PHARMACOLOGICAL EFFECTS OF MONOCAINE HYDROCHLORIDE *†

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(*Continued from the May issue*)

Local Effects on Tissues

In their paper on the clinical effects of monocaine, Tainter and Throndson (4) reported that it caused more local tissue irritation than procaine as indicated by the frequency of painful injections and post-operative reactions at the site of injection. Therefore, several methods were used to determine the local toxic effects on tissues in order to evaluate the importance of this action. The first and least quantitative of these was the direct detection of signs of irritation in the tissues used in measuring local anesthetic power. Monocaine killed a greater percentage of the frogs' sciatic nerves than it should have, if the compound was non-injurious to such tissues as claimed. However, evidences of irritation were not seen in other preparations and tissues. Thus, the injury to sciatic nerves alone was not fully convincing. Direct study of tissue irritation was therefore made, comparing monocaine and procaine by tests with trypan blue, microscopic study of injected tissues, and through the concentrations producing sloughs after infiltrations. These results may now be described in detail.

Trypan Blue Test.—A comparison of irritation from monocaine and procaine in the subcutaneous tissues of rats was attempted by the trypan blue test for capillary damage. Inflamed or irritated tissues of animals injected intravenously with trypan blue allow the dye to escape through the hyperpermeable capillaries and to stain deeply blue the irritated tissue. Each of 12 rats was given subcutaneous injections of the various anesthetic solutions under the abdominal skin, in concentrations covering the clinical range. Control injections of equal volumes of physiological saline solution and 0.5 per cent hydrochloric acid were made in each animal at the same time, but in different regions. Solutions of 1.0 and 2.0 per cent procaine and 1.0 per cent monocaine caused about the same amount of capillary irritation as the salt solution; that is, a negligible amount. However 2.0 per cent monocaine produced definite irritation as shown by the increased intensity of blue staining, al-

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though this damage was not marked when compared with that from hydrochloric acid.

Histological Examination of Tissues.—Two rats were injected subcutaneously in the abdominal region with 0.1 cc. of 1.0 per cent monocaine, 1.0 per cent monocaine plus 1:75,000 epinephrine, 2.0 per cent procaine, and 2.0 per cent procaine plus 1:50,000 epinephrine, with controls of physiological saline solution and needle-jabs alone. Twenty-four hours later these injected areas and some normal uninjected skin were excised, the tissues fixed and sectioned, and slides prepared with hematoxylin-eosin stain.* Many sections from each block of tissue were examined for evidences of inflammatory reactions.

A slight amount of inflammation was present in all the sections, except the normal skin and that pierced only by the needle. In the procaine and monocaine areas the reaction was slight and no difference in the degree of inflammatory change could be detected. However, all the skin-sections after injection with monocaine showed definite irritation, whereas only about two-thirds of those after procaine and one-half of those after saline solution were abnormal. The presence of epinephrine apparently did not modify these inflammatory reactions. Therefore, the results as a whole indicated that the injury to subcutaneous tissues was not extensive, but that there was slightly more injury from monocaine than from procaine.

Slough Test.—The foregoing tests were only qualitative indicators of tissue injury. Therefore, a quantitative procedure was developed to compare the degree of irritation. Sixty-one subcutaneous injections of 0.5 cc. of monocaine or procaine solution of graded concentrations were made into the subcutaneous tissues of the abdomen of rats, and the areas observed for necrosis and sloughing for eight days. The concentrations of monocaine tested ranged from 0.1 to 3.0 per cent, and of procaine from 0.5 to 6.0 per cent. The weakest monocaine solution which killed the skin in any animal was 0.5 per cent, as compared to 2.0 per cent for procaine. Comparison of the concentrations which produced sloughing in one-half the tests also showed that monocaine was far more irritating, since 1.4 per cent was required for this as contrasted to 3.4 per cent for procaine. These results indicated that monocaine was more than twice as injurious to tissues as was procaine. This greater local toxicity is of increased importance in view of the recent introduction of ampules of 1.5 per cent monocaine for clinical use.

ACUTE FATAL TOXICITIES

The acute fatal toxicities of monocaine were determined in several species of animals by various routes of administration. In each series, the volume of solution injected was kept constant while the concentration was varied to give the required dose, the intravenous injections

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being made as rapidly as possible without overdistending the vein. The dosage intervals were increased in proportionate increments. The cumulative frequency of mortality at each dosage level was computed and plotted against dose on log-probability graph paper. A straight line was drawn through the points from which corrected mortalities could be read for each dose. These values were used to calculate the median lethal dose and its standard error, according to the approximate methods of Kärber (10) and Irwin and Cheeseman (11). Check calculations showed that this method gave values closely agreeing with those obtained from the exact but more laborious "maximum likelihood" method of Bliss (12). Approximately equal numbers of males and females were used in each series, but separate curves for the two sexes revealed no sex difference in mortality, so the data have been combined for presentation here. The results are summarized in table 7, together with some other results on toxicity previously reported for the same compounds and animals.

