Analgesics and ENT surgery

A clinical comparison of the intraoperative, recovery and postoperative effects of buprenorphine, diclofenac, fentanyl, morphine, nalbuphine, pethidine and placebo given intravenously with induction of anaesthesia

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- 1 Vomiting and restlessness following ENT and eye surgery are undesirable, and may be related to the emetic and analgesic effects of any analgesic given to augment anaesthesia during surgery.
- 2 To rationalise the choice of analgesic for routine ENT surgery we examined the intraoperative, recovery and postoperative effects following the administration of either buprenorphine (3.0 to 4.5 $\mu\text{g kg}^{-1}$), diclofenac (1 mg kg^{-1}), fentanyl (1.5 to 2.0 $\mu\text{g kg}^{-1}$), morphine (0.1 to 0.15 mg kg^{-1}), nalbuphine (0.1 to 0.15 mg kg^{-1}), pethidine (1.0 to 1.5 mg kg^{-1}) or saline (as control) given with the induction of anaesthesia in 374 patients. A standardised anaesthetic technique with controlled ventilation using 0.6–0.8% isoflurane in nitrous oxide and oxygen was employed. The study population constituted 7 similar groups of patients.
- 3 Intraoperatively, their effects on heart rate and blood pressure, airway pressure and intraocular pressure, were similar. This implies, most surprisingly, that neither their analgesic nor their histamine releasing effects were clinically evident during surgery. By prolonging the time to extubation at the end of anaesthesia, only buprenorphine, fentanyl, morphine and pethidine provided evidence of intraoperative respiratory depression.
- 4 Postoperatively, buprenorphine was associated with severe respiratory depression, prolonged somnolence, profound analgesia and the highest emesis rate. Diclofenac exhibited no sedative, analgesic, analgesic sparing, emetic or antipyretic effects. Fentanyl provided no sedative or analgesic effects, but was mildly emetic. Morphine provided poor sedation and analgesia, delayed the requirement for re-medication and was highly emetic. Nalbuphine and pethidine produced sedation with analgesia during recovery, a prolonged time to re-medication and a mild emetic effect. None provided evidence, from analysis of postoperative re-medication times and analgesic consumption, of any pre-emptive analgesic effect.
- 5 We conclude that nalbuphine (mean dose 0.13 mg kg^{-1}) and pethidine (mean dose 1.35 mg kg^{-1}), given individually as a single i.v. bolus during induction of anaesthesia, are the most efficacious analgesics for routine in-patient ENT surgery.

Keywords Anaesthesia: ear nose throat in-patient
Analgesia: intraoperative recovery postoperative pre-emptive
Analgesics: buprenorphine diclofenac fentanyl morphine nalbuphine
pethidine saline (placebo)

Introduction

The provision of intra- and postoperative analgesia is an integral part of anaesthetic practice [1], and postoperative pain may be pre-empted or reduced by giving analgesics prior to the surgical stimulus [2]. Such pain may first manifest in the recovery ward where a smooth recovery, a rapid return of reflexes, with a minimum of restlessness and vomiting are important following ENT and eye surgery [3, 4]. During anaesthesia with controlled ventilation, changes in heart rate and blood pressure may occur in response to pain, and an increase in airway pressure may reflect an increase in bronchomotor tone. The latter may be secondary to histamine released in response to analgesic drugs given intravenously. During head and neck surgery an increase in airway pressure may cause an undesirable increase in central venous pressure, intracranial pressure, intraocular pressure and bleeding. Opioid analgesic drugs given with anaesthesia are also known to depress respiration. Following general anaesthesia with controlled ventilation such depression may manifest as an increase in the time to onset of spontaneous respiration at the end of anaesthesia. Of the alternative non-opioid analgesics gaining use in anaesthetic practice, the non-steroidal anti-inflammatory drugs (NSAIDs) have the potential advantages of an antipyretic effect and lesser emesis in the postoperative period. Fentanyl, papavaretum, alfentanil, morphine and pethidine are the most commonly used analgesics in anaesthetic practice in the United Kingdom while phenoperidine, levorphanol, diamorphine, methadone, cyclomorph, nalbuphine, buprenorphine and diclofenac are less popular [5].

With these considerations in mind, and in order to rationalise our choice of analgesic for routine ENT, and possibly eye surgery, a prospective study of the efficacies and adverse effects of the above analgesics available here was undertaken. Three narcotic-agonists, fentanyl, morphine and pethidine, two agonist-antagonists, buprenorphine and nalbuphine, and one NSAID, diclofenac, were compared with saline control.

Certain aspects were particularly considered. These were:

- 1) Intraoperatively, their effects on heart rate, blood pressure, airway pressure and respiratory depression
- 2) During recovery, their residual emetic, sedative, analgesic and respiratory depressant effects
- 3) In the surgical ward, their residual analgesic and adverse effects (emesis and pruritus), and their influence on postoperative fever.

Methods

With Hospital Ethics Committee approval and patient (or guardian) consent, 374 consecutive ASA Grade I–II Saudi nationals of all ages scheduled for elective ENT surgery (ear—tympanomyringoplasty; nose—septorhinoplasty; throat—adenotonsillectomy) were

studied. On arrival in the operating theatre each patient was randomly allocated, depending on gender and site of surgery (to ensure treatment groups of similar size), to receive one of the analgesics or saline as control.

