Effect of Local Anesthetics on the Cardiovascular System of the Dog

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THE ACUTE systemic toxic effects of an overdose of local anesthetic are manifested by (1) excitement or convulsions, (2) unconsciousness, (3) respiratory depression, and/or (4) cardiovascular depression, not necessarily in this order. The first three manifestations may very well be life threatening by compromising alveolar ventilation. However, these detrimental effects may be reversed readily by establishing effective mechanical ventilation. Cardiovascular depression, however, may be extremely difficult to reverse, especially in the patient with pre-existing cardiovascular disease. This study was undertaken to determine the specific effects of some of the commonly employed local anesthetic agents on the cardiovascular system and their relative toxicities from this standpoint.

Method

The studies were conducted in 30 healthy mongrel dogs weighing from 7.5 to 14 kg. Anesthesia was induced with 25 mg./kg. of pentobarbital intravenously, the trachea cannulated, and adequate artificial ventilation with room air maintained with a Harvard respirator. Arterial blood pressure (BP) was recorded via a femoral artery from an indwelling polyethylene catheter inserted to the level of the descending aorta. A second polyethylene catheter for drug injection was placed, via a femoral vein, into the inferior vena cava at about the second lumbar vertebral level. The chest was opened either by a right intercostal or by a sternal-splitting incision, and a Walton-Brodie strain gauge arch was sutured directly to the right ventricle.[1, 2] The strip of myocardium between the two feet of the arch was stretched to a length 30–35 per cent longer than end-diastolic length. Myocardial adjustments secondary to hemodynamic changes were insignificant because of the fixed initial length of the muscle segment. In some animals, aortic blood flow was measured with a Carolina Electronics Company square-wave electromagnetic flowmeter[3] inserted around the ascending aorta just distal to the coronary ostia. This provided a satisfactory index of cardiac output (aortic flow equals cardiac output minus coronary flow). Heart rate, aortic blood pressure, myocardial contractile force (MCF), aortic blood flow and lead 2 of the electrocardiogram were monitored and recorded on a Grass polygraph or a Sanborn polyvisograph.

The drugs tested were procaine, chloroprocaine, lidocaine, hexylcaine, cocaine, and tetracaine. All were employed as the hydrochloride salt and doses calculated as the salts. Each dose of drug was diluted to 10 ml. volume and injected into the vena cava over a two-minute period by a constant speed syringe driver. After control recordings, doses of the different drugs were administered which produced similar levels of myocardial depression, *i.e.*, contractile force recordings reduced to approximately 50 per cent of control value. The effects of procaine and of at least one other drug were studied in every animal. The order of injection was reversed at least once for each drug studied; there was no significant alteration of effect. The interval between injections varied according to the time required for all parameters to return to control levels, usually 45 minutes to 2 hours.

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Results

Seventy-six drug injections were made in thirty animals. Figure 1 represents a typical tracing of parameters studied. It is to be noted that maximal depression of myocardial contractile force (MCF) paralleled that of blood pressure, heart rate and aortic blood flow. The diphasic response seen in figure 1 is representative of the response observed in the majority of injections. The initial cardiovascular depression was followed by a partial recovery with a secondary depression preceding return to the control state. This diphasic response to local anesthetic injection has been observed by other investigators.[4] It is possibly due to a sympatho-adrenal discharge although