In rats, monocaine was found to be 36 per cent more toxic than procaine intravenously, and 48 per cent more toxic intraperitoneally. In mice, the toxicity intravenously was less than in rats for both monocaine and procaine, but there was about the same ratio of relative lethal dosage. However, intraperitoneal and subcutaneous injections indicated an opposite situation, i.e. procaine being approximately one-third more toxic than monocaine. The lower toxicity of monocaine than procaine according to results of intraperitoneal and subcutaneous injections in mice suggests a slower rate of absorption of monocaine from these two regions in this species, since the intravenous injections showed monocaine to be more toxic after it got into the circulation.

The symptoms accompanying the lethal doses of both monocaine and procaine were spasticity, intermittent clonic convulsions and respiratory failure. The speed of onset and duration of symptoms depended upon the route of administration and dosage. Thus, the symptoms of monocaine poisoning were indistinguishable from those of procaine, and in fact those known for other local anesthetics.

Using subcutaneous injections in white mice, Butts and Koelle (3) reported "M.L.D." values of 350–400 mg. per kilo for monocaine and 400–500 mg. per kilo for procaine, and Abramson and Goldberg (2) reported 750 mg. per kilo for both monocaine and procaine. Thus, according to Butts and Koelle monocaine was 20 per cent more toxic than procaine, and according to Abramson and Goldberg these drugs have the same toxicity, whereas we found procaine to be more toxic under the same conditions. It should be pointed out that Butts and Koelle and Abramson and Goldberg expressed toxicity as the "M.L.D.," without defining the term, rather than median lethal dose. The median lethal dose was used by us because it is the most reliable value for expressing toxicity since it is at the midpoint of the dose-response curve, where each animal gives information of maximum significance, rather

TABLE 7

COMPARISON OF ACUTE TOXICITY OF MONOCAINE AND PROCAINE ACCORDING TO MEDIAN LETHAL DOSES (LD_{50}) IN MG. PER KILO

Species	Method of Injection Used	Monocaine		Procaine		Relative Toxicity of Monocaine (Procaine = 1)	References
		No. Animals Used	$LD_{50} \pm SE$	No. Animals Used	$LD_{50} \pm SE$		
White rat	i.v.*	150	28.2± 1.26	155	38.3± 1.60	1.36	
	i.p.†	48	182.3± 4.8	28	269.4± 5.8	1.48	
White mouse	i.v.	100	43.2± 0.95	100	56.9± 1.5	1.32	
	i.p.	130	203.0± 7.9	120	123.8± 7.1	0.61	
	Subcut.	32	449.1± 26.1	36	339.1± 42.4	0.76	
RESULTS IN LITERATURE							
White rat	i.v.				51		15
	i.p.			70	250		13
				129	255		14
					300		15
White mouse	i.v.				60-70		15
	Subcut.	60	350–400 "MLD"	27	400–500 "MLD"	1.2?	3
			750 "MLD"		750 "MLD"	1.0	2
					800		15

* Intravenous. † Intraperitoneal.

than at either end, where the information from each animal rapidly decreases. By "M.L.D.," Abramson and Goldberg may have meant the dose which killed all their animals, since they also gave values in other series for the "lowest individual M.L.D." This would account for their high values for toxicity. It is impossible to determine from the published report of Butts and Koelle what these authors meant by "M.L.D."

Reinjections of monocaine and procaine were made intravenously, after about ten days, into the 72 mice and 76 rats which survived the first doses of these drugs. The mice were injected with 39 mg. procaine, and the rats with 25 mg. monocaine, or 40 or 45 mg. procaine,

doses which were thought to be approximately the LD_{50} from the data available at the time the reinjections were made. The percentage mortalities resulting from the reinjections agreed closely with those from the first doses. The Chi-square calculations showed that there were not statistically significant differences in the percentage mortalities of these groups of animals from which, supposedly, the more susceptible members had been eliminated. These results indicated that there were probably no cumulative toxic effects beyond ten days from the monocaine or procaine. That is, there was no enhanced toxicity from the second dose, nor was there increased tolerance. The results also suggest that variabilities in susceptibility to local anesthetics is a matter of spontaneous daily fluctuation for each animal rather than the expression of an inherent fixed physiological state characteristic of an individual. However, there is the remote possibility that the decreased mortality which might be expected to be demonstrated in such a group of survivors was counterbalanced by the persistence of a toxic action tending to produce an increased susceptibility. Whatever the explanation, this is something that would be worth while looking into further by experimenters, because, if animals surviving such tests for fatal doses can be used over again without distorting average results, there would be a considerable saving in animals and expense.

