Down regulation of receptors depends on maintaining a continuously raised agonist concentration. While daily administration of high concentrations of the superactive agonist luteinising hormone releasing hormone analogue is capable of maintaining activity for prolonged periods, the fluctuation of blood concentrations may be the reason why rises in testosterone are sometimes seen during long term administration. Indeed, it is recognised with other peptide systems that maintaining a constant plasma concentration is critical in producing down regulation (unpublished observation). Thus there is every reason to suppose that a constant availability such as is produced by depot administration is likely to be more effective in maintaining the down regulation.

The regulatory peptide control system in the body has been relatively recently discovered but it is clear that it is highly complex and has an important role in the control of every organ system. Pharmaceutical intervention in the regulatory peptide system therefore offers considerable therapeutic potential. This has already been exploited with such agents as captopril, preventing the production of an active peptide, and naloxone, blocking the natural peptide receptor. It has not been possible, hitherto, to contemplate long term administration of peptide as treatment except in extreme circumstances, such as diabetes mellitus, where a poor drug delivery system is tolerable only in the face of a dire alternative. The availability of a safe, effective long term depot, which is capable of fulfilling this role, may therefore have a wide application, particularly as other superagonist regulatory peptides are developed.

Urinoma complicating papillary necrosis in diabetes

The term urinoma describes an encapsulated collection of urine that has extravasated from the upper renal tract. We describe a case in which a urinoma formed secondary to ureteric obstruction caused by a sloughed papilla.

Case report

A 76 year old woman with maturity onset diabetes normally controlled by diet presented with left sided abdominal pain, polydipsia, polyuria, and confusion of one week’s duration. She was severely dehydrated with tenderness in the left flank. On admission her blood glucose concentration was 39 mmol/l (703 mg/100 ml) with no evidence of ketonuria or hypernatraemia. The white cell count was 20.8 x 10^9/l with 83% neutrophils. Blood and urine cultures were sterile despite the lack of previous antibiotic treatment. She rapidly improved after administration of insulin and intravenous fluids, but the abdominal pain persisted.

Abdominal ultrasound (figure) showed the presence of a transonic mass adjacent to the left kidney. Ultrasound of the left kidney (Conray 325) intravenous urography confirmed the presence of an extrinsic mass causing lateral displacement of the kidney. The left collecting system was slightly distended and contained several lucent filling defects, particularly in the upper group of calices. The right lower pole of the kidney was displaced by the extrinsic mass, without evidence of obstruction of the ureter or renal pelvis. This suggests the tumour was arising from either the renal sinus or from the perinephric fat. There was no evidence of hilar or renal vessel involvement. The mass was confirmed histologically to be a renal cell carcinoma.

The patient was discharged from hospital with an intention of a planned right nephrectomy. The patient remains well except for debility due to diabetes with frequent hospital admission for fluid replacement. She is not a candidate for nephrectomy due to a previous myocardial infarction and her deteriorating general condition.

Respiratory depression after alfentanil infusion

Alfentanil (Rapifen) is a synthetic, short acting opioid, roughly one quarter as potent as fentanyl with one third the duration of action. Its pharmacokinetics render it suitable for administration by continuous intravenous infusion. We have been assessing the use of alfentanil by continuous infusion and report two cases of unexpected respiratory depression after its use.

Case reports

Case 1—A 72 year old man weighing 81 kg was scheduled to undergo cervical decompression. Premedication was with temazepam 30 mg by
Management of retained biliary calculi: relaxation of sphincter induced by ceruleide

Several non-operative techniques have been reported as effective in the management of retained stones after exploration of the common bile duct. Infusion of saline is of doubtful efficacy and infusion of cholate unreliable.\(^1\) Infusion of glyceryl mono-octanoate via a T tube is effective but induces erosive duodenitis.\(^2\) Other methods of proved efficacy include endoscopic sphincterotomy and extraction of stones, and percutaneous removal via the T tube tract.\(^3\) The first of these requires special skill, which is not available in many hospitals. Extraction via the T tube tract with a catheter that may be guided and a flexible choledochoscope is effective but requires six weeks' delay to allow for maturation of the T tube tract.\(^1\) I describe a simple method of treatment in which maximal relaxation of the sphincter was induced pharmacologically by ceruleide, which allowed large volumes of saline to be infused via the T tube without a deleterious rise in biliary pressure. Ceruleide is the synthetic analogue of caerulein and elicits a powerful cholecystokinin response with relaxation of the sphincter of Oddi.\(^5\)

Patients, methods, and results

Four patients with retained ductal calculi were treated according to a preset protocol. All had undergone cholecystectomy during the same admission, with exploratory and arterial blood gas and plasma potassium, and calcium values were all within the normal range. The patient gradually woke up and was extubated, talking and moving all four limbs within 180 minutes of the arrest.

Case 2—A 54 year old woman weighing 64 kg scheduled for vascular decompression of the fifth cranial nerve was premedicated with temazepam 30 mg by mouth. After alfentanil 32.5 μg/kg and thiopentone 200 mg an infusion of alfentanil 7 μg/kg/min was given for 10 minutes and then 16 μg/kg/min was given for 110 minutes. Curare 45 mg was used for neuromuscular blockade. Fifty minutes after stopping the infusion and after atriope 1-2 mg and neostigmine 2-5 mg she woke up and was conversing normally, saying that her facial pain was completely cured. Thirteen minutes later she stopped breathing and was immediately reintubated. Spontaneous ventilation was returned after alfentanil 0.4 μg/kg/min was given intravenously. The radial pulse remained palpable throughout. Plasma alfentanil concentration at the time of the respiratory arrest was 95 μg/l.

Comment

Respiratory depression is a well recognised complication after administration of opioid analgesics. The interesting feature of these two cases is that both patients had initial rapid, clear recovery from anaesthesia, with sudden respiratory arrest. Furthermore, the plasma alfentanil concentration in the second case was below that which would be expected to cause respiratory arrest. Unfortunately, the plasma alfentanil concentration was not measured in the first patient. These two respiratory arrests are unlikely to be due to second peaks in plasma alfentanil concentration as have been described for fentanyl,\(^2\) since all the available pharmacokinetic data suggest that plasma alfentanil concentrations decline exponentially after stopping administration.\(^1,3,4\) Possibly a decrease in ambient stimulation after transfer to the recovery ward may have been a contributory factor. Possibly also age was relevant in the first patient, as alfentanil elimination is prolonged with increasing age.\(^6\) Other workers have used infusion regimens with higher doses that were in 15 patients without problems for short duration of arterial respiratory depression.\(^7\) One such case, however, occurred in a series of 26 patients who had received alfentanil. We therefore recommend that when alfentanil infusions are used, as with other opioids, respiration should be monitored very closely in the initial postoperative period.

Neither the Committee on Safety of Medicines nor the manufacturers, Jansen Pharmaceutical Ltd, were aware of this potential problem with alfentanil. Nevertheless, since submitting this report we have learnt of a further, similar episode described in a patient in Canada.\(^7\)

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