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Benzodiazepine-opiate antagonism – a problem in intensive-care therapy

C. F. McDonald[1], S. A. Thomson[1], N. C. Scott[2], W. Scott[3], I. W. B. Grant[1] and G. K. Crompton[1]

[1]Respiratory Unit, Northern General Hospital, [2]Department of Pharmacy, Heriot-Watt University and [3]Department of Pharmacy, Western General Hospital, Edinburgh, Scotland, UK

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Abstract. A 14-year-old previously fit schoolboy was admitted with staphylococcal pneumonia secondary to influenza A infection. His condition deteriorated as he developed adult respiratory distress syndrome (ARDS); during a stormy recovery exceptionally high doses of benzodiazepines and opiates were given in order to suppress voluntary breathing during a successful period of assisted ventilation. It is possible that benzodiazepine-opiate antagonism developed. Subsequent studies in laboratory mice indicate that the respiratory depressant effects of morphine can be antagonized by prior treatment with lorazepam.

Key words: ARDS – Respiratory depression – Opiates – Benzodiazepines – Interaction

Reports of interactions between benzodiazepines and opiate analgesics have been contradictory. In man, chlordiazepoxide has been shown to prolong the respiratory depression caused by pethidine [1]. An earlier study suggested that diazepam did not alter the effect of pethidine in reducing responses to carbon dioxide [2]. It has, however, been reported that diazepam counteracts the respiratory depressant effects of pethidine in healthy volunteers [3]. In laboratory mice, chlordiazepoxide antagonizes morphine-induced analgesia [4] and intracerebroventricular diazepam or midazolam have been found to antagonize the antinociceptive effects of morphine [5]. In another study intraperitoneal diazepam could not be shown to antagonize morphine analgesia in mice [6], but it has also been reported that diazepam increases the respiratory depression caused in mice by morphine [7].

We describe a patient whose tolerance of extraordinarily large doses of diamorphine may have been related to the concurrent administration of lorazepam.

Case history

A fourteen-year-old previously fit schoolboy was admitted with staphylococcal pneumonia secondary to an influenza A infection. On admission he was moribund with a partial pressure of oxygen in the arterial blood (PaO_2) of 5.98 kPa, and a carbon dioxide tension ($PaCO_2$) of 3.87 kPa with a hydrogen ion concentration of 35 $nmol^{-1}$. He was immediately intubated and ventilated but his condition deteriorated and he developed ARDS. He had a stormy course with a number of complications including pneumothorax, severe bone marrow depression, liver function abnormalities, hyperkalaemia and metabolic alkalosis.

A major management problem was the extreme difficulty encountered in sedating him sufficiently to allow him to tolerate assisted ventilation with a volume-cycled machine (CAPE). In keeping with Unit policy at that time phenoperidine, combined with the benzodiazepine, diazepam, was given on an ad hoc basis as assessed by medical and nursing staff. Figure 1 shows the high doses of phenoperidine and diazepam which were soon required and were continued over 10 days. On day 11 the drug regimen was changed because of failure to ablate the patient's respiratory drive. Phenoperidine was changed to diamorphine, and lorazepam was substituted for diazepam. Although the administered doses of these drugs (Fig. 2) were very large and diamorphine was given by continuous infusion, this regimen was also ineffective. On day 17, despite very high plasma drug levels (lorazepam 5.3 μg/ml and morphine 320 μg/ml), the patient was conscious, his pupils were not constricted and he did not have any other features suggesting excessive opiate administration. A decision not to use muscle relaxants was made because of our inability to sedate him adequately. Facilities for alternative ventilation techniques such as high frequency ventilation

