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Effects of Hepatectomy on the Disappearance Rate of Lidocaine from Blood in Man and Dog

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DEPENDING on their chemical configuration, local anesthetic agents are inactivated chiefly either in the plasma or in the liver. Lidocaine hydrochloride, an anesthetic with an amide structure, has been thought to be primarily metabolized in the liver with little or no extrahepatic degradation.[1-3] This contention was tested in hepatectomized dogs with nearly normal cardiodynamics and, during the anhepatic period, in 2 patients undergoing liver transplantation.

MATERIALS AND METHODS

Anhepatic Dogs — Five mongrel dogs, weighing between 14 and 17 kg., were anesthetized with 30 mg./kg. of pentobarbital sodium injected intravenously. The femoral vein and artery were cannulated. After a 5 ml. control arterial blood sample was obtained, a 2 percent solution of lidocaine HCl, 2.5 mg./kg. intravenously, was administered during a 30-second period. Arterial blood samples were drawn 2, 5, 10, 15, 30, 60, 90, and 120 minutes later. One hour after procurement of the last sample, portacaval shunt and total hepatectomy were performed, leaving the inferior vena cava intact.[4] This was followed by control sampling, lidocaine injection, and the procurement of blood samples as before.

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Since hepatectomy is known to be accompanied by hypoglycemia and metabolic acidosis,[5] arterial blood gases and pH and blood glucose were measured every 15 minutes. A solution of 50 percent glucose was used to maintain the glucose level between 130 and 175 mg./100 ml. Arterial blood pressure and heart rate were continuously monitored. After hepatectomy two animals (dogs 11 and 12) also received an infusion of 5 percent glucose in 0.9 percent saline solution at a rate of 20 ml./kg./hr., whereas dogs 13, 14, and 15 were not given the extra infusion.

Anhepatic Patients — Two adult patients undergoing orthotopic liver transplantation, as described by Starzl,[6] were studied while under anesthesia. Thiopental sodium and succinylcholine were administered to induce sleep and facilitate orotracheal intubation. Thereafter, fluroxene-nitrous oxide-oxygen was given by inhalation in a semiclosed-circle system. After obtaining a control arterial sample, lidocaine HCl, 2.5 mg./kg., was given intravenously, and other arterial aliquots were obtained at the same intervals as described in the dog experiments. During this time, the diseased host liver was being dissected preparatory to removal but the blood supply was intact.

At least 3 hours after lidocaine injection, total host hepatectomy was performed, at which time a second injection of lidocaine was given and subsequent samples obtained at the same time intervals as earlier. The homograft was revascularized 50 minutes after the local anesthetic agent had been injected. However, the schedule of sampling was continued as in the preanhepatic studies, except in patient A, from whom an extra sample was obtained 240 minutes after lidocaine injection.

Blood and solutions of glucose and sodium bicarbonate were infused during these operations to replace blood loss, prevent hypoglycemia, and correct metabolic acidosis during the anhepatic phase. The lidocaine level in the blood was determined according to the technic described by Keenaghan,[7] using a dual-column Aerograph Model 1520 gas chromatograph, which is sensitive to concentrations as low as 0.5 mcg./ml. of the local anesthetic in blood.

RESULTS

Animal Studies — Blood levels of lidocaine observed in intact anesthetized dogs declined similarly in every instance, being 0.7 mcg./ml. or less at 60 minutes and 0.5 mcg./ml. or less at 2 hours after injection.

After hepatectomy, the 2 dogs that received dilute glucose in the intravenous saline solution had lidocaine values between 3.3 and 4.2 mcg. in the immediate postinjection period. At 2 hours, these remained above 1.2 mcg./ml. (fig. 1). In contrast,

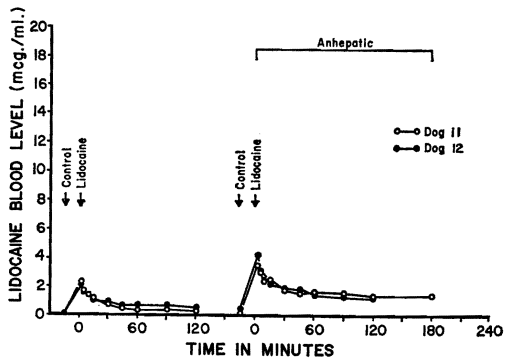
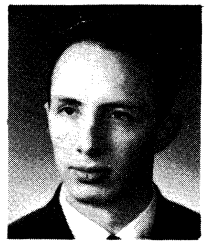


FIG. 1. Blood levels observed after intravenous injection of lidocaine (2.5 mg./kg.) into 2 dogs under control conditions and after hepatectomy. A solution of 5 percent glucose in 0.9 percent saline was infused at a rate of 20 ml./kg./hr.



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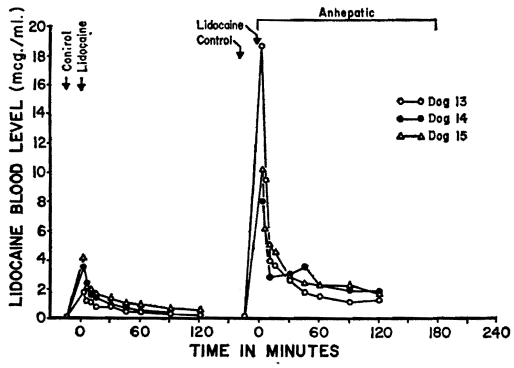

FIG. 2. Changes of blood levels observed after intravenous injection of 2.5 mg./kg. into 3 dogs before and after hepatectomy. The glucose demand in these animals was supplied with a concentrated solution of dextrose (50 percent).

the 3 animals that received concentrated glucose alone and were not, therefore, hemodiluted, had initial lidocaine levels ranging from 7.9 to 18.4 mcg./ml. rapidly declining to levels between 3 and 5 mcg./ml. (fig. 2). However, the lidocaine concentrations remained above 1 mcg./ml. at 120 minutes after injection and even at 180 minutes in the one sample (figs. 1 and 2).

