CIMETIDINE AND PROLONGED POST-OPERATIVE SOMNOLENCE

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ABSTRACT

A case of prolonged post-operative somnolence is described. The patient was on concurrent benzodiazepine and cimetidine therapy. Cimetidine can cause impairment of metabolism of the benzodiazepines by inhibiting the hepatic microsomal enzyme system and its possible role in causing the prolonged somnolence is discussed.

KEY WORDS: INTERACTION (DRUG), cimetidine, benzodiazepine.

CIMETIDINE, a histamine antagonist frequently used for treatment of peptic disease, has been advocated as prophylactic agent against acid aspiration in anaesthetic practice.¹⁻⁵ Benzodiazepines are also frequently prescribed as premedicants to allay anxiety before operation. Recent pharmacokinetic studies have shown, however, that cimetidine can have significant interactions with the benzodiazepines, prolonging their action and exaggerating their clinical effects.^{6,7} The following report describes a case of prolonged post-operative somnolence in a patient on concurrent cimetidine and oxazepam therapy before operation.

CASE REPORT

A 65 year old man was admitted to University Hospital for investigation and surgical repair of hiatus hernia. He was 161 cm tall and weighed 52.2 kg. His past medical history included two ear operations, cholecystectomy and vagotomy with pyloroplasty, from which he recovered uneventfully. He was a smoker for forty-five years but a non-drinker. His medication at home included Maalox and an occasional aspirin for arthritis in the right arm. Laboratory investigations in hospital were all within normal limits. He was admitted eight days before operation and placed on cimetidine 300 mg four times daily. Oxazepam 30 mg was prescribed for night sedation; he took it for three nights and received

an extra dose the night before the operation. Pantopon 10 mg was administered intramuscularly as premedication 45 minutes before induction. The patient arrived in the operating room in satisfactory condition, calm but not overly sedated. Because of the hiatus hernia and reflux symptoms he was considered a potential risk for aspiration. The lungs were pre-oxygenated for three minutes, and following administration of thiopentone 300 mg and succinylcholine 100 mg, cricoid pressure was applied and a cuffed tracheal tube inserted without difficulty. The lungs were ventilated using a Bain circuit⁸ and maintenance of anaesthesia included nitrous oxide 66 per cent, enflurane 0.5 to 1.0 per cent and pancuronium 4.5 mg. Intravenous fentanyl to a total of 125 µg was also administered intermittently; 50 µg was given initially, 50 µg after 30 minutes and the final dose of 25 µg was administered 80 minutes after start of the operation. Enflurane was decreased to 0.5 per cent 45 minutes before the end of the operation and was discontinued 20 minutes later. Vital signs were stable throughout the operation, which was completed in three hours. Neostigmine 2.5 mg and atropine 1.2 mg were administered at the end of the operation and reversal of neuromuscular blockade was confirmed by a peripheral nerve stimulator demonstrating a normal train-of-four and sustained tetanus.⁹ However, the patient remained apnoeic and unconscious. Naloxone 0.2 mg was administered intravenously with no response. He was then transferred to the recovery room and placed on a ventilator. He remained somnolent after 20 minutes and a venous blood sample was drawn for analysis of enflurane blood level by gas chromatography. This was found to be less than 0.133 kPa (1 torr) or approximately 0.17 per

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cent.* After another 25 minutes he began to rouse and the trachea was extubated after one hour. He remained very drowsy and gradually improved over the next five hours.

DISCUSSION

As a histamine antagonist cimetidine decreases gastric acidity and is frequently prescribed for treatment of peptic disease. Cimetidine is also used prophylactically to prevent the development of stress ulcer, a not infrequent complication of major surgery. Recently it has also been advocated as a pre-medicant to decrease the risk of acid aspiration during induction of anaesthesia,⁴ tracheal extubation³ and particularly in obstetrical anaesthesia.⁵ Due to these medical, surgical and anaesthetic indications an increasing proportion of the surgical population confronting the anaesthetist is on cimetidine therapy. Anaesthetists therefore should be aware of the potential adverse effects associated with cimetidine therapy. This case report describes one of these.

