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Extracorporeal Pump Assistance – Novel Treatment for Acute Lidocaine Poisoning* **

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Summary. Accidental bolus administration of lidocaine ranging in dosages from 1000 mg to 2000 mg has caused death in humans. Because lidocaine clearance depends upon hepatic blood flow, drug clearance in a hypotensive overdosed patient is poor so that a drug overdose is likely to be irreversible. Traditional approaches to drug removal include hemodialysis and charcoal hemoperfusion. Neither treatment would be effective for lidocaine overdose because the drug is a myocardial depressant and because the clearance rates of these techniques are 100–200 ml/min. Hepatic clearance of lidocaine is 1000 ml/min in a human with normal cardiac output. We have tested a new concept for removal of high clearance drugs that are associated with myocardial depression. Cardiac bypass support was used in a dog experiment to demonstrate that restoration of cardiac output could restore high clearance of lidocaine. Sixteen anesthetized dogs were given 30 mg/kg boluses of lidocaine. In one group of eight dogs, toxicity was treated with antiarrhythmic drugs, pressor drugs and cardioversion. Six out of eight of these animals died within 30 min after lidocaine infusion. In the second group of eight dogs, an extracorporeal bypass pump was used for 90 min after the lidocaine injection. None of these assisted animals died. Drug clearance in dogs treated with the extracorporeal pump was compared to drug clearance in eight dogs that received non-toxic lidocaine doses of 3 mg/kg. Drug clearance was 39.75 ± 4.16 ml/kg/min in the overdosed animals compared to 38.29 ± 8.6 ml/kg/min in the non-toxic animals. Thus, drug clearance was normal in dogs treated with the extracorporeal pump. These experiments suggest that short-term support of the circulation with an extracorporeal pump could theoretically be effective in reducing patient mortality from acute massive lidocaine overdose.

Key words: lidocaine overdose; lidocaine kinetics, extracorporeal pump, hepatic clearance, cardiac output

Acute lidocaine poisoning secondary to massive overdosage is being recorded with increasing frequency [1–3]. The drug has found widespread use for suppressing ventricular ectopy in the setting of suspected or documented myocardial infarction [4–6]. Initial administration is usually by a 1.5 mg/kg intravenous bolus supplemented by secondary boluses and then by a continuous infusion to maintain therapeutic serum levels of 1.4–6.0 μg/ml [7, 8]. Accidental overdoses typically occur at the time of bolus loading and have been reported as high as 2000 mg (30 mg/kg) with catastrophic results [1]. Convulsions, refractory arrhythmias, and cardiovascular collapse are common terminal events. Hemodialysis and charcoal hemoperfusion are the conventional techniques for removing toxins from blood. Either of these treatments is unsuitable for a lidocaine overdose for two reasons. First, cardiac output is low making both procedures difficult to perform. Second, the maximal clearances of these techniques is 100–200 ml/min. When cardiac output is normal, the liver can metabolize lidocaine with a clearance of 900–1000 ml/min. We propose a new concept for treating overdoses of high clearance drugs that depress myocardial func-

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** *Editorial's Remarks:* According to our editorial rules this journal does not accept experimental studies in animals. In the following paper an exception seems to be justified, in so far as the study suggests a new approach to the treatment of certain intoxications in man. F. G. and H. J. D.

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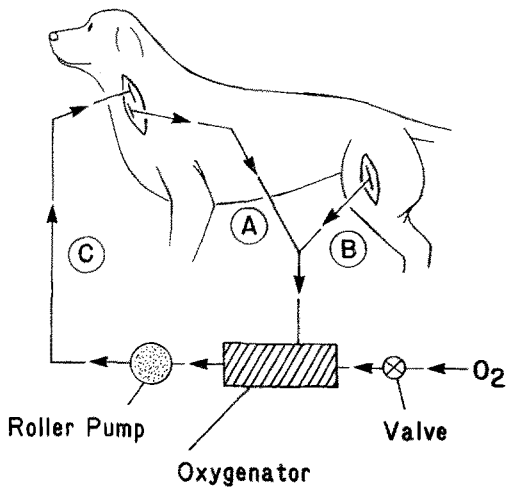

Fig. 1. Schematic diagram of extracorporeal pump bypass circuit. Ⓐ From Jugular Vein. Ⓑ From Femoral Vein. Ⓒ To Carotid Artery

tion. Extracorporeal cardiac bypass support may be a technique for not only maintaining critical perfusion but also restoring normal hepatic blood flow to permit rapid drug clearance.