Fatal doses from continuous intravenous injections were also determined, using clinical concentrations of monocaine, in 5 cats anesthetized with pentobarbital, 35 mg. per kilo intraperitoneally. Blood pressure and respiratory changes were recorded on a kymograph and the femoral vein was cannulated for continuous intravenous injection. One per cent monocaine in physiological saline solution was injected at a constant rate of 0.5 cc. per kilo per minute until death of the animal, as indicated by a fall of blood pressure to the zero level on a mercury manometer. The mean lethal dose under these conditions was 35.1 ± 1.7 mg. per kilo. Under the same conditions, in this laboratory, Tainter and Throndson (14) found the mean lethal dose of procaine to be 30.9 ± 2.3 mg. per kilo. The difference between these values is so small as to indicate that monocaine and procaine are practically equally toxic when given intravenously in pentobarbitalized cats. In rabbits, Butts and Koelle (3) reported intravenous lethal doses of 30 and 45 mg. respectively, and Abramson and Goldberg (2) 32 and 53 mg. for rapid injections and 43 and about 60 mg. respectively, for slower ones. Thus, the data of these reporters indicate monocaine to be more toxic than procaine in unanesthetized rabbits, in contrast to an equality of toxicity in pentobarbitalized cats used by us.

Summary.—Injected intravenously into healthy mice and rats, monocaine is 30 to 48 per cent more toxic than procaine, but is of equal toxicity for anesthetized cats by the same route. When injected intraperitoneally into rats, monocaine is about 50 per cent more toxic than procaine, but is less toxic intraperitoneally or subcutaneously in mice.

This reversal of the relative toxicities suggests that in mice absorption of monocaine is considerably slowed, the mechanism of which is not indicated by the data on toxicity. Since this difference was not present in rats, the possibility of a local vasoconstrictor action of monocaine seems improbable unless it be assumed that this is peculiar to mice, which appears untenable. Experimental tests for the alleged vasoconstrictor action of monocaine are described next.

EFFECTS ON CIRCULATION AND RESPIRATION

The effects of monocaine and procaine on the blood pressure, pulse and respiration of rabbits and cats were determined after intravenous injections of the drugs. Fourteen rabbits and 16 cats were anesthetized with chlorbutanol (0.75 to 1.0 cc. of 40 per cent solution per kilo) and prepared in the usual manner for recording blood pressure and respiratory movements. The local anesthetics in isotonic solution were injected into a cannulated saphenous vein, each dose being washed in by a small volume of 0.9 per cent sodium chloride solution.

Monocaine did not consistently increase the blood pressure, either in different animals or in the same animal at different times, more than did the same volume of salt solution. In 5 rabbits of between 2 and 3 kilo body weight, monocaine alone in doses of 0.25 to 0.5 cc. of 1.0 per cent solution produced a slight rise of blood pressure averaging less than 10 mm. Hg. The same dose in 4 other rabbits produced a slight fall, while 3 rabbits showed no significant changes. The rises observed were no greater than those caused by the same volumes of salt solution injected as controls. Apparently this elementary control test was not carried out by some of the other investigators who reported pressor effects for monocaine. When the dose of monocaine administered was increased, any pressor effects were lost, until, with large doses, the blood pressure dropped abruptly, the pulse rate slowed, and the respiration was depressed. Death was due primarily to respiratory failure, quickly followed by cardiac stoppage. Injections of procaine consistently decreased the blood pressure, the magnitude and duration of the fall depending upon the dose. Procaine is known to be a vasodilator, and our results on blood pressure agreed with this.

Claims are being continually made by the manufacturer and some clinical reporters that monocaine is a pressor drug, based apparently on individual responses of the inconclusive type observed by us. It should be pointed out that, while vasoconstrictor substances may increase the blood pressure, pressor agents are not necessarily vasoconstrictors. Central nervous system, cardiac and other effects must be eliminated before vasoconstrictor action can be inferred from pressor changes alone. Therefore, more direct tests of the mechanisms involved appeared necessary, particularly after destruction of the central nervous system. Potentiation or synergism was also looked for by comparing

responses to test doses of epinephrine in the presence and absence of monocaine and procaine.