Premedication comprised diazepam (0.5 mg kg^{-1} to age 12 years, 0.3 mg kg^{-1} for those over 12 years) and metoclopramide (0.15 mg kg^{-1}) given orally, and EMLA cream applied topically to the dorsum of the hand, 2 h prior to surgery. In theatre, following venous cannulation and preoxygenation, anaesthesia was induced with thiopentone (sleep dose) and atracurium (0.6 mg kg^{-1}), and endotracheal intubation performed after the larynx was sprayed with lignocaine 10%. Anaesthesia was maintained with nitrous oxide (67%) and isoflurane (0.6–0.8%) in oxygen. Respiration was controlled at a rate of 10 to 16 breaths min^{-1} as required in adults and children respectively, an inspiratory:expiratory ratio of 1:3, a tidal volume of 10 ml kg^{-1} and a fresh gas flow (FGF) of $70 \text{ ml kg}^{-1} \text{ min}^{-1}$ using the Bain Circuit to maintain an end-tidal carbon dioxide concentration [EtCO_2] of 4.5–5.0 kPa. At the end of anaesthesia, residual neuromuscular blockade was reversed with neostigmine (0.035 mg kg^{-1}) and atropine (0.017 mg kg^{-1}). Pethidine, paracetamol and prochlorperazine were prescribed for the relief of postoperative pain, pyrexia and emesis.

Patients were positioned supine for pharyngeal procedures, or tilted 5 to 10° head up for nasal and aural procedures. The latter received hypotensive anaesthesia using labetalol (1 mg kg^{-1}) and nitroglycerine by infusion to maintain a mean arterial pressure of 55–65 mm Hg. Ringer lactate or dextrose-saline was infused intraoperatively ($8.0 \text{ ml kg}^{-1} \text{ h}^{-1}$), and continued postoperatively ($2.0 \text{ ml kg}^{-1} \text{ h}^{-1}$) until oral fluids were tolerated. Intraoperative monitoring of ECG (Hewlett Packard 80300A), blood pressure (Dinamap Critikon 1846SX), oxygen saturation (Ohmeda Biox 3700), EtCO_2 (Hewlett Packard 47210A Capnometer), inspired oxygen concentration (Oxychek Critikon) and respiratory parameters (Ohmeda AV7700 ventilator) provided data sources. The Schioetz Tonometer was used to record intraocular pressure.

Analgesic drug dosages (Table 1) were based on the literature [6–9], current practice in this department, and on the principle that smaller doses are appropriate for children [10] and the elderly [11, 12].

Table 1 Analgesic drug dosages

Drug	<i>The young, the elderly (< 12 years) (> 60 years)</i>	<i>Adults (13–59 years)</i>
Buprenorphine	$3.0 \mu\text{g kg}^{-1}$	$4.5 \mu\text{g kg}^{-1}$, max. 300
Diclofenac	1 mg kg^{-1}	1 mg kg^{-1} , max. 75
Fentanyl	$1.5 \mu\text{g kg}^{-1}$	$2 \mu\text{g kg}^{-1}$
Morphine	0.1 mg kg^{-1}	0.15 mg kg^{-1} , max. 10 mg
Nalbuphine	0.1 mg kg^{-1}	0.15 mg kg^{-1}
Pethidine	1.0 mg kg^{-1}	1.5 mg kg^{-1} , max. 100 mg
Saline	1.0 ml	2.0 ml

The analgesics and saline were coded (A = buprenorphine, B = fentanyl, C = diclofenac, D = morphine, E = nalbuphine, F = pethidine and G = saline) and, to ensure blindness, all documentation was appropriately endorsed.

To assess the effects of these analgesics on bronchomotor tone, as indicated by the peak airway pressure (Paw), and on intraocular pressure (IOP), the test drug was administered after controlled ventilation had been established and the baseline values of Paw and IOP had been recorded.

Data were recorded on customised forms in the operating theatre, recovery and surgical wards. Prior to induction of anaesthesia note was made of patient details, site of surgery, analgesic group, heart rate (HR), systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure. Following induction and the establishment of controlled ventilation, but prior to administering the test drug, the baseline HR, MAP, Paw and IOP were recorded. During surgery, thereafter, (at 10 min intervals for 1 h following the test drug), note was made of HR, MAP, and Paw. At the end of surgery, prior to the reversal of neuromuscular blockade and discontinuation of isoflurane and nitrous oxide, the cardiovascular, pulmonary and ocular parameters were again recorded, as was the duration of anaesthesia. Following reversal of neuromuscular blockade and discontinuation of the anaesthetic agents, note was made of the extubation time, defined as the time from cessation of anaesthesia to the re-establishment of spontaneous respiration and extubation.

Nurses in the recovery ward, blind to the test drug given, recorded details of vomiting, antiemetic requirements and residual analgesic effects. The latter was assessed according to the need to administer analgesia to restless patients, using a four point score (0 = restful, pain free; 1 = mild restlessness, mild pain, responding to nursing care; 2 = moderate restlessness, moderate pain, requiring i.v. analgesia; 3 = severe restlessness, severe pain, requiring i.v. analgesia and physical restraint), in the absence of hypoxia or inadequate reversal of neuromuscular blockade. Recovery from anaesthesia was monitored by recording the awakening time (used as an index of the residual sedative effect of the test drug), the presence of residual respiratory depression and the overall time spent in the recovery ward. Awakening time was defined as the time to eye opening in response to a command. Respiratory depression was considered present in any of those patients admitted with an endotracheal tube *in situ*, those requiring assisted ventilation in the recovery ward, those who were non-rousable with a respiratory rate of $< 8 \text{ min}^{-1}$, and in those who required doxapram or naloxone to stimulate respiration.

