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An isobolographic analysis of diamorphine and levobupivacaine for epidural analgesia in early labour

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Background. Few data describe the pharmacological interactions between local anaesthetics and opioids. The aim of this study was to measure the median effective concentration (MEC) of diamorphine and levobupivacaine when given separately and as mixtures for epidural analgesia, and determine whether the combination is additive or synergistic.

Methods. One hundred and twenty patients were enrolled in this prospective randomized, two-phase, double-blind study. In the first phase, 60 women were randomized to receive a fixed 20 ml volume of either levobupivacaine or diamorphine epidurally . Dosing was determined using up-down sequential allocation with testing intervals, respectively, of 0.01%w/v and 12.5 $\mu g\ ml^{-1}$. After estimations of the MEC of levobupivacaine and diamorphine, a further 60 patients were randomized in the second phase to one of the three mixtures: (a) diamorphine 70 $\mu g\ ml^{-1}$ (fixed) and levobupivacaine (testing interval 0.004%w/v, starting at 0.044%w/v); (b) levobupivacaine 0.044%w/v (fixed) and diamorphine (testing interval 7 $\mu g\ ml^{-1}$, starting at 70 $\mu g\ ml^{-1}$); and (c) bivariate diamorphine and levobupivacaine (testing intervals of 7 $\mu g\ ml^{-1}$ and 0.004%w/v starting at 70 $\mu g\ ml^{-1}$ and 0.044% w/v respectively).

Results. The MEC estimates from the first phase were 143.8 $\mu g\ ml^{-1}$ (95% CI 122.2–165.3) for diamorphine and 0.083%w/v (95% CI 0.071–0.095) for levobupivacaine. In the second phase, the MEC and interaction index (γ) of the three combinations were: diamorphine 65.5 $\mu g\ ml^{-1}$ (56.8–74.2), γ=0.99; levobupivacaine 0.041%w/v (0.037–0.049), γ=0.98; and for the fixed combination diamorphine 69.5 $\mu g\ ml^{-1}$ (60.5–78.5) and levobupivacaine 0.044%w/v (0.039–0.049), γ=1.02.

Conclusion. The combination of diamorphine and levobupivacaine is additive and not synergistic when used for epidural analgesia in the first stage of labour.

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The clinical efficacies of local anaesthetics[1] and opioids[2] have been shown to be concentration-dependent when used as the sole epidural analgesic in labour. However, in practice, epidural administration of a mixture of local anaesthetic and opioid is more commonplace during labour[3 4] or after surgery.[5 6] Use of a combined approach often decreases the incidence of side-effects while maintaining a similar level of pain relief.[7] Despite widespread use of combinations of local anaesthetics and opioids, there are few data describing the pharmacological interactions between these drug groups,[8 9] and a wide range of combination therapies are used clinically. Therefore, the aim of this study was to measure the median effective concentration (MEC) of diamorphine and levobupivacaine when given separately and as mixtures for epidural analgesia, and determine whether the combination is additive or synergistic.

Methods

One hundred and twenty patients were enrolled in his prospective randomized, two-phase, double-blind study after informed, written consent, and approval by the Tayside Committee on Medical Ethics. Patient information sheets describing the study protocol and procedure were distributed within the antenatal clinic to patients between 36 and 38 weeks gestation. Patients were approached for consent early in labour and before induction. Criteria for inclusion in the study were request for epidural analgesia when in active labour, cervical dilatation $\leq$5 cm, no opioids administered within the previous 12 h and no history of significant antenatal or maternal illness.

After i.v. infusion of crystalloid solution, and with the patient in the left lateral position, a lumbar epidural catheter was inserted caudally at the L 2/3 interspace using loss of resistance to saline. Saline injection was minimized to $<$2 ml. All epidural injections were performed by one anaesthetist (B.M.), using the standard technique.

In the first phase, 60 women were randomized, using computer-generated numbers and sealed envelopes, to receive a fixed 20 ml volume of either epidural levobupivacaine (n=30) or diamorphine (n=30). No test dose was given and time zero was designated as the time at which the epidural injection was completed. Once the injection was given, the anaesthetist left the room. Both the patient and midwife were blinded to the syringe contents. Non-invasive blood pressure was measured every 5 min for the first 20 min according to the labour ward epidural protocol. The pressure at 15 min was used for analysis.

