Blood Lidocaine Levels and Kinetics following High-Dose Intramuscular Administration

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SUMMARY
In order to evaluate further the potential benefit of prophylactic intramuscular lidocaine administration in coronary artery disease, 24 patients with suspected acute myocardial infarction were given an intramuscular injection of lidocaine (10% solution) in the deltoid and gluteal muscles on consecutive days. Twelve patients received an intermediate dose (4 mg/kg), and 12 received a high dose (6 mg/kg) of lidocaine, and blood lidocaine levels were measured over a 4-hour study period.

Intradeltoid injection produced higher blood lidocaine levels and more rapid development of peak blood levels than did intragluteal injection. Administration of high-dose lidocaine (average dose 450 mg) into the deltoid muscle produced the ideal combination of rapid peak blood levels (6.5 μg/ml ± 2.1 SEM at 5 min) and persistence of therapeutic levels (>1.5 μg/ml) for over 2 hours. Although drowsiness, paresthesias, slurred speech, and tinnitus occurred in seven of the 12 patients in the high-dose group, no major neurotoxicity, such as grand mal seizures, were observed, nor was there evidence of hypotension or increase in atrioventricular block. Prophylactic administration of high-dose 10% lidocaine into the deltoid muscle appears to have potential for reducing the early mortality following acute myocardial infarction.

Additional Indexing Words:
Prophylactic administration Pharmacokinetics Lidocaine turnover rate

Previous studies have demonstrated that the major mortality following myocardial infarction occurs prior to hospitalization. In one study, 25% of coronary deaths occurred within 5 min, and 35% occurred within 1 hour of the onset of symptoms. Ventricular arrhythmias leading to ventricular fibrillation are considered the most common mechanism of this early mortality. Since prophylactic administration of intravenous lidocaine has been shown to reduce the in-hospital incidence of ventricular tachycardia and fibrillation in acute myocardial infarction, it has been suggested that early prophylactic administration of intramuscular lidocaine prior to hospitalization in patients developing symptoms might reduce this early arrhythmic mortality.

Several reports have shown that the intramuscular administration of 200-300 mg of lidocaine results in plasma lidocaine levels in the lower therapeutic range within 10-30 min, which persist for over 1 hour. The present study was designed to evaluate: (1) the effects of higher doses of intramuscular lidocaine, injected in two different sites, on both the rate of drug absorption and on the magnitude of lidocaine blood levels; and (2) the safety of administering large doses of lidocaine intramuscularly to patients with acute myocardial infarction.

Methods
Twenty-four patients, mean age 58 years (range 37-75 years) admitted to the Stanford Coronary Care Unit with suspected acute myocardial infarction, participated in this study within 4 days of hospitalization. Following informed consent, 12 patients received an intermediate dose of lidocaine hydrochloride, 4 mg/kg (average dose 321 mg) im into the gluteal muscle and the deltoid muscle on consecutive days. The lidocaine was administered as a 10% solution with a pH of 5.7 and an osmolality of 660 milliosmoles/liter. The sequence of injection sites was randomized by giving all intragluteal injections on odd and all intradeltoid injections on even days of the month. Twelve additional patients received two injections of a high dose of...
lidocaine, 6 mg/kg (average dose 456 mg), im administered in the same manner. Venous blood obtained just before and 5, 10, 15, 30, 60, 90, 120, and 240 min following each injection was assayed for lidocaine concentration by gas chromatography and expressed as lidocaine base (lidocaine base = 0.81 x lidocaine hydrochloride). Study of the distribution of 14C-labeled lidocaine in rats has shown equal distribution of the drug between red cells and plasma. This concept has recently been questioned. However, whole-blood and plasma concentrations of lidocaine are considered equivalent in this study, since the question remains open.

Of the 24 patients studied, 14 were subsequently classified as definitely, and five probably, sustaining an acute myocardial infarction. In the remaining five there was no evidence of acute myocardial damage. Excluded from the study group were all patients with atrioventricular block greater than first degree, with preceding cardiac arrest or cardiogenic shock. Patients with a moderate degree of congestive heart failure were not included.

All study patients were under continuous electrocardiographic monitoring; vital signs were obtained prior to the injection and at 2-hour intervals thereafter. The patients were closely observed and questioned regarding signs and symptoms of lidocaine neurotoxicity throughout each 4-hour study period.

Results

Blood lidocaine levels were related to both the dose and the location of injection. Following administration of the intermediate dose (4 mg/kg), mean blood levels peaked at 15 min reaching low (1.5 µg/ml) and moderate (2.5 µg/ml) therapeutic levels after intragluteal and intradeltoid injection, respectively (fig. 1). With each patient serving as his own control, significantly different lidocaine blood levels (P < 0.05) occurred only at 30 min following injection of the intermediate dose at the two different sites. From 2 to 4 hours after intermediate-dose injection at either site, blood lidocaine levels were identical and in a subtherapeutic range.

High-dose (6 mg/kg) im lidocaine resulted in significantly higher blood levels (P < 0.05) compared to the intermediate dose from 10 through 150 min following both intradeltoid and intragluteal injections (fig. 2). In addition, at the higher dose the rate of drug absorption from the two injection sites differed markedly. Intradeltoide administration resulted in the much more rapid development of peak blood levels than did the intragluteal injection (5 vs 30 min). Mean blood lidocaine levels from 5 through 120 min were also significantly higher following intradeltoid than following intragluteal injection. Blood lidocaine levels after high-dose intradeltoide injection persisted in the high therapeutic range for at least 30 min and remained over 1.5 µg/ml for more than 2 hours. Only one of the 12 patients failed to develop a blood level over 2.0 µg/ml within 10 min of the high-dose intradeltoid injection.