During the first 24 h postoperative period, further note was made by nurses, also unaware of the test drug given, of vomiting (its time of onset and severity [13]) and of the residual analgesic effect of the drug. This was assessed according to analgesic usage (its overall requirement and whether given for headache, surgical pain or pyrexia), and the time to

the first requirement of postoperative analgesia. The patient's body temperature was also recorded every 4 h using an IVAC 821A oral thermometer.

On the day following surgery a participating doctor, also blind to the agent given intraoperatively, visited the ward to review drug, temperature, fluid balance and nursing records. In addition, each patient was interviewed with regard to headache, pruritus and their overall perception of the pain experienced in the first 24 h postoperative period. The latter was rated by the patient on a verbal analogue scale of 0 to 3, with 0 = not painful to 3 = severely painful.

Analysis

Patient data were analysed using the Chi-squared, analysis of variance and Fishers Exact tests where appropriate. Intraoperative data was analysed using analysis of variance and Student's *t*-tests. Recovery room and postoperative surgical ward data were analysed using the Chi-squared, Fishers Exact, Student's *t* and Mann Whitney U tests. Tests were two tailed, with Yates' Correction where appropriate. Statistical significance was assumed at $P < 0.05$, with 95% confidence limits.

Within the surgical site subgroups (ear, nose, throat), analyses compared data pertaining to each test drug with the saline controls. In the overall groups, analyses compared data relating to each test drug with each other and with the saline control group. For illustrative purposes, the restlessness of patients during recovery and the rating of pain by patients in the surgical ward are presented in the tables as the means of these scores. The large number of recordings required to be made resulted in occasional omissions. Accordingly, some differences exist between the number of recordings and the number of patients in some of the tables.

Results

Comparability of groups

The three hundred and seventy-four patients studied formed seven study groups, each of 53 or 54 patients. These groups were comparable for sex, age, weight and duration of anaesthesia. Two patients were in their second years of life, and two patients were older than 60 years. Each study group also comprised three comparable subgroups of patients having either ear, nose or throat surgery (Table 2). The patients undergoing adenotonsillectomy had a mean age of 13 years and a mean duration of anaesthesia of 31 min, while those undergoing septorhinoplasty or tympanomyringoplasty had mean ages of 28 and 29 years and mean durations of anaesthesia of 53 and 74 min respectively.

Intraoperative effects

Cardiovascular In each of the study subgroups (*t*-tests) and overall (Figure 1, ANOVA) there were

Table 2 Demographic characteristics of patients and actual drug dosage

Variable	Buprenorphine	Diclofenac	Fentanyl	Treatment groups			
				Morphine	Nalbuphine	Pethidine	Saline
<i>Overall</i>							
<i>n</i> (M:F)	53 (34:19)	53 (36:17)	54(34:20)	54(35:19)	53(33:20)	54(35:19)	53(34:19)
Age (years)	19 ± 15	19 ± 11	22 ± 16	21 ± 13	22 ± 15	22 ± 14	21 ± 15
Weight (kg)	43 ± 24	49 ± 24	48 ± 27	51 ± 22	50 ± 23	47 ± 24	50 ± 27
DOA (min)	43 ± 26	48 ± 29	40 ± 21	49 ± 32	44 ± 32	51 ± 30	45 ± 30
Overall drug dose	4.15 µg kg ⁻¹	0.99 mg kg ⁻¹	1.93 µg kg ⁻¹	0.14 mg kg ⁻¹	0.13 mg kg ⁻¹	1.35 mg kg ⁻¹	1–2 ml
<i>Surgical procedures</i>							
<i>Ears (TM)</i>							
<i>n</i> (M:F)	10(6:4)	10(6:4)	10(6:4)	10(6:4)	10(6:4)	10(6:4)	10(6:4)
Age (years)	31 ± 13	26 ± 8	29 ± 10	25 ± 9	31 ± 10	30 ± 11	28 ± 12
Weight (kg)	59 ± 14	55 ± 11	56 ± 15	56 ± 15	63 ± 15	57 ± 12	65 ± 19
DOA (min)	74 ± 21	74 ± 22	55 ± 23	74 ± 40	78 ± 24	77 ± 39	89 ± 35
Drug dose	3.6 µg kg ⁻¹	1.03 mg kg ⁻¹	1.75 µg kg ⁻¹	0.13 mg kg ⁻¹	0.14 mg kg ⁻¹	1.32 mg kg ⁻¹	1–2 ml
<i>Noses (SR)</i>							
<i>n</i> (M:F)	16(14:2)	15(15:1)	16(14:2)	16(14:2)	16(13:3)	17(14:3)	15(13:2)
Age (years)	30 ± 9	24 ± 9	33 ± 11	30 ± 9	29 ± 12	21 ± 11	27 ± 10
Weight (kg)	70 ± 14	63 ± 17	70 ± 13	68 ± 11	67 ± 17	66 ± 9	66 ± 16
DOA (min)	50 ± 27	55 ± 40	49 ± 23	61 ± 34	48 ± 33	64 ± 30	46 ± 21
Drug dose	4.04 µg kg ⁻¹	0.92 mg kg ⁻¹	2.02 µg kg ⁻¹	0.14 mg kg ⁻¹	0.13 mg kg ⁻¹	1.43 mg kg ⁻¹	1–2 ml
<i>Throat (AT)</i>							
<i>n</i> (M:F)	27(14:13)	28(16:12)	28(14:14)	28(15:13)	27(14:13)	27(15:12)	28(15:13)
Age (years)	9 ± 11	14 ± 10	14 ± 16	15 ± 13	14 ± 14	12 ± 11	15 ± 15
Weight (kg)	24 ± 12	39 ± 25	33 ± 25	39 ± 22	35 ± 20	32 ± 25	36 ± 27
DOA (min)	28 ± 13	34 ± 14	26 ± 9	34 ± 17	30 ± 22	33 ± 12	30 ± 13
Drug dose	4.3 µg kg ⁻¹	1.0 mg kg ⁻¹	2.0 µg kg ⁻¹	0.15 mg kg ⁻¹	0.14 mg kg ⁻¹	1.16 mg kg ⁻¹	1–2 ml

