Module 2.5
Clinical Overview

Drug Products:

Bupivacaine 0.1% -Fentanyl 2 µg/ml [redacted]
Bupivacaine 0.125% -Fentanyl 2 µg/ml [redacted]

[redacted]

Redacted under section 40 of the FOI Act

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2.5.1. PRODUCT DEVELOPMENT RATIONALE

Pain is a common problem in the early postoperative period and in obstetrics. The advantages of providing pain relief to patients in different clinical situations include earlier ambulation, as well as earlier recovery or discharge from hospital.

Non-steroidal anti-inflammatory agents do not produce a sufficiently effective analgesic effect and parenteral narcotics or local anaesthetics alone have been disappointing, due to side effects or inadequate analgesia. In the search for a therapeutic tool providing effective and long lasting analgesia free from side effects, it was found that the co-administration of narcotics and anaesthetics via the epidural route could fulfil this aim.

Epidural analgesia was introduced in the 1940s, but not frequently used until the 1960s, when anaesthesiologists began administering bupivacaine epidurally to relieve pain associated with labour [redacted]). Since then, epidural blockade with local anaesthetic agents has become the most widely used technique of neural blockade for relief of pain in obstetrics in the United States, Canada, Australia, and other countries.

In 1979 for the first time, the effectiveness of intrathecal administration of morphine in humans for the alleviation of cancer related pain was shown. Since then the intrathecal, and to a much greater extent, epidural administration of narcotics has rapidly expanded to include management of postoperative pain [redacted]). Epidural narcotic analgesia is widely used because it provides intensive analgesia with a rapid onset and without motor or autonomic blockade. The efficacy of opioids administered by this route is superior to that of systemic administration and is associated with a low incidence of side effects when properly monitored [redacted]).

Narcotics and anaesthetics differ in their mechanism of action. Their combination offers the advantage of a reduction in the dose requirement for each agent and a decrease of potential toxicity, while still providing effective analgesia. Bupivacaine is a local anaesthetic and fentanyl a narcotic analgesic. Whilst bupivacaine is a local anaesthetic belonging to the amino amide group, fentanyl is a fast acting opioid analgesic. It has been demonstrated in several controlled trials that the epidural association of fentanyl and bupivacaine may improve both the onset and the duration of the analgesia and provide better quality of analgesia.

In labouring women the addition of epidural fentanyl to epidural bupivacaine has been reported to hasten the onset of analgesia, increase its duration, diminish perineal discomfort and reduce the amount of bupivacaine required to achieve pain relief without motor block ([redacted] . In one study of 46 women in the first stage of labour, treatment of perineal pain with fentanyl plus bupivacaine (100µg plus 10mg, respectively) produced reliable analgesia quicker in onset and longer in duration (140 minutes) than either fentanyl (100 µg, 114 minutes) or bupivacaine alone (25 mg, 99 minutes) ([redacted]).

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Bupivacaine 0.1% -Fentanyl 2 µg/ml
Bupivacaine 0.125% -Fentanyl 2 µg/ml

When bupivacaine is used alone, 0.5% -0.75% is often used to provide a long-term block [redacted] In pregnant women lower concentrations are frequently used (0.25%, 0.125%, 0.0625%) in combination with fentanyl 2µg/ml to provide adequate analgesia during labour [redacted]

The association of fentanyl and bupivacaine has been shown to provide improved maternal satisfaction and may also reduce the need of instrumental delivery [redacted] . In one randomised study involving 80 primaparous women requesting epidural analgesia during labour, those receiving bupivacaine and fentanyl expressed higher satisfaction than those receiving bupivacaine alone. Using a visual analogue scale to measure satisfaction the median difference was 3 mm, (95% CI: 1 to 5, P=0.012) ([redacted] .

Several studies have demonstrated that following major abdominal surgery the combination of epidural opioids and local anaesthetics results in better pain relief than a local anaesthetic alone ([redacted]). The choice of perioperative analgesia may affect the rate of recovery ([redacted]) and so a balance is needed between effective analgesia and side effects in order to maintain efficient postoperative recovery and time to fulfilment of discharge criteria ([redacted] .

The formulations of the products in the application are:

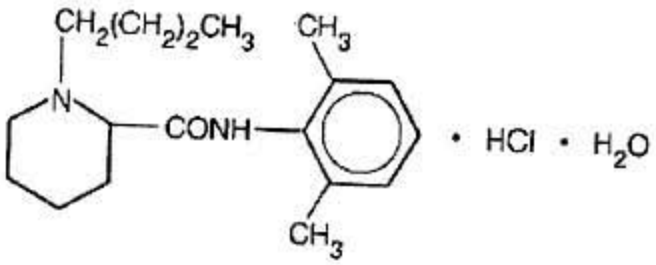
Solution for infusion	Composition per 1 ml
Bupivacaine 0.1% + Fentanyl 2µg/ml 250ml	[redacted]
Bupivacaine 0.125% + Fentanyl 2µg/ml 250ml	[redacted]

* base provided as fentanyl citrate

Bupivacaine hydrochloride is a well characterised local anaesthetic of the amide type, monohydrate ([redacted]) designed chemically as (2RS) 1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide monohydrochloride (Figure 1).

Empirical formula: $C_{18}H_{28}N_2O.HCl.H_2O$
Molecular weight: 342.9

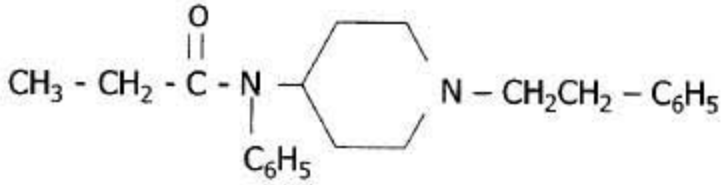
Figure 1 **Bupivacaine hydrochloride chemical structure**



Fentanyl is a highly lipophilic opioid analgesic, [redacted] designed chemically as N-(I-phenethyl-4-piperidyl)propionanilide (Figure 2).

Empirical formula: $C_{22}H_{28}N_2O$ and
Molecular weight: 336.5

Figure 2 **Fentanyl chemical Structure**



At present bupivacaine and fentanyl are individually licensed for use in the UK. According to the British National Formulary bupivacaine is licensed for use in relieving pain during labour and surgery and fentanyl for analgesia during operations, and enhancement of anaesthesia (also licensed for respiratory depression in assisted respiration and analgesia in other situations).

However, the combination of bupivacaine and fentanyl is commonly used in clinical practice, with different doses administered either as epidural bolus or epidural infusion or a combination of both [redacted]

In Switzerland, several amide class local anaesthetics have been licensed for use in the treatment of acute post-operative and labour pain. The prescribing information for these products provides information regarding their association with opioid analgesics using the epidural route (Bupivacaine [redacted], Carbostesin®, Chirocaine®, Naropin®). In France, the epidural administration of bupivacaine has been authorised for use for several decades and fentanyl since 1995.

Bupivacaine and fentanyl epidural infusion has also been authorised for use in other non-EU countries such as Australia ( ) and New Zealand ( ). In Australia the bupivacaine (1.25 mg/mL) and fentanyl (5 µg/ml) epidural infusion is indicated after surgery to treat postoperative pain and also for use during childbirth. In New Zealand the bupivacaine hydrochloride (0.125%) with fentanyl citrate (2 µg/mL) infusion solution for epidural analgesia is intended for use in post-operative analgesia.

Worldwide, various concentrations of bupivacaine plus fentanyl (generally, 0.0625-0.125% bupivacaine plus 2-5 µg/ml fentanyl) are infused epidurally after extemporaneous preparation by hospital pharmacies or units or manufactured by admixture services, using the individual products licensed over 40 years ago. In 2006, at the request of the Swiss Health Authorities an application was submitted with the rationale of providing ready to use infusions at the concentrations currently used in clinical practice, in order to avoid the need for extemporaneous preparation and the inherent risks of such practice. ( )

A postal survey of obstetric units throughout the UK conducted to obtain information about the provision of epidural analgesia for labour reported continuous infusions of low-dose bupivacaine and opioid mixtures were the most popular method of maintenance epidural analgesia ( ) In this survey 24% of units were found to offer combined spinal-epidural analgesia. The most frequently used technique was reported as an intrathecal injection of 2.5 mg bupivacaine plus 25 µg fentanyl followed by either intermittent bolus top-ups or an infusion via the epidural catheter of bupivacaine 0.1% and fentanyl 2 µg. In the UK, the mixture generally used is 0.1 % of bupivacaine with fentanyl 2 µg/ml given by epidural infusion ( )

The rationale for this current application is to provide a ready to use infusion containing bupivacaine and fentanyl at the concentrations currently used in clinical practice, in order to avoid the need for extemporaneous preparation and the inherent risks associated with this practice.

This current application is submitted to support the use of bupivacaine with fentanyl for epidural infusion used for post-operative analgesia and for maintaining epidural analgesia in labour.

The use of bupivacaine and fentanyl in combination are supported by, and are in keeping with, recommendations from both the American Society of Anesthesiologists and UK National Institute for Health and Clinical Excellence ( ):

The Task Force on Obstetrical Anesthesia in the US recommends that for uncomplicated labour and delivery, the lowest possible concentrations of local anaesthetic agents that provide adequate maternal analgesia be used, for example, bupivacaine ≤0.125%. The recommendations also include the addition of an opioid to a low concentration of epidural local anaesthetic to help improve analgesia and minimize motor block, ( )

The Task Force on Acute Pain Management recommends the use of multimodal pain management therapy, whenever possible, which consists of administration of two analgesic agents that act by different mechanisms via a single route. This is reported as providing better analgesic efficacy with equivalent or reduced adverse effects. Examples include epidural opioids administered in combination with epidural local anaesthetics, [redacted]

The NICE guidelines recommend low concentration local anaesthetic and opioid solutions (0.0625–0.1% bupivacaine or equivalent combined with 2 µg/ml fentanyl) for maintaining epidural analgesia in labour ([redacted]). Current medical practice in UK hospitals also follow these recommendation (East Kent Hospital NHS Trust and Nottingham City Hospital NHS Trust).

2.5.2. OVERVIEW OF BIOPHARMACEUTICS

In opioids, analgesia results from a regional rather than a systemic effect, although there may be some initial contribution from the latter ([redacted]). Pharmacokinetic studies have found no relationship between the quality of analgesia and plasma concentrations of opiates such as morphine, which have been well below the reported "analgesic" concentrations administered systemically [redacted]). Spinal opioids administered epidurally or intrathecally, provide analgesia that is superior to that achieved after systemic administration, with a lower incidence of side effects ([redacted]).

Local anaesthetics act through a local effect and are not reliant on plasma concentrations. To minimise risk of block beyond the required area, the recommendation is that the lowest concentration and volume of local anaesthetic should be employed whilst still maintaining the required level of analgesia ([redacted] .

Because spinal opioids and local anaesthetic agents have different modes of action, administering them in combination was proposed as a way to reduce the dose of each agent and therefore decrease the potential for toxicity associated with the individual component ([redacted] .

These are the premises on which the formulation of the analgesic combination of bupivacaine and fentanyl in solution for epidural administration are based. This pharmaceutical form can be given as epidural infusion or patient-controlled epidural analgesia (PCEA) allowing adequate analgesia with the minimal effective dose, thereby lowering the risks of adverse effects.

2.5.3. OVERVIEW OF CLINICAL PHARMACOLOGY

Pharmacokinetics

Bupivacaine

Bupivacaine half-life has been reported to be 1.5-5.5 hours in adults and 2-7 hours in neonates and children. Bupivacaine is metabolised in the liver and its metabolites are excreted in the ne. Only 5-6% of the drug is eliminated in the unchanged form [redacted]

The pharmacokinetics of bupivacaine in neonates, infants and children are somewhat different when compared with adults. Neonates and younger infants show longer half-lives, lower α_1-acid glycoprotein concentration and 20% higher free bupivacaine fraction than adults. The result is higher levels of unbound local anaesthetic and hence increased risk of toxicity ([redacted]). Although the relationship between unbound bupivacaine concentration and toxicity has not been evaluated in infants and children, this information suggests a threshold toxic dose when compared with adults. In adults the accepted toxic threshold for total plasma bupivacaine is 4 µg/ml which corresponds to a free bupivacaine concentration of 0.2 µg/ml ([redacted]). Hence measuring free bupivacaine concentrations of >0.2 µg/ml would be of concern ([redacted]).

A dual-perfused single cotyledon human placental model has been used to compare the maternal pharmacokinetic properties of ropivacaine and bupivacaine. In this model, bupivacaine was reported as diffusing into the CSF and crossing the placenta. The reported ratio of maternal to foetal concentration was relatively low with maternal-to-foetal transfer reported to be around 0.4% ([redacted]).

Small amounts of bupivacaine have also been detected in breast milk. In one study, the mean milk/serum ratio for bupivacaine based upon area under the curve values were 0.34 (SD ± 0.24) ([redacted]). In this study, 27 pregnant women admitted for caesarean delivery received epidural anaesthesia with 0.5% bupivacaine and 2% lidocaine. Blood and milk samples were simultaneously collected at 2, 6 and 12 h after the beginning of the epidural infusion. No adverse reactions related to the excretion of bupivacaine into breast milk were reported.