Case Report

A 58 year old female was admitted to the coronary care unit of a community hospital with a four day history of progressively severe chest pain that was retrosternal in location and was relieved by oral nitrates. The patient also had symptoms and physical findings consistent with congestive heart failure. Relevant past medical history included a provious myocardial infarction. Electrocardiogram on admission revealed normal sinus rhythm, rate 72, axis $-60°$, PR = 0.13 s. QRS = 0.08 s with evidence of old inferior wall infarction and anterolateral infarction of undetermined age. No ectopy was noted at the time of admission. At midnight while in the intensive care unit, the patient was noted to have 8–10 ventricular premature beats per min and 50 mg of lidocaine was ordered for bolus administration. Instead of 50 mg, 50 ml of 4% lidocaine was drawn (2000 mg), and initially, 800 mg was administered. Shortly thereafter the patient appeared to be gasping for breath and was asystolic by ECG. Cardiopulmonary resuscitation was initiated immediately. Following 30 min of intensive resuscitative effort, the patient was noted to be transiently in a normal sinus rhythm which deteriorated to ventricular tachycardia. At this time the remaining 1200 mg of lidocaine was administered. It was only after this second bolus that the initial dosage error was realized. At this point the cardiac rhythm was atrioventricular bradycardia. A pacemaker was inserted and appeared to be capturing, but no blood pressure could be obtained. After 2.5 h of resuscitation, the patient was without spontaneous respiration or blood pressure, had fixed and dilated pupils, and ECG showed infrequent ventricular complexes. Shortly thereafter the patient was pronounced dead.

As demonstrated by this case, the treatment of massive acute lidocaine overdosage is unsatisfactory. Barbiturates, benzodiazepines, and ventilatory support have been recommended for seizures and respiratory arrest caused by lidocaine [9, 10] but accompanying shock and pump failure have been refractory to therapy in clinical cases.

Proposal

Lidocaine; 2-diethylamino-2′, 6′-acetoxylidide; is rapidly metabolized in the liver by a microsomal oxidation system. Less than 10% is excreted unchanged in the urine [4]. Lidocaine clearance is directly related to liver blood flow so that with normal hepatic perfusion, lidocaine has a relatively short half-live of approximately 90 min in man. In diseases such as congestive heart failure there is a dramatic reduction in hepatic blood flow and a profound fall in lidocaine clearance [11, 12].

Death from lidocaine overdose might be avoided if the circulation could be mechanically supported for a few hours to maintain liver blood flow at near normal levels in order to sustain high lidocaine clearance. Using this reasoning, we have studied the value of temporary venoarterial pump bypass for preventing death from acute lidocaine overdose.

Methods

Twenty-four mongrel dogs weighing an average of 25 kg were anesthetized with morphine sulfate 1–2 mg/kg and pentobarbital 25 mg/kg. At no time was spontaneous respiration absent during induction of anesthesia. Pulmonary arterial pressure was monitored via a Clarke triple lumen (Swan-Ganz) central venous catheter and systemic arterial pressure was measured by a femoral artery catheter. Both catheters led to separately calibrated Clarke physiologic pressure transducers coupled to an Electronics for Medicine Simultrace VR-6 amplifier/recorder. Cardiac output was established by thermal dilution using a Lyons DT CCO-07 cardiac output calculator. The electrocardiogram was monitored throughout the experiment. Arterial blood gases were determined every 30 min. Arterial blood for lidocaine concentra-

