Respiratory effects of analgesia after cholecystectomy: comparison of continuous and intermittent papaveretum

J A CATLING, D M PINTO, C JORDAN, J G JONES

Summary and conclusions

Two methods of administering papaveretum for relieving postoperative pain were compared in two groups of patients who had undergone cholecystectomy. In one group a loading dose of papaveretum was administered by continuous intravenous infusion (1 mg/min) until the patient could breathe deeply without undue pain. Eight times this loading dose was given as a continuous intravenous infusion over the subsequent 48 hours. This regimen was compared with a conventional intermittent intramuscular dose (0·25 mg/kg at four hourly intervals as necessary) in a second group of patients. The intravenous regimen relieved pain better than the intramuscular regimen, which may have reflected the larger dose of papaveretum given to the intravenous group, but it was accompanied by a greater degree of respiratory depression and potentially life-threatening changes in respiratory pattern.

These findings suggest that the fear which often accounts for inadequate postoperative pain relief—that larger doses of analgesics will cause respiratory complications—is well founded.

Introduction

Many patients complain of the lack of adequate pain relief after surgery.[1 2] The commonest method of relieving pain during this period is to administer intermittent parenteral doses of powerful narcotics. The two principle drawbacks of this procedure are the intermittent nature of the pain relief and the unpredictable danger of fatal respiratory depression. Because of the unpredictable respiratory effect of these narcotics the dose and the frequency of administration are minimised arbitrarily. Furthermore, no record is made of the complaint of pain, and evaluation of the respiratory effect is confined to measuring respiratory rate.

In this study we used a continuous intravenous administration of papaveretum and measured the analgesic and respiratory effects over five days after surgery. This procedure was compared with the conventional regimen of intermittent intramuscular administration of papaveretum. The aim of the intravenous regimen was to provide full and prolonged pain relief, so the dose of opiate exceeded that used in the conventional intermittent regimen.

Patients and methods

Twenty-two patients undergoing elective cholecystectomy were included in the study, which was approved by the hospital ethical committee. They were divided at random into two equal groups, one of which received papaveretum intramuscularly at intervals while the other was given a continuous intravenous infusion of papaveretum. Each patient was examined before operation, the procedure explained at length, and informed consent obtained. Preoperative medication (papaveretum 0·3 mg/kg and hyoscine 0·006 mg/kg) was given one hour before surgery. After Allen's test had been performed to check for ulnar artery blood flow, blood from a radial artery was taken for blood gas estimation before induction of anaesthesia (thiopentone 3-5 mg/kg followed by pancuronium 0·1 mg/kg). The patient was intubated and ventilated with 33% oxygen in nitrous oxide, and anaesthesia was supplemented as required with fentanyl 1 μg/kg.

A respiratory inductance plethysmograph was attached to the patient at the end of the operation before mechanical ventilation had been discontinued. This device consisted of two zig-zag loops of wire attached to elastic belts, one around the upper chest and the other round the abdomen.[3] Signals from these transducers were proportional to volume excursions of the rib cage and abdomen and were recorded on a tape recorder (Medilog, Oxford Instruments Ltd). The signals were summed while the tapes were being replayed to give a signal proportional to tidal volume. The tidal volume signal was calibrated using a Wright respirometer to measure the tidal volume administered by the ventilator. This technique enabled tidal volume to be measured continuously during the first 24 hours after surgery without interfering with the patient's airway. The tape recordings were later replayed and the adequacy of respiration assessed by examining the recordings for periods of small tidal volume (<300 ml) persisting for at least 10 minutes, apnoeic periods (>20 s), and periods of slow respiratory rate (<8/min) for at least 10 minutes.

Before discontinuing anaesthesia a 22-gauge cannula was inserted into the radial artery and flushed with heparinised saline. Muscle relaxation was reversed with neostigmine and atropine, spontaneous respiration was re-established, and the patient was extubated. When postoperative analgesia was required the group receiving intramuscular injections were given 0·25 mg/kg papaveretum and this dose was repeated every four hours as necessary. Those receiving continuous intravenous papaveretum received an intravenous loading dose at a rate of 1 mg/min until they could take a deep breath and cough effectively without undue pain. Eight times this dose was then given by continuous intravenous infusion over 48 hours using a Wright syringe pump (type MS16, Pye Dynamics Ltd). This infusion was discontinued within the 48 hours if pain had ceased.