Patient acceptance of the intramuscular lidocaine injection was excellent. The injection resulted in minimal immediate discomfort, although mild tenderness at the injection site developed in some
patients within 4 hours, persisting up to 24 hours. No evidence of local inflammation was noted. Symptoms consistent with lidocaine neurotoxicity developed in two of the 12 patients in the intermediate, and seven of the 12 patients in the high-dose group. These included drowsiness, paresthesias of the tongue and lips, slurred speech, and tinnitus. No major toxicity, such as muscle tremor or convulsions, developed, and all symptoms cleared within 90 min of the injection. No hypotension was noted. Continuous electrocardiographic monitoring revealed no bradycardia or increase in atrioventricular block. The only significant arrhythmia observed during the total 48 study periods was one episode of ventricular tachycardia which developed 2 hours following intragluteal injection of high-dose lidocaine when the blood level had fallen below 1.5 µg/ml.

Discussion

The ideal antiarrhythmic drug to reduce the early mortality of coronary artery disease would be an effective, long-acting oral agent without significant side effects or cardiodepressant activity. In the absence of such an agent, new routes of administration have been explored for the in-hospital drug of choice, lidocaine. The oral route for lidocaine has not proved satisfactory, due to subtherapeutic plasma lidocaine levels attained despite large doses, the delay in peak blood levels (30–60 min after ingestion), variable gastrointestinal symptoms, and the prominence of neurotoxic symptoms.10,14 Several reports indicate that the i.m. administration of 200–300 mg of lidocaine results in low-to-moderate therapeutic blood levels within 10–30 min, which persist for over 1 hour.6–11 Since ventricular arrhythmias occur most frequently at the onset of myocardial infarction and may be relatively lidocaine-resistant,15 the rapid development of high therapeutic lidocaine blood levels is desirable. The use of combined i.v. and i.m. lidocaine administration has been suggested for this goal,16 but is not practical for prophylactic self-administration at the onset of severe chest pain. Our data indicate that intramuscular administration of high-dose (450 mg) 10% lidocaine into the deltoid muscle combines the virtues of both the i.v. and i.m. routes, i.e., the rapid development of high therapeutic blood levels and the persistence of therapeutic levels for over 2 hours.

Pharmacokinetic analysis (fig. 3) of blood lidocaine concentration following high-dose intra-deltoid injection reveals an initial exponential decay with a half-time (T½) of 21 min compared to a T½ of 5–10 min (without curve peeling) described following i.v. bolus administration of 1–2 mg/kg lidocaine.17 The prolongation of the initial slope following intramuscular lidocaine probably represents continued absorption of the drug during the phase of initial distribution of lidocaine from the blood to highly perfused tissues. The second exponential phase after intramuscular injection with T½ of 75 min is intermediate between the T½ of the second and third decay curves (40 and 120 min) following an i.v. bolus injection,17 and reflects primarily hepatic metabolism.18

The influence of injection site on the time and magnitude of peak lidocaine blood levels has been noted previously.11,19 Lidocaine absorption appears to occur most rapidly following intradeltoid injection with injection into the thigh and buttock yielding progressively later and lower peak lidocaine concentrations. Thus, in our study, intradeltoid administration consistently produced higher blood levels of lidocaine than the gluteal injections, but it is not possible to determine with certainty why more rapid absorption of the lidocaine occurred. However, several possible factors may contribute to the more rapid absorption. First, the blood flow to deltoid muscle groups may be greater than the flow to the gluteal muscles. Second, injection into the gluteal area may result in placement of the needle in fat tissue, leading to less rapid absorption. Third, since patients were hospitalized and in bed, there was minimal exercise of the gluteal muscles, while movement of the deltoid
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groups was less restricted. Clearly these observations have important implications for other drug administrations, and further studies have been initiated to elucidate the exact mechanisms involved.

The effect of lidocaine concentration on absorption following intramuscular injection remains controversial. The injection of 200 mg of lidocaine into the hamstrings of dogs in concentrations varying from 2 to 64% resulted in essentially identical blood concentrations.19 Similar blood concentrations of lidocaine were also obtained in healthy young men following injection into the lateral thigh of 200 mg of lidocaine, either as a 2% or 10% solution.20 Cohen and associates, however, recently reported that lidocaine plasma levels attained in man were inversely related to the concentration of the drug in the range of 6–10%.11 These findings should be confirmed by other investigators, since the administration of larger volumes will be required with lower concentrations. Even with the use of 10% solutions and reasonable volumes, we were able to achieve adequate blood levels in all patients studied.

The ability of lidocaine to suppress ventricular irritability resulting from acute myocardial infarction has been documented and appears to correlate with blood lidocaine concentration as previously described following i.v. administration.10, 21

The present study indicates that the im administration of high-dose (6 mg/kg) lidocaine is safe in patients with acute myocardial infarction, in the absence of marked bradycardia or cardiogenic shock. No hypotension nor increase in atrioventricular block was noted. The one episode of significant arrhythmia, ventricular tachycardia, developed 2 hours after the injection, when the plasma lidocaine level had already fallen to a subtherapeutic level.

A controlled study of prophylactic self-administration of high-dose im lidocaine at the onset of severe chest pain should now be undertaken in a group of patients at high risk of sustaining an acute myocardial infarction. Since other studies have demonstrated different patterns of absorption with concentrations of lidocaine from 6 to 10%, controlled prophylactic studies should utilize more than one concentration of the drug.

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