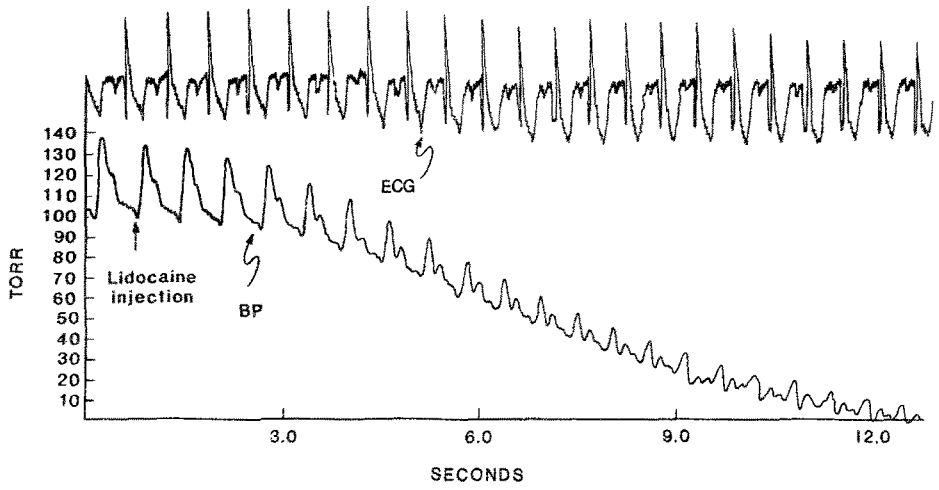

Fig. 2. Lidocaine induced cardiovascular collapse in an overdosed animal. The electrocardiogram shows that the heart rate does not increase during cardiovascular collapse

tion was drawn initially at 2 min after dosing and subsequently every 15 min. Lidocaine was assayed using a Perkin-Elmer 3920 gas chromatograph with a nitrogen-phosphorous detector utilizing a method previously described [13]. One ml of plasma was adjusted to pH 8.3 with borate buffer to which chloroform was added for extraction. After centrifugation and evaporation, the residue was reconstituted in toluene, 100 µl of which was injected into a 3% OV-1 (Sigma) column at 200 °C. Internal standard used was 6′-chloro-α-methyl-l-pyrrolidineaceto-o-toluidide hydrochloride (Aldrich Rare Chemicals #S39818-7). This lidocaine assay is linear over the range of 0.2–100 µg/ml lidocaine with a coefficient of variation of 8% at 4 µg/ml. Respiratory support was provided if necessary by an Emerson ventilator. Metabolic acidosis was treated with sodium bicarbonate infusion. Norepinephrine bitartrate, 1,6 µg/ml in normal saline, was used in an effort to maintain blood pressure above 85 Torr. Isoproterenol, 0.4 µg/ml in normal saline, was tried if norepinephrine was ineffective. Ventricular tachycardia or fibrillation was managed with electroshock. Attempts were made to reverse asystole by calcium chloride, epinephrine and isoproterenol. Third degree atrioventricular block was treated with atropine and isoproterenol and sinus bradycardia was treated with atropine.

Group A consisted of eight dogs given 30 mg/kg lidocaine intravenously over 20 s. Hypotension and ensuing arrhythmias (if any) were treated with the therapeutic regimen outlined above.

Group B consisted of eight dogs also given 30 mg/kg lidocaine intravenously over 20 seconds. However, these dogs were provided with a standby extracorporeal veno-arterial circuit (Fig. 1). The bypass apparatus provided shunting of blood from the left femoral and jugular veins to a Schiley type 1045-A bubble oxygenator, then to a calibrated occlusive roller pump with blood return to a cannulated left carotid artery. The entire circuit was primed with physiologic saline and kept on a standby basis. After the lidocaine infusion, the pump was turned on only if the dog had at least 5 min of hypotension (less than 30 Torr) which was unresponsive to intravenous norepinephrine. The extracorporeal circuit and intravenous norepinephrine were then used to support the circulation for 90 min. At that time, the animals were cardioverted if necessary and weaned from the pump support.