All patients breathed 28% oxygen via a Ventimask for four hours after operation. Blood gases were measured before analgesia, one-and-a-half hours after analgesia, and with the patient breathing air before discharge from the recovery ward. Blood gases were also measured on the first, second, and fifth days after operation with the patient breathing air. Respiratory monitoring was continued for 24 hours after surgery.

The use of the linear analogue scale[4] to assess the severity of pain was fully explained to each patient before operation. The scale comprised a single 10-cm horizontal line, one end representing no pain and the other the worst pain imaginable. Pain scores were recorded on the first three days after operation.

Results

The distribution of patients in the two groups and doses of papaveretum are shown in table I. There were wide individual differences in analgesic dose. The mean analgesic dose was significantly greater in the intravenous group than in the intramuscular group ($p=0·033$, two-sample t test).

The mean pain scores recorded by the patients in the two groups are shown in fig 1. The scores were obtained 24, 48, and 72 hours after operation. There was a significant difference between the groups on day 1 and day 2 (two-sample t test) but no significant difference on day 3.

Satisfactory tape recordings of respiratory movements were obtained in seven patients in each group (table II). Six patients in the

Clinical Research Centre, Divisions of Anaesthesia and Surgery, Harrow, Middlesex HA1 3UJ

J A CATLING, FFARCS, senior registrar (present address: department of anaesthetics, Queen Mary's Hospital for Children, Carshalton, Surrey)

D M PINTO, FRCS, Clinical Research Centre scientific staff (present address: department of surgery, Tyrone County Hospital, Omagh, Northern Ireland)

C JORDAN, BTECH, research officer

J G JONES, MD, Clinical Research Centre scientific staff

intravenous group showed a sharp increase in tidal volume and decrease in respiratory rate after the dose of papaveretum. A representative recording in one patient is shown in fig 2. A typical example of the apnoeic periods in the respiratory trace is shown in fig 3. The respiratory trace before papaveretum was quite regular, but after the intravenous dose there were prolonged apnoeic periods. Pronounced variations in respiratory pattern were seen during the 24 hours of monitoring, the greatest effects being found in the first 12 hours (table II). The number of patients showing adverse respiratory effects was reduced in the 12-24-hour period in both groups. Low tidal volume (<300 ml) was more common in the intramuscular group,

TABLE I—*Age, sex, and body weight of patients and dose of papaveretum in 48 hours in the intramuscular and intravenous groups*

Case no	Age and sex	Weight (kg)	Dose (mg)
	Intramuscular group		
1	60 F	65	90
2	52 F	63	30
3	49 M	71	90
4	52 F	51	30
5	46 M	82	100
6	43 F	58	225
7	55 M	68	90
8	29 F	69	60
9	58 M	46	30
10	30 F	53	105
11	51 F	47	40
Mean ± SD	47·7 ± 10·2	61·2 ± 11·2	80·9 ± 56·4
	Intravenous group		
12	69 M	67	192
13	73 F	64	37
14	53 F	49	140
15	38 F	78	224
16	31 F	50	232
17	69 F	64	184
18	46 F	65	104
19	37 F	61	175
20	58 F	80	160
21	51 M	74	142
22	55 M	62	0
Mean ± SD	52·7 ± 14·0	64·9 ± 10·0	144·5 ± 72·8

