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62:67–70, 1985

Plasma Levels of Beta-blocking Drugs prior to Coronary Artery Bypass Surgery

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The duration of action of beta-adrenergic blocking drugs such as propranolol and metoprolol is determined by the dose administered and by the plasma half-life. Propranolol has a half-life of approximately 2–5 h[1,2] and metoprolol one of 3–6 h,[2,3] and although the half-lives are relatively long, effects may be short lasting following small drug doses. This study was undertaken to determine whether or not commonly prescribed but relatively small dose schedules of propranolol and metoprolol, when continued until the day before or morning of coronary artery bypass graft surgery, reliably resulted in beta-blocker plasma levels within the therapeutic range at the time of anesthesia and surgery.

A therapeutic beta blocker plasma range has been proposed for awake patients with coronary artery disease, and, in both awake and anesthetized patients, a relationship between the logarithm of plasma propranolol level and beta-blocking effect has been demonstrated.[2,4–7] In awake patients, therapeutic effects of propranolol and metoprolol have been observed in the range of approximately 50–100 ng/ml,[8,9] although propranolol plasma levels from about 30 ng/ml have been reported to reduce the frequency of angina attacks,[5] and metoprolol levels above the 50–100 ng/ml range may be required to suppress heart rate (HR) exercise response in healthy volunteers.[10] A therapeutic range during anesthesia and surgery has not been established, although propranolol 50–100 ng/ml has been shown to significantly ameliorate the hemodynamic responses to stressful perioperative stimuli.[7]

METHODS

Sixty-eight patients, (57 men and 11 women, ages 40–75 yr) who chronically took propranolol or metoprolol, and who were scheduled for elective coronary artery bypass graft surgery, were investigated following institutional approval and informed consent. Patients had been taking either propranolol, 10 mg, 20 mg, or 40 mg, four times a day, or metoprolol, 50 mg, twice a day, for the preceding 1 month to 10 years. Beta-blocker therapy was continued until the day before or morning of surgery. In addition to beta blockers, 68 patients took dipyridamole (Persantine®), and 64 took nitrates. Patients taking cimetidine, phenothiazines, or heparin were excluded from the study, as these drugs alter propranolol kinetics,[11,12] and patients with renal, hepatic, gastrointestinal, or thyroid

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Received from the Departments of Anesthesiology and Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Accepted for publication June 14, 1984. Presented in part at the International Anesthesia Research Society, New Orleans, Louisiana, March 15, 1983.

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Key words: Anesthesia: cardiac. Heart: beta-adrenergic blockade. Pharmacokinetics: propranolol; metoprolol. Surgery: coronary artery. Sympathetic nervous system: beta-adrenergic blockade; propranolol; metoprolol.

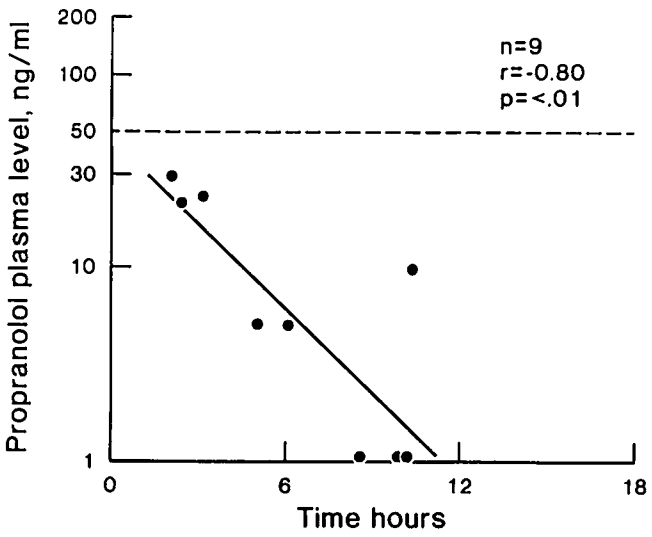

FIG. 1. Plasma levels following propranolol, 10 mg, four times per day. The relationship between plasma levels measured at anesthetic induction and time elapsed since the final preoperative oral dose is shown. The lower limit of the therapeutic range for propranolol (50 ng/ml) is indicated.

disease and those with congestive heart failure also were excluded, as such conditions alter propranolol metabolism.[13] Premedication was morphine 5–10 mg and diazepam 5–10 mg given im approximately 60 min prior to departure for the operating room.

In the operating room, prior to anesthetic induction, an arterial blood sample was removed for determination of plasma propranolol or metoprolol concentration and time interval between the preoperative beta-blocker administration and blood sample removal was noted. In addition, in 10 patients, propranolol concentration was measured during anesthesia, prior to skin incision and following sternotomy. (No intravenous propranolol was given in this period.) A high-pressure liquid chromatographic assay with fluorescence detection and pronethalol as internal standard was used to determine plasma beta-blocker concentrations.[14] Data were analyzed by plotting the time elapsed between preoperative beta-blocker administration and sample removal *versus* the corresponding beta-blocker log plasma concentration and concentration–time relationships for each group of patients were established. Linear regression analysis was used to determine correlation coefficients and P values; $P < 0.05$ was regarded as significant.