Group C consisted of eight dogs anesthetized in the same way as Groups A and B but administered only 3 mg/kg lidocaine by intravenous bolus. This group was used to determine kinetic data for anesthetized dogs receiving non-toxic doses of lidocaine.

Lidocaine clearance was determined for each animal in Groups B and C by measuring area under the plasma concentration-time curves for times 0–90 min. Lidocaine half-life was determined for each of these animals using the elimination phase of the plasma decay curve. Lidocaine plasma levels from 15 to 90 min were used for comparative values since these data points were beyond the distribution phase and included the times on the extracorporeal pump. Data were fit by the method of least squares to a one compartment first order model. Volume of distribution was calculated for individual animals using clearance, the elimination rate constant, and the equation $Cl = k_e V_d$ where $k_e = \frac{0.693}{t_{1/2}}$.

Individual volumes of distribution were then averaged to provide group mean data. Comparisons between group data were accomplished using an unpaired Student's *t*-test.

Table 1. Cardiopulmonary response to lidocaine overdose

	Group A Overdose 30 mg/kg drug support	Group B Overdose 30 mg/kg extra-corporeal pump
Cardiovascular		
Supraventricular tachycardia	1/8	0/8
Cardiovascular collapse	8/8	8/8
Ventricular tachycardia	1/8	0/8
Ventricular fibrillation	2/8	2/8
Asystole	6/8	2/8
Pulmonary		
Respiratory arrest	8/8	8/8
Survival at 120 min	2/8*	8/8*

* Fischer's Exact Test p = 0.0035

Table 2. Cardiovascular responses to lidocaine overdose

	Mean arterial pressure (Torr)		
	Group A*	Group B	Group C
Control	107 + 3.45	96.25 ± 6.39	101.2 ± 7.93
2 min	3.9 ± 1.90	5.0 ± 2.50	103.0 ± 6.04
15 min	3.5 ± 1.00	90.0 ± 6.40	102.0 ± 7.52
30 min	85.0	95.0 ± 8.70	100.0 ± 6.94
45 min	86.5	91.0 ± 4.40	101.0 ± 7.35
60 min	82.5	87.0 ± 4.70	103.0 ± 5.03
75 min	82.0	100.5 ± 5.60	106.0 ± 8.43
90 min	87.5	98.8 ± 5.70	109.6 ± 6.76
105 min	90.0	91.0 ± 11.27	110.8 ± 8.22
120 min	93.5	94.6 ± 6.54	111.0 ± 8.86
	Central venous pressure (Torr)		
	Group A*	Group B	Group C
Control	7.0 ± 2.0	6.93 ± 2.44	5.50 ± 0.50
2 min	17.1 ± 0.69	8.93 ± 2.24	5.50 ± 0.50
15 min	17.64 ± 3.50	7.39 ± 1.42	6.83 ± 3.36
30 min	19.0	7.67 ± 0.77	6.67 ± 3.22
45 min	18.0	8.57 ± 1.26	6.75 ± 3.68
60 min	17.0	9.25 ± 2.45	6.88 ± 3.71
75 min	12.0	7.5 ± 1.99	6.67 ± 4.04
90 min	17.0	8.83 ± 2.56	7.50 ± 3.91
105 min	17.0	13.25 ± 4.01	7.17 ± 3.77
120 min	18.0	12.64 ± 3.33	7.42 ± 3.91
	Cardiac output (l/min)		
	Group A*	Group B	Group C
Control	2.76 ± 0.31	3.05 ± 0.47	3.55 ± 0.4
30 min	2.0	extracorporeal pumping	4.46 ± 0.3
60 min	2.2	extracorporeal pumping	3.55 ± 0.1
90 min	3.0	2.79 ± 0.30	3.46 ± 0.1
120 min	2.7	3.43 ± 0.70	3.50 ± 0.3

* In Group A, only 2 dogs remained alive after 30 min
In Group B and C, $n = 8$.

