Clinical Reports

Maternal and fetal effects of intravenous patient-controlled fentanyl analgesia during labour in a thrombocytopenic parturient

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The use of intravenous (iv) patient-controlled fentanyl analgesia during labour in a parturient with unexplained thrombocytopenia ($70 \times 10^3 \cdot ml^{-1}$) is described. The patient self-administered boluses of 25 μg of fentanyl with a lock-out interval of ten min. In addition, a concurrent fentanyl infusion of 25 $\mu g \cdot hr^{-1}$ was given. Effective analgesia was achieved during labour and a total of 1025 μg of fentanyl was infused over 11 hr 55 min until delivery of a vigorous infant with Apgar scores of 9 after one and five min. Respiratory depression or undue sedation were not observed in the mother either during labour or in the post-partum period. At birth, maternal total plasma fentanyl concentration was 1.11 $ng \cdot ml^{-1}$, whereas neonatal umbilical total plasma fentanyl concentration was 0.43 $ng \cdot ml^{-1}$. Newborn plasma protein binding of fentanyl was lower compared to the mother (63% vs 89%). Thus, free fentanyl concentrations (0.16 $ng \cdot ml^{-1}$) were identical in the mother and newborn at delivery.

Les auteurs décrivent l'usage de l'ACP intraveineuse au fentanyl durante le travail d'une parturiente porteuse d'une thrombocytopénie ($70 \times 10^3 \cdot ml^{-1}$). La patiente s'est administrée elle-même des bolus de 25 μg de fentanyl avec un intervalle réfractaire de dix minutes. En même temps, elle recevait une perfusion continue de fentanyl de 25 $\mu g \cdot hr^{-1}$. Une analgésie efficace a été obtenue pendant le travail. Une dose totale de 1025 μg de fentanyl a été administrée sur une période de 11 heures 55 minutes jusqu'à la naissance d'un bébé vigoureux. L'Apgar a été de 9 après une et cinq minutes. On n'a pas observé de dépression respiratoire ou de sédation excessive chez la mère pendant le travail ou dans le post-partum. A la naissance, la concentration maternelle plasmatique totale de fentanyl a été mesurée a 1.11 $ng \cdot ml^{-1}$ et celle du sang veineux ombilical a été de 0,43 $ng \cdot ml^{-1}$. La fraction de fentanyl liée aux protéines plasmatiques du nouveau-né était plus basse que celle de la mère (63% vs 86%) de sorte que les concentrations de fentanyl libre (0,16 $ng \cdot ml^{-1}$) ont été indiques pour les deux.

Key words
ANAESTHESIA: obstetrical;
ANALGESIA: PCA;
ANALGESICS: fentanyl;
PHARMACOKINETICS: intravenous; fentanyl.

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Epidural anaesthesia is an effective and safe method of analgesia during labour. However, epidural anaesthesia is contraindicated in patients with coagulopathies, infection or haemodynamic instability.[1] Therefore, we elected to provide *iv* patient-controlled analgesia (PCA) for labour in a parturient who had a platelet count of $70 \times 10^3 \cdot ml^{-1}$ at the onset of labour. In this report we describe the use of *iv* PCA fentanyl during the labour and also provide transplacental pharmacokinetic data of fentanyl during delivery.

Case report

A 34-yr-old, 66 kg primigravida was admitted to the High Risk Unit (HRU) for investigation of maternal

thrombocytopenia and for intermittent fetal supraventricular tachycardia at 38 weeks gestation. The patient had a platelet count of $218 \times 10^3 \cdot ml^{-1}$ during the first trimester, but decreased to $143 \times 10^3 \cdot ml^{-1}$ at 28 wk gestation. On admission her platelet count had decreased to $79 \times 10^3 \cdot ml^{-1}$, and five days later, when labour was induced, the platelet count was $70 \times 10^3 \cdot ml^{-1}$. Prothrombin time, partial thromboplastin time and serum fibrinogen were all normal throughout her stay in the HRU. Liver function tests were within normal limits with the exception of serum alkaline phosphatase which was elevated at 231 $U \cdot L^{-1}$ (normal 36–135). Plasma analysis for antiplatelet antibody and antinuclear antibody (ANA) were both negative. Serum sodium, potassium, chloride, creatinine and uric acid were also within normal limits. Urinalysis was negative for protein, glucose and ketones.

There was no maternal history of systemic lupus erythematosus, immune thrombocytopenic purpura or hypertension. The patient had not taken any medication other than iron and vitamin supplements during pregnancy. Physical examination revealed a healthy, normotensive parturient with no evidence of purpura. Fetal echocardiogram showed supraventricular tachycardia (200–225 min^{-1}) on two occasions before labour.