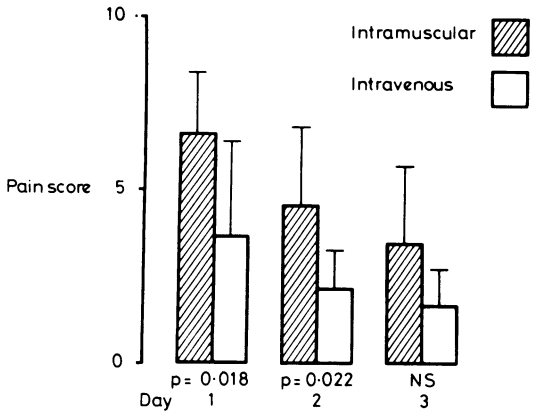

FIG 1—Pain scores recorded in the intramuscular and intravenous patient groups. Data on days 1 and 2 represent scores at the end of 24 and 48 hours ± 1 SD. Day 3 represents the scores when no papaveretum was administered. P values indicate significant differences between groups using two-sample *t* test.

TABLE II—*Changes in breathing pattern recorded in seven patients in each group. Numbers identify patients listed in table I. Cases 5 and 18 showed no significant deleterious change*

	Intramuscular group			Intravenous group		
	0–4 h	4–12 h	12–24 h	0–4 h	4–12 h	12–24 h
Tidal volume <300 ml	2,3,4,6,	2,3,6,	3	16	16	
Apnoea >20 s	1	1		13,14,21,	21	12
Respiratory rate <8/min	9	1		13,14,15	12,13,14,	12,13,

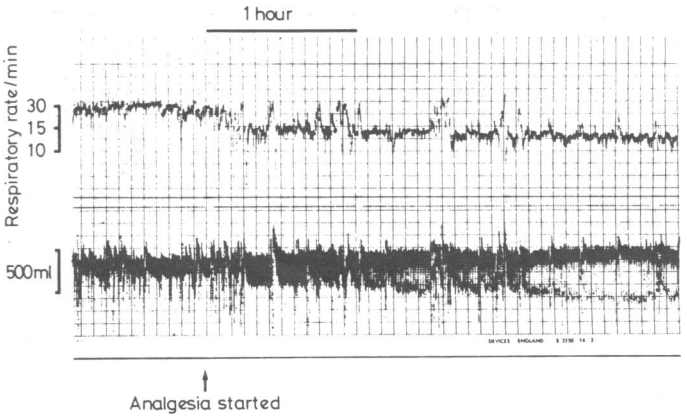

FIG 2—Fall in respiratory rate and increase in tidal volume after administration of intravenous papaveretum in one patient.

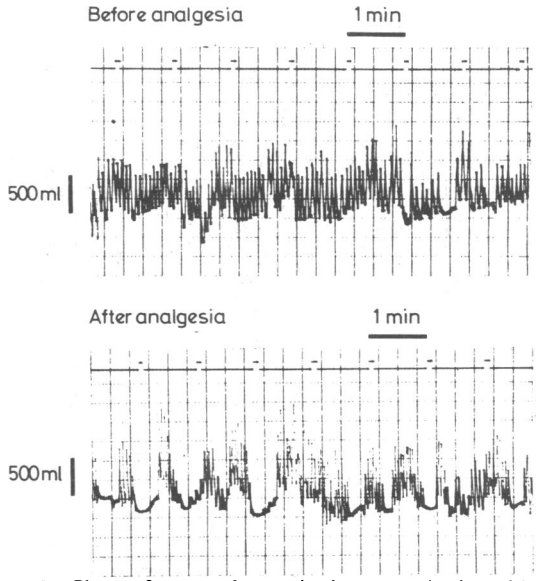

FIG 3—Change from regular respiration to respiration with prolonged apnoea after papaveretum.

while irregular breathing with apnoeic episodes of up to 40 s occurred in four of the seven patients in the intravenous group but in only one of the seven in the intramuscular group. These observations on respiration were reflected in the blood gas data as indicated by a tendency towards higher arterial carbon dioxide tensions and lower arterial oxygen tensions in the continuous infusion group. There was no obvious correlation in individuals between respiratory effects and the dose of analgesic. This indicated a large individual variation in susceptibility of the respiratory centre to the depressant effects of the analgesic drug.

