has not been studied in the hypertensive pregnant patient. In this study we have compared the effects of alfentanil 10 μg kg⁻¹ and those of fentanyl 2.5 μg kg⁻¹ as part of the anaesthetic induction technique on the pressor response to tracheal intubation in patients presenting with severe PIH.


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PATIENTS AND METHODS

The study was undertaken with the approval of the Ethics and Professional Standards Subcommittee of the Faculty of Medicine, University of Natal. Forty patients undergoing emergency Caesarean section were studied. All patients were older than 25 yr, were multiparous and had presented with a sustained diastolic arterial pressure >110 mm Hg with or without significant proteinuria, peripheral oedema, or both.

Following diagnosis, patients were admitted to the labour ward, where a central venous catheter (for measurement of central venous pressure (CVP)) and a 14-gauge peripheral infusion cannula were inserted under local anaesthesia. Hypertension was treated by the obstetric team and CVP was corrected to 4-6 cm H2O when necessary by infusion of crystalloids. Patients were transferred to the operating theatre in the left lateral position and on arrival were given 30 ml of sodium citrate 0.3 mol litre\(^{-1}\) orally and positioned on the operating table with a wedge (15°) under the right buttock. All patients received metoclopramide 10 mg i.v.

An electrocardiograph was connected and the ECG (Lead II) monitored continuously. A radial artery cannula was inserted under local anaesthesia and connected to an HP78034A monitoring system with twin-channel hard copy recorder. Whilst the patients were breathing air, arterial blood was withdrawn for baseline analysis of blood-gas tensions and acid–base status. Heart rate and arterial pressure were allowed to stabilize and preoxygenation with 100% oxygen commenced via a face mask.

Patients were given an i.v. injection of glycopyrrolate 0.2–0.4 mg and droperidol 5 mg, 5 min before induction. Particular attention was paid to the level of consciousness, which was monitored continuously by eliciting responses to verbal questioning. Patients were allocated randomly to receive either fentanyl 2.5 \(\mu\)g kg\(^{-1}\) or alfentanil 10 \(\mu\)g kg\(^{-1}\). Induction of anaesthesia was undertaken approximately 3 min after fentanyl and 1 min after alfentanil was administered.

Induction consisted of lignocaine 1 mg kg\(^{-1}\), followed by etomidate 0.3 mg kg\(^{-1}\) and suxamethonium 1 mg kg\(^{-1}\) given in rapid sequence. Cricoid pressure was applied when consciousness was lost during the administration of etomidate or if there was any impairment of conscious level preceding induction. The trachea was intubated with a cuffed tracheal tube approximately 1 min after administration of suxamethonium and the time marked on a recorder. Maintenance of anaesthesia was with enfurane up to 0.8% and 50% nitrous oxide in oxygen; the patient’s lungs were ventilated to \(P_{\text{acO}_2}\) 4.3 kPa. Neuromuscular block was produced with alcuronium 150 \(\mu\)g kg\(^{-1}\) or intermittent suxamethonium in those patients who had received magnesium sulphate as part of the antihypertensive therapy.

An infusion of syntocinon was administered after delivery and in the alfentanil group additional analgesia was provided with further administration of alfentanil, pethidine or papa-veretum. Glycopyrrolate and neostigmine were used to antagonize residual neuromuscular block at the end of surgery in those patients who had received a non-depolarizing neuromuscular blocking agent.

Maternal arterial blood was taken immediately before delivery and neonatal blood samples obtained at delivery from a double-clamped segment of umbilical cord. Samples were analysed using a semi-automatic blood-gas analyser (Corning 170 pH/blood-gas analyser). A record was made of the time from induction to delivery (I–D) and of the time from uterine incision to delivery (U–D).

All neonates were examined immediately after delivery by staff experienced in neonatal resuscitation. Assessment of the time to sustained ventilation (TSV) was measured and a modified Apgar (minus colour) score (0–8) obtained at 1 and 5 min. When necessary, naloxone 0.01 mg kg\(^{-1}\) was administered in divided doses i.m., i.v. or both. All neonates were transferred to the neonatal intensive care unit as soon as possible.

The record of ECG and arterial pressure was reserved for subsequent analysis. Measurements of pre-induction, post-induction and peak post-intubation values of heart rate and systolic and diastolic arterial pressures were analysed. Pre-induction and post-induction values were defined as average values over a 15-s period in which values varied by less than 10% from the average. There were two patients with eclampsia in each group. Comparisons between and within groups were undertaken using Student’s \(t\) test with a significance level of \(P < 0.05\) (two-tailed). Non-parametric data were compared using chi-square analysis. Data are presented with both \(t\) and \(P\) values as appropriate.
The difference in mean heart rate between the groups before induction was not statistically significant \( (P = 0.06) \) (table III). One patient in the fentanyl group underwent \( \beta \)-block before induction, but the preinduction heart rate in this patient was 130 beat \( \text{min}^{-1} \). There was no significant change in mean heart rate after induction in each group, but after tracheal intubation both groups showed a significant increase in heart rate compared with preinduction values. There was a significant \( (P < 0.001) \) decrease in systolic arterial pressure after induction in both the groups, followed by a significant increase after tracheal intubation. However, there were no statistically significant differences in mean systolic arterial pressure, before induction and after intubation, within or between the groups. Both groups showed a small (10.9 and 9.3 mmHg), but significant increase in mean diastolic pressure following tracheal intubation, with no differences between the two groups.