In rabbits, monocaine did not potentiate the pressor effects of epinephrine on blood pressure. Monocaine, 1.0 per cent, containing a range of concentrations of epinephrine, when injected intravenously produced rises of blood pressure which were less than the rise from the same amount of epinephrine alone in the same animals. A typical response is shown in figure 1, and the numerical data are summarized in

FIG. 1. Effects of epinephrine intravenously with and without addition of monocaine on the blood pressure and respiration of a rabbit.

table 8. This was true for procaine also, but to a more striking degree. Hyatt (16) states that a mixture of monocaine and epinephrine produces a blood pressure rise which is never followed by a fall, as may occur with a mixture of procaine and epinephrine. Hyatt's explanation of this is that the vasodilator action of procaine is uncovered after the epinephrine has worn off, and that, since monocaine is a vasoconstrictor, the fall does not occur when this drug is used instead of procaine. Our results showed that the rise in blood pressure after injection of a mixture of monocaine and epinephrine might be followed by a fall below normal, and that the same amount of epinephrine alone might produce a similar response. It was clear that monocaine did not interfere with this typical effect of epinephrine.

TABLE 8

RISE OF BLOOD PRESSURE IN RABBITS AFTER INTRAVENOUS INJECTION OF EPINEPHRINE ALONE AND WHEN COMBINED WITH MONOCAINE; BEFORE AND AFTER DESTRUCTION OF THE CENTRAL NERVOUS SYSTEM

Volume Injected cc.	Concentration of Solution		No. of Injections	Av. rise B. P. mm. Hg.
	Monocaine	Epinephrine		
Rabbits (Chlorbutanol Anesthesia)				
0.25	None	1 : 75,000	4	32.5
0.25	1 : 100	1 : 75,000	4	35
0.5	None	1 : 75,000	15	56
0.5	1 : 100	1 : 75,000	17	40
1.0	None	1 : 50,000	3	44
1.0	1 : 100	1 : 50,000	3	30
1.0	None	1 : 75,000	6	44
1.0	1 : 100	1 : 75,000	6	42
1.0	None	1 : 150,000	6	30.5
1.0	1 : 100	1 : 150,000	3	27
Cats (Chlorbutanol Anesthesia)				
0.25	None	1 : 75,000	12	52
0.25	1 : 100	1 : 75,000	12	56
0.5	None	1 : 75,000	7	39
0.5	1 : 100	1 : 75,000	6	46
1.0	None	1 : 75,000	2	33
1.0	1 : 100	1 : 75,000	2	34.5
Cats (Decerebrated and Pithed)				
0.25	None	1 : 75,000	3	61
0.25	1 : 100	1 : 75,000	8	39
0.5	None	1 : 75,000	14	58
0.5	1 : 100	1 : 75,000	8	30.5

In cats, intravenous injections of 0.25 to 0.5 cc. of 1 per cent monocaine did not change the blood pressure appreciably, although respiration was depressed in both rate and depth. As indicated by the summary in table 8 and the responses of figure 2, monocaine plus epinephrine produced a slightly greater rise in blood pressure in cats than did the same dose of epinephrine alone, as was also the case in dogs used by Butts and Koelle (3). But the difference was only a few millimeters, and it did not increase as the dose of injected monocaine was raised. Certainly, the difference was not great enough, nor consistent enough,

to justify claims for potentiation nor for recommending the use of monocaine over procaine.

To determine whether the slightly greater pressor effect of the monocaine-epinephrine mixture in cats was due to vasoconstriction of central or peripheral origin, the central nervous system was first destroyed by pithing and decerebration, and the injections repeated. Again monocaine alone caused no change in blood pressure, and when combined with epinephrine there were generally smaller rises than the same doses of epinephrine alone, as is shown in figure 2, and table 8. Therefore, the apparent slight increase in pressor effect of the mixtures in intact cats was not due to a direct effect on the smooth muscle of the

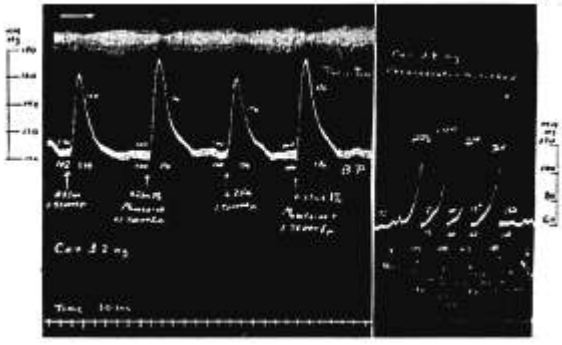

FIG. 2. Effects of epinephrine intravenously with and without addition of monocaine on the blood pressure of cats with the central nervous system intact and after decerebration and pithing.

blood vessel walls, but rather to some slight central irritation from monocaine super-imposed on the peripheral vasoconstriction of epinephrine. Thus, there is no indication from our results that monocaine is a direct vasoconstrictor, and it does not potentiate the peripheral action of epinephrine which is important in local anesthesia. Under the same conditions, procaine reduced the epinephrine responses an average of 7 mm. Hg, so it also caused no demonstrable potentiation.

