disease, as contrasted with improved prevention, did not play a major part in the overall decline in mortality from the disease during this period.

Category IV—Only one mother had been immunised by blood transfusion, bringing the total for 1977-83 to five.

Category V—As expected, the number of deaths from haemolytic disease due to antibodies other than anti-D varied little during 1977-83 being four, three, three, three, two, three, and four. Almost all were due to anti-c.

Category VI—The number of infants entered wrongly (in our opinion) as dying of haemolytic disease remained substantial. Although the number fell from 45 and 49 in 1977 and 1978 to 21 and 28 in 1979 and 1980, perhaps partly as a result of our earlier reports, the numbers scarcely changed subsequently, being 14, 19, and 17 in 1981, 1982, and 1983, respectively.

Category I (a and b) included five cases in which a woman had been treated with anti-Rh immunoglobulin after the immediately preceding pregnancy but had not been treated with it after one or more earlier pregnancies. It is debatable whether these five cases should rather have been included in category III.

Deaths of liveborn infants and stillbirths were considered together because obstetric practice plays a substantial part in determining whether a severely affected infant is born alive prematurely or dies in utero. Our results show that over 40% of the deaths of liveborn infants and of the stillbirths occurred at 28-30 weeks of gestation. Three deaths occurred in infants born alive before the 28th week of gestation. It is, of course, an anomaly that these deaths are registrable whereas stillbirths occurring before the 28th week are not, a fact that must lead to an underestimate of the overall mortality of fetuses from rhesus haemolytic disease.

The number of deaths due, indirectly, to the failure to give

anti-Rh immunoglobulin to the mother after previous deliveries continues to diminish. Our data, however, indicate that even if anti-Rh immunoglobulin were given postnatally to all mothers who were Rh (D) negative there would still be between 11 and 22 deaths from rhesus haemolytic disease each year in England and Wales (based on the figures for 1977-83). These deaths occur in women who develop anti-D by the end of a first pregnancy or in a second or subsequent pregnancy despite having received anti-Rh immunoglobulin postnatally. Evidence suggests that in a high proportion of such cases rhesus immunisation can be prevented by giving anti-Rh immunoglobulin antenatally.^{6,7} Clearly, the virtual elimination of rhesus haemolytic disease can be achieved only by giving anti-Rh immunoglobulin antenatally as well as postnatally.

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Relief of pain by infusion of morphine after operation: does tolerance develop?

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Abstract

To see whether continuous intravenous infusion of opiates provides more effective postoperative relief of pain than conventional intramuscular injection these regimens were compared in a prospective double blind trial. Thirty patients undergoing elective cholecystectomy were allocated randomly to receive an infusion of morphine or an infusion of placebo (control group) for 24 hours. Both groups were allowed supplementary morphine

boluses as requested. During the first 48 hours after operation the degree of pain was almost identical between the groups. Surprisingly, the group that was given the infusion of morphine received as much supplementary morphine as the control group during the first 24 hours and appreciably more during the 24 hours after the infusion had been withdrawn. Nausea and vomiting were more prevalent among the patients given the infusion of morphine.

These results suggest that continuous infusion of morphine may be an inferior regimen to intermittent bolus administration in the relief of postoperative pain. This may be explained by the development of tolerance in patients who received the infusion of morphine.

Introduction

The effective relief of pain after operations is a major problem in clinical practice.¹ After abdominal operations early post-operative analgesia is usually provided by opiates² administered by intramuscular injection when the patient's tolerance to pain

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has been exceeded. The alternative method of continuous intravenous infusion of opiates has been recommended on the basis that more effective relief of pain may be achieved, a lower total dose of drug is required, and fewer side effects are experienced.³

The aim of this study was to compare the effectiveness of continuous intravenous infusion of morphine with the conventional method of pulsed intramuscular administration of morphine in the relief of postoperative pain in patients after upper abdominal operations.

Patients and methods

Thirty patients undergoing elective cholecystectomy were studied. Patients were excluded if they were over the age of 70, had severe respiratory disease, were known to be allergic to morphine, or were already receiving treatment with opiated analgesics. Informed consent and approval from the ethics committee were obtained in all cases.

Anaesthesia was standardised and consisted of intramuscular morphine 10 mg one hour before operation and induction with a sleep dose of thiopentone followed by intravenous morphine 10 mg. Patients were paralysed with pancuronium, and anaesthesia was maintained with intermittent positive pressure ventilation of the lungs with 67% nitrous oxide and 0.5-1.0% halothane in oxygen. Cholecystectomy was performed through a right upper paramedian incision with routine drainage of the gall bladder bed by a tube drain. All abdominal wounds were closed in two layers with absorbable sutures. Deep tension sutures were not used. Skin was closed with interrupted silk stitches.