Reported adverse effects associated with cimetidine therapy have been rare and have included possible bone marrow depression,^{10,11} decreased sperm count¹² and mental depression.¹³ These were felt to be dose-related and associated with long-term therapy, and generally are of no relevance to the practice of anaesthesia. Recently, however, two cases of cimetidine-potentiated warfarin toxicity were reported and clearance of warfarin and antipyrine were shown to be inhibited by therapeutic doses of cimetidine.^{6,14} This interaction was attributed to inhibition of the hepatic microsomal enzyme system by cimetidine. Subsequently, it was shown that cimetidine impairs the clearance of chlorthalidopoxide,⁷ diazepam and desmethyldiazepam.⁶

*Blood tension of enflurane was measured in a 10 ml sample of blood collected in a heparinized syringe. This was then equilibrated with an equal volume of air in a syringe which rotated in a water bath maintained at 37°C. The equilibrated air was carefully separated from the blood and injected into the gas sampling loop of a Hewlett-Packard Gas Chromatograph (#5730 A), which had been calibrated with known enflurane concentrations for determination of enflurane content. The remaining blood sample was then re-equilibrated with another equal volume of air and the process repeated. This process of serial extraction allowed a plot of enflurane content versus sample number. The intercept on the Y axis represented the concentration of enflurane in the gas phase which would have produced the original blood concentration. This, converted to tension at B.T.P.S. was the blood tension.

Hexobarbitone sleep time in rats was also prolonged by pretreatment with cimetidine.¹⁵ More significantly, in the diazepam study,⁶ five of six subjects pretreated for one day with cimetidine fell asleep after the diazepam injection, while the control group did not. The metabolic pathway of oxazepam being different from diazepam, it has been suggested that its metabolism might not be influenced to the same extent by cimetidine,¹⁶ but this has not been well documented and not studied in anaesthetized subjects.

The patient reported here admittedly had received a number of central depressant drugs other than the benzodiazepine and cimetidine. He received pantopon 10 mg as a premedicant and fentanyl 125 µg during operation; but as the last dose of fentanyl was administered more than one and a half hours before termination of the anaesthetic and as he had little response from naloxone, it was unlikely that his prolonged somnolence was narcotic-induced. However, it has been demonstrated that chronic cimetidine therapy can reduce liver blood flow and, to this extent, can prolong and exaggerate the effects of drugs such as morphine, whose clearance is primarily dependent on extraction by the liver.¹⁷ Such interference may potentiate the effects of pantopon and fentanyl, and the possibility that a larger dose of naloxone might improve the response remained.

Low dose enflurane was also used, but again this was discontinued twenty-five minutes before the end of the operation and the low blood level confirmed that enflurane was not a significant factor. Unfortunately blood gases were not measured, but the lungs were not hyperventilated and ample time was allowed for the arterial carbon dioxide tension to rise at the end of the operation.

There was no evidence of residual muscle paralysis as confirmed by the response to peripheral nerve stimulation. Nitrous oxide, due to its low blood solubility, would have been rapidly washed out of the body upon discontinuation. It is conceivable that the metabolism of thiopentone is also impaired, given the prolongation of hexobarbitone sleep time.¹⁵ However, this alone would not cause the prolonged somnolence, as recovery of consciousness after a single sleep dose of thiopentone is virtually independent of its metabolism.¹⁸ We are thus led to believe that the interaction of cimetidine with oxazepam, causing a higher steady state concentration of the benzodiazepam, has contributed significantly to this

patient's prolonged somnolence. While the other depressants administered can not individually account for the somnolence, they probably contributed to it in an additive fashion. Moreover, cimetidine may well interfere with clearance of opiates¹⁹ and this would help to explain the accompanying apnoea. Whether cimetidine would also interfere with the metabolism of inhalational agents is not known and this, as well as its effect on morphine clearance, is under investigation in our institution.

In summary, a case of prolonged post-operative somnolence is described and the possible role of cimetidine is discussed. It is important that anaesthetists be aware of this potential interaction with benzodiazepines and opiates when dealing with patients on cimetidine therapy.

ACKNOWLEDGEMENT

The authors wish to thank Dr. R. L. Knill for his permission to use the gas chromatograph and Mr. J. Strupat for his technical assistance.

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RÉSUMÉ

Les auteurs rapportent un cas de somnolence post-opératoire prolongée. Durant les jours précédant l'intervention le patient était sous traitement à la cimétidine; il recevait également une benzodiazépine au coucher. La cimétidine peut gêner le métabolisme des benzodiazépines au niveau du foie par une inhibition du système enzymatique microsomial. Son rôle possible comme facteur étiologique dans le cas rapporté est discuté.