In both cats and rabbits, lethal doses of either monocaine or procaine caused respiratory paralysis followed by circulatory collapse. The actual doses for this have been presented above in the discussion of acute fatal doses. Table 9 shows that the mean fatal doses of procaine and monocaine were equal within the limits of variation of individual animals. However, we have previously shown for procaine (14) that since the cause of death is respiratory paralysis, artificial respiration raises the dose required to stop the heart to 454 mg. per kilo., which is a decrease in toxicity of practically fifteen times. Therefore, a series of

TABLE 9

MEAN FATAL DOSES OF MONOCAINE AND PROCAINE AS MODIFIED BY THE USE OF ARTIFICIAL RESPIRATION

Cats were given 1 per cent monocaine or 2 per cent procaine intravenously at the rate of 0.5 cc. per kilo per min., under pentobarbital anesthesia. The values for fatal doses are the means in mg. per kilo and the standard error of the mean.

Solution	Without Artificial Respiration		With Artificial Respiration		Cardiac-Respiratory Toxicity Ratio
	No. Cats	Mean Fatal Dose	No. Cats	Mean Fatal Dose	
Monocaine.....	5	35.1±1.7	6	111.3±23.0	3.2
Procaine.....	5	30.9±2.3	10	454.5±117.1	14.7

cats was studied similarly with monocaine, using artificial respiration throughout the period of intravenous injection. This procedure raised the fatal dose to 111 mg. per kilo., or only an increase of about three times. Apparently, therefore, monocaine is four times more toxic than procaine for the cardiovascular system, although monocaine and procaine are equally paralytic for the respiratory center.

SYNERGISM WITH EPINEPHRINE

The results on blood pressure discussed above did not indicate that monocaine was synergistic with epinephrine. However, addition of epinephrine to monocaine enhanced the local anesthetic efficiency, but this increase was not more marked than that of procaine under the same conditions. More direct evidence was therefore sought on the question of the alleged synergism or potentiation of local vasoconstriction with epinephrine by monocaine.

Slough Test.—The slough test has been described above as a method of comparing the necrotizing effects of monocaine and procaine on tissues. It may also be used to indicate the intensity of vasoconstriction, since this can cause necrosis from too prolonged anoxia. Graded concentrations of epinephrine were therefore injected and the frequencies of sloughs compared with those observed when 1 per cent monocaine or 2 per cent procaine was added. The results are summarized in table 10.

Monocaine caused sloughs in 18 per cent and procaine in 11 per cent of the animals when these agents were used alone. This necrotizing action of the two local anesthetics does not necessarily establish a vasoconstrictor action for them since these actions can be explained as readily by direct tissue damage independent of vasoconstriction or vasodilatation. Similarly, the various concentrations of epinephrine caused increased incidence of sloughs as the concentrations were raised and the vasoconstriction became more intense. The data in table 10 show that, when monocaine and epinephrine were combined, the incidence of necrotic areas was practically identical with what would be expected from a simple additive action of the two independently acting agents. Hence,

TABLE 10

INCIDENCE OF SLOUGHS AFTER SUBCUTANEOUS INJECTIONS IN RATS OF 0.5 CC. OF MONOCAINE, PROCAINE AND EPINEPHRINE ALONE AND IN COMBINATION IN A SERIES OF CONCENTRATIONS