The pharmacokinetics of bupivacaine and ropivicaine in healthy volunteers were compared and evaluated during continuous epidural infusion of bupivacaine 2.5 mg/ml for 21 h, infusion rate 25 mg/h, ([redacted]). In subjects receiving bupivacaine, total plasma levels reached a plateau after about 5 h and remained constant for around 10 h. The mean value 5-10 h after the start of the infusion was 0.65 mg/L and at the end of infusion (21 h) the mean total plasma level was 0.90 mg/L. Mean free drug concentration 12 h and 21 h after the start of infusion was reported as 0.037 mg/L and 0.042 mg/L, respectively. No patient showed signs of toxic systemic plasma levels ([redacted]

Fentanyl

After parenteral administration, fentanyl has a rapid onset and short duration of action. It is metabolised in the liver by N-dealkylation and hydroxylation ([redacted] Metabolites and some unchanged drug are excreted mainly in the urine; they are inactive and devoid of toxic effects.

The short duration of action is probably due to rapid redistribution into the tissues rather than metabolism and excretion. An elimination half life of about 4 hours reflects slower release from tissue depots. About 80% has been reported to be bound to plasma proteins. The pharmacokinetics of fentanyl follow a three-compartment model with a distribution time of 1.7 minutes, a redistribution time of 13 minutes, and a terminal elimination half-life of 219 minutes. Administration of repeated, or large doses, or continuous infusions, may result in an accumulation. Fentanyl crosses the placenta and small amounts have been detected in breast milk ([redacted] .

In a prospective, randomised, double-blind study the placental transfer and neonatal effects of epidural sufentanil and fentanyl infused with bupivacaine for labour analgesia were studied [redacted]). In this study healthy parturient women were randomly assigned to receive one of three treatments:

Group	Regimen
B (n=13)	12 ml epidural bolus 0.125% bupivacaine followed by 10 ml/h infusion 0.125% bupivacaine
B-F (n=14)	12 ml epidural bolus 0.125% bupivacaine with 75 µg fentanyl followed by 10 ml/h infusion 0.125% bupivacaine with 1.5 µg/ml fentanyl
B-S (n=9)	12 ml epidural bolus 0.125% bupivacaine with 15 µg/ml sufentanyl followed by a 10 ml/h infusion 0.125% bupivacaine with sufentanyl 0.25 µg/ml

Groups were similar with respect to the duration of labour and the mode of delivery. Maternal venous (MV), umbilical arterial (UA) and umbilical venous (UV) bupivacaine, sufentanyl and fentanyl concentrations were determined [redacted] . The study found significant placental transfer of sufentanyl and fentanyl after epidural administration during labour and the authors report sufentanyl transfer appeared greater than that of fentanyl. The UV/MV ratio for sufentanyl was larger than that of fentanyl (0.81 vs. 0.37; P = 0.003). Neonatal conditions were assessed using Apgar score, and neurobehavioural testing (assessed by the Neurologic and Adaptive Capacity Score [NACS]) at delivery, 2 hours and 24 hours of life. Neonatal conditions were good and generally similar in all groups. While total NACS were similar among the groups at 15 min and 2 h after delivery, at 24 h, NACS in the B-F group (34.7±0.8) were significantly lower than in groups B (36.8±0.5) and B-S (37.1±0.4); P=0.02 (B-F versus B and B-S). When NACS component scores were compared, there were no statistically significant differences among the groups ([redacted]

[redacted] . None of the newborns had clinically significant depression. The authors concluded that although the numbers in the study were small, the anaesthetic techniques provided adequate analgesia for labour and delivery with no severe side effects in any of the groups.

In the clinical setting, labour analgesia using epidural infusions of low-dose bupivacaine and fentanyl may be maintained for many hours. Hence, the potential of bupivacaine and fentanyl accumulation, when a low-dose infusion is continued over a long period, has been investigated. [redacted] measured maternal and umbilical drug levels at delivery and correlated these measurements with length of infusion time. Women (n=21) received a 10 mL/h continuous infusion with 0.125% bupivacaine and 2 µg/mL fentanyl. Infusion times ranged from 70 min - around 15 h with total dose of epidural drug received varying from about 27 mg bupivacaine and 22 µg fentanyl (shortest infusion time) to 200 mg bupivacaine and 300 µg fentanyl (longest infusion time). All patients in the study had satisfactory analgesia for labour and did not require additional anaesthesia for delivery. Apgar scores were recorded and Scanlon Neonatal Neurobehavioural testing was performed on all neonates during the first hour of life.

Maternal (MV) and neonatal (UV) drug concentrations remained relatively constant throughout the infusion period (Table 1) and infant neurobehavioural scores were within the normal limits. With increasing infusion times, no statistically significant increases in UV or MV, fentanyl or bupivacaine, concentrations were detected. Similarly, the UV/MV ratios for both drugs did not change significantly over the infusion times studied. All Apgar scores at 1 and 5 min were ≥8. Hence in this study, continuous infusion for labour analgesia did not appear to result in significant foetal drug accumulation. No adverse neonatal effects were seen and none of the neonates showed evidence of respiratory depression ([redacted]).

Table 1 Maternal and neonatal drug concentrations

	MV concentration (mean ± SD)	UV concentration (mean ± SD)	UV/MV ratio
Bupivacaine (µg/ml)	0.50 ±0.16	0.15 ±0.06	0.30
Fentanyl (ng/ml)	0.17±0.10	0.16±0.09	0.94

MV = maternal vein; UV = umbilical vein

The pharmacokinetics and transplacental distribution of fentanyl in epidural anaesthesia have been studied in normal pregnant women who delivered by caesarian section ([redacted]). Ten normal parturients were treated with 5 ml of 2% lidocaine hydrochloride followed by epidural injection of 2 ml fentanyl citrate (0.05 mg/ml) and 15 ml of 0.5% bupivacaine hydrochloride (with 1:200,000 epinephrine, and 10 ml 2% lidocaine hydrochloride without a vasoconstrictor). Maternal blood plasma for fentanyl determination was collected at various times after injection (1-840 min) and pharmacokinetics parameters of fentanyl measured (Table 2). Pharmacokinetic parameters of clearance and volume of distribution corrected for body weight were reported as 6.9 ml/min/kg and 4.4 L/kg, respectively.

Table 2 Pharmacokinetic parameters of fentanyl in parturients

Parameter*	Parturients (n=10) Median (P25-P75**)
$t_{½}\alpha$ (min)	13.5 (9.0-24.5)
α (min^{-1})	0.05 (0.03–0.08)
$t_{½}\beta$ (min)	192.5 (119.3-242.5)
β (min^{-1})	0.004 (0.003–0.006)
$t_{½}\gamma$ (min)	620 (526.3-752.5)
γ (min^{-1})	0.001 (0.001–0.001)
$AUC^{0-\infty}$ (ng.min/ml)	137.4 (99.0–150.8)
C_1/f (ml/min)	465.0 (422.0–657.6)
$C_1/f/kg$ (ml/min/kg)	6.9 (6.3–8.9)
V_d/f (L)	300.0 (149.8–400.2)
V_d/f/kg (L/kg)	4.4 (2.4–5.6)

*t½α=Distribution half-life; α=distribution rate constant; $t_{½}\beta$= elimination half-life; β=elimination rate constant; $t_{½}\gamma$=terminal half-life; γ= terminal rate constant; $AUC^{0-\infty}$ = area under the curve for plasma concentration versus time; C_1/f= apparent clearance; V_d/f= apparent distribution volume
**P25, 25th percentile; P75, 75th percentile

The latency between drug administration and birth was 28.5 min. At delivery, maternal and foetal plasma concentrations were 0.310 and 0.245 ng/ml (median foetal/maternal ratio: 0.892) indicating a rapid passage of fentanyl from epidural space to maternal blood and transfer of maternal fentanyl of about 90%. No postnatal respiratory depression occurred.

Pharmacodynamics

A pain model was used to evaluate analgesia, side effects and pharmacokinetics of epidural fentanyl in a double-blind crossover study in 12 healthy volunteers (aged 22-28 years) receiving study drug at low and high doses (fentanyl, 30 and 100 µg, alfentanil, 300 and 1,000 µg, and sufentanil, 3 and 10 µg). Study drug doses were half log increments, chosen based on intravenous dose equivalents for analgesia, and administered in a 6 ml volume over 3-5 minutes. Ventilatory drive, pupil size, and subjective ratings of alertness, nausea, and pruritus were measured using visual analog scales ([redacted]).

The pain model was cutaneous electrical stimulation of sufficient intensity to produce a pain report of 5 on a 0 (faint sensation) - 5 (strong pain) scale and delivered alternatively to the finger and toe. After baseline measurements, an epidural catheter was placed at the L2-3 or L3-4 interspace. Subjects received the lower dose of study drug and analgesia was tested at 2, 55, and 95 minutes after treatment, and repeated with the higher dose 2 h later. Onset of analgesia with the low dose occurred within 15 minutes (mean peak achieved after about 60 minutes), and with the high dose within 10 minutes (mean peak 15 minutes). ([redacted])

For the drugs tested, including epidural fentanyl, reduction in reported pain was greater for the lower versus upper extremity, suggesting a selective spinal action ([redacted]). Additionally, the degree of analgesia was dose-dependent with the effect lasting about 2 hours for both doses. When using the lower dose of each drug, plasma drug concentrations were below the minimum effective plasma concentrations (MEACs). After 30µg fentanyl, mean peak plasma concentration was 0.19±0.08 ng/ml (reported MEAC for systemic fentanyl 0.6 ng/ml, Gourlay et al, 1989) and time to peak was 10 - 30 minutes. Plasma levels decreased to 0.11±0.08 ng/ml by 2 h after administration ([redacted]). Following administration of the higher dose, plasma opioid concentrations were near MEACs (for fentanyl, mean peak plasma concentration 0.36±0.05 ng/ml was reached in 15 minutes). Although numbers were small, the incidence of side effects was reported as low. Five subjects reported pruritus with 100 µg fentanyl. The 2 subjects reporting nausea following 100 µg fentanyl, also reported nausea following 1000 µg alfentanil ([redacted]).

The minimum local analgesic concentration (MLAC) has been defined as the effective concentration in 50% of subjects (EC50) and the MLAC for bupivacaine is reported as 0.065% (95% confidence interval [CI] 0.045-0.085), equivalent to a 2 mmol solution ([redacted]). In a double-blinded, sequential allocation trial, the ability of epidural fentanyl to reduce the requirement for epidural bupivacaine was assessed in women (n=223) in labour. In this trial the bupivacaine sparing effect was assessed by the addition of four different doses of extradural fentanyl and measuring bupivacaine MLAC ([redacted] .

The analgesic effect was measured by a visual analogue pain score (100 mm VAPS). Women were assigned one of five treatments with doses of fentanyl constant for each group (n=40 subjects/group):

Group 1: Bupivacaine (control) starting concentration 0.1%

Group 2: Bupivacaine with fentanyl 1 µg/ml, starting concentration 0.07%

Group 3: Bupivacaine with fentanyl 2 µg/ml, starting concentration 0.06%

Group 4: Bupivacaine with fentanyl 3 µg/ml, starting concentration 0.05%

Group 5: Bupivacaine with fentanyl 4 µg/ml, starting concentration 0.04%

Drugs, dissolved in 20 ml were given over 5 minutes in the epidural space at L2-3 or L3-4. Efficacy of the first dose was assessed (at 0, 15 and 30 minutes after injection of test solution) using a 100 mm visual analogue pain scale (VAPS), where 0 represented "no pain" and 100 "the worst pain ever." Three outcomes were possible:

Effective	VAPS decreased to ≤10mm at height of contraction within 15-60 minutes. Indicated end of study and a decrease of 0.01% w/v bupivacaine for the next woman
Ineffective	Failure of VAPS to reach 10 mm within 30 minutes of test solution. At 30 min rescue analgesia offered and if VAPS ≤10 mm study ended and an increase of 0.01% w/v bupivacaine for the next woman
Repeat	Failure to reach VAPS of 10mm and pain outside T10-L1 distribution, or when rescue medication failed. Same concentration repeated for next

woman

The addition of fentanyl produced a dose-dependent reduction in the requirements for bupivacaine (Table 3). Significant reductions were reported with fentanyl 2, 3 and 4 µg/ml, with the highest dose most effective.

Table 3 MILAC of bupivacaine and fentanyl concentrations, compared with MLAC control

	MLAC (w/v)	P (95% CI)	P* (95% CI)
Bupivacaine	0.069%		
fentanyl 1 µg/ml	0.057%	0.14 (-0.003 to 0.027)	0.52 (-0.008 to 0.032)
fentanyl 2 µg/ml	0.048%	0.008 (0.006 to 0.036)	0.03 (0.0013 to 0.041)
fentanyl 3 µg/ml	0.031%	<0.0001 (0.022 to 0.054)	<0.0001 (0.018 to 0.058)
fentanyl 4 µg/ml	0.015%	<0.0001 (0.039 to 0.069)	<0.0001 (0.035 to 0.073)

MLAC = minimum local analgesic concentration; P= P value (95% CI) using modified t test versus MILAC control; P*= P value (95% CI) with Bonferroni correction

However, compared with the bupivacaine control group, the incidence of pruritus was significantly higher with fentanyl 4 µg/ml (P=0.0015). Hence the authors recommend a concentration lower than 4 µg/ml be used in a bupivacaine sparing regimen ([redacted]).

A prospective, randomised, double-blind study was conducted to determine whether, in the presence of local anaesthetics, epidural fentanyl elicited analgesia by a predominantly spinal mechanism ([redacted] Epidural and IV continuous infusions of fentanyl were compared for their local anaesthetic sparing effects during the maintenance of epidural analgesia in the first stage of nulliparous labour.