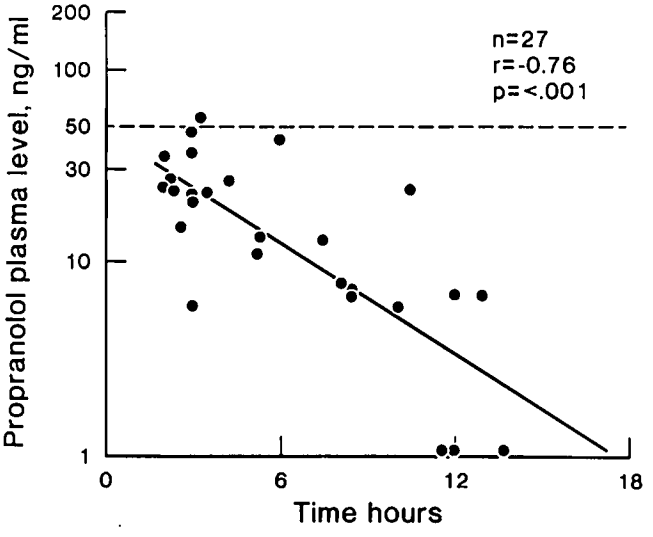

FIG. 2. Plasma levels following propranolol, 20 mg, four times per day. The relationship between plasma levels measured at anesthetic induction and time elapsed since the final preoperative oral dose is shown. The lower limit of the therapeutic range for propranolol (50 ng/ml) is indicated.

RESULTS

Figures 1–4 show the relationships between time elapsed since the final preoperative beta–blocker administration and log plasma drug levels at the time of anesthetic induction. The period that plasma concentration remained within the therapeutic range was estimated from the regression lines, and the duration of therapeutic concentrations can be seen in figures 1–4. Although correlations indicate that, on cessation of chronic oral therapy, beta-blocker plasma levels declined predictably with time, individual variation in drug level occurred following a given oral dose. This variation can be seen in Figures 1–4, where both regression lines and individual patient plasma drug levels are plotted. Propranolol, 10 mg, four times per day, and propranolol, 20 mg, four times per day, were ineffective in producing therapeutic plasma levels. Propranolol, 40 mg, four times per day resulted in levels within the therapeutic range for approximately 2 h, while metoprolol 50 mg twice a day produced therapeutic levels for about 4.5 h.

Prior to anesthetic induction, mean propranolol plasma level (10 patients) was 29.5 ± 30.5 ng/ml (mean ± SD). Plasma level decreased during anesthetic induction and antiseptic skin prepping to 20.9 ± 23.6 ng/ml (mean ± SD) immediately prior to skin incision ($P < 0.01$). Following sternotomy, mean level was 20.6 ± 29.9 ng/ml (mean ± SD), again significantly lower than the awake value ($P < 0.01$).

DISCUSSION

Maintenance of beta blockade prior to coronary artery bypass graft surgery generally is considered to be desirable, especially as awaiting surgery is emotionally stressful and surgery itself is associated with marked adrenergic stimulation.[15] However, results shown here

demonstrate that low but commonly prescribed dose schedules of propranolol and metoprolol did not consistently result in plasma levels within the therapeutic range at the time of anesthesia and surgery. Furthermore, even when therapeutic levels were achieved, they were only likely to occur at the time of anesthesia and surgery if the final beta-blocker dose had been administered within a few hours of departure for the operating room. Patients who had received propranolol 10 mg or 20 mg four times per day did not achieve therapeutic plasma levels and patients maintained on propranolol 40 mg four times per day would not be likely to have therapeutic levels unless oral therapy were maintained carefully until the time of surgery. Patients who received metoprolol 50 mg twice per day were better protected against subtherapeutic levels, providing oral therapy was continued to within a few hours of surgery.

Between anesthetic induction and skin incision, propranolol levels decreased sharply. The cause of this abrupt decline is unknown, but it may be related to intravenous fluid administration during induction. If supplemental intravenous propranolol is not given, then plasma levels that are therapeutic at induction may decline below the therapeutic range by the time of surgical stress.

Plasma propranolol and metoprolol ranges of 50–100 ng/ml have been suggested to be therapeutic.[2,4–7] This range is an indication of therapeutic beta blockade, although the clinical value of measuring plasma levels is not so clearly evident for beta blockers as it is for other drugs. It generally is agreed that a relationship exists between the logarithm of the plasma level and beta-blocking effect[2,4–7] (assessed by HR response to exercise or isoproterenol challenge), however, the dose–response relationship is flat such that a tenfold reduction in concentration results in only a halving of beta blockade. Plasma propranolol levels in excess of 30 ng/ml in awake patients reduce angina frequency by 25% or more, while at 100 ng/ml a high degree of beta blockade exists in exercising young volunteers.[4] Plasma propranolol levels in the range of 50–100 ng/ml during morphine–diazepam–halothane anesthesia have been associated with considerable attenuation of the hemodynamic response to coronary artery bypass surgery.[7]

