EXTRADURAL PETHIDINE WITH AND WITHOUT ADRENALINE DURING LABOUR: WIDE VARIATION IN EFFECT

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SUMMARY

The pain-relieving effect of a single extradural dose of pethidine 25 mg with and without adrenaline was studied in 20 healthy women during labour. The study was open regarding the effects of pethidine but double-blind regarding the addition of adrenaline. In 14 of 19 women good or excellent analgesia was achieved for a period of 50–160 min. Pethidine with adrenaline 25 μg was not more effective than pethidine alone. Eight of the 14 women showed signs of regional analgesia to pin-prick and temperature discrimination. The patients had small (45–188 ng ml⁻¹) concentrations of pethidine in plasma. In eight patients the plasma concentrations of pethidine were maintained for at least 1.5 h. Extradural pethidine thus induces analgesia of short and variable duration. Repeated doses may be needed, resulting in accumulation of the drug in plasma with the risk of respiratory depression in mother or child.

Extradural analgesia with local anaesthetics is accepted as a reliable and safe method during labour (Moir, 1976; Bromage, 1978). However, even with segmental analgesia (Zador and Nilsson, 1974; Høllmén et al., 1977) the efficiency of uterine contractions in the first stage of labour is slightly decreased and weakness of the abdominal muscles and inhibition of the pushing reflex in the second stage of labour results in an increased number of outlet extractions (Willdeck-Lund, Lindmark and Nilsson, 1979). In uncontrolled studies small extradural doses of opiates gave long-lasting relief of postoperative and chronic pain with unimpaired muscular function (Bahar et al., 1979; Bromage, Camporesi and Chestnut, 1980; Graham, King and McCaughey, 1980). This type of selective opiate-induced analgesia would be a more physiological way to relieve pain during labour. However, small doses of morphine (2–4 mg) in the extradural space have failed to provide sufficient analgesia during labour (Booker et al., 1980; Husemeyer, O'Connor and Davenport, 1980; Magora et al.; 1980; Nybell-Lindahl et al., 1981). By virtue of its higher lipophilicity (Goodman and Gilman, 1975; Yaksh, 1981) pethidine might reach the spinal cord more rapidly than morphine. Addition of adrenaline might decrease the absorption of pethidine to the systemic circulation and thereby increase the local concentration of the drug.

This study was undertaken to investigate the analgesic effect and duration of a single extradural dose of pethidine 25 mg with and without adrenaline during the first stage of labour. Another aim was to study the relation between the analgesia and the plasma concentrations of pethidine.

METHODS

Twenty healthy women with normal pregnancies were studied. All patients were at term; 10 were nulliparous. The study was approved by the Department of Drugs of the National Board of Health and Welfare and by the ethics committee of the hospital. All patients gave their informed consent.

The extradural catheter was introduced when the cervix was dilated to 3–4 cm. Extradural puncture was performed by paramedian technique (Bonica, 1972) at the L2–L3 interspace and the catheter was introduced 2–3 cm.

The women were randomly allocated to one of two groups. Both groups were given a single dose of pethidine 25 mg in 5 ml of saline with or without adrenaline 5 μg ml⁻¹. Balanced saline solution 400–500 ml was administered prophylactically to prevent a decrease in arterial pressure. Systolic and diastolic arterial pressures and respiratory rates were monitored.

If adequate analgesia was not achieved within 30 min, 5 ml of 0.25% bupivacaine containing adrenaline 5 μg ml⁻¹ was administered via the catheter.
Pain relief was estimated with a 10-cm horizontal visual analogue scale (VAS) before and 20 min after the administration of pethidine or bupivacaine (Huskisson, 1974; Scott and Huskisson, 1976). An unused scale was shown on each occasion. The duration of analgesia was calculated as the time in minutes until the patient required additional analgesia consisting of bupivacaine 5 ml or until the time of delivery.

To determine the plasma concentrations of pethidine blood samples were taken before and 5, 15, 30, 60, 90 and 120 min after the administration of pethidine and thereafter hourly until delivery. Mixed blood from the umbilical cord was withdrawn immediately after birth. The samples were centrifuged within 30 min and the plasma was withdrawn and frozen at $-20^\circ\text{C}$. Pethidine analyses in duplicate were carried out with mass fragmentography with deuterium-labelled pethidine as an internal standard. The limit of sensitivity of this method in 100-μlitre plasma samples is $5\,\text{ng}\cdot\text{ml}^{-1}$ (G. Tomson and colleagues, in preparation).

Tests for discrimination of temperature, pin-prick and sensation of heavy legs were carried out before and 20 min after the injection of pethidine or bupivacaine. The infants were assessed with Apgar scores at 1 and 5 min. Any sign of respiratory depression was monitored. All blocks and the assessment of the analgesic effect, the segmental distribution and the duration of analgesia were performed by the same senior anaesthetist.