Drug Concentration			Observed Incidence of Sloughs	Expected Incidence of Sloughs from Additive Actions
Monocaine	Procaine	Epinephrine		
1%			18%	
	2%		11%	
		1 : 5,000	100%	
		1 : 10,000	70%	
		1 : 20,000	46%	
		1 : 40,000	17%	
		1 : 60,000	0%	
1%		1 : 10,000	85%	88%
1%		1 : 20,000	62%	64%
1%		1 : 40,000	33%	35%
1%		1 : 60,000	22%	18%
1%		1 : 80,000	10%	18%
	2%	1 : 20,000	100%	57%
	2%	1 : 40,000	90%	28%
	2%	1 : 60,000	74%	11%
	2%	1 : 80,000	69%	11%
	2%	1 : 100,000	45%	11%

no evidence was obtained of any synergistic or potentiated effect of monocaine in increasing the epinephrine ischemia. However, with procaine the frequency of necrosis was much greater than could be accounted for by a simple additive action with the epinephrine. The solutions behaved as if epinephrine were present in from five to eight times the actual concentration, a difference which could not be accounted for by weak necrotizing action of procaine alone. Many reports have been published to the effect that procaine can potentiate epinephrine actions under special conditions, and our results are consistent with such an effect. However, that monocaine should fail to do the same thing is very striking in view of the categorical claims made for it of a synergistic vasoconstrictor effect with epinephrine.

Strychnine Test.—Another indirect test of vasoconstriction in monocaine was the simultaneous use of strychnine in fatal doses. This alkaloid produces its action rapidly, and is quickly eliminated if survival is sufficiently prolonged. Any vasoconstrictor agent added to a strychnine solution injected subcutaneously would delay its absorption and require administration of a larger dose for fatal effects. Use was made of this to test the vasoconstrictor power of monocaine and procaine in the presence and absence of epinephrine. Spoto has used the same principle to measure local vasoconstriction in the pulmonary system (17).

One control series of mice was given subcutaneous injections of 10 cc. per kilo of strychnine solutions of strengths adjusted to contain the re-

quired dose, and the median lethal dose determined. Two series were injected with strychnine plus 1 per cent monocaine or 2 per cent procaine, and 4 more series with graded strengths of epinephrine and strychnine instead of the local anesthetics. Then 4 series were injected with solutions of strychnine containing one of the anesthetics and various strengths of epinephrine. By comparing the median lethal doses, the amount of interference with the strychnine absorption as the result of any vasoconstriction could be estimated. A summary of the results is presented in table 11.

TABLE 11

EFFECTS OF EPINEPHRINE, MONOCAINE AND PROCAINE ON THE ABSORBABILITY OF STRYCHNINE SOLUTION FROM THE SUBCUTANEOUS TISSUES OF MICE

Each mouse was given 10 cc. per kilo of physiologic salt solution containing the required amounts of the drugs indicated and strychnine.

Concentration in Solution of Strychnine			No. Mice Used	LD_{50} of Strychnine mg. per kilo.
Epinephrine	Monocaine	Procaine		
			65	1.40
	1 : 100		40	1.39
		1 : 50	40	1.43
1 : 100,000			40	2.40
1 : 75,000			65	2.90
1 : 50,000			40	3.70
1 : 25,000			40	3.00
1 : 75,000	1 : 100		50	1.39
1 : 50,000	1 : 100		30	1.63
1 : 25,000	1 : 100		10	1.56
1 : 50,000		1 : 50	38	1.65

Strychnine alone killed one-half the mice with a dose of 1.40 mg. per kilo, which was not significantly altered by addition of either monocaine or procaine alone. Hence, no evidence of direct vasoconstrictor action of either of these agents was demonstrable. Epinephrine, 1:100,000 slowed the absorption of the strychnine so that the LD_{50} was raised to 2.40 mg. per kilo; 1:75,000 and 1:50,000 raised it to 2.90 and 3.70 mg. per kilo, respectively. The still higher concentration of epinephrine of 1:25,000 gave a somewhat lower fatal dose of strychnine, namely 3.00 mg. per kilo, indicating possibly some direct toxicity of epinephrine itself coming into play. When monocaine 1 per cent was added to the epinephrine-strychnine mixtures practically all the antidotal power of epinephrine was lost as shown by LD_{50} values of 1.39, 1.63 and 1.56 mg. per kilo, respectively. Procaine, 2 per cent, had the same effect, i.e., reducing the LD_{50} in the presence of 1:50,000 epinephrine from 3.70 to 1.65 mg. per kilo. These results indicate that clinical concentrations of the local anesthetics depress the peripheral vascular mechanisms enough to prevent nearly all the vasoconstriction of epinephrine, and certainly do not show any evidence of potentiation. The observations are also of interest in demonstrating why it is necessary to use as much as 1:25,000

to 1:75,000 epinephrine in local anesthetic solutions, when concentrations as low as 1:10,000,000 will cause powerful constriction of vessels in the absence of anesthetic drugs.