After five days of maternal and fetal observation it was decided to induce labour using prostaglandin E_2 cervical gel. Lumbar epidural analgesia (LEA) was felt to be contraindicated because of the increased risk of epidural haematoma due to the low platelet count ($70 \times 10^3 \cdot ml^{-1}$). A bleeding time was not performed, as it was decided that it would be unwise to proceed with LEA in this otherwise healthy parturient even if the bleeding time was within normal limits. The patient was offered the alternative of *iv* fentanyl infusion using a PCA device. The risks and benefits of the technique were explained to the patient and consent was obtained to initiate therapy. The PCA pump (Abbott Lifecare® PCA II Plus 4100, Chicago IL) was set to deliver a background infusion of 25 μg fentanyl per hr and to deliver PCA doses of 25 μg of fentanyl with a lock-out period of ten min. The PCA pump was also set to deliver a four-hour maximum dose of 600 μg. The patient was experiencing painful, regular contractions at the onset of PCA fentanyl therapy when the cervix was two centimeters dilated. The first stage of labour proceeded, augmented by an *iv* oxytocin infusion, for ten hr. This was followed by a second stage of labour that lasted 1 hr 55 min. The fetal heart rate tracing showed good variability throughout labour without evidence of fetal tachycardia. The obstetrician administered a bilateral pudendal nerve block prior to the spontaneous delivery of a vigorous 3220 gm female infant with Apgar scores of 9 at one minute and five minutes. Maternal as well as umbilical venous blood from a double-clamped segment of the umbilical cord

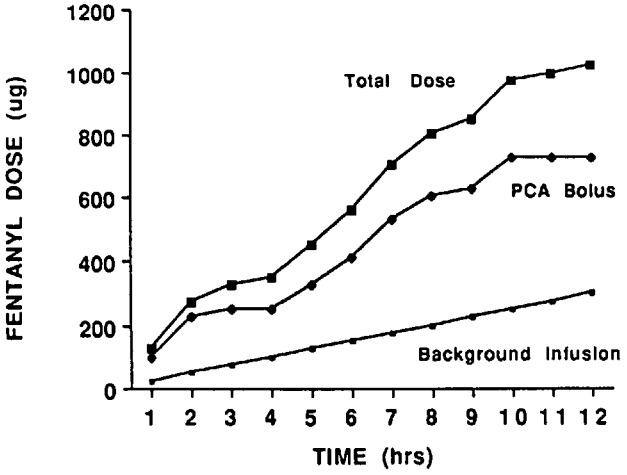

FIGURE 1 Details of fentanyl administration – PCA bolus, infusion and total dose.

were obtained immediately after delivery for radioimmunoassay of maternal and fetal plasma fentanyl concentrations. Measurement of protein binding of fentanyl was performed by filtration of serum samples through an Amicon centrifree micropartition system.[2] The commercial immunoassay for fentanyl has a 0.1 $ng \cdot ml^{-1}$ lower detection limit. The coefficient of variation of this test in our laboratory is less than 5%. A hard copy was subsequently obtained from the PCA computer using a text printer (TPW Electronic Products Inc. San Louis Obispo CA). Analysis of the data showed that 732 μg of self-administered fentanyl were given during the first stage of labour whereas no additional PCA doses were requested during the second stage of labour. The cumulative fentanyl dose given by continuous background fentanyl infusion was 293 μg. The patient received a total of 1025 μg of *iv* fentanyl over 11 hr and 55 min of labour (Figure 1). There was no nausea or pruritus associated with *iv* PCA fentanyl administration. The respiratory rate was monitored hourly and was noted to be 16–20 min^{-1} throughout labour. The sedation score (Table I) was 0 or 1 except on two occasions (for four hours and eight hours after the start of the PCA infusion) when a score of 2 was noted. The patient became progressively more tired as labour progressed which might have influenced the sedation score. The mother was observed for one hour in the recovery room before she was transferred to postpartum floor. On direct questioning the patient felt that the degree of analgesia was satisfactory during early first stage labour. However, during the accelerated first stage of labour (7–10 hr after start of *iv* PCA fentanyl therapy), coinciding with intravenous oxytocin augmentation (Figure 1), pain relief was not adequate and she lost confidence in the ability of the PCA

TABLE I Sedation scale

0 Alert
1 Occasionally drowsy
2 Frequently drowsy, easy to arouse
3 Somnolent, difficult to arouse
4 Unresponsive

pump to give her satisfactory analgesia during that time. During the second stage of labour the pain intensity was much less and she did not self-administer any fentanyl during this period.

