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Prolonged Alfentanil Effect Following Erythromycin Administration

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Alfentanil is a potent synthetic opioid with a relatively short duration of action.[1] Alfentanil can be used for anesthetic induction and maintenance as a component of balanced anesthesia. We encountered a case where the time course of alfentanil was much longer than expected. The patient involved had received erythromycin preoperatively. A recent controlled study[2] confirmed that erythromycin can inhibit metabolism of alfentanil. This study used a small fixed dose of erythromycin (500 mg bid) in healthy volunteers and determined the change in alfentanil pharmacokinetic parameters. It did not, however, address the full extent of this interaction in the clinical setting such as prolonged respiratory depression and sedation. It also left unresolved the question of how much erythromycin must be given, and over what time interval, before an interaction will be seen. We therefore present this case and review the literature for other examples that document the clinical consequences and setting wherein this interaction might occur.

CASE REPORT

A 32-yr-old, 80-kg man was scheduled for an exploratory laparotomy because of persistent lower abdominal pain. He had been in good health until 6 weeks earlier when the pain began. He had no history of chronic illness and was taking no medications at the time of admission. Physical examination results revealed only a tender 7-cm mass in the right lower quadrant.

Laboratory results were normal. In the 24 hours before surgery, he received 1 g of erythromycin and 1 g of neomycin po three times ending on the morning of surgery and 10 mg of diazepam po 1 h before arriving at the operating room. While breathing oxygen *via* mask, he received 1.6 mg of pancuronium followed by 4.0 mg of alfentanil and 175 mg of thiopental for anesthetic induction. Tracheal intubation was accomplished after administration of 120 mg of succinylcholine. Anesthesia was maintained with 67% N_2O in O_2. Immediately after intubation, an alfentanil infusion was started at 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Additional pancuronium was administered to maintain one to two twitches of a train-of-four.

As surgical stimulation became more intense, the patient's heart rate and arterial pressure began to increase. In response, four bolus doses of 50 μg alfentanil were given over a 20-min period during which the infusion rate was increased to 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion was maintained at this rate for 45 min and then decreased to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over the next 30 min. At that point, 25 min before the end of surgery, the infusion was discontinued. Surgery to remove a large appendix took 2 h and 15 min during which time he received 14.9 mg of alfentanil in the infusion. Total alfentanil administered, including induction and bolus doses, was 20.9 mg or 260 μg/kg. A total of 9.5 mg of pancuronium was administered in five doses throughout the procedure. With three visible twitches on the monitor, muscle relaxation was reversed with neostigmine (2.5 mg) and atropine (1.0 mg) while 100% oxygen was administered. When the patient was still unresponsive and apneic 9 min later, despite the return of four strong twitches in the train-of-four, 0.1 mg of naloxone was administered. This was repeated after 3 min when no response was seen. Within 2 min, the patient began breathing and awoke, and his trachea was extubated.

The patient was taken to the recovery room where he was awake and alert. During his stay, he was described as comfortable, sleeping intermittently, and easily aroused with unobstructed respirations of 16–18 breaths per min. After 1 h, he was awake, alert, and oriented and was discharged to his room. He received no further medications during this time. One hour later, the patient was lethargic, *i.e.*, sleeping and unarousable to his wife (an emergency physician) and the floor nurse. His respiratory rate was 5 breaths per min. The patient was given 0.4 mg of naloxone im and rapidly returned to an alert state with normal respirations (above 10 breaths per min) as assessed by the same floor nurse. Approximately 1 h later, he began to complain of pain for the first time and received a single dose of 2 mg im morphine sulfate. For further postoperative pain, his physician ordered meperidine (75 mg) and hydroxyzine (25 mg) im. He had adequate pain relief and no unusual response to this regimen. The rest of his course was uneventful.

DISCUSSION

A recent study[2] in six volunteers showed that clearance of alfentanil was significantly reduced by 7 days of erythromycin administration (500 mg bid) but not by a single 500-mg administration. While these changes were significant, the average effect was not so great as to lead to

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obvious clinical effects. The average clearance in that study decreased from 3.9 to 2.9 $ml \cdot kg^{-1} \cdot min^{-1}$, which was associated with an increase in terminal half-life from 84 to 131 min. Furthermore, all of the subjects were not affected equally. Two subjects had a marked reduction in clearance, and in two others, clearance was hardly affected. The case presented here represents a different dose regimen of erythromycin administration than was given in the study. The patient received 3,000 mg of erythromycin over a 24-h period. This is a larger dose over a shorter time interval than that which was found to decrease clearance in the volunteer study.