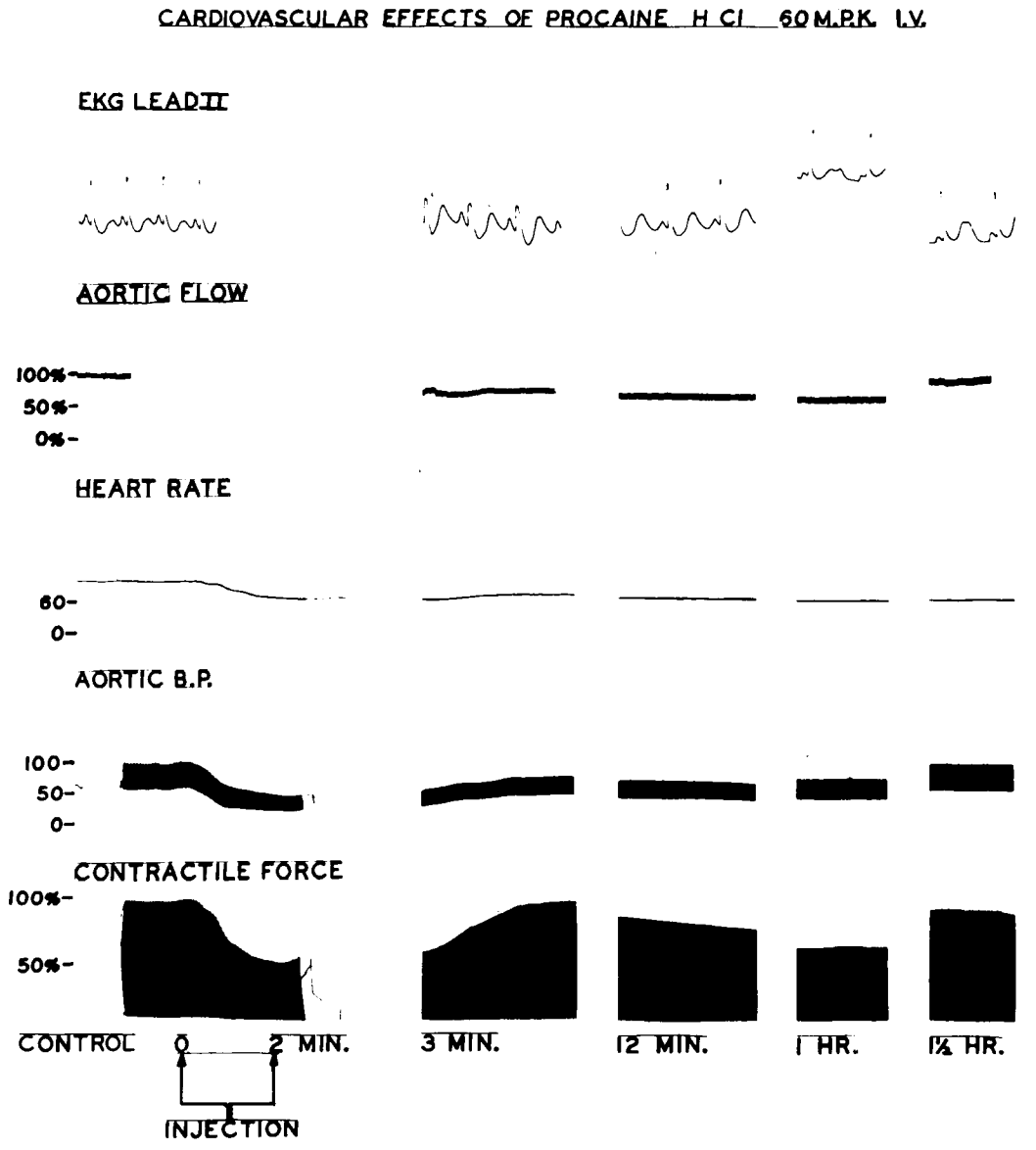

FIG. 1. Typical effects of local anesthetics as exhibited by procaine HCl on electrocardiogram, aortic blood flow, heart rate, aortic blood pressure (aortic B.P.) and right ventricular contractile force (contractile force).

TABLE 1. Effects of Intravenous Local Anesthetics on Myocardial Contractile Force (MCF), Arterial Pressure and Aortic Flow in the Dog

Drug	Dose Median and (Range) (mg./kg.)	Number of Experiments	Percentage Decrease in MCF Mean and (Range)	Relative MCF Toxicity (Procaine = 1.0)	Percentage Decrease in Systemic Blood Pressure Mean and (Range)	Percentage Decrease in Heart Rate Mean and (Range)	Percentage Decrease in Aortic Flow Mean and (Range)
Procaine	65 (60–65)	42	40 (20–73)	1.0	42 (20–66)	26 (11–38)	32 (14–83)
Chloroprocaine	26 (25–33)	6	40 (24–56)	2.2	36 (19–58)	18 (11–28)	44 (30–57)
Lidocaine	17 (14–28)	10	50 (25–78)	4.6	40 (20–70)	20 (10–39)	32 (8–50)
Hexylcaine	15 (10–30)	4	53 (29–81)	5.3	33 (17–67)	9 (4–20)	
Cocaine	10 (8–10)	5	41 (18–71)	6.6	5 (14 incr.–24 decr.)	12 (10–13)	
Tetracaine	8.0 (4.6–10)	9	44 (25–58)	8.3	36 (5–70)	23 (16–32)	33 (29–38)

the present evidence is not conclusive. ECG changes suggestive of an intraventricular conduction block was a frequent finding. Though this block was transient, there were frequent T-wave changes, *i.e.*, inversion, depression, or peaking, which persisted after other parameters had returned to control levels.

Although we were concerned primarily with acute changes, it is interesting to note in figure 1 that the cardiovascular depression lasted approximately one hour. Most of our experiments reflected this prolonged action which is at variance with other reports of similar type experiments.[10–13] An evaluation of the data in this respect is inconclusive.

Two animals died unexpectedly following injection of the local anesthetic. The first developed ventricular fibrillation after a 60 mg./kg. dose of procaine. The second developed asystole with persistent widely spaced ventricular complexes on the ECG following administration of 8 mg./kg. of tetracaine. In both cases, the arrhythmia was diagnosed by ECG and by direct observation of the heart.

Table 1 summarizes the results obtained and indicates the degree of similarity of depression in the parameters under observation. The similarity in depression of myocardial contractile force is consistent. The arterial blood pressure response to cocaine was inconsistent since two of five animals exhibited elevation of blood pressure during the period of maximum depression of all other parameters. No determinations of aortic blood flow were made during cocaine or hexylcaine injection.