Hepatectomized Patients—Preoperatively, both patients had severe hepatic insufficiency, recipient A owing to chronic rejection of a previously transplanted liver and recipient B as a result of long-standing cirrhosis with repeated hematemesis. Two minutes after intravenous injection of lidocaine, the blood levels were 6.6 and 5 mcg./ml., respectively, and fell to 1.5 and 1.7 mcg./ml. at 1 hour, and to 1.1 and 1.4 mcg./ml. at 2 hours (fig. 3). After revascularization, a downward trend of the arterial blood levels was apparent, to a degree that 4 hours after injection, the concentration of lidocaine was only 0.4 mcg./ml.

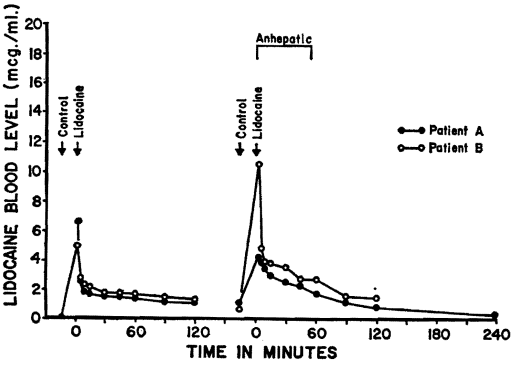

FIG. 3. Comparison of the rate of lidocaine disappearance from blood after intravenous administration of 2.5 mg./kg. in 2 patients with terminal cirrhosis undergoing orthotopic transplantation. Blood samples in the second series were obtained during the anhepatic stage, which lasted 50 minutes in both cases. Thereafter, decline of lidocaine levels is presumably due to restoration of normal function by the homograft.

Neither dogs nor patients showed toxic manifestations from the lidocaine injections.

DISCUSSION

After entry into the blood stream, the disposition of a number of local anesthetic agents such as procaine occurs by prompt degradation subserved by the enzyme pseudocholinesterase.[8,9] Disappearance of lidocaine HCl is less dependent upon metabolic degradation and more upon its high lipid solubility permitting rapid distribution in tissue.[1] However, the ultimate metabolism of lidocaine has been said to take place in the liver by microsomal enzymes with reduced Nicotinamide-adenine dinucleotide phosphate and oxygen,[1,3,10] undergoing either oxidation first, or hydrolysis followed by oxidation prior to sulfate conjugation.[11]

A prediction, based on the foregoing facts, that the early phase of lidocaine disappearance would be less affected by the liverless state than the late phase, proved valid both in dogs and in man. The canine experiments were the most decisive, since transfusions were not ordinarily required during hepatectomy and because an excellent cardiodynamic state could be maintained at all times. With these conditions, most of the lidocaine disappeared from the blood in the first hour, although at a somewhat slower rate than normal. Thereafter, the fall in blood levels either declined very slowly or not at all, suggesting that equilibration had occurred. Presumably, further elimination would then depend upon other routes (kidney or gastrointestinal tract). If extrahepatic degradation occurred at all, it must have been at an imperceptible pace.

Despite the seriously diseased livers in the 2 human subjects, early disappearance of lidocaine was rapid, presumably because of prompt tissue distribution. In the ensuing 40 minutes, blood concentrations decreased

slowly but steadily. During the anhepatic state, the tissue distribution phase was also noted but the subsequent decline of lidocaine concentration was not so rapid, the levels remaining above 2.5 mcg./ml. even 45 minutes after the new liver had been revascularized. Ultimately, the homograft apparently assumed the burden of lidocaine degradation, since by 4 hours after revascularization, the concentration was only 0.4 mcg./ml. Although not of practical significance, lidocaine clearance from blood could be interpreted as a sign of acceptable liver homograft function.

In this investigation, it was necessary to give two doses of the drug tested. A criticism of the protocol might be that the administered agent could accumulate in the tissues and contribute to an artificially high value after the second injection.[12] Such an explanation would not seem to account for the results in the present study, first because the doses were small; second, because lidocaine disappeared almost completely before the second injection in the presence of the liver; and finally, because, in the human experience, the restoration of liver function with the homograft was attended by a secondary late acceleration of lidocaine disappearance.

SUMMARY

The disappearance from blood of intravenously injected lidocaine HCl was studied in 5 dogs before and after total hepatectomy. In the intact state, the lidocaine concentrations in the blood fell rapidly at first and more slowly in the late phase. After hepatectomy, the disappearance rates were reduced both early and late after injection. The findings were consistent with the hypothesis that the liver is responsible for the ultimate disposition of lidocaine.

Analogous experiments were performed in 2 patients with terminal cirrhosis undergoing orthotopic liver transplantation. The results indicated that the conclusions from the animal experiments pertained as well in humans.

Generic and Trade Names of Drugs

Lidocaine (HCl)—Xylocaine
Procaine (HCl)—Novocain
Pentobarbital sodium—Nembutal
Sodium thiopental—Pentothal Sodium
Succinylcholine—Anectine, Quelicine
Fluoroxene—Fluoromar
Sodium bicarbonate

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