Data given as mean ± s.d.; *n* = Patient numbers; M:F = Male:Female; TM = Tympanomyringoplasty; SR = Septorhinoplasty; AT = Adenotonsillectomy; DOA = Duration of anaesthesia.

similar changes in the means of the heart rates and mean arterial pressures in response to the induction of anaesthesia, injection of test drug, ensuing anaesthesia and surgery, and ultimately, to awakening from anaesthesia. Transient initial increases were followed by gradual intraoperative reductions which culminated in similar increases in the means of those two parameters at the end of surgery.

Peak airway pressure and intraocular pressure The injection of the study drugs produced no significant changes in the peak airway pressure throughout the course of anaesthesia and surgery. The airway pressure remained almost constant in each group at about 20 cm water pressure. There were also no differences between the intraocular pressures measured prior to the administration of the test drugs and those measured at the end of anaesthesia (Figure 1, ANOVA).

Intraoperative respiratory depression Following discontinuation of the inhalational anaesthetic agents and the administration of neostigmine and atropine at the end of anaesthesia, the mean times to extubation were similar and brief in all those subgroups given diclofenac, saline or nalbuphine, but were prolonged to varying extents in many of those given buprenorphine, fentanyl, morphine or pethidine (Table 3). Overall, the mean times to extubation, of between 4.5 and 6.3 min, in those who received the latter drugs were significantly longer than the mean extubation time of 3.3 min in those given saline.

Recovery ward features

Emetic sequelae The incidences of vomiting in the recovery ward were similarly low in all of the groups and subgroups, occurring in 0% to 9% of patients (Chi-squared, Fishers Exact Tests). There was a correspondingly low need, in 0% to 4% of instances, for nursing staff to administer antiemetics.

Analgesic usage In three of the 21 study subgroups, analgesic requirements were significantly less than in the saline control subgroups. All three had undergone adenotonsillectomy. Of these, only two (7%, $P < 0.02$, Fishers Exact Test) of the 27 patients in each of the subgroups given buprenorphine or nalbuphine, and three (11%, $P < 0.05$, Fishers Exact Test) of the 27 patients in the subgroups given pethidine required analgesia in the recovery ward, compared with the higher requirement rates for analgesia in those given saline (9 of 28, 32%).

In the overall study groups (Table 4), patients who received buprenorphine, nalbuphine and pethidine had significantly less analgesic requirements (4%, 6% and 9% of patients respectively) than patients who received saline (25%) and diclofenac (26%). The intermediate incidences of analgesic requirements, of 13% and 15%, seen in those patients who received fentanyl and morphine were, however, similar to these lower and higher requirement rates respectively.

Restlessness Of the surgical subgroups only that which underwent adenotonsillectomy and received

Figure 1 Intraoperative cardiovascular, pulmonary and ocular pressure responses to anaesthesia and surgery (□ buprenorphine, ○ diclofenac, ▼ fentanyl, ■ morphine, ◇ nalbuphine, ◆ pethidine, △ saline).

buprenorphine was more restful ($P < 0.01$, Mann Whitney U Test, $Z = -2.66$). Overall (Table 4), patients who had received diclofenac and saline were most restful in the immediate postoperative period. Conversely, those who had received buprenorphine, nalbuphine and pethidine were the most restful.

Awakening time (sedation) The mean times to awakening tended to be shorter in those given diclofenac and saline, and longer in those given opioids. In the subgroups, these times were longer in all those given buprenorphine ('aural' $P < 0.01$; 'nasal' $P < 0.001$; 'pharyngeal' $P < 0.01$, Student's t -tests) and in some of those who underwent nasal surgery (those receiving morphine ($P < 0.01$), nalbuphine ($P < 0.05$) or pethidine ($P < 0.001$) Student's t -tests). Overall (Table 4), a significantly prolonged time to eye opening on command was seen only in those having received buprenorphine, nalbuphine and pethidine.

Respiratory depression Significant respiratory depression in the recovery ward was evident only in patients who had received buprenorphine. Of the buprenorphine subgroups, six ((60%); $P < 0.01$, Fishers Exact Test) of the 10 patients who had 'aural' surgery, and five ((31%); $P < 0.05$ Chi-squared) of the 16 patients who had undergone 'pharyngeal' surgery had respiratory depression. Overall (Table 4), this morbidity was present in 28% of those given buprenorphine, a highly significant difference compared with the similar infrequent incidences of respiratory depression, of between 2% and 7%, observed with the other drugs.

