aspirates, *B. catarrhalis* was recovered in 15 patients (14.4%); other series have shown rates of recovery of 4%¹⁶ and 7%.¹⁷ In our series *B. catarrhalis* was isolated from bronchial secretions obtained by transtracheal puncture, which is widely accepted as the procedure of choice to collect uncontaminated material from the lower respiratory tract.^{2, 17, 18}

As we discarded transtracheal aspirates that included epidermoid cells, the possibility of contamination of these aspirates by oropharyngeal secretions can be ruled out.

In nine of the 10 patients who were followed up bacteriologically *B. catarrhalis* was isolated as a pure culture and the organism could be observed intracellularly in the leucocytes on the Gram stain. In one case it was associated with *H. influenzae*. Two bacterial species are often found to be associated in acute bronchopulmonary infection.¹⁹ *H. influenzae* and *Str. pneumoniae* were observed in 10 of our 104 patients and *H. influenzae* and "viridans" streptococci in another one.

We observed a positive correlation between resolution of the clinical features and the disappearance of *B. catarrhalis* from the respiratory tract. One patient (case 9) showed no clinical improvement despite ampicillin treatment, and a repeat transtracheal puncture yielded the same β -lactamase-producing, ampicillin-resistant, *B. catarrhalis* strain that had been present at the initial puncture. When cefuroxime, a cephalosporin active against this strain, was given clinical and bacteriological improvement ensued. β -Lactamase-producing strains of *B. catarrhalis* have recently been isolated from nasopharyngeal swabs obtained from children with suspected whooping cough.²⁰

B. catarrhalis, a normal inhabitant of the nasopharynx, presumably becomes pathogenic by spreading downwards to the lower respiratory tract, producing pneumonia. Similarly, pathogenesis of acute otitis media in children due to *B. catarrhalis* is most probably explained by an upward spread of the organism to the middle ear.¹³ But additional factors present in our patients most probably predisposed them to a *B. catarrhalis* pulmonary infection. Because of their clinical characteristics, our patients could be considered to be compromised hosts. They were all miners of anthracosilicotic coal who had altered pulmonary function; they had all suffered repeated infectious episodes, which must have damaged the bronchial ciliary mechanism; and they all received frequent corticosteroid treatment, which has been shown to have immunodepressant activity.²¹ The recently reported case of fatal *B. catarrhalis* pneumonia also

occurred in an immunodeficient host. Thus, *B. catarrhalis* seems to behave as an opportunistic pulmonary invader rather than a primary pathogen.

B. catarrhalis is sensitive to the penicillins commonly used in respiratory infections. But these antimicrobial agents will not be effective against β -lactamase-producing strains. Thus when usual treatment fails a transtracheal puncture is essential to identify accurately the causative organism and determine its in-vitro sensitivity to antibiotics.

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SIDE EFFECTS OF DRUGS

Delayed respiratory depression after use of fentanyl during anaesthesia

Concern about polluting operating theatres with anaesthetic gases and the wish to avoid using volatile inhalational agents have led to the increased use of potent narcotics given intravenously during anaesthesia. Drugs such as fentanyl and phenoperidine used as supplements to controlled ventilation with nitrous oxide, oxygen, and a muscle relaxant ensure that the patient remains asleep during surgery, and their analgesic effects are useful in the immediate post-operative period.

We describe three cases in which fentanyl was used as described above but in which severe respiratory depression occurred several hours after apparent recovery from the anaesthetic.

Case 1

An 18-year-old Pakistani man weighing 64 kg was admitted for condylotomy under general anaesthesia because ankylosis of the left temporomandibular joint, caused by a typhoid infection at the age of 2, restricted jaw opening to 7 mm. Papaveretum 10 mg and hyoscine 0.2 mg were given intramuscularly one hour preoperatively with little sedative effect. Anaesthesia was induced with intravenous propofol 450 mg, and blind nasal intubation was performed with a 7.5 mm cuffed, streamlined endotracheal tube while the patient breathed halothane in oxygen. Intravenous pancuronium (Pavulon) 7 mg and fentanyl (Sublimaze) 0.2 mg were given and the lungs ventilated by using an East-Radcliffe ventilator and Bain anaesthetic circuit with a fresh-gas flow of nitrous oxide and oxygen of 7 l/min. During the operation more fentanyl (0.275 mg) and pancuronium (5 mg) were given in divided doses. At the end of surgery, which took three and three-quarter hours, atropine 1.2 mg and neostigmine 3.75 mg were given. The patient was extubated when spontaneous breathing resumed. He coughed immediately and was talking within a few minutes.

The patient's condition remained satisfactory while he was in the recovery room, and one hour later he was returned to the ward, where he talked coherently to visitors. About four hours after the last increment of fentanyl he became increasingly drowsy with a slow, grunting respiration of three per minute. When he could not be roused laryngoscopy was performed and he was ventilated with oxygen by means of an Ambu bag. Some pharyngeal oedema was present. An anaesthetist, noting the pinpoint pupils, gave intravenous naloxone (Narcan) 0.4 mg with dramatic effect: the patient awoke immediately and respiration returned to normal. He needed no further naloxone and made an uneventful recovery. No postoperative medication had been given.

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Case 2

A 74-year-old woman weighing 48 kg was admitted for a simple mastectomy 14 months after advanced carcinoma of the breast had been treated by radiotherapy. She was in good general health, her only complaint being dyspnoea on exertion. Examination showed a pansystolic murmur, which was attributed to mild mitral incompetence. Arterial pressure was 180/65 mm Hg. There was no evidence of cardiac failure, but an electrocardiogram contained some evidence of myocardial ischaemia. Haemoglobin was 12.1 g/dl; serum urea and electrolyte concentrations were normal. Drug treatment at the time of surgery was digoxin 0.25 mg and frusemide 40 mg once daily and one potassium chloride (Slow-K) tablet thrice daily.