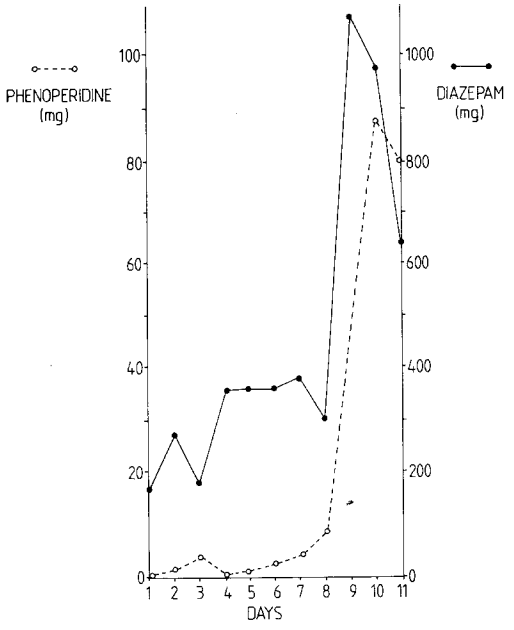

Fig. 1. Sedation requirement days 1 – 11

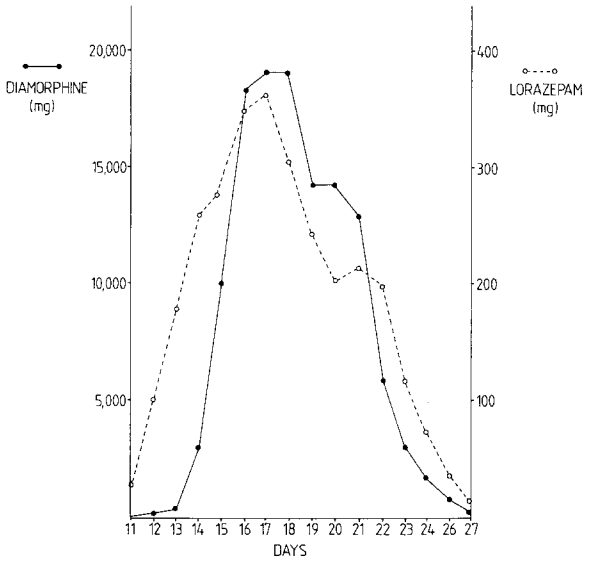

Fig. 2. Sedation requirement days 12 – 27

were not available. He made a gradual recovery but required a prolonged period of ventilation with positive-end-expiratory pressure and a high inspired oxygen tension in order to maintain an adequate PaO_2. Diamorphine and lorazepam were reduced in a stepwise fashion as his condition improved and were withdrawn 4 days before he was weaned off the ventilator.

Animal studies

The difficulties encountered in sedating this patient when the combination of benzodiazepine and opiate was used caused us to consider the possibility of benzodiazepine-opiate antagonism. To investigate this possible interaction in an animal model the effects of lorazepam on morphine-induced respiratory depression were studied in restrained mice. The index of respiration measured was the respiratory interval (the mean interval of time between respiratory excursions) using a bead thermistor activated device described by Crossland and colleagues [8].

In order to facilitate a constant restraint on the animals, they were encouraged to enter a 3-cm diameter perspex tube which contained a sensing device at the opposite end. Mice will usually readily investigate and enter a tube of such diameter spontaneously. Those reluctant to do so were excluded from the investigation. Respiratory intervals were measured 30 min after subcutaneous injections of morphine (10 mg/kg). The following day, the same mice received lorazepam (4 mg/kg) subcutaneously 30 min before the same morphine dose, and the respiratory intervals were measured as before (Table 1). There was a significant depression of respiration 30 min after morphine was given. After pretreatment with lorazepam, however, the same dose of morphine had a significantly reduced effect. Lorazepam alone (4 mg/kg) caused a small increase in respiratory interval (Table 1). The respiratory depression caused by morphine returned to control levels when tested on the same animals on the day after combined benzodiazepine/morphine, suggesting that the decreased effect seen in the presence of the benzodiazepines was not due to tolerance.

Discussion

Although both clinical observation and animal experiments supported the hypothesis that this patient's resistance to opiate sedation was due to benzodiazepine-opiate antagonism, other possible reasons for this phenomenon were considered.

