Fentanyl and midazolam anaesthesia for coronary bypass surgery: a clinical study of bispectral electroencephalogram analysis, drug concentrations and recall

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Bispectral index (BIS) was assessed as a monitor of depth of anaesthesia during fentanyl and midazolam anaesthesia for coronary bypass surgery. In 10 patients given morphine premedication, anaesthesia was induced with a combination of midazolam and fentanyl and thereafter maintained with a continuous infusion of a mixture of midazolam and fentanyl 5 and 50 µg kg⁻¹ h⁻¹, respectively. BIS was recorded continuously but not shown to the attending anaesthetist. Plasma concentrations of midazolam and fentanyl were measured five times during the procedure. An auditory stimulus was given during bypass. All patients were interviewed twice after operation for explicit and implicit recall. No patient had any anaesthetic complications. BIS decreased during anaesthesia, but varied considerably during surgery (range 36–91) with eight patients having values >60. Midazolam and fentanyl drug concentrations did not correlate with BIS. No patient reported explicit or implicit recall. During clinically adequate anaesthesia with midazolam and fentanyl BIS varies considerably. The most likely reason is that BIS is not an accurate measure of the depth of anaesthesia when using this combination of agents.

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Patients about to undergo general anaesthesia may fear that they will be aware of the operation and be able to remember it afterwards. Awareness with recall is rare, though, occurring in about 0.2% of patients undergoing anaesthesia for general surgery.¹ A greater incidence, >1%, has been reported during cardiac surgery.²

The bispectral index (BIS), derived from bispectral analysis of the electroencephalogram, has recently been introduced to monitor the depth of anaesthesia. Ideally such a monitor should measure the depth of anaesthesia irrespective of the anaesthetic agent(s) used or the type of surgical procedure. We investigated the clinical value of BIS during fentanyl and midazolam anaesthesia for coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB). A standardized auditory stimulus was presented at predetermined times during CPB and patients were interviewed for explicit and implicit recall. Plasma concentrations of fentanyl and midazolam were measured.

Methods
Ten patients with a mean age of 69 yr (range 50–83 yr) and scheduled for elective CABG surgery were studied after approval from the hospital ethical committee and informed consent. All patients were seen the day before surgery and informed about the study and its objectives. They were told that a sound (not specified in detail) would be presented during anaesthesia that they would later be asked to recall. About an hour after intramuscular premedication with morphine 5–15 mg, anaesthesia was induced with midazolam 0.05 (0.03–0.12) mg kg⁻¹ and fentanyl 10 (7–12) µg kg⁻¹. Pancuronium 0.1 mg⁻¹ was given as a muscle relaxant to facilitate endotracheal intubation. A continuous infusion of fentanyl and midazolam was started (5 and 50 µg kg⁻¹ h⁻¹, respectively) and maintained until completion of surgery; supplementary doses of fentanyl or midazolam were given at the discretion of the anaesthetist.

Standard procedures were used for CPB. Core temperature was reduced or was allowed to drift to 34°C. An auditory stimulus (100 dB, duration 60 s) was presented five times during CPB. BIS (Aspect Medical Systems; version 3.12, Natick, MA, USA) was measured continuously; the attending anaesthesiologist was not shown the output values.

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Fig 1 Bispectral index at various times during coronary bypass surgery (n=10): 1, before induction; 2, sternotomy; 3, heparin; 4, start of bypass; 5, end of bypass; 6, skin closure.

![Fig 1 Bispectral index at various times during coronary bypass surgery](image1)

Fig 2 Bispectral index plotted against midazolam plasma concentration (ng ml\(^{-1}\)) during bypass surgery (n=10).

![Fig 2 Bispectral index plotted against midazolam plasma concentration](image2)

Fig 3 Bispectral index plotted against fentanyl plasma concentration (ng ml\(^{-1}\)) during bypass surgery (n=10).

![Fig 3 Bispectral index plotted against fentanyl plasma concentration](image3)

Blood samples were drawn from the radial artery catheter before induction, at sternotomy, when heparin was given, at the start, middle and end of CPB, and at skin closure. Samples were stored in a freezer for blinded, batch analysis.

Patients were interviewed on each of the first 2 days after the operation using a fixed predefined questionnaire. At the first interview they were asked to describe their experience of anaesthesia. At the second meeting the patients were also asked specifically about recall of any special sound. They were given a number of associative proposals. If there was still no recall, the actual sound was presented and the patients were asked again for recollections from the surgical procedure.

**Results**

The 10 patients studied had mean (SD) body weight of 78 (13) kg. All patients had an uncomplicated surgical course, with a mean surgical time 158 (19) min and mean anaesthesia time 198 (35) min. Haemodynamic measurements were stable.

All patients were awake and fully oriented at arrival in the operating theatre and at induction BIS was between 96 and 99. BIS decreased in all patients with induction, but during surgery it varied between 36 and 91. Almost 40% of BIS values at the time of blood sampling were >60 (Table 1, Fig. 3).