Postoperatively, patients were allocated randomly to receive an intravenous infusion of either 50 ml morphine sulphate (20 µg/kg/hour in isotonic saline) or 50 ml of isotonic saline (control group) for 24 hours after the operation. These infusions had been prepared previously by the pharmacy at the hospital, and their contents were unknown to the patient and the medical and nursing staff. Infusions were started at the end of the operation and administered with an infusion pump (Hospal K pen infusion pump, Electromedical Systems, Scotland) through an 18 gauge intravenous cannula into the contralateral arm to that into which routine intravenous fluid had been administered.

Additional postoperative relief of pain was available to both groups. All patients were asked regularly by the nursing staff if they were in pain and required analgesia. Those who had mild or more severe pain were given morphine sulphate 10 mg intramuscularly (not more often than four hourly). The cumulative dose of intramuscular morphine administered was recorded. Intramuscular morphine 10 mg (up to four hourly) was the only analgesic available to the patients in both groups during the second 24 hour period (24-48 hours after operation).

Postoperative pain was measured on a four point scale⁴: 0 for no pain, 1 for mild pain, 2 for moderate pain, and 3 for severe pain. Patients were familiarised with this scoring system before operation, and recordings were made one, six, 12, 24, and 48 hours after operation. In addition, any nausea or vomiting was recorded.

Data were compared using the Mann-Whitney U test unless indicated.

Results

Seventeen patients received infusions of morphine and 13 patients received infusions of saline (control group). Patients in both groups were comparable in age, weight, and sex (table I). No difference was seen between the groups in pain scores after operation; the percentage of measurements in each band of the scale of pain was similar between the groups. Pain scores were also similar when compared one, six, 12, 24, and 48 hours after operation. The groups therefore had similar profiles of pain (figure).

Table II shows the means and standard deviations of the cumulative doses of morphine given to patients in both groups during the first and second 24 hour periods. The patients who were given infusions of morphine received a mean (SD) of 31.6 (5.1) mg morphine by intravenous infusion during the first 24 hours, significantly more than the control group, who during the same period were given 20.8 (15.5) mg by intramuscular injection ($p < 0.05$). In addition, the patients who were given infusions of morphine also required a mean

TABLE I—Age and weight of patients and ratio of men to women

	Patients given morphine infusion (n = 17)	Control group (n = 13)
Mean (range) age (years)*	51.8 (32-70)	53.3 (24-66)
Mean (SD) weight (kg)*	65.4 (10.6)	66.3 (9.5)
Men: women*	2:15	3:10

*All differences between groups not significant.

Mean (SD) pain scores taken one, six, 12, 24, and 48 hours after operation. 0 = No pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain.

TABLE II—Mean (SD) doses of morphine (mg) administered by infusion and intramuscular injection

Method of administering morphine	Group given morphine infusion (n = 17)	Control group (n = 13)	p value
0-24 hours			
Infusion	31.6 (5.1)		
Intramuscular injection	24.7 (18.2)	20.8 (15.5)	NS
24-48 hours			
Intramuscular injection	21.2 (10.5)	11.5 (8.0)	<0.002
0-48 hours			
Intramuscular injection	45.9 (15.0)	32.3 (13.0)	<0.05
Total morphine administered	81.2 (31.7)	32.3 (13.0)	<0.002

dose of 24.7 mg by intramuscular injection in the first 24 hours. This was similar statistically to the dose of intramuscular morphine required by the patients in the control group during the same period.

When the patients received only intramuscular morphine, 24 to 48 hours after operation, those who had had an infusion of morphine required significantly more morphine than those in the control group (21.2 (10.5) mg *v* 11.5 (8.0) mg, $p < 0.002$). Patients who had infusions of morphine received a total dose—that is, intramuscular morphine plus intravenous morphine—of 81.2 (31.7) mg during the first 48 hours, whereas the patients in the control group received only 32.3 (13.0) mg morphine during the same period. This represented a significantly greater requirement for morphine by the group given infusions of morphine ($p < 0.002$).

Of the 17 patients who were given infusions of morphine, 14 experienced either nausea or vomiting compared with six of the 13 patients in the control group ($p < 0.05$, Cox's logistic empirical transfer⁵).

Discussion

Other studies have suggested that continuous infusion of opiates confers advantage over bolus intramuscular injection as better relief of pain is achieved with a lower total dose, resulting in fewer side effects.³⁻⁹ The mean doses used

in these studies ranged from morphine 12 mg/24 hours to papaveretum 72 mg/24 hours. Various protocols were used, but we were unaware of any double blind study used to test this hypothesis. Our study was performed double blind with a dose of 31.6 (5.1) mg given over 24 hours. An identical procedure (cholecystectomy) was performed in all patients so that the stress caused by having an operation was similar for both the treated and control groups.

