Hypocalcaemia increases the narcotic effect of codeine

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Summary

Severe narcosis occurred in a patient with hypoparathyroidism given therapeutic doses of codeine phosphate.

Case report

A 50-year-old woman had suffered from rheumatoid arthritis for many years. Removal of a goitre in 1975 revealed amyloid which was also found in a renal biopsy later that year when chronic renal failure was diagnosed. Also in 1975 she developed troublesome diarrhoea and was given codeine phosphate up to 60 mg 8 hourly, although only initially with benefit.

In April 1978 she was admitted to hospital after several convulsions. Serum calcium was 1.37 mmol/l, phosphorus 2.37 mmol/l and albumin 37 g/l. A serum parathyroid hormone concentration of 0.45 ng/ml supported a diagnosis of hypoparathyroidism. Her serum calcium was initially controlled with 1, α -hydroxycholecalciferol and no further fits occurred, but subsequently the drug was stopped owing to hypercalcaemia. The patient stopped taking codeine because of lack of therapeutic effect.

In September 1978 admission was again required because of diarrhoea, which was controlled effectively by codeine phosphate 30 mg 6 hourly. Although her blood urea had only risen from 14 mmol/l to 20 mmol/l her condition deteriorated rapidly. Myoclonic jerks were prominent and there was a progressive diminution in her level of consciousness. An EEG showed generalized slow wave abnormalities consistent with metabolic disturbance. Because the serum calcium was again low at 1.87 mmol/l, calcium gluconate was injected i.v. but no clinical improvement occurred despite restoration of serum calcium to normal. Six days after admission she was rousable only with difficulty and, despite an arterial pH of 7.07 and plasma bicarbonate of 9 mmol/l (due at least partly to renal tubular acidosis), her breathing was strikingly slow and shallow.

Arterial PO_2 and PCO_2 were 12.3 kPa and 4.0 kPa respectively, breathing room air. The 'normal' response to this degree of metabolic acidosis would

be a PCO_2 of 1.2–2.8 kPa (Bone *et al.*, 1974). Sodium bicarbonate 150 mmol i.v. largely corrected the acidosis but caused no change in the clinical state. Although the pupils were not markedly constricted, the possibility of codeine poisoning was considered. No other sedative drugs were being given and there was no clinical or biochemical evidence of liver cell failure. Naloxone 0.4 mg was injected i.v. Within 30 sec she awoke and began to hyperventilate. The pupils dilated and severe retching occurred. Several further doses were given and by the following day she had recovered completely. Plasma concentrations of codeine and norcodeine before naloxone was given (16–18 hr after the last recorded dose of codeine) were 18.0 μ g/l and 11.0 μ g/l respectively by immunoassay, well within the therapeutic range (Findlay, Butz and Welch, 1977).

Three days later codeine and norcodeine were undetectable and no morphine was detected on either occasion. Since then she has remained well again taking 1, α -hydroxycholecalciferol.

Discussion

The reversal of narcosis by naloxone indicates that codeine or an endogenous opiate-like peptide had caused the clinical state. A number of mechanisms might explain an acquired intolerance to therapeutic plasma concentrations of codeine. The contribution of acidosis cannot be discounted simply because of lack of effect of i.v. bicarbonate but no evidence exists directly to link pH to opiate action. An interaction with hypocalcaemia is more likely. Tests on animals show that depletion of brain calcium can increase the analgesic effect of morphine. Intraventricular administration of calcium ion can antagonize the analgesic effect of morphine but the effect of peripheral injections of calcium is much less, possibly because morphine inhibits calcium uptake into the brain (Snyder, 1977). This might explain the lack of effect of i.v. calcium in the present patient. Changes in production or release of enkephalins within the brain probably account for many features of exogenous opiate administration (Kaneto, 1971).

As calcium has been implicated as a mediator of release of several other polypeptides, an interaction at this level is certainly possible.

It will be noted that the plasma levels of codeine, although within the therapeutic range, are inappropriately high in relation to the time since the last recorded dose. There are several possible explanations for this finding. Firstly, although detailed data on narcotic metabolism in renal failure are lacking there is quite likely to be a prolongation of plasma half-life of codeine with diminished renal function. Codeine is, however, commonly prescribed where renal function is as bad as or worse than in this patient, and unwanted effects other than constipation are rarely reported. Secondly, it is possible that larger or more frequent doses of codeine than those recorded on the prescription sheet were actually given. Although the patient's reduced level of consciousness was actually the main factor in preventing further doses being given it is also possible that the final dose given was closer than had been thought to the time of plasma sampling and that the dose had not been charted correctly. Although these latter hypotheses would explain the inappropriately high plasma concentration they cannot be tested and appear rather unlikely.

It is suggested that there may be unexpected problems in using codeine and other narcotic analgesics in hypocalcaemic patients.

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