The results of this test are not entirely consistent with those of the previous section on the necrotizing effects, since no evidence of interference with vasoconstrictor action was discovered there. In the slough test, there may have been factors in the irritative effects other than these due to vasoconstriction. This uncertainty in the interpretation of the results made it imperative that direct observations of the actions of these drugs on blood vessels be made for an unequivocal answer. Recourse was therefore had to perfusion of the living vascular bed.

Perfusion of Rabbit Ear Vessels.—Rabbits were killed by a blow on the head, and the ears immediately removed. A cannula was tied into the central artery for perfusion with Ringer-Locke solution at room temperature and a pressure of about 1 meter of water. The efferent veins were exposed and the fluid running out was collected quantitatively each minute as a measure of the degree of constriction or relaxation present. Injections of monocaine and procaine, with and without epinephrine, were made into the inflowing fluid, using constant technic to avoid pressure artefacts.

In only one of 9 ears did monocaine 0.1 to 1.0 mg. alone cause a decrease in flow, and therefore, vasoconstriction. In all the other ears there was no evidence of vasoconstrictor action. In 7 ears 0.2 to 2.0 mg. procaine constricted once, dilated twice, and had no effect in the remaining 4 ears. Hence, this drug also was practically devoid of direct vasomotor actions. Constriction from epinephrine was decreased by both monocaine and procaine in doses of 0.1 to 2 mg. in 8 out of 9 ears, the decrease being greater as the amount of local anesthetic in the epinephrine solution increased. In one representative series of responses, three injections of 0.1 micrograms of epinephrine caused constrictions averaging 72 per cent, whereas when 0.1 mg. monocaine was added to the epinephrine, in injections alternating with these, the average constriction was reduced to 48 per cent; when 1 mg. was added, this was reduced to 29 per cent. Therefore, monocaine not only failed to exert a direct vasoconstrictor action, but even diminished the intensity of the vasoconstriction produced by epinephrine. From all this it follows that the claims for vasoconstrictor action of, or potentiation of epinephrine by, monocaine are disproved by these clear-cut negative results. These negative results are also consistent with those of the strychnine absorption tests and of blood pressure responses.

DISCUSSION

The major claims made for monocaine which are susceptible of experimental verification or refutation are (1) increased anesthetic potency, (2) decreased toxicity, and (3) vasoconstrictor or synergistic actions with epinephrine. The results of this report show that monocaine,

like procaine, was a poor surface anesthetic, and therefore need not be considered from this standpoint, since much more effective agents are available and in common use. For injection purposes, its local anesthetic potency was no greater than that of procaine upon direct application to the exposed sciatic nerve (frog); it was possibly weaker upon infiltration of the orbital tissues, and only somewhat stronger for other tissues in the rabbit. Although stronger than procaine in wheals in human skin, when used alone, this superiority was lost when epinephrine was added. Accordingly the claim of greater anesthetic efficiency than procaine could not be confirmed. While direct injury to tissues from monocaine was not particularly marked, it was greater than that of procaine according to different tests. The systemic toxicity of monocaine was definitely greater than that of procaine, as indicated by fatal doses intravenously in rats and mice and intraperitoneally in rats. However, it was less toxic than procaine when injected intraperitoneally or subcutaneously in mice, and possibly slightly so intravenously in cats anesthetized with pentobarbital. When the respiratory paralysis was prevented by artificial respiration, monocaine paralyzed the heart in about one-fourth the dose required by procaine under the same conditions. Hence, the systemic toxicity as indicated by lethal actions showed no consistent advantage of monocaine over procaine.

A vasoconstrictor action for monocaine was not demonstrable by direct perfusion through blood vessels or intravenous injection in intact animals. What may have been mistaken for a vasoconstrictor effect of monocaine by others was demonstrated to be due to some central actions rather than a peripheral vasoconstrictor action or, it may have been a misinterpretation of small differences resulting from the volumes of fluid injected, which were apparently not accurately discounted by appropriate controls. Similarly, combinations of monocaine and epinephrine had no demonstrable potentiated vasoconstriction, as indicated by a variety of tests, both direct and indirect. Hence, the claims for a special vasoconstrictor efficiency of combinations of epinephrine and monocaine also were not sustained by the extensive and varied tests made by us.

These results leave little doubt that the slight chemical change made in the procaine molecule which led to monocaine resulted also in only slight changes in its useful actions quantitatively, but probably not qualitatively. The local irritant actions, however, were not lessened in monocaine, but made worse, if anything. There is, therefore, little if any experimental justification of monocaine over procaine as a local anesthetic, just as was previously shown by us to be the case clinically.