Recovery ward times The overall mean times spent by the patients in the recovery ward (of between 26 and 31 min) were similar, irrespective of the varying residual analgesic, sedative and respiratory depressant effects observed between the test drugs.

Table 3 Intraoperative respiratory depression as inferred from the extubation time

Drug group	Ears		Noses		Extubation time (min)		All ENT	
	(n)	Mean s.d. 95% confidence limits	(n)	Mean s.d. 95% confidence limits	(n)	Mean s.d. 95% confidence limits	(n)	Mean s.d. 95% confidence limits
Buprenorphine	(10)	8.0 ± 3.4 6–10	(15)	7.5 ± 3.7 6–9	(26)	4.3 ± 2.1 3.5–5	(50)	6.3 ± 4.4 5–7.5
Diclofenac	(6)	3.2 ± 0.41 2–3.5	(13)	3.8 ± 1.1 3–4	(25)	3.5 ± 1.4 3–4	(53)	3.5 ± 1.2 3–4
Fentanyl	(10)	5.4 ± 3.2 3–7	(13)	4.8 ± 2.1 4–10	(27)	4.9 ± 3.0 4–6	(50)	4.9 ± 2.8 4–6
Morphine	(8)	7.5 ± 7.1 3–12	(13)	7.0 ± 4.4 5–10	(27)	3.5 ± 1.6 3–4	(48)	4.5 ± 3.0 4–5
Nalbuphine	(8)	4.0 ± 2.0 3–5	(14)	5.1 ± 3.4 3–10	(25)	3.3 ± 1.4 3–4	(47)	3.9 ± 2.4 3–5
Pethidine	(10)	7.0 ± 4.6 4–10	(14)	5.9 ± 3.5 4–8	(24)	4.6 ± 3.1 3–6	(45)	5.1 ± 3.5 4–6
Saline	(10)	3.4 ± 1.3 3–4	(15)	3.4 ± 1.1 3–4	(28)	3.3 ± 2.2 2.5–4	(53)	3.3 ± 1.8 3–4

Data given as (n) mean ± s.d. = (Number of recordings) mean value ± standard deviation; t = Student's t -tests.

Table 4 Recovery ward: analgesic usage, restlessness, awakening time and respiratory depression

Drug	N	n	Analgesic effect				Awakening time (min)				Respiratory depression			
			Analgesic usage		Restlessness pain score		Mean		P value		Mean		P value	
			%	P value	Mean	± s.d.	CL	± s.d.	(MW)	(t)	N	n	%	P value
			CL	(FET)	CL								CL	(FET)
Buprenorphine	53	2	4% 1–13	<0.005	0.31 0.14–0.48	±0.64		<0.001	44	13.2 10–17	±12	<0.01	46	13
Diclofenac	53	14	26% 16–40	NS	0.92 0.62–1.22	±1.11		NS	43	4.6 3–6	±5.2	NS	48	1
Fentanyl	54	7	13% 6–26	NS	0.60 0.36–0.84	±0.90		NS	47	7.6 10–9	±6.0	NS	48	1
Morphine	54	8	15% 7–28	NS	0.65 0.41–0.89	±0.91		NS	46	8.2 6–11	±9.2	NS	48	3
Nalbuphine	53	3	6% 1–16	<0.01	0.40 0.18–0.62	±0.81		<0.005	44	8.7 7–11	±7.0	<0.02	44	2
Pethidine	54	5	9% 3–20	<0.05	0.56 0.31–0.87	±0.92		<0.05	44	10.7 8–14	±9.6	<0.01	45	3
Saline	53	13	25% 14–40	—	0.94 0.65–1.23	±1.09		—	49	5.4 4–7	±5.4	—	52	1

N = Overall patient numbers, n = Patient incidence, P = P value, χ^2 = Chi-squared, MW = Mann Whitney U Test, t = Student's t-test, FET = Fisher's exact test, CL = 95% confidence limits.

Surgical ward features

Vomiting and antiemetic usage Vomiting occurred in the surgical ward more frequently in the 'nasal' subgroups of patients given either buprenorphine or pethidine (in 12 (80%; $P < 0.001$, Fishers Exact Test) and nine (60%; $P < 0.05$, Fishers Exact Test) of 15 patients each respectively), and after 'pharyngeal' surgery in those given morphine (in 13 (46%; $P < 0.05$ Chi-squared Test) of 28 patients). Overall (Table 5), however, the vomiting incidences following buprenorphine (58%) and morphine (48%) were similar and significantly greater than those in the diclofenac (26%) and saline (25%) groups. The rate of vomiting following buprenorphine was also greater than that after nalbuphine ($P < 0.025$), fentanyl ($P < 0.025$) and pethidine ($P < 0.05$). However, the vomiting rate associated with morphine was similar to the lower rates seen following nalbuphine, fentanyl and pethidine. The latter vomiting rates, in turn, were similar to the lowest vomiting rates seen in those given diclofenac and saline.

Those who had received diclofenac and saline tended to have more single postoperative emetic episodes, while the opioids were associated with more multiple vomits. This observation only reached significance ($P < 0.05$, Chi-squared test), however, when all 105 patients who had received a non-opioid (diclofenac or saline) were compared with all 268 patients who had received opioids.