Before operation there was no significant difference in $Paco_2$ or Pao_2 between the two groups. There was the usual postoperative hypoxia,[5] but the intravenous group showed a significantly greater fall in Pao_2 than the intramuscular group in the first 24 hours after the operation (fig 4). The fall in Pao_2 in the intravenous group was out of proportion to the rise in $Paco_2$, implying an unusually low gas exchange ratio or a greater ventilation-perfusion abnormality in the intravenous group. There was no significant difference in $Paco_2$ between the two groups from 24 hours after operation (fig 5).

Discussion

There was a wide individual variation in dose of papaveretum, which ranged from zero in one patient who had no pain after the operation to 0·8 mg/kg given as an intravenous loading dose. This indicated wide differences in pain thresholds and susceptibility to the analgesic effect of the drug and the problem of titrating a

dose against an endpoint that was not easy to define accurately. We expected that the intravenous group would be given a larger mean dose than the intramuscular group, as in Church's study.[6] This was confirmed and reflected the different priorities in administering papaveretum to the two groups of patients. In the intravenous group papaveretum was administered in response to specific questions about pain until the patient became relatively free of pain. In the intramuscular group the dose was determined by the response of the nurse to a specific complaint of pain by the patient. The latter regimen represents standard clinical practice and may explain the general complaint of inadequate postoperative pain relief, which stems mainly from poor

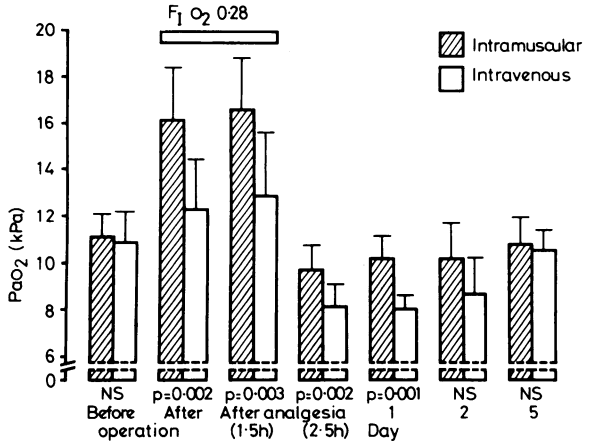

FIG 4—Changes in arterial Po_2 tension during the study (±1 SD). p values indicate significant differences between groups using two-sample *t* test. F_IO_2 = Fractional inspired oxygen.
Conversion: SI to traditional units—Pao_2: 1 kPa ≈ 7·5 mm Hg.

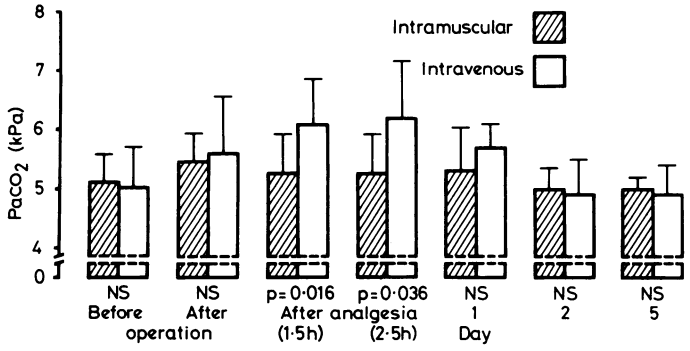

FIG 5—Changes in arterial Pco_2 tension during the study.

communication between nurse and patient and the fear of respiratory complications if larger or more frequent doses of analgesics were to be administered. Our study suggests that this fear is well founded.

Despite the fact that papaveretum was administered to achieve a pain-free state, patients in the intravenous group registered an appreciable amount of pain on their visual analogue scales on day 1 of the study. Nevertheless, there were significant differences in the pain indicated on the visual analogue scales between the two groups on the first two days of the study, and there was a striking clinical difference between the two groups. Those receiving continuous analgesia were alert and moved more easily while those receiving intermittent papaveretum tended to lie still and were reluctant to move because of pain. The reduction in pain with time was notable and was consistent with the findings of Rutter *et al.*[7]

