Propranolol Postoperative Maintenance by Continuous Intravenous Infusion

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In patients with coronary artery disease receiving propranolol and undergoing surgery, propranolol can be given up to the morning of surgery without adverse hemodynamic effects.1–4 If propranolol administration is terminated postoperatively for more than 24 h, the withdrawal rebound syndrome may occur,4 consisting of tachycardia, hypertension, worsening angina pectoris, ventricular arrhythmias, myocardial infarction, and even sudden death.5 During abdominal surgery, postoperative maintenance of propranolol by an iv administration seems logical when patients cannot take the drug orally for at least 24 h.

Few reports on the iv administration of propranolol in patients with coronary artery disease undergoing abdominal surgery procedure are available.6 We describe below the clinical benefits and the hemodynamic effects of a continuous iv propranolol infusion maintaining postoperatively the plasma propranolol concentration within the 14 to 90 ng/ml range. According to Pine et al.7 such a concentration range is associated with optimal relief of angina pectoris and with a 64–98% blockade of exercise-induced tachycardia.

PATIENTS AND METHODS

Seven patients (49–61 yr) scheduled for abdominal surgery and receiving propranolol therapy because of a documented history of angina pectoris (Grade III) gave informed consent to this study, which was approved by our medical staff (table 1). Preoperatively, propranolol therapy was well tolerated; no patient had clinical, radiologic, or ECG evidence of congestive failure or atrioventricular block. Blood urea and serum creatinine as well as liver function tests were all within normal levels.

The patients received their last oral dose of propranolol...
12 h preoperatively. Premedication comprised 20 mg diazepam orally, 2 h before induction of anesthesia. Patients were anesthetized with fentanyl iv (5 μg/kg), thiopental iv (4 mg/kg), and pancuronium iv (0.1 mg/kg) following which the trachea was intubated. Ventilation was controlled with 50% nitrous oxide and oxygen. Infusion of propranolol was begun approximately 6 to 8 h after the beginning of surgery when patients were normothermic and had normal blood gases during spontaneous ventilation. After an initial rapid infusion of propranolol (0.2 mg/kg during 10 min), a constant infusion rate of 1.0 mg·kg\(^{-1}\)·day\(^{-1}\) was maintained during at least 24 h until patients could resume oral propranolol therapy. Propranolol was administered in a 5% glucose solution through a central catheter by means of a constant infusion pump.

Blood samples for serum propranolol determinations were first obtained from an arterial catheter 12 h preoperatively, just before the last oral dose, and second, just before starting the infusion and from then on at intervals throughout the infusion (fig. 1). Each 10-ml sample was collected in a glass flask containing dry heparin, centrifuged and frozen at −20°C. Serum propranolol concentrations were determined in duplicate within 48 h using a fluorometric method. The sensitivity of the method was 3 ng·ml\(^{-1}\) in standard solution. Hemodynamic data (mean arterial pressure [MAP], pulmonary wedge pressure [PWP], and cardiac index [CI]), were collected via a thermodilution Swan Ganz catheter and a cannula inserted into a radial artery. Clinical status was evaluated for heart rate (HR), length and intensity of angina, D2 lead electrocardiographic monitoring and a twice daily ECG. Holter monitoring (V5 lead) was carried out over the 12-h period immediately prior to surgery and throughout the duration of propranolol infusion.

The plasma propranolol levels and hemodynamic data were analyzed by analysis of variance. Paired t tests were used to assess intragroup differences.

**RESULTS**

Propranolol infusion was performed for at least 24 h in all patients (range 24 to 66 h). The mean data for plasma propranolol concentrations observed during the study are summarized in figure 2. About 18 h after the last oral dose of propranolol, the plasma concentration was zero. The highest mean propranolol concentration value was obtained 5 min after the beginning of the rapid propranolol infusion. Thereafter, the slow infusion during 24 h produced a steady mean plasma propranolol concentration in the desired therapeutic range. The variations in mean plasma propranolol concentrations observed between the first and the 24th hour were not statistically significant. Considering individual results during propranolol infusion, plasma propranolol concentration was never less than 35 ng·ml\(^{-1}\) and exceeded 90 ng·ml\(^{-1}\) for three patients, respectively at the 18th, 42nd, and 66th hours of infusion.