The use of antiemetics was least in those given diclofenac or saline, and greatest in those given buprenorphine. In the subgroups given buprenorphine, six (38%, $P < 0.05$, Chi-squared test) of 16 patients undergoing nasal surgery, and six (22%; $P < 0.05$, Chi-squared test) of the 27 patients having 'pharyngeal' surgery required prochlorperazine. Overall (Table 5) the requirements for prochlorperazine by patients given buprenorphine (32%) or morphine (20%) were only greater than those requirement rates following diclofenac (2%) and saline (6%).

Residual analgesia The requirements for analgesia and the ratings of postoperative pain within the first 24 h postsurgical period were similar in the subgroups (Fishers Exact and Mann Whitney U tests). Overall (Table 6), the time to the first requirement for postoperative analgesia was significantly longer (> 7.5 h) following surgery in those given buprenorphine, morphine, nalbuphine and pethidine. Conversely, those given diclofenac, fentanyl and saline required postoperative analgesia earlier (within 5.3 to 6.2 h of surgery) (Table 6). Despite these differences, however, the patients, overall, rated as similar the pain that they had experienced in the first 24 h postoperative period.

Headache, pruritus and postoperative pyrexia Within the surgical site subgroups and overall, there were similar incidences of headache (30% to 45%), and of pruritus (0% to 7%). Similar mean maximum postoperative oral temperatures ($37.7 \pm 0.4^\circ \text{C}$ to $37.7 \pm 0.7^\circ \text{C}$) were also recorded in each drug group.

Discussion

The anaesthetic protocol used for this study was chosen in order to control those variables which may influence the perioperative effects of the analgesics being studied, and is not necessarily advocated as the most appropriate method of anaesthesia for ENT surgery. ENT patients generally have no ophthalmic pathology. This, in conjunction with the numerous anaesthetic [3, 4] and perioperative morbidity [14] considerations common to ENT and eye surgery renders ENT patients suitable for the study of intraocular pressure. The Schiøtz Tonometer is sufficiently accurate and widely used [15, 16] to record IOP, measurements of which only at the start of and at the end of surgery are considered to reflect the intraoperative IOP [17–19]. While ocular pressures are only relevant in intraocular surgery, bronchomotor tone is important in both eye and ENT surgery. An increased

Table 5 Surgical ward: post operative vomiting and antiemetic usage

Drug	N	Vomiting										Time to first vomit (h)		Antiemetic					
		Total vomits		Single vomits		Multiple vomits				Mean CL	s.d. (t)	P value	n	CL	P value (FET)				
		%	CL	%	CL	%	CL	%	CL							%	CL		
Buprenorphine	53	(31)	58%	48-70	<0.001	(15)	49%	32-66	(16)	51%	34-69	NS	6.4	±4.4	NS	(17)	32%	21-44	<0.0005
Diclofenac	52	(14)	26%	15-39	NS	(11)	79%	50-95	(3)	21%	5-51	NS	5.6	±3.2	NS	(1)	2%	0.1-10	NS
Fentanyl	54	(19)	36%	23-48	NS	(9)	46%	24-71	(10)	53%	29-76	NS	4.5	±3.8	NS	(7)	13%	6-26	NS
Morphine	54	(26)	48%	35-61	<0.01	(13)	50%	30-70	(13)	50%	30-70	NS	5.6	±3.3	NS	(11)	20%	11-34	<0.025
Nalbuphine	53	(18)	34%	21-47	NS	(8)	44%	22-67	(10)	56%	33-79	NS	4.7	±2.7	NS	(6)	11%	4-23	NS
Pethidine	54	(21)	39%	26-52	NS	(15)	71%	48-88	(6)	29%	12-53	NS	4.8	±3.1	NS	(7)	13%	6-26	NS
Saline	53	(13)	25%	14-38	—	(9)	69%	38-91	(4)	31%	9-62	—	7.3	±6.7	—	(3)	6%	1-16	—

Data given as N = patient numbers, n = numbers vomiting/requiring antiemetic, (χ^2) (t) = Chi squared/Student's t-test, FET = Fisher's exact test, CL = 95% confidence limits.

Table 6 Surgical ward: analgesic requirements and patients, rating of postoperative pain

Drug	N	n	Headache		Surgical pain		Pyrexia		Total		Time to first analgesia (h)		Pain rating score	
			%	CL	%	CL	%	CL	%	CL	Mean	s.d.	Mean	s.d.
			P (FET)	n	P (χ^2)	n	P (χ^2)	n	P (χ^2)	n	CL	(t)	CL	(MW)
Buprenorphine	53	6	11	4-23	NS	20	NS	25	47	NS	39	74	1.41	±1.09
Diclofenac	53	5	9	3-21	NS	22	NS	24	45	NS	45	85	1.54	±0.92
Fentanyl	53	7	13	6-26	NS	17	NS	27	51	NS	40	75	1.65	±0.99
Morphine	54	5	9	3-20	NS	19	NS	29	54	NS	43	80	1.70	±1.04
Nalbuphine	53	5	9	3-21	NS	20	NS	24	45	NS	40	75	1.41	±1.05
Pethidine	54	4	7	2-18	NS	22	NS	30	56	NS	48	89	1.60	±0.98
Saline	53	3	6	1-16	NS	19	NS	26	49	—	43	81	1.49	±1.05

N = patient numbers, n = numbers requiring analgesia, P = P value, χ^2 = Chi squared, t = Student's t-test, MW = Mann Whitney U test, FET = Fisher's exact test, CL = 95% confidence limits.

airway pressure may increase central venous pressure, IOP [20, 21] and surgical bleeding. As further aims of this study were to assess the effects of the analgesics on airway pressure and IOP, and not on the hypertensive response to intubation [22], the analgesic was administered following the establishment of controlled ventilation and recordings of the baseline airway pressure and IOP. The recovery and surgical ward assessments were made by British, Filipino and Arabic nurses on Arabic speaking patients. Accordingly, objective assessments of pain (as described) were used rather than the alternative subjective visual analogue pain scoring systems.