Women (n=40, and in active labour) receiving lumbar epidural analgesia with 20-30 ml bupivacaine 0.125% until pain free, were then randomised (20 patients/group) to either IV or epidural fentanyl infusion groups (delivering fentanyl 30 µg/h). All received an epidural infusion of bupivacaine (20 ml/h), with the concentration determined by the response of the previous woman in the same group to the analgesic regimen used.

Epidural catheters were placed at the L2-3 or L3-4 interspace and incremental doses 0.125% bupivacaine administered to a minimum volume of 20 mL. The initial epidural bupivacaine concentration was 0.07% for the first patient in both groups.

Analgesia was measured using a 100 mm VAPS and adequate analgesia considered to be achieved if the VAPS reduced to ≤10 mm. Three outcomes were possible:

Effective — No supplemental analgesia requested until ≥8 cm cervical dilation or supplemental analgesia requested: vaginal examination immediately after administration was ≥8 cm. Consequence: next patient in group had a 0.01% w/v reduction in the bupivacaine concentration for the epidural infusion.

Failure — Supplemental analgesia requested (and where doses of up to 12 mL of 0.25% bupivacaine provided adequate analgesia), vaginal examination

	performed immediately after its administration was <8 cm. Consequence: the next patient in group had a 0.01% w/v increase in the bupivacaine concentration for the epidural infusion.
Reject	As for "failure" but where doses up to 12 mL of 0.25% bupivacaine failed to relieve labour pain within 15 min, or need for supplemental analgesia within 2 h from the start of the study infusion, or progression to full cervical dilation within 2 h from the start of the study infusion, or the progression to caesarean delivery before 8 cm cervical dilation without any prior request for supplemental analgesia.

$MLAC_{infusion}$ for the maintenance of analgesia throughout the first stage of labour was determined. The $MLAC_{infusion}$ of epidural bupivacaine was 0.063% (95%CI, 0.058–0.068) and 0.019% (95%CI, 0.000–0.038) in the fentanyl IV and epidural groups respectively. The relative potency ratio for the epidural:IV route of administration was 3.3 (95% CI, 1.7–10.7) and was highly significant (P=0.0017; 95% CI difference, 0.021– 0.068). Since continuous infusion of fentanyl was more than three times as potent when administered by the epidural route than by the IV route, the results of this study suggest a predominantly spinal mechanism of action for infused epidural fentanyl in the presence of local anaesthetics. Although pruritus, affected 11/16 patients in the epidural group and 1/15 patients in the IV group (P<0.005) no patient in either group required treatment for pruritus and there was no difference in maternal satisfaction between groups reported.

Patient Controlled Epidural Analgesia (PCEA) during labour offers several advantages including flexibility of dosing, benefits of self-administration, reduced demand on professional time and high patient satisfaction. As the optimal drug dose and PCEA pump setting were not defined, three modes of pump settings were compared in a randomised double-blind study, in order to determine the optimal combination of bolus dose and lockout interval ([redacted]). The epidural solution used during the study was bupivacaine 0.1 % with fentanyl 2 µg/ml. Epidural catheters were placed at the L2-3 or L3-4 interspace.

Parturient women were assigned to one of three groups (n=20 per group) and were able to self-administer a demand dose with a lock out interval: group A, 3 ml, lockout interval 6 minutes; group B, 6 ml, lockout interval 12 minutes; group C, 9 ml, lockout interval 18 minutes.

All patients received a background drug infusion at a rate of 6 ml/h. Visual analogue pain scores (measured on a 10 cm scale), pinprick analgesia and motor block ([redacted]) were assessed hourly by a blinded observer. The physician-administered supplementation and the cumulative dose of analgesic were also compared. The three modes of PCEA provided similar pain relief with no statistical difference between treatments noted. Patient's satisfaction was rated good to excellent with no difference between groups detected. A trend for decreased rescue analgesia in the group with a larger bolus dose and a longer lockout interval was reported (group C versus Group A, P=0.1). Motor block was minimal in all the patients. The duration of both stages of labour did not differ between groups.

The use of the combination of bupivacaine with fentanyl through the epidural route in labour was further endorsed by [redacted]) who compared a continuous epidural drip to the PCEA route. Having randomised 43 patients both methods achieved effective analgesia, similarly low adverse events and comparable maternal satisfaction.

2.5.4. OVERVIEW OF EFFICACY

The clinical application and efficacy of epidural bupivacaine in combination with fentanyl has been extensively reported in the literature. This overview examines and summarises important information taken from published studies, and covers the efficacy of bupivacaine in combination with fentanyl when used in obstetric, surgery, and paediatric indications (summarised below).

Specific efficacy studies on special populations have not been reported in the literature; however where patients over 65 years were enrolled in the trials no critical issues were noted.

Overview of Efficacy Studies			
Study Reference	**Comparators**	**Endpoints**	**Main Outcome**
Obstetrics			
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Maternal satisfaction and perception of epidural analgesia. Side effects.	Satisfaction higher, more normal deliveries, greater self control, reduced unpleasantness of motor and sensory blockade and shivering in fentanyl/bupivacaine
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Motor power. Time to first painless contraction. Progress of labour. Instrumental delivery rate	Reduction in the length of the second stage (P=0.0003; 95% CI: -1.17, -0.27 h) and instrumental delivery rate (P=0.032) in fentanyl/bupivacaine
[redacted]	• fentanyl/bupivacaine • sufentanyl/ bupivacaine	Analgesia. Motor block. Adverse events.	No difference between treatments. In the sufentanyl group, motor blockade (P=0.03) and pruritus (P=0.02),were significantly lower
[redacted]	• fentanyl/bupivacaine • ropivacaine	Quality of epidural analgesia. Delivery mode. Patient assessment of motor blockade	More ropivacaine patients pain-free throughout first stage of labour (51% versus 33.7% , P=0.01). No difference in 2nd stage. Higher percentage patients in bupivacaine group had minimal motor block (51% versus 42%, NS).
[redacted]	• fentanyl/ bupivacaine • morphine/bupivacaine • bupivacaine alone	Duration of pain relief	Pain relief duration in fentanyl/bupivacaine greater than placebo group: (132.5 versus 97.2 minutes, P<0.05). Level of pain relief in morphine and placebo groups were similar.

Study Reference	Comparators	Endpoints	Main Outcome
[redacted]	• fentanyl/bupivacaine • bupivacaine alone • fentanyl alone	Analgesia at rest and on coughing. Sensory and motor blocks	Adding fentanyl to bupivacaine reduced bupivacaine dose by up to 68%. The combination improved analgesia at rest and decreased PCEA use. Motor and sensory block were decreased
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Analgesic efficacy: pain and motor block assessed	Two regimens produced similar analgesic effect, less motor block in the bupivacaine/fentanyl group considered a tangible benefit.
[redacted]	• fentanyl/bupivacaine • fentanyl alone	Pain relief recorded every hour	No difference in number of instrumental deliveries, or duration of second stage. Fentanyl/bupivacaine group demonstrated lower need for rescue epidural analgesia.
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Analgesia, the level of sensory block and the degree of motor block	No differences in: the duration of first and second stage of labour; time from loading dose to delivery; sensory and motor block. In fentanyl/bupivacaine patients pain relief more consistent and sustained longer.
[redacted]	Fentanyl/bupivacaine administered as either combined spinal-epidural analgesia (CSE) or epidural infusion (EPI)	Midwife assessed analgesic efficacy; delivery mode, patient assessed first, second stage and overall analgesia; motor block; complications	No difference between groups for quality of analgesia and motor block. Overall analgesia judged excellent: 61.6% and 56.4% (P=0.02), CSE and EPI group respectively. Overall analgesia 'excellent' in 74.8% of CSE compared with 71.7% EPI (P=0.14).

Study Reference	Comparators	Endpoints	Main Outcome
[redacted]	Comparison of three methods of continuing analgesia in labour: midwife top-ups (MW), PCEA and CI • fentanyl/bupivacaine	Mother assessed pain hourly; midwife evaluated motor power; overall experience	Significant dose-sparing effect of fentanyl/bupivacaine in group MW compared with groups CI and PCEA reported. Analgesia, and overall satisfaction similar between the three groups
[redacted]	• bupivacaine boluses • fentanyl/bupivacaine combined spinal–epidural analgesia (CSE) • fentanyl/bupivacaine low dose infusion	Assessment of pain	Mean usage of bupivacaine/woman, significantly lower in the CSE group (first stage, P<0.001; second stage, P<0.01). CSE associated with a more rapid onset of analgesia.
[redacted]	During second stage • fentanyl/bupivacaine • placebo	Analgesic efficacy and influence on instrumental delivery	Fentanyl/bupivacaine provided better analgesia, particularly for second stage labour ≥60 minutes; did not significantly increase incidence of instrumental delivery
[redacted]	At first request for analgesia received either intrathecal fentanyl or systemic hydromorphone, then • fentanyl/bupivacaine • bupivacaine (both PCEA)	Time to analgesis, rate of caesarean or instrumental delivery	No significant difference in rate of caesarean section, or instrumental delivery. Median time from initiation of analgesia to complete dilatation and time to vaginal delivery significantly shorter after intrathecal analgesia. Pain scores after the first intervention were significantly lower after intrathecal analgesia.

Study Reference	Comparators	Endpoints	Main Outcome
Surgery			
[redacted]	Three concentrations of epidural fentanyl with 0.1% bupivacaine in patients undergoing thoracotomy for lung resection	Pain on coughing assessed	Epidural fentanyl 5 µg/ml with bupivacaine 0.1% appeared to provide a good balance between pain relief and adverse effects
[redacted]	In patients undergoing thoracic surgery through a posterolateral thoracotomy • bupivacaine + morphine • fentanyl/bupivacaine	Quality of analgesia and effects on pulmonary function	No significant difference observed between groups in relation to respiratory parameters (P=0.27) or side effects
[redacted]	Patient (scheduled to have elective major abdominal surgery) supplemented epidural analgesia (PSEA) with either • ropivacaine/fentanyl or • bupivacaine/fentanyl mixtures	Analgesic efficacy and occurrence of motor block and other side effects	No differences in the degree of pain relief but median number of incremental doses given and final solution were higher in patients treated with bupivacaine combination. Incidence of motor blockade similar.
[redacted]	Analgesic effect of PCEA fentanyl or morphine in combination with a low dose of bupivacaine in patients undergoing abdomino-perineal resection	Analgesia and weakness	Both methods effective in preventing pain, because of fewer side effects, fentanyl may be preferable to morphine
[redacted]	Anaesthesia for out patient ano-rectal surgery • Bupivacaine and Fentanyl (spinal) • Bupivacaine alone (spinal)	Anaesthesia efficacy Time to recovery Time to discharge analgesia	Both equally effective Better recovery and discharge times for Bupivacaine and Fentanyl
[redacted]	Post thoracotomy pain relief • PCEA bupivacaine and fentanyl • IVPCA morphine	Analgesia failure	Better analgesia post operatively for PCEA group

Study Reference	Comparators	Endpoints	Main Outcome
Paediatrics			
[redacted]	Children received either intermittent morphine administered every 8 hours, or a continuous infusion of bupivacaine/fentanyl	Postoperative pain evaluation	Both regimens provided effective analgesia, however fentanyl/bupivacaine was superior to intermittent morphine for pain relief
[redacted]	Compared two different concentrations of morphine in a fixed dose of bupivacaine in children undergoing selective dorsal rhizotomy	Pain evaluation	Higher dose of continuous intrathecal morphine combined with bupivacaine, significantly reduced the pain score and postoperative intravenous analgesic requirements without increasing adverse effects
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Quality of postoperative analgesia. Time to clinical recovery of infants after thoracotomy	Infants in fentanyl/bupivacaine experienced significantly less pain. Time to first analgesic rescue was significantly longer in fentanyl/bupivacaine

NS=not significant; PCEA= patient controlled epidural analgesia; CI=continuous infusion

Obstetrics

The analgesic effect of the combination of bupivacaine and fentanyl in comparison with an opioid or anaesthetic alone during labour, or after caesarian section, has been evaluated in many clinical trials. In these studies drugs were administered epidurally as bolus or as patient controlled epidural analgesia (PCEA) or as continuous epidural infusion.

A prospective, randomised pilot study has been reported comparing a combination of epidural fentanyl and bupivacaine with bupivacaine alone for epidural analgesia in labour ([redacted]). Factors, other than analgesia, that influenced maternal satisfaction were also evaluated. Initially 4 ml of 0.25% bupivacaine was administered epidurally, and topped up, as needed, with the same dose at 5 minute intervals.

Mothers were allocated to either:

Group 1 (n=42): topped up with 5 ml 0.25% bupivacaine, repeated after 5 minutes if necessary and topped up at hourly intervals *or*

Group 2 (n=43): received either 4ml 0.25% bupivacaine for pain restricted to the abdomen or 10 ml 0.1% bupivacaine containing 50µg fentanyl if they had perineal pain. A maximum amount of fentanyl was allowed 200µg in first 6 h plus and extra 50µg for each subsequent 2 h.

Maternal satisfaction, maternal perception of epidural analgesia and its side effects, and aspects of mothers' psychological states during labour, were quantified using separate 0-100 mm VAS (0 was lowest score and 100 the highest). The frequency of normal and operative deliveries; and measurements of neonatal wellbeing were also monitored.