![Image](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931421/)
Prior to surgery and during propranolol infusion, no patient complained of chest pain. Postoperatively, just as propranolol infusion was to begin, one patient had an attack of angina pectoris, with hypertension (220/120 mmHg) and tachycardia (130 beats/min). The rapid propranolol infusion then was started immediately and the symptoms disappeared within 5 min.

During propranolol infusion, as compared with preoperative Holter traces, there was no further depression of the ST segment, no lengthening of the PR interval, and no change in ventricular arrhythmias.

Figure 3 shows the mean hemodynamic results observed during the study. Postoperatively, about 18 h after the last oral dose of propranolol and before infusion, there was a statistically significant increase in HR (P < 0.01) and rate pressure product (RPP) (P < 0.01), as compared with preoperative data. During propranolol infusion, a significant reduction in HR and RPP (P < 0.01) was obtained, as compared with the data observed just before starting the infusion with those observed from the 10th min up to 24 h. In addition, the variations in HR, RPP, CI, PWP, and MAP between

**Fig. 2.** Mean plasma propranolol concentration (±SE) before and during propranolol infusion. B1: 12 h preoperatively, just before the last oral dose. B2: 6-8 h postoperatively, just before starting the infusion.

**Fig. 3.** Mean hemodynamic variables ± SE collected during the study. B1 and B2 = see legend for figure 2. *Value differs from B1 (P < 0.01). **Value differs from B2 (P < 0.01).
preoperative and +10 min, preoperative and +24 hrs, and +10 min and +24 hrs, respectively, were not statistically significant.

**DISCUSSION**

Shand and Wood\(^9\) claim that the propranolol withdrawal syndrome characterized by worsening of angina pectoris, ventricular arrhythmias, and myocardial infarction is a real but rare phenomenon, while Müller et al.,\(^5\) in a prospective controlled and blind trial in 20 ambulatory patients with coronary artery disease, report the syndrome in six patients with one death. These authors agree that the withdrawal syndrome is most frequent in patients with the most severe pretreatment symptoms, or those in whom propranolol had provided the greatest symptomatic relief, and in patients who remain physically active when the propranolol is discontinued. Although the exact causes of the withdrawal rebound phenomenon are not known, probably an inappropriate sympathetic hyperactivity or hypersensitivity is involved.\(^4,6\) When propranolol is discontinued before surgery in patients with coronary artery disease, myocardial imbalance between oxygen supply and demand may occur, either by an appropriate increase in \(\beta\) adrenergic activity consistent with anesthesia and surgical trauma, or by a true rebound phenomenon. To prevent such a myocardial strain, a postoperative prophylactic propranolol infusion may maintain a constant plasma propranolol concentration.

In the present study, in order to avoid deleterious hemodynamic effects in hemodynamically unstable patients, we started the propranolol infusion when postoperative problems such as anemia, hypovolemia, electrolyte disturbances, and hypothermia were corrected, about 16 to 18 h after the last oral dose of propranolol. When the propranolol infusion started, all plasma propranolol levels were zero. This complete absence of propranolol in the serum may be surprising, particularly for one patient receiving propranolol 40 mg \(\times\) 3 daily, associated with a 66 ng \(\cdot\) ml\(^{-1}\) preoperative plasma concentration, since the theoric elimination half-time is about 4 h. Although this fall in plasma concentration to zero in 18 hours is in the same magnitude of that observed by Wells et al.\(^10\) from 90 ng \(\cdot\) ml\(^{-1}\) to 20 ng \(\cdot\) ml\(^{-1}\) 16 h after a last oral dose of 40 mg \(\times\) 4 daily, a shorter elimination half-life\(^6\) may explain these findings. Since postoperative plasma propranolol concentrations were undetectable in our study, perhaps an inadequate \(\beta\) blockade existed during surgery and the immediate postoperative period. However, these zero levels do not indicate necessarily the complete absence of clinical propranolol effects.\(^11\) During surgery we observed no electrocardiographic signs related to myocardial ischemia, but postoperative tachycardia and increase in rate pressure product should have been a significant problem as demonstrated by a patient who exhibited clinical and ECG patterns of myocardial ischemia in the late postoperative period.