Histamine is released by a variety of drugs used in anaesthesia, and may influence the cardiovascular system and bronchomotor tone. Pethidine, morphine, fentanyl and diclofenac given either subcutaneously or intravenously release histamine [23, 24, 25], whereas nalbuphine [23] and buprenorphine [26] reputedly do not. Changes in heart rate and blood pressure also occur in response to painful operative stimuli, and occur at different times during adenotonsillectomy, septorhinoplasty and tympanomyringoplasty. Despite these various factors, the intraoperative cardiovascular and bronchomotor responses of our patients were similar. Our recording of heart rate, mean arterial pressure and peak airway pressure at 10 min intervals after the injection of the analgesic may have missed immediate histamine mediated responses [24], as well as any short lived changes in IOP. However, our observation of similar effects during surgery on the cardiovascular, pulmonary and ocular dynamics in all the patient groups suggests that the histamine released by these drugs is of no consequence in routine anaesthetic practice.

Anaesthetised patients provide suitable subjects for the study of respiratory depression induced by analgesic drugs [27]. The time to resumption of spontaneous respiration and extubation after anaesthesia with controlled ventilation is an index of this depression [28]. The respiratory depression induced by opioids given during anaesthesia has clinical significance in that it may slow the turnover of patients on operating lists. In this study, respiratory depression occurred with buprenorphine ($t_{1/2}$ 5 h, duration of action 4–5 h), morphine ($t_{1/2}$ 2 h, duration 4–5 h) and pethidine ($t_{1/2}$ 3–4 h, duration 3–5 h) [6], which are reputed to be long acting drugs. This was not as unexpected as was that produced by fentanyl ($t_{1/2}$ 3–4 h, duration 1–2 h) [6] which is described as being short acting. Such respiratory depression following low dose fentanyl, however, is well known [28–30]. Only nalbuphine ($t_{1/2}$ 2–3 h, duration 4–6 h) [6] and diclofenac ($t_{1/2}$ 1–2 h, duration 3–6 h) [31] were not associated with intraoperative respiratory depression. The greater propensity of buprenorphine compared with nalbuphine to depress respiration is documented [32], but the lack thereof with diclofenac appears not to be so.

Only the respiratory depression induced by buprenorphine extended into the recovery ward, where it was accompanied by prolonged awakening. Both are features of buprenorphine when used in con-

ventional [33–35] and high [36] doses, especially in patients premedicated with benzodiazepines [33, 34]. Nalbuphine and buprenorphine are central kappa receptor agonists [37]. This may explain their similar or greater sedative effect when compared with morphine [35, 38–41], which is a medullary MU-2 receptor agonist. In our study, sedation (as inferred from the time to eye opening) followed all the opioids, but only that produced by buprenorphine, nalbuphine and pethidine was significant. The absence of sedation following morphine was surprising, as this effect is well known. However, our findings confirm that buprenorphine and nalbuphine have a greater sedative effect than morphine, and suggest that pethidine may be more sedating than morphine in the doses studied here.

A significant residual analgesic effect in the recovery ward was provided by the long acting opioids buprenorphine, nalbuphine and pethidine, but not, surprisingly, by morphine. These four analgesics, however, prolonged (to >7.5 h) the time to the requirement for analgesia in the surgical ward, while shorter re-medication times (of about 5–6 h) occurred in those groups receiving the shorter acting agents diclofenac and fentanyl, or saline. Despite these group differences, however, both the overall quantities of analgesia consumed and the rating of pain by all patients within the immediate 24 h postoperative period were similar. These observations suggest that the duration of action of the drugs given with anaesthesia only affects the comfort of patients in the early postoperative period.

The design of this study allows some assessment of the pre-emptive analgesic properties of these drugs. It is postulated that pain felt after an injury may be diminished if analgesia is given before the injury, that this initial analgesia may be more effective than if the same analgesic is given following the injury, and that such 'pre-emptive' analgesia may also reduce the consumption of analgesics in the postoperative period [2]. In our study, all patients received either paracetamol orally or pethidine i.m. to treat postoperative pain. Since the same analgesic was not given to treat postoperative pain as was given during anaesthesia, a strict assessment of these results with respect to a pre-emptive analgesic effect of the study drugs is not possible. However, our observations reveal that all the patient groups had similar requirements (of between 74–89%) for analgesics within the first 24 h postsurgical period, and that the times to re-medication in these groups was related to the known duration of action of the drugs given. These data infer that no obvious pre-emptive analgesic effect was exerted by any of these drugs when used in this manner.