Satisfaction was reported as higher in group 2 mothers (Table 4). They also had more normal deliveries; greater self control and reduced unpleasantness of motor blockade, sensory blockade, and shivering. Mild itching was worse in this group ([redacted] . Group 1 mothers found restricted movements more unpleasant and were more sedated. The addition of fentanyl to bupivacaine reduced the requirement for local anaesthetic (median difference -33 mg, 95% CI: -55 to -15, $p<0.001$) without compromising analgesia. No adverse effects were considered related to fentanyl in the neonates of mothers who were treated with this drug. Two neonates (one in each group) were treated with naloxone after ventilatory depression was diagnosed.

Overall, the authors concluded that a combination of epidural fentanyl and bupivacaine can improve maternal satisfaction.

Table 4 Maternal satisfaction with analgesia

VAS Measure* (mm)	Group 1 n=42	Group 2 n=43	P value;	Median difference (95% CI)
Overall satisfaction	85-96	92-99	0.012	3 (1 to 5)
Self control	6-47	3-25	0.003	-7 (-17 to -2)
Weakness in legs	5-46	0-9	<0.001	-10 (-19 to -5)
Numbness	3-46	0-14	0.002	-5 (-11 to -2)
Shivering	0-56	0-29	0.046	-5 (-18 to 0)
Itching	0-0	0-5	<0.001	-
Restricted movements	0-41	0-5	0.006	-1 (-11 to 0)
Sedation after epidural	5-75	1-47	0.032	-4 (-20 to 0)

*0 is the lowest score and 100 the highest

A double-blind, randomised, controlled study compared two epidural drug regimens during labour ([redacted]). Group A patients (n=35) received 15 ml of 0.1 % bupivacaine with fentanyl 50 µg and analgesia maintained, on request, with 10 ml bolus doses of 0.1% bupivacaine with fentanyl 2 µg/m1. Group B patients (n=38)

received 15 ml of 0.25% bupivacaine and analgesia was maintained, on request, with 10ml bolus doses of 0.25% bupivacaine. An epidural catheter was sited at the second lumbar interspace. Analgesia was measured with VAS (0-100 mm) and a verbal scoring system (0=no pain, 3 =a distressing pain or pressure) at several time intervals until delivery.

Motor power was assessed using a modified Bromage score 30 minutes after each bolus administration and on request to get out of bed ([redacted]). All patients reported pain free contractions by 30 minutes. Time to first painless contraction were similar and the total VAPS as well. Women in group A retained motor power in their legs and 60% (versus 5%) chose to get out of bed.

For those in group A, there appeared to be beneficial effects on the progress of labour, with a clinically important reduction in the length of the second stage (P = 0.0003; 95% CI: -1.17, -0.27 h) and instrumental delivery rate (P = 0.032). Maternal satisfaction with epidural analgesia, as assessed by VAS, was also higher in group A (P = 0.04; 95% CI -0.001, 10.001). In this study the combination of bupivacaine and fentanyl produced similar analgesia but less motor blockade than bupivacaine alone ([redacted]).

In a prospective, double blind clinical trial, patients were randomly assigned to receive 0.125% bupivacaine with either fentanyl 2µg/ml (n=105) or sufentanyl 0.25 µg/ml (n=101) using patient controlled epidural analgesia (PCEA) (Le Guen 2001). After epidural catheterisation, 10 ml of 0.25% bupivacaine was injected to achieve a sufficient level of analgesia. The continuous infusion pump was set to deliver 4 ml with a lockout interval period of 10 minutes. In case of inadequate analgesia, supplementary injection of 0.25% bupivacaine (5 ml) was provided. Analgesia was assessed by a visual analog scale (100 mm YAPS) before epidural administration, 1 and 3 hours after, at full cervical dilatation and at delivery. Motor block was assessed by the Bromage scale at delivery. Overall analgesia was good and no difference observed between the sufentanyl-bupivacaine and the fentanyl-bupivacaine groups. The number of boluses and of supplementary injections were similar between groups. In the sufentanyl group, motor blockade (P=0.03) and pruritus (P=0.02),were significantly lower than in the fentanyl group. Nausea was not recorded in any patients.

A randomised, double-blind trial compared bupivacaine 0.1% with fentanyl 2 µg/ml (n=101) to ropivacaine 0.2% (n=102) for quality of epidural analgesia, mode of delivery, and patient assessment of motor blockade ([redacted]). Drugs were infused at a rate of 8 ml/h and additional bolus injections of 10 ml were given as required. Patient VAS for first and second stage pain, motor blockade and overall satisfaction with the epidural were obtained 24 h after delivery.

After 30 minutes from the start of treatment, the number of patients pain free was the same for both treatments; significantly more ropivacaine patients remained pain-free throughout the first stage of labour (51% versus 33.7% , P=0.01). Patients receiving ropivacaine received fewer routine top-ups (median 1 versus 2, P=0.001) and fewer escape top-ups (9.8% versus 21.8%, P=0.02). No difference in pain scores between the treatment groups were seen in the second stage of labour. Although not

statistically significant, a higher percentage of patients in the bupivacaine group had a minimal motor block compared with the ropivacaine group (52% versus 43%). Pain relief and satisfaction scores from patients and midwives were not statistically different between the groups (.

A prospective, randomised double-blind clinical trial, has evaluated the efficacy of fentanyl 80 µg (fentanyl group, n= 81), 4 mg morphine (morphine group, n=83); or placebo (placebo group, n= 85) added to 0.25% bupivacaine for control of labour pain ( ). An extradural catheter was inserted at L2-3 or L3-4 space and drugs (8 ml) injected as bolus. Analgesia was considered successful and adequate when contractions were painless. The mean duration of pain relief induced in the fentanyl group was significantly greater than in placebo group: (132.5 versus 97.2 minutes, $P<0.05$). In comparison, the level of pain relief in the morphine group was similar to placebo. The rate of inadequate pain relief for residual pain was similar for fentanyl and placebo (4.7 and 4.9%, respectively), but was significantly higher in the morphine group (14.4%, $P<0.05$). Considering, persisting painful contraction and lateralised analgesia, the fentanyl group (6.2% and 0%, respectively) had the lowest incidence of inadequate pain relief (placebo: 13% and 4.7%, morphine: 27.7% and 4.8%, respectively, $P<0.05$). In this trial fentanyl, and not morphine, was shown to improve the quality of analgesia induced by bupivacaine ( ).

The pain relief, provided by epidural bupivacaine and epidural fentanyl administered either alone or in combination after caesarean section was evaluated in a randomised, double blind study ( ). Women received either 0.1 % bupivacaine, or fentanyl 4 µg/ml, or 0.05% of bupivacaine with fentanyl 2 µg/ml by PCEA (20/group). An extradural catheter was inserted at L2-3 or an adjacent space. The pump was programmed to allow a 5 ml bolus with a 10 minutes lockout interval. The study lasted 24 h from the end of the operation. Analgesia was recorded with a VAS for pain (100 mm) at rest and on coughing. Sensory and motor blocks were also examined.

Adding fentanyl to bupivacaine reduced the dose of bupivacaine by up to 68%. For patients who completed the study, overall reductions in doses were 62% and 53% for bupivacaine and fentanyl respectively. The combination improved analgesia at rest (but not on coughing) and decreased PCEA use. Motor and sensory block were also decreased (Table 5).

Adding bupivacaine to fentanyl reduced the dose of fentanyl by up to 57% without altering pain scores or PCEA use, however the incidence of pruritus was unchanged (89%) and sensory block was increased (Table 5). The overall incidence of nausea and vomiting was low and no difference between groups observed.

Table 5 Incidence of sensory/motor block

	Bupivacaine	Fentanyl	Bupivacaine/fentanyl
Assessed study end	n=11	n=18	n=19
Sensory block (%)	90	11	74*†
Motor block (%)	73	0***	16**
Inability to walk (%)	82	24**	53

* P<0.05, **P<0.01, ***P<0.001 when compared with bupivacaine, †P<0.001 compared with fentanyl

In a randomised, double-blind study, the analgesic efficacy of continuous epidural infusion during labour, of 0.0625% bupivacaine with 0.0002% fentanyl (n=41 subjects) was compared with the infusion of 0.125% bupivacaine alone (n=39 subjects) ([redacted]). When the cervix was at 3-7 mm dilatation, a catheter was inserted into the epidural space via the L3-4 interspace; patients received a test dose (3 ml of 0.5% bupivacaine with epinephrine) and 5 minutes later 6 ml of 0.125% bupivacaine/0.0008% fentanyl or 0.25% bupivacaine alone. Five minutes later, a continuous infusion (12.5 ml/h) of 0.0625% bupivacaine/0.0002% fentanyl or 0.125% bupivacaine alone was started. Infusion was discontinued when the cervix was noted as fully dilated. Pain was scored on a 100 mm VAS at different times during the infusion and motor block assessed according to Bromage.

During the first stage of labour 88% of bupivacaine/fentanyl subjects and 95% of bupivacaine subjects had analgesia of excellent or good quality (Chestnut et al, 1988). Patients were asked to rate (excellent, good, fair, poor and very poor) the quality of analgesia during the first and second stages of labour. During the second stage 59% of the combination group (versus 66%) rated their analgesia as excellent or good. Partial or almost complete motor block was present in 60% of the subjects of the bupivacaine group, compared with 5% of the bupivacaine-fentanyl group. Duration of second stage, and of pushing and method of delivery were similar in the two groups. Although the two regimens produced a similar analgesic effect, less motor block in the bupivacaine/fentanyl group was considered a tangible benefit. Women in the bupivacaine/fentanyl were more likely to experience mild pruritus (22% versus 5%, P<0.05).

A double-blind randomised, controlled trial compared the efficacy of epidural infusion of fentanyl alone (1.6 µg/ml) with bupivacaine (0.125%) plus fentanyl (1.6 µg/ml) in the second stage of labour ([redacted]). An epidural catheter was inserted via the L2-3 or L3-4 interspace. After epidural analgesia with a continuous bupivacaine/fentanyl mixture (0.125%/1.6 µg/ml, 10 ml/h) in the first stage, women (40 subjects/group), at full dilatation, were assigned to receive either a continuation of the same solution or a change to fentanyl-only solution (1.6 µg/ml given at the same rate). Additional analgesia was provided during the second stage if requested. Pain relief on a VAS (0-4, where 0 =pain free and 4=painful contraction) was recorded every hour.

There was no difference in the number of instrumental deliveries (30% versus 27.5%) or the duration of the second stage (141 versus 147 minutes) between the bupivacaine/fentanyl and fentanyl groups, respectively [redacted] . The bupivacaine/fentanyl group demonstrated a lower need for rescue epidural analgesia (1 versus 6, RR 0.2, 95% CI 0.02–1.3) and significantly fewer high pain scores at delivery (11 versus 20, RR 0.6, 95% CI 0.3–1.0)

A randomised, double-blind study was conducted to investigate the analgesic effect of epidural bupivacaine in comparison with bupivacaine and fentanyl during labour ([redacted] . An extradural catheter was inserted at the first lumbar interspace. One group of parturients (n=20) received a loading dose of 0.5% of bupivacaine (6 ml) with fentanyl 100 µg (2 ml), then an extradural infusion of 0.08% bupivacaine 15 ml/h with fentanyl 37.5 µg/h. The other group (n=19) received a loading dose of 0.5% of bupivacaine (6 ml) with saline (2 ml), then 0.08% bupivacaine 15 ml/h alone. The extradural infusion was continued until delivery. Analgesia, the level of sensory block and the degree of motor block (evaluated using the Bromage scale) were assessed at 30 min following the loading dose. The analgesic level was defined as the upper dermatomal level with diminished sensation to pinprick. Additional bolus (bupivacaine 0.25% 10 ml) was given when requested and the analgesic level and motor block were evaluated immediately before, and 30 minutes after the administration.

There were no differences between the two groups in the duration of first and second stage of labour and the time from the loading dose to delivery; sensory and motor block did not differ. However, pain relief was more consistent and sustained longer in patients treated with fentanyl in addition to bupivacaine compared with bupivacaine alone (303 minutes versus 150 minutes, P<0.001). Significantly less bupivacaine plus fentanyl was used (mean dose 21.32 mg/h versus 25.93 mg/h). The only significant side effect was a high incidence of mild pruritus in the fentanyl group. The addition of fentanyl to the extradural loading dose and subsequent infusion of local anaesthetic was considered by the authors to be a satisfactory alternative to giving higher doses of local anaesthetic alone ([redacted]).

Combined spinal-epidural analgesia (CSE) has been proposed as alternative to epidural infusion (EPI) in the initial phase of analgesia and uses a low-dose combination of bupivacaine and fentanyl. A randomised study was conducted to compare the efficacy of the two techniques ([redacted] . In the EPI group (n=484) 20 ml of 0.1% bupivacaine with fentanyl 2 µg/ml were given epidurally for initial analgesia, followed by an infusion (12 ml/h) with the same mixture. In the CSE group (n=524) initial analgesia was induced with a spinal injection of plain bupivacaine 2.5 mg with fentanyl 25 µg (total volume 1.5 ml), followed by the same infusion as the EPI group.