Pethidine concentrations in plasma and percentage pain relief are given as median values.

**RESULTS**

Various degrees of pain relief were achieved at 20 min after administration of pethidine (fig. 1). Ten patients indicated 71–100% pain relief ("excellent analgesia"), four patients indicated 31–70% pain relief ("good analgesia") and five patients had 0–30% pain relief ("poor analgesia"). Seventy-four per cent of all patients thus indicated good or excellent analgesia. One patient who delivered her child before analgesia was achieved was excluded.

Median values of pain relief at 20 min in patients who received pethidine with and without adrenaline were 74% and 61% respectively. Patients with good or excellent pethidine analgesia noted an incipient analgesic effect after 5–10 min and fully established analgesia after 10–15 min.

In the group with excellent or good analgesia none of the patients required additional injections during the first 50 min (fig. 2). Six patients experienced pain relief lasting for more than 115 min and in three patients the effect remained at delivery.

Table I shows how pethidine in the extradural space influences temperature and pin-prick discrimination and the sensation of heavy legs. In the group with good or excellent analgesia eight of 14 patients had a segmental involvement of at least one of these three variables. In two of the five patients

![Fig 1. Analgesic effect after 20 min expressed as per cent pain relief derived from the visual analogue scale. The patients are grouped in three categories, corresponding to the subjective judgements of pain relief.](image1.png)

![Fig 2. Duration of analgesia of the 14 patients with good or excellent pain relief. The time limits in the three groups are arbitrarily chosen. In the group with a duration of more than 115 min the accurate duration could not be decided because in three patients the duration of analgesia outlasted the delivery.](image2.png)
TABLE I. Number of patients with segmental effects of extradural pethidine. The two patients with impaired pin-prick discrimination in the group with poor analgesia had this effect in T3–9 and T9–11 respectively. In the group with good or excellent analgesia the four patients with effect on temperature discrimination and the six patients with heavy legs all had effect on pin-prick discrimination.

<table>
<thead>
<tr>
<th>Segmental effect</th>
<th>Poor analgesia (n = 5)</th>
<th>Good or excellent analgesia (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pin-prick</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Temperature</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Heavy legs</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

with poor analgesia impaired pin-prick discrimination was found in T3–9 and T9–11 respectively. No patient in this group had any involvement of the entire segment T10–L1 whereas all of the patients in the group with good or excellent analgesia had a segmental distribution that included T10–L1 or more.

Respiratory depression was not observed in any of the women. Two infants had an Apgar score less than 7 at 1 min, and one was still less than 7 at 5 min. In both of these infants instrument-assisted delivery was necessary because of threatening asphyxia.

The plasma concentrations of pethidine varied widely in both groups (table II) and the median value was less for the group who had received pethidine with adrenaline. Figure 3 shows a representative plasma concentration curve for one patient and demonstrates that the concentration of pethidine was comparatively stable for several hours. No relationship between plasma concentrations of pethidine and analgesic effect after 20 min was found.

The plasma concentrations of pethidine in mixed umbilical blood ranged from 10 to 96 ng ml⁻¹ with a median value of 32 ng ml⁻¹. They were slightly less than the maternal plasma concentration at birth (fig. 3).

In one of the patients nausea occurred 30 min after the administration of pethidine. In no patient did hypotension or itching occur.

DISCUSSION

A single extradural dose of pethidine 25 mg provided good or excellent analgesia in labour in 14 of the 19 women studied. The duration of pethidine-induced analgesia was evaluated only indirectly, taking the time of required additional analgesia as end-point. Thus it was estimated that the duration lasted for 50–160 min, which constituted 13–100% of the total delivery time (fig. 4). The small difference in the median values for pain relief between the two groups cannot serve as a basis for any conclusions since, in the group of 10 patients with adrenaline, three were nulliparous and in the group of nine without adrenaline six were nulliparous.

To obtain effective analgesia during the first stage of labour T10–L1 should be blocked (Bonica, 1979). We found signs of segmental analgesia with reduced temperature and pin-prick discrimination or sensation of heavy legs, or both, in 57% of the patients with effective pethidine analgesia. This contrasts with reports from others (Husemeyer, O’Connor and Davenport, 1980; Perriss, 1980). Bromage, Camporesi and Leslie (1980) reported a dose-dependent regional decrease of discrimination for pin-prick and temperature after extradural doses of methadone, hydromorphone or morphine.