Table 3. Serum pH

	Group A[a]	Group B[b]
Control	7.50 ± 0.06	7.44 ± 0.06
30 min	7.23 ± 0.13	7.33 ± 0.09
60 min	7.42	7.26 ± 0.08
90 min	7.30	7.30 ± 0.11
120 min	7.42	7.30 ± 0.12

[a] $n = 8$ for control and 30 min, but $n = 2$ thereafter
[b] $n = 8$, all time points

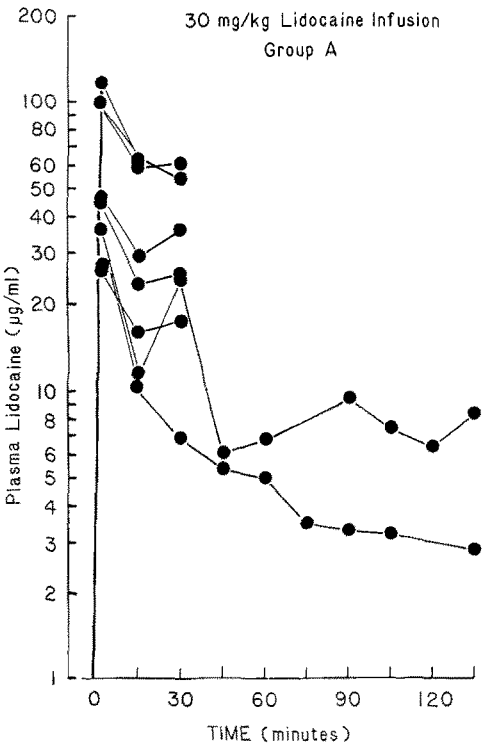

Fig. 3. Lidocaine blood levels following a 30 mg/kg infusion at time 0 in Group A animals. Animals in this group were treated only with respiratory and drug support. By 30 min 6/8 dogs had died despite resuscitative efforts

Results

All animals in Groups A and B had respiratory arrest within 30 s of injection of lidocaine. Within 2 min, these animals experienced cardiovascular collapse with hypotension to less than 10 Torr. Interestingly, no animal had a significant reflex tachycardia. This is demonstrated by a sample recording seen in Fig. 2. A summary of cardiopulmonary effects of a lidocaine overdose for the two groups is shown in Table 1. Comparison of mean arterial pressure, central venous pressure, and cardiac output between Groups A, B and C are shown in Table 2 and serum pH values are given in Table 3. In group A animals receiving an

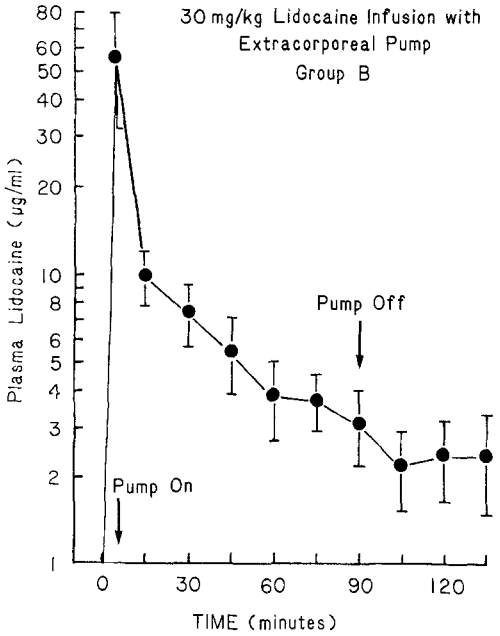

Fig. 4. Lidocaine blood levels following a 30 mg/kg infusion at time 0 in Group B animals in which the extracorporeal pump was initiated at PUMP ON and discontinued at PUMP OFF designations. Because all eight animals survived, data was averaged and is shown as mean ± SEM