The newborn was admitted to the Special Care Nursery (SCN) for observation where she was monitored continuously using an apnoea monitor, transcutaneous oximetry and continuous ECG monitoring. There were no apnoeic spells or fetal tachyarrhythmias noted, and the baby was transferred to the normal newborn nursery following 12 hr of surveillance. The remaining stay in the hospital was uneventful for both mother and baby and they were discharged on the third postpartum day.

Discussion

Epidural anaesthesia for labour is safe if the platelet count is higher than $100 \times 10^3 \cdot ml^{-1}$ (normal $>150 \times 10^3 \cdot ml^{-1}$).[3] Disruption of dilated epidural veins may inadvertently occur by the epidural needle or during epidural catheter insertion for continuous LEA during labour.[4] Platelets initiate clot formation; therefore adequate quality and quantity of platelets is important to prevent epidural haematoma formation with subsequent neurological compromise. Case reports of uneventful epidural anaesthesia during labour when the platelet count is less than $100 \times 10^3 \cdot ml^{-1}$ have been published,[3,5] but we felt that *iv* PCA opioid administration was a preferable choice for labour analgesia in this patient since she did not have any associated medical condition where epidural anaesthesia would be of particular benefit. Thrombocytopenia in the parturient is often associated with disorders such as pre-eclampsia, immune thrombocytopenic purpura (ITP) or systemic lupus erythematosus (SLE), whereas infrequent causes of thrombocytopenia in this patient population include drug-induced thrombocytopenia or thrombotic thrombocytopenic purpura (TTP).[6] Unexplained peripartum thrombocytopenia, a diagnosis of exclusion, is often characterized by an early return to normal platelet count following delivery of the infant.[7] The platelet count in our patient increased to $110 \times 10^3 \cdot ml^{-1}$ on the third postpartum day.

We considered transcutaneous electrical nerve stimulation (TENS) therapy as an alternative to epidural analgesia. However, studies of its use during labour[8] and for other painful conditions[9,10] have only demonstrated a placebo effect with no decrease in pain intensity. Furthermore, TENS therapy during labour interferes with electronic fetal heart rate monitoring. This was unacceptable in this parturient since episodes of fetal supraventricular tachycardia had been documented before labour.

Intermittent *im* injections of meperidine has been the most common analgesic therapy for labour in our unit if there was a contraindication to epidural analgesia. However, inadequate analgesia, pain at injection site, maternal sedation and neonatal respiratory depression can be associated with *im* meperidine injections. Patient-controlled analgesia using intravenous meperidine can result in improved labour analgesia and reduced meperidine requirements when compared with an *im* meperidine regimen.[11] However, meperidine crosses the placenta rapidly and following prolonged administration accumulation of meperidine and its metabolite normeperidine will occur.[12,13] Normeperidine has been implicated in causing neonatal depression and may produce epileptiform EEG patterns.[14] Fentanyl is a potent, lipophilic opioid without active metabolites. When administered in hourly *iv* increments of 50–100 μg fentanyl provided maternal labour analgesia with only mild sedation. There was no evidence of neonatal respiratory depression at birth, and Apgar and neurologic and adaptive scores were similar to neonates that did not receive narcotics during labour.[15] In a randomized study comparing the efficacy of *iv* fentanyl and *iv* meperidine for labour analgesia it was found that there was less maternal sedation, nausea and vomiting in the fentanyl group.[16] Similar pain relief was obtained by patients in both study groups.[16] Nalbuphine, an agonist-antagonist narcotic with a reported ceiling effect for respiratory depression has also been studied. In a study with *iv* PCA meperidine (15 mg) vs nalbuphine (3 mg) nalbuphine was reported to be superior in decreasing pain intensity with a similar incidence of side-effects.[17] However, in a case report by Feinstein *et al.*, nalbuphine administration during labour has been associated with sinusoidal fetal heart rate patterns.[18]

We chose fentanyl as the preferred *iv* opioid agent, and used a combined background fentanyl infusion and PCA regimen during labour in our patient. Although the usefulness of a background infusion is controversial in postoperative pain management,[19] we felt that labour pain, where there is constant discomfort with periods of exacerbations, would respond well to this treatment modality. Our PCA dosing regimen is similar to postoperative *iv* PCA infusion schedules.[20,21] However, the relatively high number of PCA demands and excess demand frequency in the first two hours after the start of *iv* fentanyl therapy (Figure 2) underscores the importance of a physician-administered loading dose (50–100 μg) at the onset of PCA therapy. This would allow the patient to achieve an