There were eight neonatal deaths in the study: five in the alfentanil group (mean gestational age 30 weeks, mean weight 1.04 kg, range 0.55–1.5 kg) and three in the fentanyl group (mean gestation 32 weeks, mean weight 1.17 kg, range 0.95–1.45 kg). All deaths were related to prematurity or growth
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Fig. 1. Modified Apgar (minus colour) scores at 1 and 5 min. ● = Fentanyl; ● = alfentanil.

Fig. 2. Time to sustained ventilation after fentanyl (●) or alfentanil (●).

Control of the pressor response to tracheal intubation is an essential part of any general anaesthetic technique in severe PIH [10]. In a previous study from this department, a technique based upon nitrous oxide and a volatile agent failed to provide a safe technique, applicable to all mothers with PIH [11] and it was confirmed that increasing age and parity were significant prog-
nastic indicators. It was suggested that for the older, multiparous patient with PIH a different anaesthetic approach should be used, particularly as a more severe pressor response to intubation may be expected. Our study has thus been confined to the elderly multigravid patient with severe hypertension.

One method of obtunding the pressor response to a rapid sequence induction is by using an opioid such as fentanyl or alfentanil. Fentanyl 200 µg, given in divided doses in an elderly, multiparous group of patients presenting for Caesarean section has been found to obtund the hypertensive response to laryngoscopy in most patients [12]. Whilst maternal safety is the overriding consideration, drug-induced neonatal depression should be minimal and alfentanil may be more appropriate in view of its physicochemical properties.

Alfentanil has been used to obtund the pressor response to tracheal intubation in both the pregnant [9] and non-pregnant patient [13]. Comparison between fentanyl and alfentanil in non-pregnant patients showed that alfentanil 15 µg kg\(^{-1}\) was effective in suppressing the increase in arterial pressure subsequent to tracheal intubation, and 30 µg kg\(^{-1}\) also suppressed the increase in heart rate, whereas fentanyl 5 µg kg\(^{-1}\) suppressed both [13]. However, the effects of alfentanil were of shorter duration than the effects of fentanyl. In the normotensive patient undergoing elective Caesarean section, alfentanil 10 µg kg\(^{-1}\) is effective in modifying the arterial pressure and heart rate response to tracheal intubation [9].

The present study showed that alfentanil 10 µg kg\(^{-1}\) was as effective as fentanyl 2.5 µg kg\(^{-1}\) when used in combination with other agents in obtunding the pressor response to tracheal intubation and may be considered as an appropriate alternative. However, both groups showed an increase in heart rate and diastolic pressure following tracheal intubation and, although mean increases in heart rate of 16 beat min\(^{-1}\) (fentanyl), 11 beat min\(^{-1}\) (alfentanil) and in diastolic pressure of 11 mm Hg (fentanyl) and 8 mm Hg (alfentanil) may not be considered clinically significant, there was wide variation. Maximum changes of 45 beat min\(^{-1}\) (fentanyl), 47 beat min\(^{-1}\) (alfentanil) and 43 mm Hg (fentanyl), 32 mm Hg (alfentanil) were observed and were considered to be clinically significant in the individual patients.

Although there were no significant differences between the groups in pressor response, this must be viewed in the context of group comparability. We consider the PIH in the alfentanil group to have been more severe, in that those patients were older and delivered neonates of lower gestational age, the latter in relation to earlier termination of pregnancy in maternal interests.

The overall neonatal mortality in the study was

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### Table IV. Maternal and neonatal blood-gas and acid-base status at delivery (mean (SD)). \(\dagger n = 19\); \(\ddagger n = 18\). BE = Base excess. * \(P < 0.05\)