The degree of pain experienced after operation was similar in both groups throughout the study (table III and figure).

TABLE III—Pain scores after operation. (Values are numbers (%) of total measurements)

Pain score*	Group given morphine infusion (85 measurements)	Control group (65 measurements)
0	20 (24)	15 (23)
1	30 (35)	25 (39)
2	25 (29)	18 (28)
3	10 (12)	7 (11)

*All differences between groups not significant.

Despite a bolus dose of morphine 10 mg one hour before induction and a second dose during induction, pain was worse immediately postoperatively (figure). The total abolition of pain by the use of narcotic analgesics may be undesirable because of the risk of respiratory depression. In this study, however, neither method achieved a satisfactory degree of analgesia as only a quarter of the measurements of pain were pain score 0. Over a third of the measurements of pain were considered to be excessive—that is, moderate or severe pain scores. The results therefore fail to substantiate the claim that continuous infusion of morphine produces better relief of pain.

Continuous infusion also failed to reduce the dose of morphine required. In addition to the fixed dose during continuous infusion, intramuscular morphine was given as required for pain; the dose delivered therefore was roughly titrated against pain. Both groups received similar amounts of intramuscular morphine during the first 24 hours. This resulted in the group who were given infusions of morphine having a significantly greater total cumulative dose of morphine (intramuscular plus

intravenous) during the first 24 hours ($p < 0.002$). During the second 24 hour period, however, after the respective intravenous infusions were withdrawn the group who had received infusions of morphine required significantly more morphine by intramuscular injection than the control group. The patients who had had infusions of morphine may have developed tolerance to morphine due to the significantly greater dose that they received during the first 24 hours.

Endogenous enkephalins, particularly β endorphin, are promoted by stress caused by operations¹⁰ and thought to represent an endogenous analgesic system.¹¹ Opiates act on endorphin receptors and produce analgesia.¹² Administration of intravenous morphine by infusion postoperatively causes a noticeable decrease in the plasma concentration of β endorphin.¹⁰ We hypothesise that the apparent tolerance shown by patients who received infusions of morphine may have been due to depression of the β endorphin system by the large dose of morphine received during the first 24 hours.

In conclusion, intravenous infusion of morphine at the dose used in this study failed to reduce the degree of pain beyond that which would require the prescription of morphine by intramuscular injection, and patients receiving morphine infusions appeared to have more side effects.

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SHORT REPORTS

Intravascular haemolysis induced by pentachlorophenol

Pentachlorophenol is a potent insecticide, fungicide, bactericide, and herbicide. It is soluble in water and organic solvents and is well absorbed through the skin, by ingestion, and by inhalation. Because of its toxicity strict precautionary measures should be taken when it is used, including wearing protective clothing and ensuring that the hands and face are well covered.¹⁻³ We report on a patient who developed intravascular haemolysis after negligent use of pentachlorophenol. To the best of our knowledge intravascular haemolysis has not previously been described as a side effect of this insecticide.

Case report

A 56 year old, previously healthy woman was admitted to our department for investigation of excessive weakness, palpitation, nausea, sweating, and systemic fever. The day before she had used an insecticide containing pentachlorophenol to clean wooden furniture. She had handled the solution and inhaled its vapour without taking any precautions.

On examination she seemed well, but pronounced pallor and mild jaundice were observed. The heart rate was 100 beats/min, blood pressure 100/

70 mm Hg, and temperature 39°C; the rest of the examination yielded normal results. The haemoglobin concentration was 7 g/dl, reticulocyte count 12%, and white cell count $8.1 \times 10^9/l$ with a shift to the left. A peripheral blood smear showed microcytosis, spherocytosis, and anisocytosis. The haptoglobin concentration was reduced, bilirubin concentration 62 $\mu\text{mol/l}$ (3.6 mg/100 ml) (indirect), and lactate dehydrogenase activity 414 IU.

During the first two days after admission she complained of excessive weakness, and the haemoglobin concentration dropped to 5.3 g/dl. She was given two units of red blood cells, and her haemoglobin concentration rose to 9.0 g/dl. Five days after admission a gradual improvement occurred paralleled by resolution of the fever, tachycardia, palpitation, and jaundice. Reticulocytosis (up to 30%) was noticed, but the haptoglobin and bilirubin concentrations and lactate dehydrogenase activity returned to normal. She was discharged two weeks later. Six months later her symptoms had not recurred.

Comment

This patient presented with intravascular haemolytic anaemia, and direct toxic injury with pentachlorophenol was postulated. There are many reports on the toxicity of pentachlorophenol, including cases with fatal outcomes.¹⁻⁴ Acute toxicity causes fever, sweating, tachycardia, tachypnoea, and pronounced generalised weakness; other features include headache, dizziness, nausea, and shock leading to