Treatment groups were compared for midwife assessment of analgesic efficacy, delivery mode, patient assessments of first stage analgesia, second stage analgesia, overall analgesia, motor block and complications. Midwives were not blinded to the treatment and assessment of pain relief was performed by a questionnaire on the day after delivery. Motor block was determined using a six-point descriptive scale. No difference between groups for quality of analgesia in the first and second stage of

labour and motor block was reported. Overall analgesia was judged excellent in 61.6% and 56.4% (P=0.02) in CSE and EPI group respectively. Patients assessed overall analgesia as 'excellent' in 74.8% of CSE compared with 71.7% of epidurals (P=0.14). Other comparisons between groups revealed no differences. The authors suggest these findings showed no clear advantage of either technique ([redacted] .

Three methods of continuing analgesia in labour were compared in a randomised study: midwife top-ups (Group MW, n=43), PCEA (Group PCEA, n=44) and continuous infusion (Group CI, n=46.) After induction of initial analgesia with an intrathecal dose containing bupivacaine 2.5 mg (0.25%) with fentanyl 25 µg (0.5 ml), patients were randomly allocated to one of the three groups ([redacted] .

All epidural solutions contained 0.1 % bupivacaine and fentanyl 2 µg/ml. The mother assessed pain hourly on a verbal analogue scale (0, no pain -10, worst pain); motor power was midwife evaluated according to the patient's ability to sustain a straight leg raise (SLR), as an indication of ability to ambulate. Overall experience was based on a 100 mm VAS (0 mm, best -100mm worst outcome).

Significant dose-sparing effect of bupivacaine/fentanyl in group MW compared with groups CI and PCEA was reported (Table 6). Four hours after combined spinal-epidural analgesia, 88.1% of women could SLR in group MW, 83.7% in group PCEA and 57.8% in group Cl (P=0.002). Analgesia, assessed hourly, was similar between the three groups and overall satisfaction was also similar (Table 6). ([redacted] .

Table 6 Mean bupivacaine and fentanyl use and reasons for reduced mobility

	MW	CI	PCEA	P
Mean (SD) use	n=43	n=46	n=44	
Bupivacaine (mg/h)	7.5 (3.1)	11.5 (3.3)	9.1 (2.1)	<0.001*
Fentanyl (µg/h)	18.8 (7.7)	29.9 (12.7)	21.8 (7.5)	<0.001**
Reason for reduced mobility	n=40	n=44	n=41	
Motor block	9	21	9	-
Syntocinon drip/CTG	10	13	16	-
Numbness	2	0	1	-
Nausea	1	0	1	-
Shivering	0	1	0	-
Median (interquartile range) experience of labour (mm)	45 (24-68)	39 (20-65)	40 (21-52)	-

* group MW versus PCEA (P=0.02); group PCEP versus CI (P<0.001)
**group MW versus PCEA (P=0.07); group PCEP versus CI (P<0.001)

Nulliparous women (n=1054) were randomized, in labour, to receive either boluses of 10 ml 0.25% bupivacaine (traditional, n=353), or combined spinal–epidural (CSE,

n=351) analgesia, or low dose infusion (LDI, n=337), both with 0.1% bupivacaine with 2 µg/ml fentanyl ([redacted]). In the traditional group, subsequent boluses of the same concentration were provided on request no more than hourly. In CSE group, analgesia was established by an intrathecal injection of 1 ml bupivacaine 0.25% and 25 µg fentanyl (total volume 1.5 ml). With the return of painful contractions, 15 ml of low dose mixture (15 mg bupivacaine and fentanyl 30 µg) were administered epidurally. On maternal request 10 ml of the same solution was given no more than half hourly. In LDI group anaesthesia was established with an epidural injection of 15 ml of low dose mixture (15 mg bupivacaine and fentanyl 30 µg) followed by an infusion at a rate of 10 ml/h of the same solution. Additional 10 ml low dose mixture was given on request, no more than hourly. Pain was assessed by 100 mm VAS through labour and delivery and 24 h post delivery.

Throughout first and second stages of labour, mean usage of bupivacaine/woman, (excluding top-ups for operative procedures), was similar in the traditional and LDI groups but significantly lower in the CSE group (first stage, $P<0.001$; second stage, $P<0.01$). Less fentanyl was used in the CSE group than in the LDI group. CSE was associated with a more rapid onset of analgesia. At 5 min after insertion, the median VAS score reported in the CSE group was significantly less than that of the traditional group (20 versus 64 mm; $P<0.001$, and was maintained up to 1 h after epidural treatment (4 versus 14 mm, $P<0.001$), but at 3 h median VAS score were higher than that of the traditional group (21 versus 15 mm, $P<0.01$). Pain scores reported by LDI group were similar to those of the traditional group throughout labour and delivery. The number of patients requiring rescue analgesia was similar across the 3 groups. In this study the authors concluded, that the beneficial impact of mobile epidural techniques on delivery mode did not compromise pain relief during labour ([redacted]

A randomised, double-blind placebo-controlled study was performed to evaluate the analgesic efficacy and influence on instrumental delivery of continuing epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl during the second stage of labour ([redacted]). When the cervix was 3-7 cm dilated, an epidural catheter was inserted via the L3-4 interspace. Each woman initially received a bolus (6 ml) of 0.125% bupivacaine-0.0008% fentanyl followed by a continuous epidural infusion of 0.0625% bupivacaine-0.0002% fentanyl (12.5 ml/h). After full dilatation, the patient received either 0.0625% bupivacaine-0.0002% fentanyl (n= 29) or saline-placebo (n=34) until delivery. Pain was assessed on a 100 mm VAS (0=no pain, 100=worst possible) every 30 minutes and motor block assessed by the Bromage scale.

During the first stage of labour the two groups had similar pain scores and assessment of analgesia. During the second stage of labour, pain scores were significantly higher in the saline group ($P<0.005$ at each 30 minute interval between 60 and 150 minutes) and global assessment of analgesia quality was significantly lower ($P<0.05$, when second stage lasted $\geq$60 minutes). Epidural infusion of bupivacaine-fentanyl did not significantly increase the incidence of instrumental delivery (21% versus 15%, bupivacaine-fentanyl versus saline). There was a low incidence of clinically significant motor block: 3% in each group at beginning of stage 2; 6% versus 0% at delivery (bupivacaine-fentanyl versus saline, respectively). The authors concluded that in this study, bupivacaine-fentanyl provided better analgesia than the saline

solution, particularly for those patients with a second stage labour lasting ≥60 minutes, nor did it significantly increase the incidence of instrumental delivery ([redacted]

A randomised trial evaluated whether, in comparison with systemic opioid analgesia, the initiation of epidural analgesia early in labour had an effect on the rate of caesarean delivery ([redacted] . In all, 750 nulliparous women at term, who were in spontaneous labour or had spontaneous rupture of the membranes and a cervical dilatation of <4 cm were assigned (at the first request for analgesia) to receive either intrathecal fentanyl (25 µg, n=366) or systemic hydromorphone (n=362). Epidural analgesia was initiated in the intrathecal group at the second request for analgesia such that: cervix <4 cm, a 15 ml epidural bolus of bupivacaine+fentanyl (0.625 mg/ml+2 µg/ml, respectively) given; or cervix ≥4 cm, a 15 ml epidural bolus of bupivacaine given (1.25 mg/ml). Epidural analgesia was initiated in the systemic group at a cervical dilatation of ≥4 cm or at the third request for analgesia, when a 15 ml epidural bolus of bupivacaine was given (1.25 mg/ml). In both instances, PCEA was used. Subjects were asked to rate their pain according to an 11-point verbal rating score for pain (0=no pain, 10= worst pain imaginable) at the first and second requests for analgesia.

No significant difference between the groups (intrathecal analgesia versus systemic analgesia, respectively) regarding the rate of caesarean section, 17.8% versus 20.7% (95%CI -9.0 to 3.0%; P=0.31) or instrumental vaginal delivery, 19.6% versus 16% (95%CI -2.9 to 10.1%; P=0.13) were found. Median time from initiation of analgesia to complete dilatation was significantly shorter after intrathecal analgesia than after systemic analgesia (295 minutes versus 385 minutes; P<0.001), as was the time to vaginal delivery (398 minutes versus 479 minutes; P<0.001). Pain scores after the first intervention were also significantly lower after intrathecal analgesia than after systemic analgesia (2 versus 6; P<0.001). The authors concluded that neuraxial analgesia initiated early in labour did not increase the rate of caesarean delivery, provided better analgesia, and resulted in a shorter duration of labour than systemic analgesia ([redacted]

Surgery

To manage post-thoracotomy pain, combinations of opioids and local anaesthetics are often administered into the epidural space for their combined effects in pain relief.

A prospective, double-blind, randomised controlled trial was conducted to investigate the analgesic and adverse effects of three concentrations of epidural fentanyl with 0.1% bupivacaine in patients undergoing thoracotomy for lung resection ([redacted] 2004).

In all, 99 patients (33/group) were randomised to receive either fentanyl 2 µg/ml, or fentanyl 5 µg/ml or fentanyl 10 µg/ml in bupivacaine 0.1% via a thoracic epidural. Postoperatively, pain on coughing was assessed using a VAS (0-100 mm) and an observer verbal rating score (OVRS, 0-5, where 0=no pain and 5=severe pain) at 2, 8, 16 and 24 h. Sedation, pruritus and nausea were also assessed. Solutions were infused

at a rate of 0.1 ml/kg/h (after a loading dose of 0.1 ml/kg) through a catheter inserted at T4-5 or T5-6 interspace.

At each of the four assessments, the number of patients with unsatisfactory pain (pain VAS >30 mm or OVRS >1) was significantly higher in patients receiving fentanyl 2 µg/ml than in those receiving fentanyl 5 or 10 µg/ml (P<0.01). Although the analgesic effect of fentanyl 5 µg/ml and 10 µg/ml was similar, the higher dose appeared to increase the incidence of sedation (50% versus 35% or 34%) and pruritus (59% versus 43% or 41%). Hence, in this study, epidural fentanyl 5 µg/ml with bupivacaine 0.1% appeared to provide a good balance between pain relief and adverse effects (.

The quality of analgesia and the effects on pulmonary function were investigated in patients undergoing thoracic surgery through a posterolateral thoracotomy (t). In this randomised study, one group received a 5-segment intercostal block plus IV patient controlled analgesia (PCA) morphine (n=16). This regimen consisted of bupivacaine 0.5%, then morphine 3 mg injected intravenously every 10 minutes until the dynamic VAS score was less than 4. PCA followed, and was programmed to administer 1 mg of morphine, with a lockout of 8 minutes, and with a maximum dose of 7 mg/h. A second group received a bupivacaine 0.5% and fentanyl 100 µg PCA infusion through a thoracic epidural catheter at the end of surgery (n=15) followed by an infusion of 0.125% bupivacaine and fentanyl 2 µg/ml, at a rate of 5 ml/h.

Analgesia was assessed by a 10 cm VAS, during a resting period (resting VAS) and after a voluntary cough (dynamic VAS). Resting and dynamic VAS values and pulmonary function (forced vital capacity and forced expiratory volume in 1 second) were measured basally at the end of surgery and hourly up to 4 hours and then 12, 24, and 48 hours later. Resting and dynamic VAS scores were slightly lower in bupivacaine/fentanyl treated patients, although only resting scores were significant (P=0.042). After the first hour, mean scores were below 4 in both groups. No significant difference was observed between groups in relation to respiratory parameters (P=0.27) or side effects ( ).

Additionally, post operative pain in thoracotomy patients was studied employing epidural bupivicaine and fentanyl (as Patient Controlled Epidural Analgesia – PCEA) or intravenous morphine (as Intravenous Patient Controlled Analgesia – IVPCA). This study of 30 patients showed that after thoracic surgery, PCEA using the combination provides better pain relief at rest and coughing versus morphine IVPCA (.

A prospective, randomised, double-blind study has been reported comparing analgesic efficacy and occurrence of motor block and other side effects during patient supplemented epidural analgesia (PSEA) with either ropivacaine/fentanyl or bupivacaine/fentanyl mixtures ( ). Patients scheduled to have elective major abdominal surgery (major bowel resection, pancreaticoduodenoctomy, hepatic resection) were randomly allocated to receive PSEA with either bupivacaine 0.125%/2 µg/ml fentanyl (n=16) or ropivacaine 0.2%/2 µg/ml fentanyl (16 patients/group). Epidural catheters were placed at T8-T10 interspaces and postoperative pain relief was provided using PSEA infusions set to deliver 4 ml/h of

the study solution with 1.5 ml incremental doses and a 20 minute lock out time. If analgesia was inadequate the background infusion rate was increased to 6 ml/h. Degree of pain and motor blockade were blindly recorded at 1, 6, 12, 24 and 48 h after the end of surgery. Analgesia was measured during coughing using a 4 score Verbal Rating Scale and motor block was assessed using the Bromage scale. Although no differences between groups in the degree of pain relief at any of the measurement times were observed, the median number of incremental doses given (5 (range: 0-20) versus 10 (range: 5-52); P=0.03) and the final solution infused (208 ml (range: 148-260) versus 236 (range:204-360); P=0.05) were higher in patients treated with the bupivacaine combination. The incidence of motor blockade was similar in the two groups (Table 7).