Only two of the 10 patients studied did not have BIS values or >60 at some point during surgery. The BIS values in each subject during anaesthesia varied, with a range that was as small as 15 or as large as 50 (median range was 30).

No drug accumulation occurred. The median plasma concentrations of fentanyl and midazolam did not change during anaesthesia (Table 1). Plasma drug concentrations varied widely between individuals. BIS did not correlate with fentanyl \(r^2=0.13\) or midazolam plasma concentration \(r^2=0.034\); Figs 2 and 3. In individual patients, there was no correlation between drug plasma concentration changes and BIS.

No patients reported explicit recall of intraoperative events at interview on the first or second day after operation. No patient could recall the acoustic stimulus presented repeatedly during CPB, either after given strong associations or when actually hearing it.

**Discussion**

General anaesthesia is a state of pharmacologically induced depression of the central nervous system causing uncon-
Anaesthesia is not an on–off phenomenon but a continuum, a gradual depression of cognitive and autonomic functions. Most anaesthetics cause a dose-dependent increase in anaesthetic depth. Many hypnotics and anaesthetics also cause varying degrees of amnesia. Recollection of a stimulus requires an initial activation of the sensory system, central processing of the information and, finally, retrieval of information. The memory process can be separated into explicit or conscious learning and implicit or unconscious retrieval of information.

Awareness with explicit recall of intraoperative events is a feared complication of general anaesthesia with potentially serious adverse psychological sequelae. The incidence of explicit awareness with recall after general anaesthesia is, however, small: about two per thousand patients. Implicit processing has been shown to be less affected by general anaesthesia than explicit memory processing and may continue subconsciously during clinically adequate anaesthesia. Implicit intraoperative awareness and postoperative values are associated with a great likelihood of awareness also being present during clinical recovery. Anaesthesia is not an on–off phenomenon but a continuum, a gradual depression of cognitive and autonomic functions. Most anaesthetics cause a dose-dependent increase in anaesthetic depth. Many hypnotics and anaesthetics also cause varying degrees of amnesia. Recollection of a stimulus requires an initial activation of the sensory system, central processing of the information and, finally, retrieval of information. The memory process can be separated into explicit or conscious learning and implicit or unconscious retrieval of information.

The considerable variation in BIS observed here is, in some respects, similar to that found during sedation of intensive care patients. In our study BIS not only varied considerably but was, in general, surprisingly large. Such values are associated with a great likelihood of awareness and the capability to follow command. A BIS value of <60 is often regarded as the criterion for adequate anaesthesia, while a value of >70 is frequently seen during awakening. Several factors may have led to the observed variation in BIS. Hypothermia may have affected the BIS measurements during bypass, as discussed by Doi and colleagues. Cardiac surgery with profound hypothermia affects electroencephalographic recordings because of changes in conductance, but our patients were operated on at 34°C and gave no problems with recording apart from during diathermy. Furthermore, the variability was present both before and after the bypass period. The variability may, of course, be explained by inadequate depth of anaesthesia. Although we detected no apparent awareness during surgery, and although haemodynamic measurements were stable, muscle relaxants, beta-blocking drugs and blood volume changes could have masked many of these clinical indicators of adequate anaesthesia. No patient reported recall when actively interviewed on two occasions after operation, even though auditory stimuli are resistant to suppression by fentanyl and midazolam anaesthesia. No consistent decrease in BIS was found with increasing plasma concentrations of either drug. The most plausible explanation for the high BIS values seems to be that BIS reflects anaesthetic depth less accurately when fentanyl and midazolam are used as anaesthetics. We have shown in a previous study that increasing concentrations of nitrous oxide have no effect on BIS, and addition of fentanyl to propofol anaesthesia causes large BIS variations. The weak correlation between decreasing BIS and an increasing fentanyl concentration supports results obtained in volunteers.

As discussed above, no patient recalled events during the operation. The timing of, and technique for, evaluating awareness and recall have considerable impact on the results. The lack of any explicit recall in this study with so few patients is not surprising, as explicit recall is
infrequent. The lack of implicit recall of the auditory stimulation during surgery, which should be detectable even in the small number of patients in this study, confirms the adequacy of the anaesthetic depth. Technique and time of stimulation are important for implicit memory testing.\textsuperscript{23}

In conclusion, this study has shown that although anaesthetic depth was adequate and no recall was reported, BIS varied widely and values that are usually related to excessively light anaesthesia or wakefulness were occasionally observed. BIS did not correlate with midazolam and fentanyl plasma concentrations. A measurement such as BIS should, ideally, be suitable for determining the depth of anaesthesia for all anaesthetics on a common scale. For coronary surgery with fentanyl and midazolam anaesthesia, the BIS algorithm too often underestimates the depth of anaesthesia and does not accurately reflect plasma concentrations. Administering more anaesthetic to try to decrease large BIS values would result in an excessive depth of anaesthesia with delayed awakening and, perhaps, haemodynamic instability. BIS may be well suited to predominantly hypnotic drugs, but it is not useful for the midazolam--fentanyl combination commonly used for cardiac surgery.

References