The efficacy of a constant infusion of propranolol is not yet well documented. In 13 patients receiving 3 mg \(\cdot\) h\(^{-1}\) of propranolol by a constant iv infusion, a mean plasma propranolol concentration of 80.75 \(\pm\) 28.5 ng \(\cdot\) ml\(^{-1}\) was observed by Smulyan et al.\(^6\) within the first 5 h of infusion. Afterwards, on nine occasions, the rate of infusion was modified, in order to maintain plasma propranolol concentration in the chosen range of 50–120 ng \(\cdot\) ml\(^{-1}\). No clinical adverse effects were noted, but hemodynamic measurements were available in only four patients, and none had Holter monitoring.

In a previous study, Wells et al.\(^10\) described a constant infusion technique (1.0 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) day\(^{-1}\)) achieving a steady mean plasma propranolol concentration of 54 \(\pm\) 4 mg \(\cdot\) ml\(^{-1}\) within 4 h. In three patients, the infusion was continued afterwards for 3 h. In our study and that of Mc Allister,\(^12\) an initial rapid infusion achieved an efficacious propranolol concentration in as little as 10 min. The decrease in plasma propranolol concentration observed, even though the priming infusion continued, may be interpreted as the temporary saturation of the liver's capacity to extract and metabolize propranolol.\(^13\) After this rapid infusion, the slow one (1.0 mg \(\cdot\) kg\(^{-1}\) \(\cdot\) day\(^{-1}\)) maintained plasma propranolol concentration in the desired therapeutic range up to 24 h.

The hemodynamic results observed during this study show that the reestablishment of therapeutic propranolol plasma levels controlled promptly the postoperative hemodynamic responses to multiple factors that influence cardiovascular function. In this regard, although propranolol is just one of the variables affecting hemodynamics in the postoperative period, the study of Mc Donald et al.\(^14\) demonstrated that iv propranolol produced a significant decrease in the responsiveness to isoproterenol of patients after coronary artery surgery.

In our patients, these results were obtained without any adverse effect on the myocardial function, as evidenced by the stability of the mean values of CI, MAP, and PWP both during the infusion and as compared with preoperative values. In addition, no patients developed bradycardia, hypotension, or myocardial failure during the infusion. Further, no adverse hemodynamic effects were noted in the three patients in whom the plasma propranolol concentration reached a value over 90 ng \(\cdot\) ml\(^{-1}\). As Zito et al.\(^15\) pointed out, the hemodynamic effects of administering propranolol to patients with coronary artery disease without left ventricular failure are the same whether the plasma propranolol concentration is high (788 \(\pm\) 134 ng \(\cdot\) ml\(^{-1}\); range 152–920 ng \(\cdot\) ml\(^{-1}\)) or conventional (43 \(\pm\) 7.2 ng \(\cdot\) ml\(^{-1}\); range 10–85
ng·ml\(^{-1}\)). However, in order to avoid clinical hazards of excessive plasma concentration, even in patients where preoperative propranolol is well tolerated, we suggest a reduction in infusion dose of propranolol in cases with poorly documented or altered left ventricular function, prolonged infusion exceeding 24 h, and abnormal liver function.

We conclude that in patients with coronary artery disease receiving long-term propranolol therapy and unable to take the drug orally because of abdominal surgery, the postoperative maintenance of propranolol by a constant infusion offers the potential of preventing the withdrawal rebound syndrome phenomenon without harmful hemodynamic and ECG effects.

REFERENCES


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Residents' Attitudes Toward Parents' Presence during Anesthesia Induction in Children: Does Experience Make a Difference?

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Allowing parents to be present with their children during induction of anesthesia may have advantages during this stressful phase of the surgical experience.\(^1–3\) Potential advantages include minimizing the need for heavy premedication, avoiding screaming and struggling if the child refuses to leave his or her parents, and possibly decreasing postoperative anxiety. Since an established practice in our Department is to allow parents to be present during induction of anesthesia, and since none of the residents who come to our program have had such an exposure previously, we designed this study to examine two specific questions. First, what was the attitude of incoming anesthesia residents toward our practice of having the parents present during anesthesia induction? Secondly, what changes, if any, occurred in the resident's attitude following a period of training where the parents actually are allowed to be present during induction of anesthesia?