UNCONSCIOUSNESS ASSOCIATED WITH MIDAZOLAM AND ERYTHROMYCIN

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SUMMARY
An 8-yr-old boy suffering from an asymptomatic ventricular septal defect was given erythromycin for antibiotic prophylaxis before adenoidectomy. Sixty minutes after premedication with oral midazolam 0.5 mg kg⁻¹ and oral atropine 0.03 mg kg⁻¹, an infusion of erythromycin 400 mg was started. When 200 mg of erythromycin had been infused, the patient lost consciousness, but other vital functions remained normal. After 45 min, he awakened spontaneously. At that time the plasma concentration of midazolam was 134 ng ml⁻¹. In order to investigate possible interactions between midazolam and erythromycin, we studied the pharmacokinetics of midazolam in six children of the same age undergoing minor otolaryngological surgery. The plasma concentration of midazolam in the patient who lost consciousness was significantly greater than in six other children without concomitant administration of erythromycin. The altered pharmacokinetics of midazolam may result from reduced hepatic clearance of midazolam caused by an enzyme inhibiting drug, erythromycin.

KEY WORDS

Midazolam is an effective oral premedicant in children. No marked side effects have been observed after doses of 0.4-0.5 mg kg⁻¹ [1]. Erythromycin inhibits metabolism of midazolam in vitro and has been thought to reduce its metabolism in man [2, 3]. We describe a child in whom the administration of erythromycin with midazolam (without any other medication) was associated with unexpectedly great plasma concentrations of midazolam and deep unconsciousness.

The pharmacokinetics of midazolam in this patient were compared with the pharmacokinetics of midazolam in children not given erythromycin.

CASE REPORT
We aimed to give an 8-yr-old boy (ASA II; weight 27 kg) erythromycin 400 mg (Abboticin, Abbott S.A., France) in saline 100 ml i.v. before adenoidectomy because of an asymptomatic ventricular septal defect. He was premedicated with oral midazolam 0.5 mg kg⁻¹ (Dormicum injection, Roche, Switzerland) and oral atropine 0.03 mg kg⁻¹ in 0.7 ml kg⁻¹ of fruit juice 60 min previously. On arrival in the operating theatre the child was fully awake. Heart rate was 96 beat min⁻¹, arterial pressure was not measured. Ten minutes after beginning the infusion of erythromycin, the child developed nausea and tachycardia. When 200 mg had been infused (40 min after commencing the infusion) the patient lost consciousness. He did not respond to verbal commands but reacted by withdrawal to noxious stimuli. He was breathing spontaneously and the airway was not compromised. No oral airway was inserted. The pupils were small and symmetrical.

The patient was transferred to the recovery room and the proposed operation was postponed. In the recovery room, heart rate and ECG were displayed continuously on an oscilloscope. Systolic and diastolic arterial pressure were measured using a sphygmomanometer every 5 min. Haemoglobin oxygen saturation was monitored by A. HILLER, M.D.; P. ISOHANNI; L. SAARNIVAARA, M.D.; Department of Anaesthesia, Otolaryngological Hospital, Helsinki University Central Hospital, Haartmaninkatu 4E, SF-00290 Helsinki, Finland. K. T. OLKKOLA, M.D., Department of Clinical Pharmacology, University of Helsinki, Pasikivenkatu 4, SF-00250 Helsinki, Finland. Accepted for Publication: June 23, 1990. Correspondence to A.H.
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Pulse oximetry (Ohmeda Biox 3700 Pulse Oximeter, Colorado, U.S.A.). The child was positioned on his side. When he was unconscious, haemoglobin oxygen saturation was 99%, systolic arterial pressure 100–120 mm Hg and heart rate 105–115 beat min⁻¹. Rectal temperature was 37.2°C. After 45 min the child awakened spontaneously and was a little drowsy but otherwise normal. No specific or non-specific antidotes to midazolam were given. At this time, 170 min after administration of premedication, plasma concentration of midazolam was 134 ng ml⁻¹. Thereafter the concentration declined rapidly and was below the limit of detection after approximately 24 h. The area under the plasma midazolam concentration–time curve from 0 to 24 h (AUC) was 601 ng ml⁻¹ h⁻¹ (fig. 1). Haemoglobin concentration, erythrocyte sedimentation rate, serum C-reactive protein, aspartate- and alanine aminotransferases, gammaglutamyltransferase and calcium concentrations were within the normal range. Serum protein electrophoresis was normal, except for the gamma fraction, which was 6.2 g litre⁻¹ (normal range 7.0–16.0 g litre⁻¹).