The results of these two studies, considered together, raise the interesting, speculative possibility whether the favorable impressions of monocaine, obtained by some clinicians, may be caused by comparisons of symptoms after 1 per cent monocaine with those after 2 per cent procaine, and after monocaine solutions containing 1:75,000 epinephrine

with those after procaine with 1:50,000 epinephrine. If 1 per cent procaine will give satisfactory anesthesia, as it apparently does in the hands of many oral surgeons, and 1:75,000 epinephrine provides adequate vasoconstriction, as is the frequent experience, would not this combination be equally as satisfactory as, or better than, the monocaine combination of the same strengths now in use? Also what is to be expected in terms of toxicity and irritation of the still stronger 1.5 per cent monocaine now being made available for clinical use?

SUMMARY AND CONCLUSIONS

1. A study has been made of the pharmacological actions of monocaine (isobutyl-aminoethyl-para-amino-benzoate hydrochloride), an isomer of procaine recently introduced for clinical use with claims of superiority over procaine.

2. The solubility of monocaine is limited, since only about a 2.6 per cent solution can be made in water and 1.5 per cent in physiological sodium chloride solution at room temperatures. The pH of 1 per cent solution is 5.59 as measured with a glass electrode. Solutions of monocaine decompose slowly on standing exposed to light and air, and during pressure sterilization. However, addition of sodium bisulfite produces adequate stability.

3. As a surface anesthetic, monocaine was found to be twice as efficient as procaine on frog's skin, when tested by the Türck method, and of about the equal potency by instillation in rabbit's conjunctiva. The motor fibers in the frog's sciatic nerve were paralyzed equally well by monocaine and procaine. Block of sensory fibers after injection into tissues around the eyes of rabbits was produced by lower concentrations of procaine than of monocaine, but the relative potency was reversed when epinephrine was added to the solutions. Sensory fibers in rabbits' skin were paralyzed by slightly lower concentrations of monocaine than procaine, but in human skin, in the presence of epinephrine, the anesthetic efficiency of both agents was the same.

4. The effects of monocaine on frog's sciatic nerve were not always fully reversible, indicating a direct injurious action on nerve tissue. Similarly, the subcutaneous tissues of rats were irritated more by monocaine than procaine, according to the trypan blue test and the presence of inflammatory changes in tissues. When injected under standard conditions, 1.4 per cent monocaine caused sloughs in the skin in one-half the animals as compared to 3.4 per cent procaine required for the same degree of local irritant action. Hence, monocaine was definitely more injurious for tissues than was procaine.

5. The systemic toxicity of monocaine was about 40 per cent greater than that of procaine, as indicated by fatal doses intravenously in rats and mice, and intraperitoneally in rats. In mice, this toxicity ratio was reversed for subcutaneous and intraperitoneal administrations, possibly indicating some lack of absorption from these two regions in this species. In cats under pentobarbital anesthesia, the fatal dose of mono-

caine was 35.1 mg. per kilo, as compared to 30.9 mg. per kilo for procaine, a difference which the standard errors showed not to be reliable. When artificial respiration was maintained in the cats, the fatal dose of monocaine was increased to 111 mg. per kilo, and that of procaine to 454 mg., indicating that monocaine was about four times as toxic for the cardiovascular system as was procaine.

6. Neither monocaine nor procaine caused pressor actions due to peripheral vasoconstriction when injected intravenously in rabbits and cats. Both agents did not increase the pressor responses to epinephrine and thus there was no demonstrable synergism or potentiation of effects between these anesthetics and epinephrine. There was the same lack of pressor and synergistic responses in perfused blood vessels where all except peripheral effects were eliminated. Indirect tests for potentiated vasoconstrictor responses to monocaine and epinephrine, consisting of comparing the incidence of tissue sloughs under quantitative conditions, and the interference with absorption of strychnine from subcutaneous tissues, failed to give evidence of any heightening of epinephrine effects in the presence of monocaine.

7. These results taken together indicate that the local anesthetic efficiency of monocaine is similar to that of procaine qualitatively and quantitatively, as is also the systemic toxicity, except for a greater cardiovascular paralyzing action of monocaine. They also fail to substantiate current claims that monocaine is a pressor agent, or that it potentiates the actions of epinephrine. Since monocaine is definitely more irritating to tissues than procaine, it lacks the advantages which would justify its selection over procaine as a local anesthetic for injection purposes. It is suggested that, since the anesthetic potencies of procaine and monocaine are so nearly the same, a 1 per cent concentration of procaine (same as that used of monocaine) with the epinephrine diluted to 1:75,000 (the strength used in monocaine solutions) might give as satisfactory clinical results as does the monocaine solution now in common use.

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