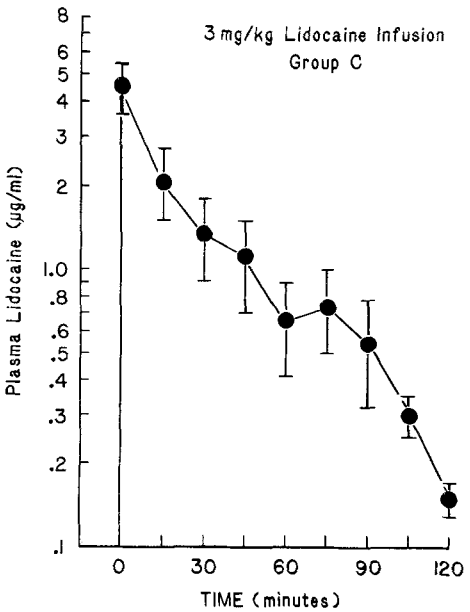

Fig. 5. Lidocaine blood levels following administration of a low dose infusion (3 mg/kg) in eight dogs. Values represent mean ± SEM

overdose of lidocaine with only conservative drug therapy, serial levels were determined as long as animals survived, or until termination of the experiment at 135 min. Only two of eight animals survived longer than 30 min. These data are shown in Fig. 3.

Table 4. Kinetics of lidocaine elimination

	Lidocaine dose	Clearance [ml/kg/min]	Volume of distribution [l/kg]	Half-life [min]
Group B	30 mg/kg	39.75 ± 4.16	3.13 ± 0.58	54.0 ± 8.4[a]
Group C	3 mg/kg	38.29 ± 8.6	2.33 ± 0.49	34.3 ± 4.2[a]

Figures represent group mean averages ± SEM
[a] $p < 0.05$ different by unpaired t-test

In Group B, all eight animals experienced hypotension within 1 min of lidocaine infusion and blood pressure was unresponsive to norepinephrine infused for 5 min (remained less than 30 Torr). At that time, the standby extracorporeal pump was turned on and animals were supported for 90 min. On the pump, blood pressure was stabilized as seen in Table 2. As shown in Table 1, arrhythmias occurred in this group of animals with the same frequency as in Group A animals despite the fact that blood pressure was being maintained with the extracorporeal pump. The animals developed electrocardiographic asystole within 10 min of lidocaine administration, but both spontaneously reverted to sinus rhythm within 30 min. Three animals stayed in normal sinus rhythm for the duration of the experiment. Two animals were in ventricular fibrillation while on the extracorporeal pump and were converted to normal sinus rhythm by electrical countershock after 90 min of circulatory support. Despite the fact that these animals had at least 60 min of ventricular fibrillation during cardiopulmonary support and were then cardioverted, lidocaine clearance in these two animals was well maintained at 53.3 ml/kg/min and 33.3 ml/kg/min. All eight animals survived the experiment and none showed electrocardiographic evidence of ischemia. Statistical comparison by Fisher's exact test showed that the extracorporeal pump led to a highly significantly improvement in survival from lidocaine overdose ($p = 0.0035$). The rate of fall of lidocaine blood levels in overdosed animals treated with the extracorporeal pump is plotted in Fig. 4 and lidocaine half-life, clearance and volume of distribution appear in Table 4.

Group C animals treated with low doses of lidocaine experienced no cardiovascular or respiratory compromise. Lidocaine blood levels are shown in Fig. 5. Kinetic data comparing the low dose lidocaine Group C animals with the overdosed extracorporeally pumped Group B animals is shown in Table 4. No statistical differences between volume of distribution and clearance were seen using unpaired Student's t-test. Lidocaine half-life was prolonged, however, in overdosed animals on the extracorporeal pump ($p < 0.05$).

Discussion

Deaths from lidocaine overdose in humans result from cardiovascular collapse and arrhythmias. Compounding this problem is a reduction in hepatic perfusion and drug clearance which leads to irreversible drug intoxication. Our results demonstrate that cardiac bypass can not only restore tissue perfusion but can lead to normal distribution and clearance of lidocaine.