A rapid return of reflexes and a quiet, non-emetic, pain-free recovery from surgery are desirable following ENT and eye surgery [3, 4]. Each of the opioids studied provided some sedation and analgesia in the recovery ward. Of those, however, only nalbuphine and pethidine did so without evidence of residual respiratory depression. Diclofenac on the contrary, provided no sedative, analgesic or analgesic sparing

effect either in the recovery ward or in the postoperative period. These findings contradict the report that diclofenac given i.v. during surgery provides analgesia following dental surgery [9] but corroborates its demonstrated lack of efficacy for the pain following tonsillectomy [42]. When given rectally, however diclofenac is efficacious in reducing pain after tonsillectomy [43, 44] and adenoidectomy [45], though its use by the intramuscular route after a variety of surgeries (hip, abdominal, dental) is both efficacious [46, 47] and inefficacious [48, 49]. Collated with these contradictory reports our findings suggest that the effect of diclofenac may be related to its route of administration and to the nature of surgery. The rectal and i.m. routes appear to be the most efficacious, and good effect appears mostly to follow orthopaedic and dental surgery. Fentanyl, likewise, provided poor postoperative analgesia. Our patients given fentanyl, as with those given diclofenac and saline, required analgesia shortly after surgery. This is well known when fentanyl is used as the adjuvant to anaesthesia [28].

The use of a saline control group in our study yielded unique perioperative data. Changes in heart rate and blood pressure during surgery are used by anaesthetists to gauge the need for analgesia during surgery [22, 50]. To our immense surprise, our findings of similar changes in heart rates and blood pressures during surgery in those given saline and in those given any analgesic strongly suggests that these doses of analgesics provide undetectable intraoperative analgesia. More importantly, they suggest that the common practice of administering a bolus dose of a short acting analgesic, such as fentanyl, only at induction of anaesthesia provides undetectable perioperative analgesia or sedation.

Vomiting following ENT and eye surgery is hazardous. Knowledge of the differential emetic potentials of the analgesics would be of value in guiding the choice of analgesic to complement anaesthesia for these disciplines. Our surgical ward observations made this information manifest. Diclofenac and saline were associated with the lowest vomiting incidences (in approximately one quarter of patients), fentanyl, nalbuphine and pethidine with moderate rates (in approximately one-third of patients) and morphine and buprenorphine with the highest rates (in approximately one half of patients). Of these differences, however, only the buprenorphine/morphine: diclofenac/saline emetic differences were statistically significant. Though the time to the first vomit and the severity of vomiting were similar for the individual drugs, the opioids, as a group, produced more severe emesis. Patients given any opioid ($n = 268$) had significantly more multiple vomits than patients ($n = 105$) given diclofenac or saline ($P < 0.05$). Comparative comprehensive studies of the emetic potentials of these drugs, as well as the lack of emetic potential of diclofenac, appear not to have been documented. Our findings, however, are consistent with reports that nalbuphine has a similar or lesser emetic potential than morphine [40, 41, 50, 51], pethidine [52–55] and fentanyl [56, 57], and that buprenorphine has a similar or greater emetic potential than morphine [35,

58–60] or pethidine [60].

Anaesthesia for head and neck surgery may be complicated by intraoperative arrhythmias and postoperative vomiting. These may be mediated via a variety of vagal reflexes [14]. In our study, a quarter of the patients not given an intraoperative opioid vomited. This confirms that anaesthesia *per se* is emetic. The higher incidences of vomiting, and correspondingly higher incidences of postoperative antiemetic usage, in those given any opioid confirms that opioids augment postoperative emesis. Though all our patients received metoclopramide to promote gastric emptying and absorption of their concomitant sedative (diazepam) premedication, such therapy is known to give unreliable antiemetic protection [61, 62]. This suggests that a more efficient antiemetic, such as prochlorperazine [61, 62], should be given prophylactically with the induction of anaesthesia when postoperative vomiting is especially undesirable.

None of the analgesics studied showed any advantage with regard to postoperative pruritus, headache or pyrexia. The possibility that diclofenac may provide an antipyretic effect, as part of its anti-inflammatory action (as has been demonstrated in intensive care patients [63]), was not shown either by measurements of body temperature or by the use of antipyretic (paracetamol) medication.

In conclusion, buprenorphine revealed itself to be an undesirable drug by virtue of profound respiratory depressant, sedative and emetic effects. We have since abandoned its use, as have others [34]. Intravenous diclofenac exhibited no analgesic, analgesic sparing, sedative or antipyretic effects. We have also abandoned its use. Fentanyl demonstrated no analgesic or sedative effect, but depressed respiration and was mildly emetic. We concur with Semple *et al.* [5] that its popularity is undeserved. Morphine provided conflicting evidence of analgesic and sedative efficacy, but was highly emetic. Its popularity, as with fentanyl, requires re-evaluation. Nalbuphine and pethidine were demonstrably analgesic and sedative, and only mildly emetic. These features suggest their greatest suitability for routine in-patient ENT and, subject to verification, eye surgery. Nalbuphine has the additional advantages of being a non-controlled drug with low abuse potential, of having a demonstrated safety in clinical practice [64] as a result of a 'ceiling' capacity to depress respiration [65], and of not releasing histamine [23]. Pethidine has the advantage of being the least expensive. However, it is a narcotic, a respiratory depressant and avidly releases histamine [24]. Finally, this study suggests that none of the opioids studied, nor diclofenac, exert any pre-emptive analgesic effect when administered i.v. with the induction of anaesthesia.

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