The peak plasma concentrations of pethidine after extradural administration were small (45–188 ng ml⁻¹) compared with the concentrations (300–650 ng ml⁻¹) found in parturients after i.m. administrations.
FIG. 3 Plasma concentrations of pethidine (ng ml⁻¹) in one patient after extradural pethidine 25 mg with adrenaline. ○ = Maternal plasma concentration, ■ = umbilical plasma concentration.

Injection of 1.5 mg/kg body weight (G. Tomson and colleagues, in preparation). However, the peak plasma concentrations were greater after extradural administration than would be expected after a similar dose administered i.m. (Tomson and colleagues, in preparation). These characteristics of extradural pethidine, with the sustained plasma concentrations observed (fig. 3) may lead to respiratory depression after repeated administration of even low doses.

Since segmental effects were observed and good or excellent analgesia was achieved, even though the plasma concentrations of pethidine were low, a direct spinal action is indicated.

We found that almost 75% of the women experienced good or excellent analgesia. This is in contrast to the inadequate or absent pain relief after administration of extradural morphine during labour (Husemeyer, O'Connor and Davenport, 1980; Magora et al., 1980; Nybell-Lindahl et al., 1981; Writer, James and Wheeler, 1981). As morphine is not as lipophilic as pethidine it probably takes longer for morphine to reach the spinal cord (Yaksh, 1981). One study reports acceptable analgesia from morphine 2.5–4.0 mg given extradurally in labour in 12 of 25 patients (Booker et al., 1980), but the reported latency periods vary between 15 and 40 min. This long latency period can be the reason why others have failed to achieve analgesia with extradural morphine during labour.
The frequency of adequate analgesia with pethidine in the extradural space is less than with local anaesthetics. With extradural bupivacaine the expected frequency of adequate analgesia is about 95% (Moir, 1976). The risk of respiratory depression in the mother or the infant following repeated doses of extradural pethidine argues against the routine use of this technique. In conclusion extradural pethidine, with or without adrenaline, does not seem to provide a safe alternative to local anaesthetics in labour.

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REFERENCES


LA PETHIDINE AVEC OU SANS ADRENALINE EN PERIDURALE AU COURS DU TRAVAIL: EFFETS EXTREMEEMENT VARIABLES

RESUME
On a étudié l'effet analgésique d'une dose périnérale unique de pethidine 25 mg avec ou sans adrénaline chez 20 femmes bien portantes au cours du travail. L'étude était découverte pour ce qui est des effets de la pethidine, mais en double aveugle pour ce qui est de l'adjonction d'adrénaline. Chez 14 femmes sur 19, une analgésie bonne ou excellente a été obtenue pendant une période 50-160 min. La pethidine additionnée d'adrénaline 25 μg n'était pas plus efficace que la pethidine seule. Huit de ces 14 femmes avaient des signes d'anesthésie régionale à la piqûre d'épingle et pour la discrimination thermique. La concentration plasmatique de pethidine était faible (45-188 mg·ml⁻¹). Chez huit patientes, on a pu retrouver de la pethidine dans le plasma pendant plus de 90 min. Ainsi, la pethidine en péridurale entraîne une analgésie de durée variable et faible. Des doses répétées peuvent être nécessaires, et entraîner une accumulation plasmatique de l'agent, avec un risque de dépression respiratoire chez la mère ou l'enfant.

EPIIDURALE PETHIDIN-GABE MIT UND OHNE ADRENALINE WÄHREND DER GEBURT: GROßE STREUUNG DER WIRKUNG

ZUSAMMENFASSUNG

PETIDINA EXTRADURAL CON Y SIN ADRENALINA DURANTE EL PARTO. GRAN VARIACION EN LOS EFECTOS.

SUMARIO
Se llevó a cabo un estudio del efecto aliviador del dolor de una dosis única extradural de 25 mg de petidina con y sin adrenalina en 20 mujeres sanas durante el parto. El estudio era abierto en lo que se refiere a los efectos de la petidina, pero doble-ciego en cuanto a la añadidura de adrenalina. En 14 de las 19 mujeres, se obtuvo una analgesia excelente por un periodo de 50–160 min. La petidina con 25 µg de adrenalina no fue más eficaz que la petidina sola. Ocho de las 14 mujeres demostraron señales de analgesia regional con picadura de alfiler y una discriminación de temperatura. Las pacientes tenían pequeñas concentraciones (45–188 ng/ml) de petidina en el plasma. En ocho de las pacientes, las concentraciones de petidina en el plasma se mantuvieron por lo menos durante 1.5 h. La petidina extradural entonces induce la analgesia de duración corta y variable. Dosis repetidas pueden ser necesarias, lo que resulta en una acumulación de la substancia en el plasma con riesgos de depresión respiratoria en la madre o en el niño.