The patient was premedicated with morphine 5 mg and atropine 0.6 mg intramuscularly two hours before surgery. Anaesthesia was induced with intravenous thiopentone 150 mg and suxamethonium 50 mg, and an 8 mm cuffed Oxford endotracheal tube was passed. When muscle tone returned she was given intravenous alcuronium 10 mg and fentanyl 0.075 mg and ventilated with nitrous oxide and oxygen using an East-Radcliffe ventilator in the "circle-without-absorber" mode, with a fresh-gas flow of 6 l/min and a tidal volume of 700 ml. Surgery lasted 45 minutes, at the end of which atropine 0.6 mg and neostigmine 2.5 mg were given. She received no other drugs. Recovery was uneventful, and on return to the ward she conducted a normal conversation and was aware of her surroundings.

Three hours later she became increasingly drowsy with a slow respiratory rate and needed a nurse to sit with her; the anaesthetist could not account for the change in her level of consciousness. No treatment was given and she eventually recovered. No postoperative medication had been given.

Case 3

A 46-year-old woman weighing 60 kg was admitted for elective cholecystectomy. She had cervical spondylosis, which restricted neck movement, but was otherwise in good health. Papaveretum 15 mg and hyoscine 0.3 mg were given intramuscularly one-and-a-quarter-hours preoperatively. Anaesthesia was induced with intravenous thiopentone 240 mg, pancuronium 6 mg, and fentanyl (Sublimaze) 0.5 mg, and the patient was ventilated by means of a Nuffield ventilator and Bain anaesthetic circuit with a fresh-gas flow of 6 l/min. Pancuronium 2 mg and fentanyl 0.1 mg were given during the one-and-a-quarter-hour operation, at the end of which she received atropine 1.2 mg and neostigmine 2.5 mg. She was extubated when spontaneous breathing resumed.

In the recovery room she talked rationally, and reversal of the neuromuscular blockade was clinically adequate. Thirty minutes later she became cyanosed and respiratory arrest occurred. Ventilation of the lungs with oxygen by facemask was instituted and intravenous naloxone 0.4 mg given. She awoke immediately and respiration returned to normal.

Comment

Some respiratory depression may be expected in the immediate postoperative period. This may be due either to central depression produced by opiates,¹ barbiturates, or volatile anaesthetic agents or to a peripheral mechanism such as inadequate reversal of neuromuscular blockade or reduction in chest-wall compliance.¹ Investigation of the extent to which opiates produce respiratory depression has shown that when the CO₂ response curve is used as an index fentanyl has a significant depressant effect.² Most workers have found consistent decreases in the slope of the curve, although some have found only a parallel displacement.

Fentanyl is widely regarded as a short-acting opiate, but at typical dosage its respiratory depressant action lasts for at least four hours, and the magnitude and duration of effect are comparable to those of an equianalgesic dose of morphine.² A recent study³ found no significant differences in the intraoperative duration of action of equianalgesic doses of morphine, fentanyl, and phenoperidine and in the duration of postoperative analgesia. There is little evidence that fentanyl is a short-acting drug, although Foldes⁴ commented on the transience of the hypnotic as opposed to the analgesic effect when compared with that of other opiates, which may well be responsible for the generally held impression of a short duration of action.

Respiratory depression in the present patients was almost certainly precipitated by opiates, as in two cases the response to naloxone, a specific narcotic antagonist, was rapid and complete. Nevertheless, the intervening period of apparent recovery requires explanation. Becker *et al*⁵ showed that fentanyl has a biphasic effect on the ventilatory response to CO₂. In 26 patients respiratory depression (manifest as a decrease in slope of the CO₂ response curve) was maximal shortly after intravenous administration of the drug and then decreased steadily. Continued monitoring showed a second phase of respiratory depression, occurring when the patient was in the recovery room and maximal about 160 minutes after the last dose of narcotic. It was suggested that either varying levels of stimulation during the recovery period alter the response to CO₂ or fentanyl, like pethidine,⁶ is

secreted into the stomach to be reabsorbed on transit to the jejunum. Serum concentrations of the drug were not measured during the study, so the authors could not distinguish between these two possibilities. The pattern of depression seen was principally a decreased slope of CO₂ response without associated hypercapnia. The authors pointed out the possible risk imposed by an otherwise minor degree of airway obstruction in a patient who has little ventilatory response to such a CO₂ challenge.

Possibly, such an airway obstruction occurred in two of our patients, since case 1 had pharyngeal oedema and case 3 had cervical spondylosis. This together with an insensitivity to a rising alveolar PCO₂ may have trapped them in a cycle of increasingly inadequate ventilation associated with increasing CO₂ narcosis.

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Effect of quinidine on plasma concentrations of digoxin

Plasma concentrations of digoxin and quinidine were extracted in 12 patients admitted for cardioversion of atrial fibrillation or flutter. They had been receiving digoxin for at least four weeks and the treatment was continued in hospital. After a loading dose of quinidine sulphate (0.6-0.8 g depending on body weight) maintenance doses of quinidine were given as Kinidin Durules (each tablet containing 250 mg quinidine bisulphate, equivalent to 200 mg quinidine sulphate), three tablets twice daily. Blood samples were taken 12-hourly over the next three to five days. Quinidine concentrations were determined by a modified version of Cramér and Isaksson's method,¹ and digoxin concentrations by radioimmunoassay with commercial kits obtained

Plasma digoxin and quinidine concentrations in one patient. Conversion: SI to traditional units—Plasma digoxin: 1 nmol/l ≈ 0.8 ng/ml. Plasma quinidine: 1 μmol/l ≈ 0.3 μg/ml.