In a previous study[3] investigating alfentanil as an induction agent in seven patients, a prolonged elimination half-life and decreased clearance were observed in one patient.‡ The only difference in the preoperative medications received by this patient was the inclusion of erythromycin (500 mg every 6 h) for nine doses prior to surgery. The patient was also studied§ for a genetic defect in metabolism by testing the elimination of Phenacetin. While a low elimination of Phenacetin was found, further investigations by others[4] showed that this particular metabolic trait is related to the debrisoquine gene but is not involved in alfentanil metabolism.

Yate *et al.*[5] reported another instance of prolonged respiratory depression following administration of alfentanil ($0.4\ \mu g \cdot kg^{-1} \cdot min^{-1}$) for postoperative analgesia and sedation during controlled ventilation. The patient in question behaved quite differently from all others similarly treated: extubation was not accomplished until 230 min after termination of infusion compared to 51 ± 24 min for the others and then only after 0.3 mg iv naloxone had been given. Respirations were described as satisfactory for an additional 420 min, and then she suddenly had a respiratory arrest that responded to 0.4 mg naloxone iv and im. They note that this patient was one of two in the study to receive erythromycin. The other patient had prolonged clearance but a normal clinical course.

These authors did not suggest that this problem was caused by erythromycin; however, they restudied[6] the patient with prolonged sedation as a volunteer at a later date. The patient was found to have a terminal half-life for alfentanil ($t_{1/2}$) of 161 min and a clearance of 1.96 $ml \cdot kg^{-1} \cdot min^{-1}$. These values are at the upper range of normal and are different from the clinical value measured during the infusion that resulted in prolonged respiratory depression, where $t_{1/2}$ was 720 min and clearance was measured as 0.66 $ml \cdot kg^{-1} \cdot min^{-1}$. While the authors were unable to account for these differences, they are similar to the changes reported for an erythromycin interaction in sensitive volunteers.[2]

The cases reviewed above describe a prolonged elevated serum concentration or effect of alfentanil. The common feature in all of the cases is the suggestion of an interaction between erythromycin administration and prolonged respiratory depression following alfentanil. Erythromycin is known to inhibit the metabolism of other drugs, most notably theophylline. After describing five children who exhibited signs of theophylline toxicity 36–48 h after beginning erythromycin therapy,[7] and finding increased theophylline concentrations in four of 11 patients taking the drugs concurrently,[8] Cummins *et al.* proposed an interaction between these drugs. Subsequently, controlled studies showed impaired clearance of theophylline after a 7-day course of erythromycin base 250 mg qid[9] and after a 10-day course[10] but not after the first two days.[10] *In vitro* studies have shown that erythromycin is N-demethylated and oxidized by cytochrome P-450 in the liver. A metabolite then forms an inactive complex with cytochrome P-450 leading to reduced oxidizing activity.[11] Alfentanil has been shown in humans to have oxidative N-dealkylation as its principal phase I metabolic pathway.[12] At present, it has not been determined which pathway is responsible for this interaction.

In summary, we described a patient receiving erythromycin who had prolonged respiratory depression following alfentanil. Based on this case and on two others reported previously, we recommend that caution be exercised when alfentanil is given to patients who have recently received erythromycin therapy.

References

1. Stanski DR, Hug CC: Alfentanil — A kinetically predictable narcotic analgesic (editorial). ANESTHESIOLOGY 57:435–438, 1982
2. Bartkowski RR, Goldberg ME, Larijani GE, Boerner TF: Inhibition of alfentanil metabolism by erythromycin. Clin Pharmacol Ther 46:99–102, 1989
3. McDonnell TE, Bartkowski RR, Williams JJ: ED50 of alfentanil for induction of anesthesia in unpremedicated young adults. ANESTHESIOLOGY 60:136–140, 1984
4. Henthorn TK, Avram MJ, Krejcie TC: Alfentanil clearance is independent of the polymorphic debrisoquin hydroxylase. ANESTHESIOLOGY 71:635–639, 1989
5. Yate PM, Short TSM, Sebel PS, Morton J: Comparison of infusions of alfentanil or pethidine for sedation of ventilated patients on the ITU. Br J Anaesth 58:1091–1099, 1986
6. Yate PM, Sebel PS: Abnormal alfentanil pharmacokinetics. Br J Anaesth 59:808, 1987