The differences in the effect of the two regimens on respiration were notable. Unrelieved pain was often characterised by shallow rapid breathing which was well relieved by intravenous analgesia but little affected by the intramuscular dose. Despite the increase in tidal volume there was an inappropriately large fall in respiratory rate, and satisfactory pain relief was associated with respiratory depression indicated by a rise in $Paco_2$, slow respiratory rate, and periods of apnoea. Of these the most serious were apnoeic periods, during which there is an inevitable fall in Pao_2. It is now well documented that profound hypoxia occurs during obstructive sleep apnoea,[8] Pao_2 falling from 10·6±(SD) 1·15 kPa (79·5±8·6 mm Hg) awake supine to 4·9±1·5 kPa (36·8±11·3 mm Hg) during sleep apnoea. The hypoxia associated with these periods of sleep apnoea may have caused the deaths of several patients with these conditions by inducing cardiac arrhythmias. The sequence of events that compound the problem is a fall in Pao_2 due to impaired gas exchange after surgery,[5 9] respiratory depression leading to a further fall in Pao_2, and a period of apnoea leading to profound hypoxia with cardiac arrhythmia. In our study the most profound respiratory effects were recorded in the 12 hours after surgery, but we did not record sleep stages and we can only speculate about the exacerbation of these effects during certain stages of sleep. The persistence of hypoxia into the postoperative period, despite good pain relief, is consistent with the findings of others.[9] It has been fairly consistently shown that when postoperative pain has been relieved and patients can breathe and cough freely, beneficial effects on pulmonary function do not necessarily occur. This may be related to changes in lung volume induced by anaesthesia due to central shifts in blood volume[10] that may persist into the postoperative period.

We have confirmed that satisfactory pain relief may be achieved by intravenous administration of analgesic drugs. In contrast to the patients of Rutter *et al*,[7] who received a mean intravenous dose of 0·5 mg/h of morphine in 72 hours, our subjects required 3 mg/h of intravenous papaveretum in 48 hours to produce a similar degree of pain relief. Rutter *et al*[7] showed that this low dose of morphine was more effective in relieving pain than a mean dose of 2 mg/h of morphine given in intermittent intramuscular injections in a regimen similar to that used in our study. This is surprising considering the similarity in surgical procedures in the two studies and is also in contrast to the higher-dose regimen of intravenous pethidine used by Church.[6] Neither Church[6] nor Rutter *et al*[7] provided information about the respiratory effects of their different regimens. If the low-dose intravenous morphine regimen is confirmed to be effective in relieving pain it is important to examine the respiratory effects of this dose using continuous respiratory monitoring.

References

1 Fry EM. Postoperative pain. *Br Med J* 1976;ii:817.
2 Anonymous. Postoperative pain. *Br Med J* 1976;ii:664.
3 Jordan C, Pinto DJ, Jones JG. Postoperative respiration monitoring. In: *Proceedings of the third international symposium on ambulatory monitoring, 1979*. London: Academic Press, 1980:373-9.
4 Scott J, Hiskisson EC. Graphic representation of pain. *Pain* 1976;ii: 175-84.
5 Diament ML, Palmer KNV. Post-operative changes in gas tensions of arterial blood and in ventilation function. *Lancet* 1966;ii:180-2.
6 Church JJ. Continuous narcotic infusions for relief of postoperative pain. *Br Med J* 1979;i:977-9.
7 Rutter PC, Murphy F, Dudley HAF. Morphine: controlled trial of different methods of administration for postoperative pain relief. *Br Med J* 1980;**280**:12-3.
8 Schroeder JS, Motta J, Guilleminault C. Hemodynamic studies in sleep apnea. In: Guilleminault C, Dement WC, eds. *Sleep apnea syndromes*. New York: A R Liss, 1978:177-96.
9 Spence AA, Logan DA. Respiratory effects of extradural nerve block in the post-operative period. *Br J Anaesth* 1975;**47**:281-3.
10 Jones JG, Faithfull D, Jordan C, Minty B. Rib cage movement during halothane anaesthesia in man. *Br J Anaesth* 1979;**51**:399-407.

(*Accepted 14 July 1980*)