These results are surprising in that beta blocker levels within the therapeutic range were observed so rarely. It may be that patients with lower plasma levels had good or adequate control of angina preoperatively, without recourse to higher dosage. However, higher dosage has been shown to result in more effective management of myocardial ischemia without much increase in incidence of side effects.[16,17] It is possible that patients who received low-dose schedules were accustomed to a sedentary life or were cautious about undue exertion and required only minimal beta blockade or perhaps had suffered side effects at higher dosage. However, such patients would be susceptible to inadequate beta blockade during surgery, as surgery is

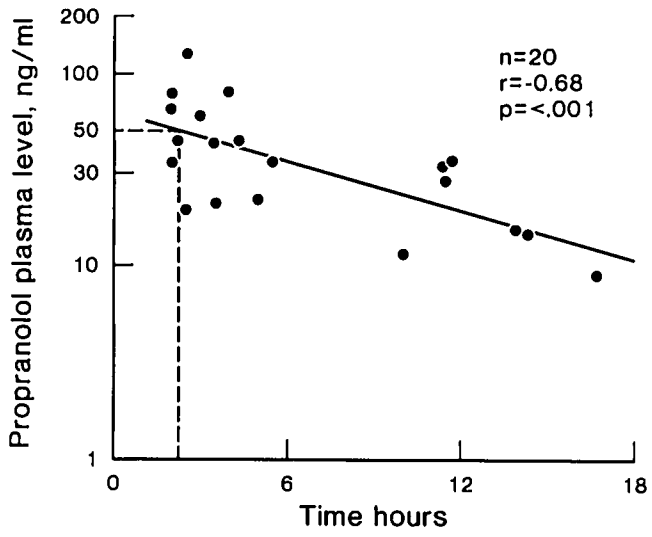

FIG. 3. Plasma levels following propranolol, 40 mg, four times per day. The relationship between plasma levels measured at anesthetic induction and time elapsed since the final preoperative oral dose is shown. The lower limit of the therapeutic range for propranolol (50 ng/ml) is indicated. The predicted duration of plasma levels within this range is approximately 2 h.

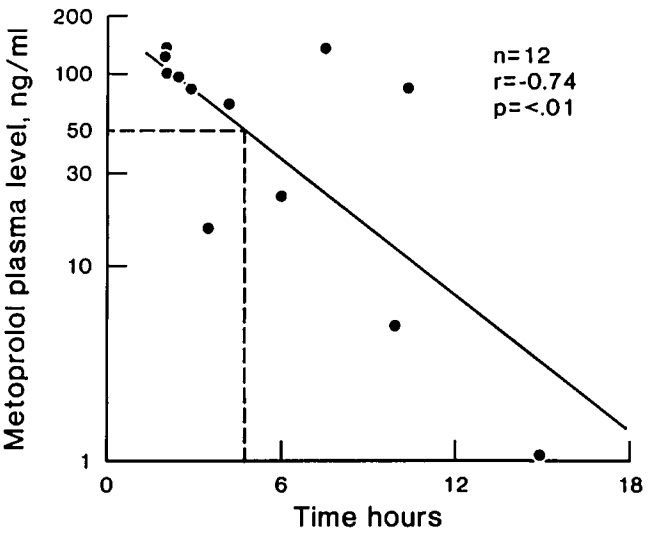

FIG. 4. Plasma levels following metoprolol, 50 mg, twice a day. The relationship between plasma levels measured at anesthetic induction and time elapsed since the final preoperative oral dose is shown. The lower limit of the therapeutic range for metoprolol (50 ng/ml) is indicated. The predicted duration of plasma levels within this range is approximately 4.5 h.

inevitably a stressful procedure. The results show that low-dose beta blocker therapy is not effective in producing therapeutic plasma levels and that medium dose therapy is not effective in producing sustained therapeutic levels. Patients receiving larger propranolol doses (>320 mg/day) have been shown to maintain therapeutic plasma levels, even if the final preoperative dose precedes surgery by as much as 24 h.[18] However in clinical practice in the United States, the average daily propranolol dose may be as low as 90 mg/24 h.[19]

We conclude that low-dose propranolol therapy (40–80 mg/day) is ineffective in producing therapeutic plasma levels, and that if therapeutic levels are desired at the time of anesthesia and surgery, then dosage ought to be increased. Medium dose propranolol (160 mg/day) and metoprolol (100 mg/day) is more likely to result in therapeutic levels, but such levels will become subtherapeutic unless oral therapy is maintained to within a short period of departure for the operating room.

The authors thank Harriet Morrow, Mae Olson, and Julie Vogen for their assistance.

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Anesthesiology
62:70–72, 1985

Misleading Mass Spectrometer Reading Caused by an Aerosol Propellant

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The mass spectrometer (Perkin-Elmer Medical Gas Analyzer, MGA-1100) displays a carbon dioxide waveform and inspired and expired partial pressures for oxygen, nitrogen, carbon dioxide, nitrous oxide, halothane, enflurane, and isoflurane. Accuracy of the partial pressure values is in part predicated on the fact that

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Key words: Equipment: mass spectrometer. Monitoring.