‡ McDonnell TE, Bartkowski RR, Bonilla FA, Henthorn TK, Williams JJ: Nonuniformity of alfentanil pharmacokinetics in healthy adults (abstract). ANESTHESIOLOGY 57:A236, 1982

§ McDonnell TE, Bartkowski RR, Kahn C: Evidence for polymorphic oxidation of alfentanil in man (abstract). ANESTHESIOLOGY 81:A284, 1984

7. Cummins LH, Kozak PP, Gillman SA: Erythromycin's effect on theophylline blood levels. Pediatrics 59:144, 1977

8. Kozak PP, Cummins LH, Gillman SA: Administration of erythromycin to patients on theophylline. J Allergy Clin Immunol 60:149, 1977

9. Prince RA, Wing DS, Weinberger MM, Hendeles LS, Riegelman S: Effect of erythromycin on theophylline kinetics. J Allergy Clin Immunol 68:427–431, 1981

10. Zarowitz BJM, Szefler SJ, Lasezkay GM: Effect of erythromycin base on theophylline kinetics. Clin Pharmacol Ther 29:601–605, 1981

11. Danan G, Descatoire V, Pessayre D: Self-induction by erythromycin of its own transformation into a metabolite forming an inactive complex with reduced cytochrome P-450. J Pharmacol Exp Ther 218:509–514, 1981

12. Meuldermans W, Van Peer A, Hendrickx J, Woestenborghs R, Lauwers W, Heykants J, Vanden Busshe G, Van Craeyvelt H, VanDerAa: Alfentanil pharmacokinetics and metabolism in humans. ANESTHESIOLOGY 69:527–534, 1988

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Preoperative Use of Erythropoietin in an Adolescent Jehovah's Witness

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Strategies used increasingly to avoid heterologous blood transfusion in the operating room include autologous transfusion, directed donor transfusion, intraoperative cell salvage, and hemodilution. Patients who are Jehovah's Witnesses will not accept heterologous transfusions on religious grounds.[1] Some Jehovah's Witnesses will accept intraoperative hemodilution and cell salvage as long as the blood remains in a circuit that is always connected to the patient. The problems of Jehovah's Witnesses are magnified in children who require major elective procedures entailing significant blood loss. While the courts will act to intervene and order transfusions in a life-threatening emergency, they have not done so in elective situations. Undertaking a major elective procedure without the use of heterologous blood may place the child at risk after the procedure is started or in the postoperative period.

Within the last several years, recombinant DNA technology has produced synthetic human erythropoietin that has provided a means to increase red cell production and red cell mass in severely anemic patients.[2] The most common use for the drug has been in treating anemia associated with renal failure.[3]

We report the preoperative use of recombinant DNA erythropoietin in an adolescent of the Jehovah's Witness faith who required placement of Cotrel-Dubousset rods for correction of scoliosis.

CASE REPORT

The patient was a 14-yr-old, 40-kg girl with progressive scoliosis. Her curvature was 42 degrees. Past medical history was significant for mitral valve prolapse and infrequent bouts of asthma. Pulmonary function study results obtained 6 weeks before surgery demonstrated mild peripheral airway obstruction (decreased forced expiratory flow at 25–75% vital capacity) and hyperinflation (increased functional residual capacity). Her hematocrit had been 39.5% 2 months prior to surgery. Initial discussions with the family revealed that her parents would accept hemodilution and use of cell salvage, but they adamantly refused to allow heterologous blood transfusion and would not permit the surgery to go ahead if transfusion was contemplated. With this background, and with the family's consent, we began erythropoietin (Epogen™, Amgen Inc.) administration to increase the patient's hematocrit before surgery. She was given 100 units/kg, subcutaneously, two to three times/week with iron supplements. She was treated with erythropoietin for 7 weeks (total of 15 doses), at which time her hematocrit increased to 47%, and surgery was scheduled. Her blood pressure at the start of treatment was 106/68 mmHg and was unchanged during the course of therapy. No side-effects of treatment were observed. The increase in hematocrit is shown in the table 1. The delay in response to erythropoietin was due to the patient not taking her iron supplements at the beginning of therapy.

On the day of surgery, she was given intramuscular morphine, glycopyrrolate, hydroxyzine, and inhaled metaproterenol preoperatively. An intravenous induction was carried out with thiopental sodium, fentanyl, and midazolam. Following induction of anesthesia, an 18-G catheter was inserted into the left radial artery. Tracheal intubation was facilitated with succinylcholine. A 4-Fr central venous catheter was inserted into the right external jugular vein. Two units of whole blood

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