Labour pain was measured using the same method as previous, similar studies[1 2] investigating the MEC of local anaesthetics in early labour. Pain after epidural injection was measured every 5 min for 30 min by midwives with a visual analogue pain score (VAPS) corresponding to the peak pain associated with the previous contraction. The outcomes of the study were defined as:

- Successful—VAPS $\leq$10 mm at any time within the 30 min study period.
- Unsuccessful—VAPS $>$10 mm within the 30 min study period, but pain relief after bolus rescue with a 10 ml solution of 0.25%w/v bupivacaine.
- Technical failure—VAPS $>$10 mm within the 30-min study period, but no pain relief after bolus rescue with a 10 ml solution of 0.25%w/v bupivacaine. After a technical failure, the next patient was randomized to the same solution and concentration.

Dosing was started at 0.12%w/v levobupivacaine and 200 $\mu g\ ml^{-1}$ diamorphine and continued using up-down sequential allocation with testing intervals of 0.01%w/v and 12.5 $\mu g\ ml^{-1}$ for levobupivacaine and diamorphine, respectively. Testing intervals approximating to 10% of the initial dose were used in accordance with previous methodology.[1 2]

After estimations of the MEC of levobupivacaine and diamorphine, a further 60 patients were randomized in the second phase to one of three mixtures (n=20):

- diamorphine 70 $\mu g\ ml^{-1}$ (fixed) and levobupivacaine (testing interval 0.004%w/v, starting at 0.044%w/v);
- levobupivacaine 0.044%w/v (fixed) and diamorphine (testing interval 7 $\mu g\ ml^{-1}$, starting at 70 $\mu g\ ml^{-1}$);
- bivariate diamorphine and levobupivacaine (fixed testing intervals of diamorphine 7 $\mu g\ ml^{-1}$ and levobupivacaine 0.004%w/v, starting at a combination dose of diamorphine 70 $\mu g\ ml^{-1}$ and levobupivacaine 0.044%w/v, respectively).

Measurement of the efficacy of analgesia in phase two used the same criteria as phase one. After the study, pain relief

Table 1 Patient characteristics of those receiving diamorphine alone, levobupivacaine alone, and the combination of diamorphine and levobupivacaine (three groups combined). Continuous data analysed using one-way ANOVA; nominal data† analysed using χ^2 or Fisher's exact test

	Diamorphine (n=30)	Levobupivacaine (n=30)	Combination (n=60)	F-ratio or (χ^2)	P-value
Age (yr)	27.7 (6.6)	27.6 (7.8)	27.5 (5.4)	0	0.99
Height (cm)	161.0 (5.8)	160.6 (5.6)	163.4 (6.6)	2.6	0.08
Weight (kg)	80.8 (13.6)	82.0 (16.0)	84.3 (15.5)	0.6	0.57
Cervical dilitation (cm)	2.8 (1.1)	2.7 (1.2)	3.1 (1.1)	1.6	0.20
Gestation (weeks)	39.9 (1.8)	40.3 (1.5)	39.6 (1.7)	1.5	0.24
Prim/Multip†, n (%)	22/8 (73/27)	20/10 (67/33)	36/24 (60/40)	1.6	0.45
Induction†, n (%)	27 (90)	23 (77)	43 (72)	3.9	0.14
Nausea and vomiting†, n (%)	12 (40)	1 (3)	11 (37)	12.8	$<$0.01
Sedation score $\geq$1†, n (%)	3 (10)	0 (0)	5 (17)	2.9	0.23
Ventilatory frequency $<$ 12†, n (%)	0	0	0		
Systolic blood pressure Pre-epidural	133.8 (14.4)	132.3 (15.1)	129.8 (14.1)	0.8	0.48
15 min after epidural injection	129.2 (13.8)	130.1 (15.7)	131.0 (12.8)	0.2	0.85
Diastolic blood pressure Pre-epidural	78.8 (7.8)	77.0 (11.9)	77.1 (11.3)	0.3	0.76
15 min after epidural injection	75.9 (9.5)	71.3 (12.5)	72.3 (9.2)	1.7	0.20
Initial VAPS (mm)	60 (13.2)	58.8 (13.4)	60.9 (12.3)	0.27	0.77