Table 1. % increase of respiratory interval in mice

Morphine	Lorazepam + morphine	Lorazepam
40.6 + 4.0 (s.e.m.)	29.1 + 3.5* (s.e.m.)	8.6 + 2.2 (s.e.m.)
($n = 28$)	($n = 28$)	($n = 10$)

An increase in respiratory interval is equivalent to a depression in respiratory rate. *Significantly different from morphine alone ($p < 0.01$) Student's t-test paired

Drug purity was tested by high pressure liquid chromatographic analysis of diamorphine which revealed that its concentration was within the British Pharmacopoeial limits. The same batch of drug appeared to be effective when used in other patients. The purity of phenoperidine was not tested although it was also found to be active in other patients.

The rapid development of tolerance seems an unlikely explanation. Firstly, very rapid increases in drug experiments are not commonly observed as part of the phenomenon of tolerance. In addition, on day 27, when the patient was given a single 2 mg dose of phenoperidine with no benzodiazepine, the desired effect was achieved. A disparity between the relatively small dose of narcotic required when given alone and the much larger doses required when benzodiazepine was given concomitantly was observed throughout the course of the patient's illness. An idiosyncratic response to opiate would also seem improbable because there was an observed appropriate response to phenoperidine both in the initial phase of therapy and later when lorazepam was discontinued. During the period of assisted ventilation many drugs were given, including intravenous benzylpenicillin, flucloxacillin, erythromycin, gentamicin, sodium fusidate, co-trimoxazole, hydrocortisone, cimetidine and subcutaneous heparin. We are unaware of any evidence suggesting that any of these drugs antagonizes either opiates or benzodiazepines. Since cimetidine reduces the clearance of diazepam [9], its addition to the drug regimen would tend to increase the benzodiazepine effect. Other reports, however, suggest that metabolic clearance of oxazepam and lorazepam are not affected by cimetidine [10], nor is the disposition of morphine altered [11]. Cimetidine has been routinely given to all patients treated by assisted ventilation in this Unit for many years in an attempt to decrease gastrointestinal bleeding from stress ulceration. We have been previously unaware of any problems of drug interaction induced by this policy.

Hypercapnia and, to a lesser extent, hypoxaemia, are known stimulants of ventilation, and since this patient's blood gases were markedly deranged, it could be postulated that persisting hypercapnia in the presence of hypoxaemia stimulated respiratory drive to such an extent that the sedation given was ineffective. Although there was initially severe hypoxaemia (PaO_2 5.98 kPa), this was quite quickly reversed, and when the highest sedative dose was being given, blood gas tensions were within the normal range. On days 4 and 10 there were significant degrees of hypercapnia ($PaCO_2$ 6.47 and 6.61 respectively) but these reflected our inability to suppress the patient's respiratory drive. There was a long lag phase (approximately 36 h) between the highest degree of hypercapnia (day 14 – $PaCO_2$ 9.94 kPa) and the highest level of sedation required. Thus, although hypercapnia may have been a contributing factor, it is unlikely to have been the sole explanation of the sedation problems encountered.

Previous animal studies have suggested that certain benzodiazepines can antagonize the pharmacological effects of narcotics. In a study which investigated the effects of benzodiazepines and morphine on locomotor and analgesic responses in mice using the tail-flick and hotplate tests, the dose-related stimulation of locomotor activity by morphine was reduced by diazepam and oxazepam in doses which, alone, did not affect locomotor activity [6]. The same drugs did not, however, alter the analgesic response curve. Diazepam and oxazepam have been shown to be effective in increasing the LD_{50} of morphine and methadone in the mouse [12]. It has also been demonstrated that intraventricular midazolam significantly decreases the antinociceptive effect of morphine as measured by the tail-flick test [5]. This effect is partially antagonized by the GABA antagonist bicuculline, suggesting a GABA-link in the action of midazolam. In a study of the pharmacology of lorazepam [13] it was found to be highly effective in preventing morphine-induced excitement as measured by the Straub tail phenomenon.