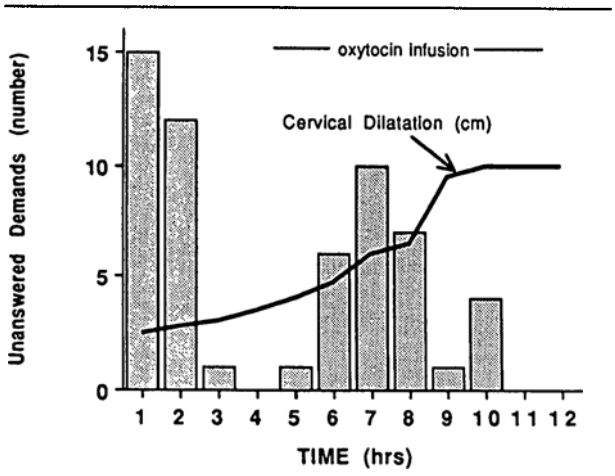

FIGURE 2 Unsatisfied demands for fentanyl bolus during labour.

analgesic plasma concentration at an earlier stage correlating with the minimum effective analgesic concentration (MEC) of that particular patient. Also, the lock-out interval which was set at ten min was probably too long and might well have prevented the patient from receiving enough opioid, especially during late first stage of labour when she became discouraged with the effectiveness of the PCA fentanyl infusion. The lock-out interval should be related to the speed of onset (time to peak analgesia) of fentanyl. Since there is a lag-time of approximately six min between blood concentration and effect,[22] a lock-out interval of five min might be more appropriate. The hourly fentanyl consumption during first stage of labour was 97.5 μg which is more than has been described for postoperative analgesia,[23] but is similar to a recent report using *iv* PCA fentanyl during labour where the patient received 113 $\mu g \cdot hr^{-1}$.[24] The maternal total fentanyl plasma concentration at delivery (1.11 $ng \cdot ml^{-1}$) is above the plasma concentration (1 $ng \cdot ml^{-1}$) that Lehmann suggested is required for postoperative pain relief,[25] and also above the mean MEC (0.63 $ng \cdot ml^{-1}$) for postoperative fentanyl analgesia.[26] The duration of action of fentanyl following intravenous bolus injection is short, due to redistribution and extensive tissue uptake.[27] A large cumulative dose (1025 μg in our patient) may cause prolonged effects due to a large volume of distribution limiting the rate at which elimination can occur. However, our patient did not exhibit respiratory depression or undue sedation during labour or in the post-partum period.

Fentanyl is a basic lipophilic molecule that crosses the placenta rapidly.[28] The principal plasma protein carrier for fentanyl is α_1-acidglycoprotein (α_1-AG).[29] Gepts *et al.* demonstrated that umbilical venous α_1-AG levels were lower than maternal plasma α_1-AG concentration.[30] Our data (Table II) indicate that maternal-fetal differences in

TABLE II Fentanyl assay

Sample	*Total fentanyl* ($ng \cdot ml^{-1}$)	*Protein binding (%)*	*Free fentanyl* ($ng \cdot ml^{-1}$)
Maternal	1.11	86	0.16
Umbilical vein	0.43	63	0.16

protein binding of fentanyl account for the differences in total concentrations. However, fentanyl rapidly achieves similar free (unbound) concentrations in the fetus and mother.

In summary, *iv* PCA fentanyl during labour is an alternative pain management regimen during labour if the patient elects not to have epidural anaesthesia or if a contraindication to performing epidural anaesthesia exists. The *iv* PCA technique avoids painful *im* injections and allows for individualized dosing of opioid analgesics leading to better titration of drug dosage minimizing interpatient pharmacodynamic and pharmacokinetic differences. It also provides the patient with a sense of control of analgesic therapy which may decrease anxiety. Although *iv* PCA has achieved popularity in postoperative pain management, its use for labour analgesia is not widespread. This is due to the effectiveness and popularity of continuous epidural labour analgesia, and from a lack of controlled clinical trials to determine *iv* infusion schedules required to achieve effective pain relief without significant maternal sedation or maternal and fetal respiratory depression. Our data give some indication of maternal and fetal distribution of *iv* PCA fentanyl during labour, but further studies are required to confirm the safety and efficacy of the technique. In this case the newborn was observed for 12 hr in SCN primarily because of a history of fetal tachycardia *in utero*. Further studies are required to determine the minimum time necessary to observe the newborn in the SCN following *iv* PCA fentanyl infusion during labour. Intravenous PCA fentanyl administration may also become a valuable alternative for relief of labour pain in hospitals without an epidural anaesthesia service, as well as in rare cases where epidural anaesthesia is technically impossible due to extensive spinal surgery and instrumentation.

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