Table 7 Degree of motor block

Bromage scale* for motor block at	Number of patients with scores 0/1/2/3		
	Ropivacaine (n=16)	Bupivacaine (n=16)	P value
1 h	15/1/0/0	15/0/1/0	0.69
6 h	16/0/0/0	16/0/0/0	0.99
12 h	16/0/0/0	14/1/1/0	0.34
24 h	16/0/0/0	14/1/1/0	0.34
48 h	16/0/0/0	16/0/0/0	0.99

*Motor block was assessed using the modified Bromage scale (0=no motor block, 1=ankle blocked, 2=ankle and knee blocked, 3=ankle, knee and hip blocked). If the patient developed motor blockade higher than 1 on the modified Bromage's score, the background epidural infusion of study solution was discontinued for one hour and restarted at 4 ml/h.

A randomised double-blind study investigated the analgesic effect of PCEA fentanyl or morphine in combination with a low dose of bupivacaine in patients undergoing abdomino-perineal resection ([redacted]). Study drugs were administered through a lumbar epidural catheter placed at the L3-4 or L4-5. After surgery, patients complaining of pain received a loading dose of 2 mg morphine (Group 1) or 50 µg fentanyl (Group 2) in 10 ml saline (20 patients/group). For PCEA, the subjects received 1 mg of morphine in 4 ml bupivacaine 0.125% (Group 1) or 20 µg fentanyl in 4 ml bupivacaine 0.125% (Group 2); the infusion rate was set at 8 ml/h with 15 minute lockout intervals. If analgesia was inadequate, supplements of 50 mg meperidine were injected im. Resting analgesia was measured by a 10 cm VAS, at baseline, and 2, 4, 6, 12, 18 and 24 h after PCEA was started. Motor weakness was assessed by a modified Bromage scale.

No difference in pain or sedation was observed between groups. The 24 hr postoperative mean opioid consumption was 15.50 (SD: ± 7.53) mg morphine and 555.10 (SD: ± 183.85) µg fentanyl. Mean bupivacaine 0.125% consumption was 58.00 (SD: ± 30.14) ml in Group 1 and 101.05 (SD: ± 36.77) ml in Group 2. One patient in Group 2 complained of motor weakness in one leg. VAS scores were similar for the two treatment groups and the mean VAS pain score was low in both groups (≤2 at each timepoint). One patient in group 2 complained of grade I motor weakness (impaired hip flexion, normal knee and ankle movements) in one leg during the first postoperative day. The number of patients reporting nausea (10% versus

45%; P < 0.05) and pruritus (5% versus 30%, P < 0.05) was less in patients receiving fentanyl (Group 2 versus Group 1).

The authors report that, although in this study, both methods were effective in preventing pain, because of fewer side effects, fentanyl may be preferable to morphine. ([redacted] .

Bupivacaine and Fentanyl as a combination in spinal surgery has proved efficacious in the out-patient setting ([redacted]. The combination was compared to bupivacaine alone (both in intrathecal use) in 35 randomised patients. There were no differences in intraopeartive outcomes (measured by the maximum motor blockade score and need for analgesic supplementation) between the two groups. However, mean recovery (measured by ambulation and urination times) and discharge times were significantly shorter in the combination group. Post-operatively, analgesic supplementation was significantly less in the bupivacaine-fentanyl group.

Paediatrics

Effective postoperative pain management in children can be achieved using combinations of opioids and local anaesthetics.

The analgesic effect of continuous epidural infusion of fentanyl and bupivacaine, with intermittent epidural administration of morphine was compared in a block-randomised, double-blind and double-dummy study. In all, 31 children aged 3 months to 6 years undergoing major abdominal or genito-urological surgery were studied ([redacted]). After induction of anaesthesia a lumbar epidural catheter was placed at L3-4 or L4-5

For post-operative pain relief, children received either intermittent morphine 30 µg/kg administered every 8 hours, or a continuous infusion of bupivacaine 1 mg/ml and fentanyl 2 µg/ml at a rate of 0.25 ml/kg/h. Postoperative pain evaluation was done 1 and 6 hours after termination of anaesthesia and every 4 hours in the first postoperative day. Children were assessed by an observer using the Objective Discomfort Pain Scale (OPS), by the parents using a 100 mm VAS, and by the number of additional administrations of morphine.

Both regimens provided effective analgesia, however the combination of fentanyl and bupivacaine was superior to intermittent morphine for pain relief (median VAS score reported by parents, 30 versus 84; P=0.041), and OPS (median score 0 [range 0-7] versus 2 [range 0-12]; P=0.021). A significant difference (P=0.043) in the mean number of supplemental morphine doses was reported (morphine versus bupivacaine combination): 0.7 (range: 0-4) versus 0.1 (range: 0-2).

Studies have also been performed using other opioids in combination with bupivacaine by the intrathecal route. Children (aged 2.7-7.4 years) undergoing selective dorsal rhizotomy to reduce spasticity, experience severe pain postoperatively. In order to help define an optimal dose of continuous intrathecal morphine and bupivacaine to treat the severe pain a study comparing two different

concentrations of morphine in a fixed dose of bupivacaine was undertaken ([redacted]).

Postoperatively the subjects were treated with bupivacaine 40 µg/kg/h and morphine 0.4 µg/kg/h (low dose group n = 11) or 0.6 µg/kg/h (high-dose group n = 15). The Behavioural Observational Pain Scale (BOPS, score 0-2, three variables) was used to evaluate pain every 3 h for the first 48 h after surgery. Better pain relief was obtained in the high dose group compared to the low dose (P=0.03). The low-dose group received seven times as much ketobemidone (over 48 hours: 0.43 [SD: ± 0.54] versus 0.06 [SD: ± 0.09] mg/kg; P = 0.0005). No statistical difference (low dose versus high dose, respectively) in pruritus (64% versus 60%) and postoperative nausea and vomiting (73% versus 87%) between the groups was found, and no incidence of respiratory and hemodynamic depression reported. In this study the authors report that the higher dose of continuous intrathecal morphine combined with bupivacaine, significantly reduced the pain score and postoperative intravenous analgesic requirements without increasing adverse effects.

A prospective, randomised, double-blind study, assessed whether the addition of fentanyl to epidural bupivacaine improved the quality of postoperative analgesia and accelerates the clinical recovery of infants after thoracotomy ([redacted]).

Inadequate postoperative analgesia, was defined as a CRIES (Crying, Requires oxygen for saturation <95%, Increased vital signs, Expression, Sleepless) score of ≥4. Infants (up to 6 months, 20/group) were randomly assigned to receive an epidural infusion containing 0.1% bupivacaine (group B) or 0.1% bupivacaine and 2 µg/ml fentanyl (group BF). Infants in group BF experienced significantly less pain than those in group B. The CRIES score in the first 24 h was significantly decreased (P<0.001) in group BF (1.5 ± 1.9) when compared with group B (2.9 ± 2.3). Time to first analgesic rescue was significantly longer in group BF (516 SD: ± 524 versus 126 SD: ± 89 minutes; P = 0.005). The incidence of side effects such as respiratory depression and urinary retention, time to first successful feeding, and time to discharge were similar in both groups.

Conclusion

The combination of bupivacaine with fentanyl for the management of pain has been shown to be effective in a large number of clinical trials. For the successful management of labour pain, the doses of bupivacaine combined with fentanyl (2µg/ml) most frequently evaluated were in the range: 0.0625% to 0.125% and for the management of post-operative pain: 0.1% to 0.125%.

The combination of bupivacaine with fentanyl was generally more effective than the opioid or the anaesthetic alone and also resulted in a lower incidence of sensory or motor block.

Epidural infusion of bupivacaine-fentanyl did not significantly increase the incidence of instrumental delivery nor did it appear to have an effect on the first and second stages of labour.

The combination of bupivacaine with fentanyl administered epidurally as bolus, as PCEA or as continuous epidural infusion has been shown to provide an effective analgesia during labour, or after caeserian section. The combination has also been shown to provide effective analgesia when managing post-thoracotomy pain, and major abdominal surgery. Effective postoperative pain management in children can be achieved using combinations of opioids and local anaesthetics, including fentanyl and bupivacaine.

2.5.5. OVERVIEW OF SAFETY

The efficacy of bupivacaine combined with fentanyl has been discussed in detail in sections 2.5.3 and 2.5.4. Many of the clinical trials detailed in these two sections evaluated the analgesic efficacy of the combination of bupivacaine and fentanyl and also assessed the safety of the dosing regimens. In these studies safety was principally assessed by examining the frequency and nature of side effects associated with the drugs.

In this section the reported safety and tolerability of bupivacaine combined with fentanyl is examined. Where details of the study designs and outcomes have already been specified in Section 2.5.3 and 2.5.4 they are not reiterated in this section. The studies are summarised below.

Overview of Safety Studies			
Study Reference	**Comparators**	**Endpoints**	**Main Outcome**
Obstetrics			
[redacted]	• Fentanyl 30 or 100 µg in bolus • Alfentanyl • Sufentanyl • Placebo	Ventilatory drive, pupil size, and subjective ratings of alertness, nausea, and pruritus	Produced side effects only at the higher dose, due mainly to systemic absorption. Sedation, increased end-tidal carbon dioxide, and pupillary constriction occurred only after the high epidural dose of all opioids
[redacted]	• fentanyl (25, 50, 100 or 200 µg) • sufentanyl (5, 10, 20 or 30 µg)	Incidence of side effects	Pruritus most common AE (n=33, 41%). Nausea occurred in four patients (5%). None requested or received treatment for pruritus or nausea. None experienced vomiting or respiratory rate <l0 breaths/min.
[redacted]	• fentanyl/bupivacaine • sufentanyl/ bupivacaine	Analgesia. Motor block. Adverse events.	Sufentanyl group, pruritus significantly lower than in the fentanyl group. Reported incidence <10% and no specific treatment required. Nausea was not recorded in any patients
[redacted]	• fentanyl/ bupivacaine • morphine/bupivacaine • bupivacaine alone	Duration of pain relief	Frequency of side effects was lower in the bupivacaine group
[redacted]	Comparison of fentanyl 25 µg with sufentanil 5 µg when added to bupivacaine 1.25 mg as the initial component of the combined spinal epidural technique in early labour	Side effects	No significant differences in the incidence of pruritus, shivering, sedation, or hypotension were found. No incidences of nausea, respiratory depression or foetal distress reported

Study Reference	Comparators	Endpoints	Main Outcome
[redacted]	• fentanyl/bupivacaine • bupivacaine alone • fentanyl alone	Analgesia at rest and on coughing. Sensory and motor blocks	Overall incidence of nausea and vomiting low with no significant difference between groups. Sedation reported as mild. In fentanyl groups incidence of pruritus was significantly more frequent than in the bupivacaine group
[redacted]	• fentanyl/bupivacaine • saline	Influence on instrumental delivery	Incidence of maternal side effects similar between groups. 6/28 (21%) women in bupivacaine-fentanyl, and 5/34 (15%) in saline group, had instrumental vaginal delivery (P=NS).
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Analgesia, the level of sensory block and the degree of motor block	Frequency of nausea, vomiting, urinary retention similar in the two groups. Frequency of pruritus higher in bupivacaine plus fentanyl group. No incidence of respiratory depression reported. In neonates, one child received naloxalone treatment (bupivacaine group). No significant difference for apgar score or birth weight.
[redacted]	• fentanyl/bupivacaine • bupivacaine alone	Analgesic efficacy: pain and motor block assessed	No significant difference frequency in nausea, emesis or urinary retention between groups. Pruritus significantly more likely (22% versus 5%, P<0.05) in Bupivacaine-fentanyl group. No significant difference in apgar score or birth weight.

Study Reference	Comparators	Endpoints	Main Outcome
[redacted]	At first request for analgesia received either intrathecal fentanyl or systemic hydromorphone, then • fentanyl/bupivacaine • bupivacaine (both PCEA)	Time to analgesis, rate of caesarean or instrumental delivery	Incidence and severity of nausea, and vomiting were significantly lower in the intrathecal fentanyl group. Incidence of 1-min Apgar scores <7 significantly higher after systemic opioid analgesia, Other neonatal outcomes not significantly different.

Study Reference	Comparators	Endpoints	Main Outcome
Surgery			
[redacted]	Analgesic effect of PCEA fentanyl or morphine in combination with a low dose of bupivacaine in patients undergoing abdomino-perineal resection	Analgesia and weakness	Incidence of nausea and pruritus lower in fentanyl group. Two patients treated with morphine required diphenhydramine for mild pruritus. No patient suffered clinical respiratory depression.
[redacted]	Three concentrations of epidural fentanyl with 0.1% bupivacaine in patients undergoing thoracotomy for lung resection	Pain on coughing assessed	Higher dose appeared to increase the incidence of sedation and pruritus. Incidence of nausea was similar across the 3 groups
[redacted]	Patient (scheduled to have elective major abdominal surgery) supplemented epidural analgesia (PSEA) with either • ropivacaine/fentanyl or • bupivacaine/fentanyl mixtures	Analgesic efficacy and occurrence of motor block and other side effects	One patient (ropivacaine/fentanyl) had pruritus. Degree of sedation similar in both groups (none higher than grade 2). Incidence and severity of changes in arterial blood pressure and heart rate same in both groups. No patient required oxygen therapy or naloxone.
[redacted]	In patients undergoing thoracic surgery through a posterolateral thoracotomy • bupivacaine + morphine • fentanyl/bupivacaine	Quality of analgesia and effects on pulmonary function. Incidence of adverse events	No significant differences in the incidence of nausea and vomiting (37% versus 20%) and itching (25% versus 12.5%) found (morphine versus fentanyl/bupivacaine, respectively)

Study Reference	Comparators	Endpoints	Main Outcome
Paediatrics			
[redacted]	Children received either intermittent morphine administered every 8 hours, or a continuous infusion of bupivacaine/fentanyl	Postoperative pain evaluation	All children experienced a varying degree of sedation. Incidence of distressing pruritus, vomiting, and need for antiemetics higher in morphine group. No incidence of clinical respiratory depression, motor blockade or seizures observed.