The demonstration in our studies that lorazepam significantly decreases morphine-induced respiratory depression in the mouse supports the case for benzodiazepine-opiate interaction, which might explain why the very large doses of diamorphine given to our patient (19.2 g in 24 h) did not suppress his respiratory drive. The animal studies, although of a preliminary nature, indicate that some antagonism does exist between lorazepam and morphine, although not to the same degree as in the reported clinical case. This quantitative difference may reflect species variation. Alternatively, it may be a function of the doses used, or may be due to the fact that the animal studies examined the effects of opiate/benzodiazepine interaction acutely. The possibility of this drug interaction requires further study, and if confirmed might suggest caution in the use of a combination of opiates and benzodiazepines in respiratory intensive therapy.

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Dr. C. F. McDonald
Respiratory Unit
Northern General Hospital
Edinburgh
Scotland

Book review

Pocket Manual of Surgical Nutrition. F. B. Cerra. Oxford, Blackwell Scientific 1985. 21 figs., 33 tables, £ 21.00

This pocket-sized volume written by the director of the University of Minnesota nutrition service sets out to clarify the principles of clinical nutrition. It begins with a short historical perspective and goes on to provide a useful description of the clinical and pathological effects of malnutrition, together with their underlying metabolic causes. The clinical and laboratory assessment of a patient's nutritional status are then described and discussed in some detail as are techniques for determining different degrees of metabolic stress. Having defined the problems of malnutrition, the author considers the merits of treatment under individual circumstances. The calculation of nutritional requirements is described and a guide is offered to daily requirements of calories and substrates under conditions of starvation and different levels of stress. Recommended doses of vitamins and trace elements are also given. The roles of branched chain amino-acids and fat are discussed together with the changes in nutritional requirements that occur in the presence of hepatic and renal failure, as well as in pregnant and burned patients. On the background of all these data the book continues with a detailed consideration of enteral and total parenteral nutrition (TPN), firstly in a chapter on the rationale behind the choice of route to be used for feeding, and the practical steps to be taken when feeding is instituted, and then in separate chapters on the two modes of nutrition. The very useful chapter on enteral nutrition describes the major types of feed that are available with indications for their use, as well as their advantages and disadvantages. The chapter on parenteral nutrition is a little disappointing inasmuch as the tables describing the different regimens providing various calorie/nitrogen ratios and fat inputs are difficult to understand. Nevertheless, the text concerning the solutions and additives is valuable, as is the section on the techniques of peripheral and cyclic TPN. The place of TPN in the management of patients with carcinoma is put in perspective, and the chapter concludes with detailed guide-lines on TPN in infants and children. Routine monitoring is dealt with in a chapter that provides comprehensive interpretation of important results. However, the basic mathematics required for calculating nitrogen balance are not described and will be missed by junior staff. The complications of nutritional support receive thorough consideration, including lists of important drugs compatible and incompatible with TPN solutions, before nutritional support at home is considered. A final chapter examines the concept of the nutritional support service, and spells out the functions of the individual members of the team. The book is comprehensive and well set out with important references at the end of most chapters (but not indicated in the text). It has an accurate and effective index, and would be a useful addition to any medical library. Allowances must obviously be made for the fact that practices in the USA sometimes differ from those this side of the Atlantic (e.g. recommended calorie/nitrogen ratios are somewhat lower than those currently used in Europe). It is nevertheless surprising to find femoral vein canulation for TPN mentioned, and it is difficult to conceive the circumstances under which small bowel obstruction from carcinomatosis would be an indication for home parenteral nutrition. As a scientific text the work is somewhat spoiled not only by incomplete data in some of the figures, and occasional editorial errors (some of which are indecipherable), but also by English that is intermittently poor. Overall however the book must certainly be considered to have achieved its goal.

N. R. Fieldman (London)