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl</th>
<th>Alfentanil</th>
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<tbody>
<tr>
<td><strong>Maternal baseline</strong></td>
<td></td>
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<tr>
<td>pH</td>
<td>7.42 (0.06)</td>
<td>7.44 (0.06)</td>
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<tr>
<td>(P_a\text{CO}_2) (kPa)</td>
<td>3.69 (0.39)</td>
<td>3.57 (0.47)</td>
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<tr>
<td>(P_{aO_2}) (kPa)</td>
<td>14.1 (1.66)</td>
<td>13.4 (1.41)</td>
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<td>BE (mmol litre(^{-1}))</td>
<td>-3.46 (2.35)</td>
<td>-2.85 (3.11)</td>
</tr>
<tr>
<td><strong>Maternal delivery (Fi(_O_2), 0.5)</strong></td>
<td></td>
<td></td>
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<tr>
<td>pH</td>
<td>7.43 (0.10)</td>
<td>7.39 (0.07)</td>
</tr>
<tr>
<td>(P_a\text{CO}_2) (kPa)</td>
<td>3.99 (0.39)</td>
<td>4.15 (0.81)</td>
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<tr>
<td>(P_{aO_2}) (kPa)</td>
<td>29.21 (6.62)</td>
<td>24.27 (7.56)</td>
</tr>
<tr>
<td>BE (mmol litre(^{-1}))</td>
<td>-3.62 (1.95)</td>
<td>-4.11 (3.42)</td>
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<td><strong>Umbilical vein</strong></td>
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<tr>
<td>pH</td>
<td>7.28 (0.12)</td>
<td>7.29 (0.06)</td>
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<tr>
<td>(P_a\text{CO}_2) (kPa)</td>
<td>6.05 (1.34)</td>
<td>6.31 (0.89)</td>
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<td>(P_{aO_2}) (kPa)</td>
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<td>BE (mmol litre(^{-1}))</td>
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<td>-3.73 (3.10)</td>
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<tr>
<td><strong>Umbilical artery</strong></td>
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<td>pH</td>
<td>7.22 (0.13)(\ddagger)</td>
<td>7.25 (0.06)(\ddagger)</td>
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<tr>
<td>(P_a\text{CO}_2) (kPa)</td>
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<td>7.13 (0.92)(\ddagger)</td>
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<td>(P_{aO_2}) (kPa)</td>
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<td>1.61 (0.68)(\ddagger)</td>
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<tr>
<td>BE (mmol litre(^{-1}))</td>
<td>-5.76 (4.97)(\ddagger)</td>
<td>-4.57 (3.23)(\ddagger)</td>
</tr>
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</table>
20%, which included one death at 22 weeks gestation. This is comparable to the mortality rate of 15% reported by Lawes and colleagues [12] and reflects the severity of the disease and the high incidence of premature delivery of low birth weight babies. None of the deaths could be attributable to the anaesthetic technique. As expected, neonatal mortality was not related to either modified Apgar scores or TSV. Neonates who died had significantly smaller mean birth weight (1.09 kg) than survivors (2.25 kg). There were no significant differences between the groups in the clinical condition of the neonates as assessed by modified Apgar scores and TSV.

The lesser fat solubility of alfentanil might be of advantage in reducing the rate of placental transfer in comparison with fentanyl, as would its increased protein binding [14], although decreased ionization at pH 7.4 (pK_a 6.5) would tend to increase placental transfer. The plasma protein largely responsible for binding alfentanil is the alpha-1 acid glycoprotein fraction [15]. This protein may be found in lesser concentrations in the fetus [16] leading to a greater fraction of unbound drug in the fetal circulation, and perhaps greater neonatal depression if delivery occurs at peak maternal plasma concentrations of drug. Although there have been a limited number of studies it appears that the calculated [17] and measured [14] unbound maternal and fetal plasma concentrations of alfentanil are similar. However, when maternal concentrations of free drug begin to decrease, back transfer from the fetus should be rapid. Following a 10-min infusion of alfentanil 50 µg kg⁻¹ in the gravid ewe, transfer back has been demonstrated within 6 min of stopping the infusion [18]. The shortest induction to delivery time in the alfentanil group in our study was 9 min. Transfer back of fentanyl appears not to occur [18].

The only significant difference found in blood-gas analysis was a lesser umbilical arterial Po_2 in the alfentanil group. Umbilical venous to arterial oxygen gradients were identical in the two groups (1.6 kPa), which suggests that the difference was caused by placental oxygen supply rather than altered fetal demand. The difference in mean maternal oxygen arterial tension between the two groups at delivery (4.5 kPa), while not statistically significant (P = 0.058), may be reflected in umbilical venous oxygen tensions. Neonatal demise was not related to umbilical blood values. In addition to an opioid, the induction sequence included other agents which could play a role in obtunding the pressor response to tracheal intubation, including droperidol [19], lignocaine [20] and magnesium [21]. Magnesium sulphate has been shown to obtund the adrenergic response to tracheal intubation in hypertensive parturients. Seventeen patients in this study received magnesium sulphate therapy before operation (eight alfentanil, nine fentanyl). Two-way analysis of haemodynamic data revealed no influence of magnesium. It is possible that magnesium concentrations were not in the therapeutic range, as they were not monitored in this study [22].

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REFERENCES

12. Lawes EG, Downing JW, Duncan PW, Bland B, Lavers N, Gane GAC. Fentanyl-droperidol supplementation of rapid sequence induction in the presence of severe