NS=not significant; PCEA= patient controlled epidural analgesia; CI=continuous infusion

Obstetrics

The epidural administration of fentanyl 30 and 100 µg in bolus (in 6ml administered over 3-5 minutes) to 12 healthy volunteers produced side effects only at the higher dose, due mainly to systemic absorption ([redacted]). Ventilatory drive, pupil size, and subjective ratings of alertness, nausea, and pruritus were measured using VAS (Table 8). Sedation, increased end-tidal carbon dioxide, and pupillary constriction occurred only after the high epidural dose of all opioids. For end-tidal carbon dioxide, compared to placebo, changes from baseline were significant for all drugs (for fentanyl mean increase of 10.1% (±2.1%), $P<0.01$).

Table 8 Number of subjects out of 12 with VAS scores ≥20 for nausea and pruritus

	Fentanyl (range)	Alfentanyl (range)	Sufentanil (range)	Placebo
Nausea				
Low dose	2 (21-22)	1 (72)	2 (21-26)	0
High dose	2 (70-80)	4 (51-90)	0	0
Pruritus				
Low dose	3 (20-73)	1 (47)	2 (26-48)	0
High dose	5 (23-71)	4 (23-65)	4 (20-32)	0

The side effects of fentanyl (25, 50, 100 or 200 µg) were compared with those of sufentanil (5, 10, 20 or 30 µg) following administration as a single postoperative epidural bolus to patients after caesarean section. No significant difference between groups in the incidence of side effects was observed. Of the 80 patients, 36 (45%) experienced at least one side effect, with pruritus the most common (n=33, 41%). Nausea occurred in only four patients (5%). No patient requested or received treatment for pruritus or nausea during the study period. No patient in any group experienced vomiting or respiratory rate <10 breaths/min throughout the study period. No increase in side effects with increasing dose for either opioid, nor any differences between fentanyl and sufentanil were noted. All groups rated drowsiness in the mild

to moderate range (mean VAS sedation 30-55 mm) at baseline without significant change in any group throughout the duration of the study period. (.

A prospective trial compared fentanyl 2µg/ml plus bupivacaine 0.125% with sufentanil 0.25 µg/ml plus bupivacaine 0.125% for the treatment of pain during labour and delivery, using PCEA ( ). In the sufentanil group, motor blockade (P=0.03) and pruritus (10 versus 2 patients, P=0.02), were significantly lower than in the fentanyl group. The reported incidence was less than 10% and no specific treatment was required. Nausea was not recorded in any patients.

Fentanyl 80 µg or morphine 4 mg added to bupivacaine 0.25% were epidurally administered in bolus (10 ml) during labour ( ). The frequency of side effects was lower in the bupivacaine group (Table 9). One patient with drowsiness in the morphine group required naloxone administration. No significant differences in foetal heart patterns or apgar score: 94.8% versus 98.4%, apgar score >7 at 1 minute and >9 at 5 minutes, were observed.

Table 9 Frequency of side effects

	Fentanyl n=81	Morphine n=83	Placebo n=85
Itching (%)	22 (27.2%)	20 (24%)	1 (1.2%)
Nausea and vomiting (%)	6 (7.4%)	27 (32.5%)	11 (13%)
Drowsiness (%)	11 (13.6%)	12 (14.4%)	1 (1.2%)
Hypotension (%)	4 (4.9%)	3 (3.6%)	2 (2.4%)
Urinary retention (%)	2 (2.4%)	5 (6%)	1 (1.2%)

A prospective, randomised study examined the duration of analgesia produced by intrathecal fentanyl 25 µg with sufentanil 5 µg when added to bupivacaine 1.25 mg as the initial component of the combined spinal epidural technique in early labour ( ). No significant differences in the incidence of pruritus, shivering, sedation, or hypotension were found (Table 10). No incidences of nausea, respiratory depression or foetal distress were reported in either group.

Table 10 Frequency of side effects

	Fentanyl	Sufentanil
Pruritus, n(%)	15 (75%)	17 (85%)
Sedation. n(%)	6 (30%)*	4 (20%)*
Hypotension, n(%)	0	1 (5%)
Motor Block, n(%)	1 (5%)	0

* All grade 1 sedtion = mild sedation

After caesarean section, patients received 0.1 % bupivacaine or fentanyl 4 µg/ml or 0.05% bupivacaine plus fentanyl 2 µg/ml by PCEA ( ). The overall incidence of nausea and vomiting was low with no significant difference between groups (Table 11). Sedation was reported as mild. Although the incidence of pruritus was similar in patients treated with fentanyl-bupivacaine and fentanyl alone, it was significantly more frequent than in the bupivacaine group.

Table 11 Frequency of side effects

	Bupivacaine	Fentanyl	Bupivacaine/fentanyl
From 30min to 24 h	n=18	n=19	n=19
Nausea (%)	11	0	0
Vomiting %)	6	0	0
Sedation %)	22	37	21
Pruritus (%)	11	89*	89*

*P<0.001 when compared with bupivacaine

A study was performed to evaluate the analgesic efficacy and influence on instrumental delivery of continuing epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl during the second stage of labour ([redacted]). The incidence of maternal side effects was similar between groups and no effect on newborn assessments was detected (Table 12). Six of 28 (21%) women in the bupivacaine-fentanyl group, and five of 34 (15%) in the saline-placebo group, underwent instrumental vaginal delivery (P=NS). No significant difference between groups in umbilical chord blood gas and pH values were noted.

Table 12 Maternal side effects incidence and newborn assessment

	Bupivacaine-Fentanyl (n=29)	Saline placebo (n=34)
Pruritus, n(%)	2 (7%)	4 (12%)
Nausea, n(%)	4 (14%)	3 (9%)
Emesis, n(%)	4 (14%)	3 (9%)
Urinary retention, n(%)	12 (41%)	12 (35%)
Newborn assessment		
Mean Infant weight, g (SD)	3258 (±528)	3314 (±390)
1-min Apgar ≥7, n(%)	25 (86%)	31 (91%)
5-min Apgar ≥7, n(%)	29 (100%)	34 (100%)
Meconium stained amniotic fluid, n(%)	2 (7%)	5 (15%)

The safety profile of an extradural infusion of 0.08% bupivacaine 15 ml/h with 37.5 µg/h fentanyl, and of 0.08% bupivacaine 15 ml/h alone was examined in patients during labour [redacted]. The frequency of nausea (45% versus 32%), vomiting (35% versus 21%) and urinary retention (45% versus 58%) was similar in the two groups (bupivacaine plus fentanyl versus bupivacaine). The frequency of pruritus was higher in the subjects treated with bupivacaine plus fentanyl than with bupivacaine alone (75% versus 5%, P<0.001). No incidence of respiratory depression was reported in either group of mothers. Considering the neonates, one child in the group receiving bupivacaine received naloxalone treatment. No significant difference between the infants from each group were reported for either the apgar score or birth weight.

Patients receiving a continuous epidural infusion during labour of 0.0625% bupivacaine with 0.0002% fentanyl were significantly more likely (22% versus 5%, P<0.05) to experience pruritus than those receiving 0.125% bupivacaine alone ([redacted]). No specific treatment for pruritus was necessary. The two groups were similar (bupivacaine-fentanyl versus bupivacaine) with regards to frequency of nausea (27% versus 31%; P=NS) and emesis (17% versus 21 %; P=NS). Although a greater incidence of urinary retention in the bupivacaine-fentanyl group was noted (63% versus 44%), it did not reach statistical significance. Effects on the neonate were monitored, and no significant differences between the two groups for

weight, meconium-stained amniotic fluid, or Apgar scores at 1 and 5 minutes were detected (Table 13). Similarly, no significant differences between groups in umbilical chord blood gas and pH values were found.

Table 13 Newborn assessment

	Bupivacaine-Fentanyl (n=41)	Bupivacainel (n=39)
Newborn assessment		
Mean Infant weight, g (SD)	3394 (±418)	3435 (±407)
1-min Apgar ≥7, n(%)	34 (83%)	32 (82%)
5-min Apgar ≥7, n(%)	41 (100%)	39 (100%)
Meconium stained amniotic fluid, n(%)	16 (39%)	12 (31%)

A trial designed to evaluate whether, in comparison with systemic opioid analgesia, the initiation of epidural analgesia early in labour had any effect on the rate of caesarean delivery, also assessed safety parameters ([redacted]). In this study, patients received bupivacaine 0.0625 mg/ml plus fentanyl 2 µg/ml as standard epidural analgesia during labour and delivery with, in addition, either intrathecal fentanyl (n=366) or systemic hydromorphone (n=362). The incidence and severity of nausea, and the incidence of vomiting were significantly lower in the intrathecal fentanyl group (Table 14). The incidence of 1-minute Apgar scores <7 was significantly higher after systemic opioid analgesia, however other neonatal outcomes were not significantly different.

Table 14 Maternal side effects incidence and newborn assessment

	Intrathecal N=366	Systemic N=362	P value (CI)
Nausea, n(%)			<0.001
None	340 (92.9%)	203 (56.1%)	-
Mild	18 (4.9%)	101 (27.9%)	-
Moderate	7 (1.9%)	47 (13%)	-
Severe	1 (0.3%)	11 (3%)	-
Vomiting, n(%)	7 (1.9%)	62 (17.1%)	<0.001
Newborn assessment			
Mean weight, g (SD))	3443 (±428)	3455 (±431)	0.85 (95%CI: -74 to 51)
1-min Apgar ≥7, n(%)	61 (16.7%)	87 (24%)	0.01 (95%CI: -13.5 to -1.3)
5-min Apgar ≥7, n(%)	5 (1.4%)	9 (2.5%)	0.28 (95%CI: -3.4 to 1.1)

Surgery

The safety of PCEA with morphine 1 mg, or fentanyl 20 µg with bupivacaine 0.125% was determined in patients following abdominal surgery ([redacted]). The incidence of nausea (45% versus 10%; P<0.05) and pruritus (30% versus 5%; P<0.05) was lower in patients receiving fentanyl. One patient in the fentanyl group and three patients in the morphine group required therapy for severe nausea. Further, two patients treated with morphine required diphenhydramine for treatment of mild pruritus. No patient suffered clinical respiratory depression.

The frequency of adverse effects associated with three concentrations of epidural fentanyl (2, 5 or 10 µg) with 0.1% bupivacaine in patients undergoing thoracotomy for lung resection has been reported ([redacted]). Sedation, pruritus and nausea were assessed (Table 15).

Table 15 Incidence of adverse effects

	Fentanyl		
	2µg/ml n=29	5µg/ml n=28	10µg/ml n=32
Nausea (%)	17 (58%)	14 (50%)	20 (62%)
Sedation %)	10 (34%)	10 (35%)	16 (50%)
Pruritus (%)	12 (41%)	12 (43%)	19 (59%)

Although the analgesic effect of fentanyl 5 µg/ml and 10 µg/ml was similar, the higher dose appeared to increase the incidence of sedation (50% versus 35% or 34%) and pruritus (59% versus 43% or 41%). Although higher, the incidence was not statistically significant. The incidence of nausea was similar across the 3 groups ([redacted]).

The incidence of side effects associated with PSEA with bupivacaine 0.125%/fentanyl 2 µg/ml or ropivacaine 0.2%/fentanyl 2 µg/ml was investigated in patients after abdominal surgery ([redacted] . Five patients in the ropivacaine group (31%) and seven in the bupivacaine group (43%) required antiemetic therapy during the study period (P=NS). One patient treated with ropivacaine/fentanyl complained of pruritus. The degree of sedation was similar in the two groups and none was higher than grade 2 (mildly sedated, easy to waken when spoken to). The incidence and severity of changes in arterial blood pressure and heart rate was the same in both groups: 5 episodes of hypotension and 2 episodes of bradycardia in each group. No patient developed major respiratory complication requiring either oxygen therapy or naloxone administration.

The safety profile of epidural fentanyl/bupivacaine and intravenous morphine was assessed in patients after thoracotomy ([redacted]). Although less frequent in the fentanyl/bupivacaine group, no significant differences in the incidence of nausea and vomiting (37% versus 20%) and itching (25% versus 12.5%) were found .(i.v. morphine versus epidural fentanyl/bupivacaine, respectively). One patient in each group exhibited a decrease in arterial blood pressure that required treatment. Before surgery, a urinary catheter was placed in 11 patients and 9 patients in the i.v. morphine and fentanyl/bupivacaine groups, respectively. Following surgery, one of the remaining patients in each group developed urinary retention.

Paediatrics

In children treated with epidural infusion of fentanyl 2 µg/ml and bupivacaine 1 mg/ml (rate of 0.25mg/kg/hr) or intermittent epidural morphine (30 µg/kg administered every 8 hours) for postoperative pain management, the occurrence of side effects was recorded ([redacted]). All children in both groups experienced a varying degree of sedation. The incidence of distressing pruritus (13% versus 27%, P=0.65) vomiting (60% versus 87%, P=0.21) and need for antiemetics (27% versus

40%, P= 0.7) was higher in children under morphine treatment. In the morphine group, two children discontinued treatment due to severe nausea or distressing itching and insufficient analgesic effect. In the fentanyl/bupivacaine group, two children discontinued therapy: one because of hypotension and headache; the other was heavily sedated and had slightly impaired cardio-vascular values. In two other children the doses were reduced due to asymptomatic bradycardia during the first postoperative night and because of distressing paresthesia of the leg. No incidence of clinical respiratory depression, motor blockade or seizures were observed. The authors report that in this study continuous epidural infusion of fentanyl/bupivacaine was found to be superior to intermittent epidural morphine.