Both human and animal data have shown decreased inotropism, increased atrioventricular block, and decreased spontaneous ventricular pacemaker rates after high doses of lidocaine [10, 14, 15–17, 18]. Previous dog data have shown that rapid intravenous administration of lidocaine in excess of 5 mg/kg is associated with a decrease in myocardial contractile force [17].

Our study demonstrates that dogs overdosed with 30 mg/kg of lidocaine and treated with conventional drug therapy and cardioversion had a high mortality rate (75%). By contrast, dogs which received overdoses of lidocaine but which were then supported with extracorporeal pump assistance for 90 min survived.

Dogs overdosed with lidocaine but supported by the extracorporeal pump had clearance rates of lidocaine equal to those seen in the animals receiving low, conventional coses of the drug. Even animals in ventricular fibrillation while on the extracorporeal pump showed good lidocaine clearance. Half-life is prolonged in the overdosed animals, possibly because of an increase in volume of distribution produced by the extracorporeal circulation apparatus.

The rapid bolus injection technique used in these experiments led to very high distribution phase levels of lidocaine (50–100 μg/ml) that were associated with respiratory arrest and hypotension. Since bolus loading is a common technique for lidocaine administration and has been one of the ways accidental overdoses have occurred, we felt justified in using this method. As shown in Fig. 3, 6/8 animals overdosed with lidocaine but not supported by the extracorporeal pump were unable to distribute the drug and had persistent high lidocaine levels. Since most of these dogs were severely hypotensive and agonal during the 30 min of drug level monitoring it is reasonable to assume that the high central compartment lidocaine concentration produced hypotension and a fall in cardiac output that prevented good tissue perfusion and dispersal of drug to the full volume of distribution. Dogs on the extracorporeal pump rapidly distributed lidocaine and, as shown in Fig. 4 and 5, completed the distribution phase in the same time as low dose control dogs. An important value of the pump is likely to have been to aid in removal of drug from the central compartment to the full volume of distribution and a consequent reduction of plasma concentration from 50–100 μg/ml to 10–20 μg/ml.

Further evidence to show the importance of high distribution phase concentrations of lidocaine comes from the study of Branch et al. [19] in which a slow infusion of 30 mg/kg of lidocaine did not cause hypotension. From data presented in that manuscript, we can compute the clearance for both 30 mg/kg and 20 mg/kg lidocaine doses to be about 35 ml/kg/min. These values are similar to those found by us for low dose and high dose lidocaine. Furthermore, in their study, when the 30 mg/kg dose was given rapidly, animals died (personal communication, R. Branch 1980). The primary kinetic benefit of the extracorporeal pump may well be to aid in the distribution of a cardiotoxic bolus dose of lidocaine.

In clinical case reports of fatal overdose with bolus injections of lidocaine, death has occurred despite immediate and prolonged cardiopulmonary resuscitation. While blood levels of drug have not been determined during these episodes, it may be that cardiopulmonary resuscitation is inadequate to distribute lidocaine to its full volume of distribution. While we have demonstrated in dogs that 90 min of cardiopulmonary pump support can prevent mortality from lidocaine overdose, it is possible that a shorter period of extracorporeal pump treatment might be effective at reducing mortality by distributing the drug out of the central compartment to the full volume of distribution.

The extracorporeal pump served two purposes in these experiments. First, it sustained blood pressure during a period of profound hypotension. Just as important, it normalized the kinetics of lidocaine by distributing the drug to the full volume of distribution and by restoring hepatic drug clearance. In conventional treatment of hypotension using pressor agents such as norepinephrine, hepatic blood flow and lidocaine clearance are actually reduced by the therapy [20, 21]. In our experiments we made no effort to give open or closed chest massage to any animal; it is possible that such support might have salvaged some animals.

We believe that the use of extracorporeal bypass to reverse drug toxicity is a novel concept. Other drug elimination techniques such as charcoal hemoperfusion or hemodialysis are not applicable or appropriate to this situation. Neither will help the hypotension associated with lidocaine toxicity and the effectiveness of both will be compromised by low cardiac output. Another basic problem with these methods is their relatively inefficient clearance rates of 100–200 ml/min. Lidocaine clearance in man approxi-

mates liver blood flow which is 750–1500 ml/min. Our animal results indicate that the extracorporeal pump can restore this high clearance rate.