The relative toxicity of the drugs was determined by the observed depression in myocardial contractile force. The toxicity of the drugs studied was calculated relative to procaine, which was arbitrarily assigned a value of 1.0. This was determined from the following formula:

$$\text{Relative toxicity} = \frac{\%\ \text{depression of MCF by drug}}{\text{mg./kg. of drug}} \Big/ \frac{\text{depression by procaine}}{\%\quad \text{mg./kg. of procaine}}$$

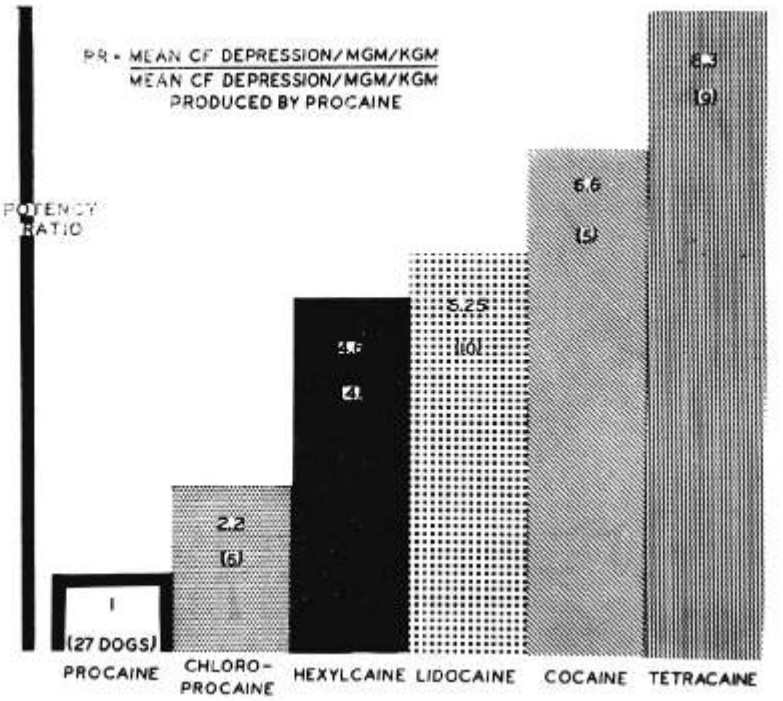

FIG. 2. Relative potency or toxicity of local anesthetics.

The relative toxicities obtained from these calculations are provided in table 1 and shown in figure 2.

Discussion

The relative toxicity of many local anesthetics in producing respiratory arrest has been determined. On this basis, the toxicity of some of the drugs used in this study have previously been reported[5, 6] as: procaine 1, chloroprocaine 0.9, cocaine 3, lidocaine 3.2, tetracaine 8. Cardiovascular depression is an indication of a more severe toxic reaction to local anesthetics and is more likely to be fatal. In animals, respiratory toxicity is generally manifest at a lower dosage than cardiovascular toxicity, but the two are not parallel for all local anesthetics.[5] Thus, cardiovascular depression is likely to be complicated by respiratory arrest, and prompt treatment of both must be instituted if a fatality is to be avoided.[7]

The results of the present study indicate that all of the local anesthetic agents investigated are capable of producing direct and intense myocardial depression. Steinhaus has shown that cocaine can produce direct myocardial depression.[7] Wollenberger and Krayer[8] used the Starling heart-lung preparation to compare the toxicity of certain local anesthetic drugs, using myocardial failure as an endpoint. Their results with cocaine, tetracaine, and procaine indicate relative toxicities of: procaine 1.0, tetracaine 6.3, cocaine 6.3. These results are of the same order of magnitude as those obtained in the present study.

Although the intravenous administration of local anesthetics does not simulate the clinical use of these drugs, toxicity is ultimately dependent upon the blood level attained.[4, 9] It is quite possible that many toxic reactions are due to accidental intravenous administration. Reproducible results are most accurately obtained by intravenous administration in the experimental animal. Topical application of some of these agents can produce a rapid rise in blood level similar to that seen following intravenous administration.[9]

In this study, the detoxification of local anesthetics by pseudocholinesterase or other enzyme systems was assumed to be minimized by the rapid attainment of high blood levels.

Summary

Six commonly employed local anesthetics were investigated with emphasis on the cardiovascular depressant effects of these drugs. All of the drugs utilized in this study were shown to be capable of producing direct myocardial depression of severe degree, and the relative toxicity was determined on this basis.

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AMNIOTIC FLUID EMBOLUS Abrupt onset of dyspnea, apprehension, and hypotension characterized 16 non-fatal cases of amniotic fluid embolism. Differential diagnosis from a thrombotic pulmonary embolus is difficult, as the patient may produce a frothy, blood-tinged sputum within minutes after the onset of the dyspnea and cyanosis. Generalized, rather than localized, moist rales and absence of pleuritic chest pain may aid in the diagnosis. Oxygen by mask, vasopressors, digitalization and possibly a bronchodilator constitute initial therapy of the cardiovascular failure. Despite prompt treatment, signs of cardiac failure may persist for 24 hours. (*Scott, M. M.: Cardiopulmonary Considerations in Nonfatal Amniotic Fluid Embolism, J. A. M. A. 183: 989 (Mar. 23) 1963.*)