Conclusion

The combination of bupivacaine and fentanyl is commonly used in clinical practice, with different doses administered either as epidural bolus or epidural infusion or a combination of both. In studies investigating the management of labour pain, the doses of bupivacaine combined with fentanyl (2µg/ml) most frequently evaluated were in the range: 0.0625% to 0.125% and for the management of post-operative pain: 0.1% to 0.125%. Taken together, the results of these clinical trials show the combination of bupivacaine plus fentanyl to be well tolerated.

In adults, reported side effects were mild when bupivacaine/fentanyl was administered epidurally in a range of therapeutic doses either by bolus or infusion or PCEA. Few required the interruption of treatment, or the administration of any other treatment intervention. The most frequently reported adverse effects were pruritus, nausea and some sedation and were primarily associated with the opiate component of the combination.

The incidence of respiratory depression and sedation was low. Motor and sensory block associated with the anaesthetic component of the bupivacaine/fentanyl combination was not frequent and in most cases allowed mobility of the patients. Adverse effects associated with the cardiovascular system were rarely reported in these trials.

In the study carried out in children, although the infusion of bupivacaine and fentanyl induced side effects similar to those reported for adults, they resulted in dose reduction or interruption in treatment, indicating that posology in children should be adjusted according to the individual.

Epidural local anaesthetics are associated with hypotension and opioids sedation, respiratory depression, pruritus, nausea and vomiting. As they are dependent on dose, these adverse effects can be minimised by using epidural solutions of lower drug concentration. Co-administration of bupivacaine with fentanyl allows dose reduction without compromising the analgesic effect.

The epidural use of bupivacaine with fentanyl has been shown to be well tolerated and is supported by the literature and clinical practice. No unexpected adverse events were reported when bupivacaine and fentanyl were administered in combination. Co-administration of the two drugs also allows a reduction in dose thereby helping to reduce the overall number of adverse events associated with the drugs.

2.5.6. BENEFITS AND RISKS CONCLUSION

The combination of bupivacaine and fentanyl administered epidurally (as bolus, infusion, or PCEA) has been shown to provide adequate pain relief in obstetrics (during labour and after caesarean section) and after major surgery (thoracotomy, abdominal surgery) in numerous, well controlled studies, and generally in the dose range bupivacaine 0.0625% to 0.125% plus fentanyl 2 µg/ml.

An additive effect of the two components has been reported. The combination of bupivacaine with fentanyl was generally reported as more effective than the opioid or the anaesthetic alone and also resulted in a lower incidence of sensory or motor block. Hence, a principal advantage of this combination is a reduction in the dose required for each agent, which in turn results in an improved safety profile while still providing effective analgesia accompanied with less motor block. The doses of bupivacaine and fentanyl relating to this application are in keeping with the doses outlined in the literature and reported as effective and well tolerated.

When considering adverse reactions, epidural local anaesthetics are associated with hypotension and opioids associated with sedation, respiratory depression, pruritus, nausea and vomiting. Since the adverse effects are dose dependent, they can be minimised by using epidural solutions thus allowing lower drug concentration whilst maintaining effective analgesia. Co-administration of bupivacaine with fentanyl has been shown to allow dose reduction without compromising the analgesic effect. Further, no unexpected adverse events were reported when bupivacaine and fentanyl were administered in combination.

Bupivacaine and fentanyl were well tolerated with the most frequent adverse events reported in clinical practice those already known to be associated with fentanyl (pruritus, nausea, and some sedation). Most were mild and did not cause discontinuation of treatment. The overall evaluation by patients concerning satisfaction and efficacy was good.

Epidural infusion of bupivacaine-fentanyl did not significantly increase the incidence of instrumental delivery nor did it appear to have an effect on the first and second stages of labour.

Bupivacaine and fentanyl epidural infusion has been authorised for use in Switzerland and other non-EU countries such as Australia and New Zealand. In Australia the bupivacaine and fentanyl epidural infusion is indicated after surgery to treat postoperative pain and also for use during childbirth. In New Zealand the bupivacaine hydrochloride (0.125%) with fentanyl citrate (2 µg/mL) infusion solution for epidural analgesia is intended for use in post-operative analgesia.

Text redacted under sections 41 and 43 of the FOI Act

Bupivacaine-fentanyl administered epidurally is currently used extensively in clinical practice for the management of acute labour pain or post-operative pain following major abdominal or thoracic surgery. When used in this way, bupivacaine-fentanyl is usually only available as extemporaneous preparation prepared by the hospital

pharmacy. The availability of sterile, ready-to-use solutions should improve patient safety by eliminating the risks associated with extemporaneous preparation such as dosing or identification errors, lack of stability, or contamination. The availability of ready-to-use solutions within the hospital should help avoid the risk of errors associated with administering the wrong dose.

Overall, the availability of an industrially manufactured, sterile, ready-to-use solution should help eliminate the risks inherent in the use of extemporaneous preparation, thus offering a benefit to patient care. Based on the available information it can be concluded that there is sufficient evidence supporting the safety and efficacy of administration of fentanyl by the epidural route in association with bupivacaine for the treatment of acute post-operative and labour pain, at the doses outlined in the Application.

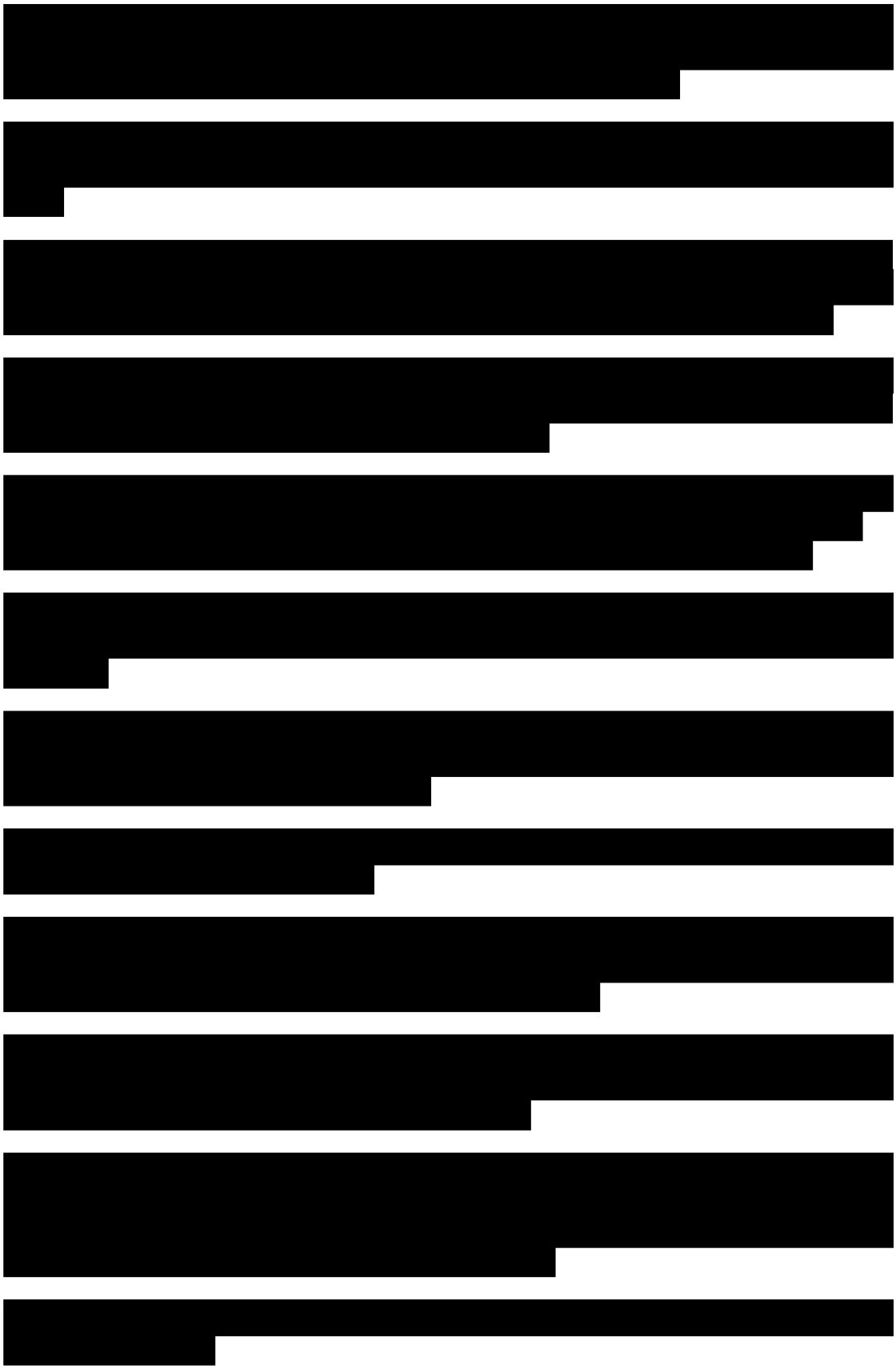
[redacted]

08 January 2010

Redacted under section 40 of the FOI Act

2.5.7. LITERATURE REFERENCES

[redacted]



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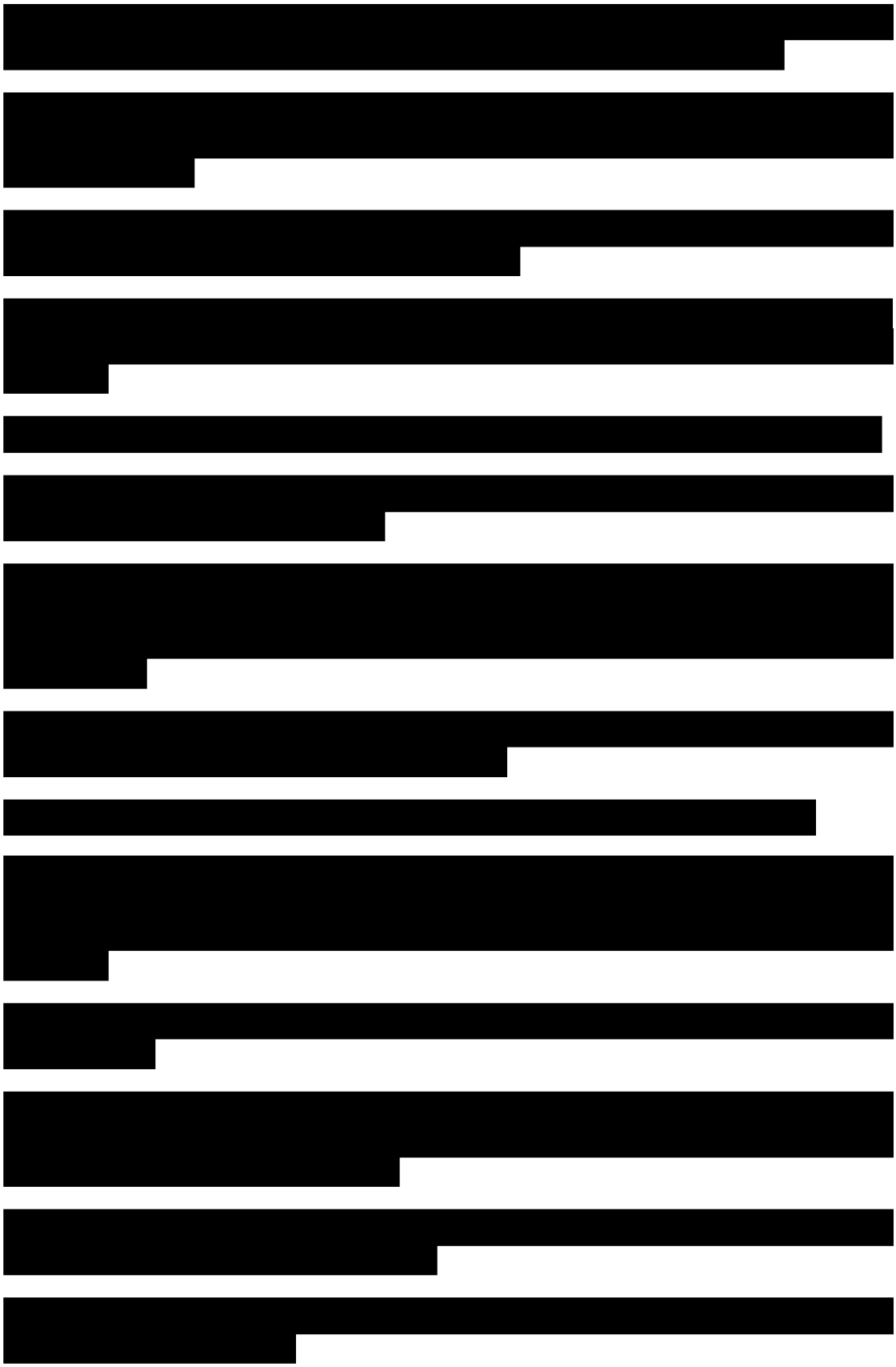

[redacted]

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