Extending these dog studies to human therapy will pose a number of technical problems. Certainly in the human overdose situation, closed chest massage would have to be performed while extracorporeal pump preparations are underway. While technical difficulties would be considerable, the extracorporeal pump may offer the only hope for reversing the cardiovascular collapse from massive lidocaine overdose.

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References

1. Burlington B, Freed CR (1980) Massive overdose and death from prophylactic lidocaine. J Am Med Assoc 243:1035
2. Finkelstein F, Kreeft J (1979) Massive lidocaine poisoning. N Engl J Med 301: 50
3. Mayer PP (1972) Lidocaine overdose and ampoule labelling. Br Med J 3: 291
4. Beckett AH, Boyes RN, Appleton PJ (1966) The metabolism and excretion of lignocaine in man. J Pharm Pharmacol 18: 76S–81S
5. Frieden J (1965) Lidocaine as an antiarrhythmic agent. Am Heart J 70: 713–715
6. Grossman JI, Lubow LA, Frieden J, Rubin IL (1968) Lidocaine in cardiac arrhythmias. Arch Int Med 121: 396–401
7. Austen WG, Moran JM (1965) Cardiac and peripheral vascular effects of lidocaine and procainamide. Am J Cardiol 16: 701–707
8. Collinsworth KA, Kalman SM, Harrison DC (1974) The clinical pharmacology of lidocaine as an antiarrhythmic drug. Circulation 50: 1217–1230
9. deJong RH, Heavner JE (1971) Diazepam prevents local anesthetic seizures. Anesthesiology 34: 523–531
10. Steinhaus JE (1957) Local anesthetic toxicity: A pharmacological re-evaluation. Anesthesiology 18: 275–281
11. Stenson RE, Constantino RT, Harrison DC (1971) Interrelationships of hepatic blood flow, cardiac output and blood levels of lidocaine in man. Circulation 43: 205–211
12. Thomson PD, Rowland M, Melmon KL (1971) The influence of heart failure, liver disease and renal failure on the disposition of lidocaine in man. Am Heart J 82: 417–421
13. Gal J, Freedman M, Kumar E, Freed CR (1981) A rapid and simple microassay for lidocaine in human blood plasma using gas liquid chromatography with nitrogen detection. Ther Drug Mon 3: 177–180
14. Brennan FJ, Wit AL (1973) Effects of lidocaine on electrophysiological properties of Purkinje fibers surrounding acute myocardial infarction. Circulation 48: 148
15. Jewitt DE, Kishon Y, Thomas M (1968) Lignocaine in the management of arrhythmias after acute myocardial infarction. Lancet 1: 266–270
16. Lichstein E, Chadda KD, Gupta PK (1973) Atrioventricular block with lidocaine therapy. Am J Cardiol 31: 277–281
17. Lieberman NA, Harris RS, Katz RI, Lipschutz HM, Dolgin M, Fischer VJ (1968) The effects of lidocaine on the electrical and mechanical activity of the herat. Am J Cardiol 22: 375–380
18. Robison SL, Schroll, M, Harrison DC (1969) The circulatory response to lidocaine in experimental myocardial infarction. Am J Med Sci 258: 260–269
19. Branch RA, Shand DG, Wilkinson GR, Nies AS (1973) The reduction of lidocaine clearance by dl-propranolol: An example of hemodynamic drug interaction. J Pharm Exp Ther 184: 515–519
20. Benowitz N, Rowland M, Forsyth R, Melmon KL (1973) Circulatory influences of lidocaine disposition. Clin Res 21: 467
21. Hoffbrand BI, Forsyth RP (1973) Regional blood flow changes during norepinephrine, tyramine and methoxamine infusions in the unanesthetized rhesus monkey. J Pharm Exp Ther 184: 656–661

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