PHARMACOKINETIC STUDY

After institutional approval and informed consent from the children and their parents we studied the pharmacokinetics of midazolam in three boys and three girls (mean age 7.7 (SD 1.1) yr, weight 28.0 (2.4) kg), all ASA grade I, undergoing minor otolaryngological surgery with thiopentone-suxamethonium or vecuronium–alfentanil–halothane and nitrous oxide anaesthesia. None was taking any other drugs. The mean duration of anaesthesia was 63 (22) min. Oral midazolam (Dormicum injection, Roche, Switzerland) 0.5 mg kg⁻¹ and atropine 0.03 mg kg⁻¹ in 0.7 ml kg⁻¹ of fruit juice were given for premedication. Plasma concentrations of midazolam were measured before the administration of midazolam and after 30, 60, 120, 180, 240, 360 and 1440 min by gas chromatography with electron capture detection using methoxydiazepam as the internal standard [4].

The mean AUC was 214 (95% confidence interval 45–384) ng ml⁻¹ h⁻¹ and peak plasma concentration (Cmax) 73 (31–114) ng ml⁻¹ (fig. 1).

DISCUSSION

The plasma concentrations of midazolam in children not given erythromycin were comparable to those observed in an earlier study of oral administration of the same preparation of midazolam to children [5]. Following i.m. administration of the same dose of midazolam, it may be expected that the plasma concentrations of midazolam would be greater, as the bioavailability after i.m. administration in children is higher than after oral administration [5] because of first-pass metabolism. It has been shown in children that the bioavailability of 0.45 or 1.0 mg kg⁻¹ of oral midazolam is approximately 15%, whereas almost 30% of midazolam 0.15 mg kg⁻¹ is absorbed after oral administration [5].

In the present study, plasma concentrations of midazolam were significantly greater in the patient given erythromycin with midazolam than in the others. Theoretically, the observed difference could be caused by methodological problems in
determining pharmacokinetics, an inappropriate dose, increased absorption or reduced hepatic clearance. The first child had nausea, which could result in delayed absorption of midazolam; this would explain the greater concentrations of midazolam in the postabsorption phase. The greatest concentration of midazolam in our patient, however, was significantly more than the mean $C_{\text{max}}$ in the others. Therefore, in addition to possible delayed absorption, there may have been other kinetic differences between the child receiving erythromycin and the other children. Because the dose given to the child was checked and found to be correct, accidental overdose would seem to be an unlikely explanation of our findings. Correspondingly, on the basis of the studies in adults, increased absorption of midazolam does not appear to explain the present findings [6].

Reduced hepatic clearance appears to be the best explanation of the high concentrations of midazolam in our patient. This may be a result of interindividual variation but, in our case, more probably of an interaction with an enzyme inhibiting drug, erythromycin [7]. Interaction between midazolam and erythromycin has been suspected previously in patients treated in the intensive care unit [2, 3]. In these patients, high concentrations of midazolam could not be attributed to co-administration of erythromycin because of the critical condition of the patients and because of the concomitant use of drugs other than erythromycin and midazolam.

On the basis of the present study, we suggest that care should be exercised when prescribing midazolam for patients receiving erythromycin. However, controlled studies are needed to study possible interactions between midazolam and erythromycin.

REFERENCES