PHARMACOLOGIC STUDIES IN SEARCH OF A SUITABLE DRUG FOR PERIDURAL SEGMENTAL ANESTHESIA *

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IN a previous paper (1), the clinical aspects and the technic of peridural anesthesia were discussed. The successful use of this method is largely dependent upon two factors: (1) The technical ability to place the anesthetic agent in the desired anatomical site and (2) a suitable local anesthetic agent for such approach.

Procaine solutions have proved inadequate for this purpose due to prolonged induction period and their erratic anesthetic action. Various agents were employed, including pontocaine, metycaine, nupercaine and intracaine; the last was the most suitable because of the speed of onset and uniformity of anesthesia which it produced.

Intracaine (beta-diethylaminoethyl para-ethoxy benzoate hydrochloride), described in detail by McIntyre and Sievers (2), possesses some marked superiorities over procaine as an anesthetic agent, for not only is it superior with regard to the minimal effective concentration, but also as to the duration of anesthesia.

$$\frac{\text{M.E.C. (Procaine)}}{\text{M.E.C. (Intracaine)}} \times \frac{\text{M.L.D. (Intracaine)}}{\text{M.L.D. (Procaine)}} = \frac{1/40\%}{1/80\%} \times \frac{565}{800} = 1.2 \text{ plus}$$

$$\frac{\text{D. (Intracaine)}}{\text{D. (Procaine)}} \times \frac{\text{M.L.D. (Intracaine)}}{\text{M.L.D. (Procaine)}} = \frac{59}{16} \times \frac{565}{800} = 1.80 \text{ plus}$$

(M.E.C. is Minimal effective concentration)

Toxicity			Anesthetic Properties		
Subcutaneous mouse	Procaine	Intracaine	Guinea pig Sciatic nerve	Procaine 16 min.	Intracaine 59 min.
	800 mg./kg.	565 mg./kg.	Block (Shackell Method) 1%		
			Human intradermal testing		
			1/10%	11 min.	13.6 min.
			1/20%	6 min.	10.6 min.
			1/40%	2 min.	7.6 min.
			1/80%	0	3.0 min.

These experimental findings have been corroborated clinically. Cullen and Rovenstine (3) observed that from a therapeutic point of

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view 0.5 per cent solution of intracaine used as an infiltration anesthetic produced results comparable to 0.7 per cent to 1.0 per cent procaine. They were unable to find any deleterious local tissue reaction as a result of administration of such solutions.

Recently, McCuskey (4) reported that subcutaneous administration of as much as 50 cc. of 2 per cent solution of intracaine produced no untoward local reactions. The duration of anesthesia was approximately twice that of procaine when used in the same concentration.

Fatalities from overdosage of local anesthetics fall into two general categories: (1) A primary cardiocirculatory failure and (2) a primary respiratory failure. From the point of view of practical therapeutics, the latter type of toxic response is somewhat less dangerous than the former, for it affords time for the institution of adequate resuscitation procedures. Nupercaine and cocaine belong to that group of agents which produced primary circulatory deaths, whereas intracaine belongs to the category which produced respiratory depression and failure prior to any serious interference with the circulatory mechanism.

Still another important consideration is the choice of a local anesthetic agent for the ease with which toxic doses may be overcome by ready available agents. The barbiturates are commonly used as antidotes for local anesthetics, and McIntyre and Sievers have demonstrated that the barbiturate group can increase the lethal intravenous dose of intracaine in dogs by a factor of 6.7 as against a factor of 2.7 for procaine.

Intracaine has a high degree of water solubility and does not break down by ordinary sterilizing procedures. Solutions have been kept over a period of three months without showing any appreciable hydrolysis. Should hydrolysis take place, however, it is readily detectable, for, unlike procaine base, it has a very low water solubility and precipitates as fine visible crystals. Attention has been called (8a) to the fact that para-amino-benzoic acid and certain of its derivatives, which include local anesthetic agents of the procaine group, are specific inhibitors of the antibacterial action of the sulfonamide group of drugs. In view of the fact that intracaine does not belong to this chemical category, it does not possess this inhibiting action.

In a previous clinical report, it was pointed out that the solution of intracaine used was modified. This modification consisted of the addition of epinephrine 1:200,000 for its local vasoconstricting action and potassium sulfate. Such modification affords an effective method of synergizing the local anesthetic action of the drug. Neither of these modifications of themselves introduced any new fundamental principles.

Braun (1903) first introduced the use of vasoconstrictors with local anesthetics. Since that time it has become the standard practice. However, the principle has not been applied to its greatest potential advantage. The usual concentration of 1:50,000 is unnecessarily high (5, 6) as well as being potentially dangerous (7) and there is no advan-

RELATIVE TOXICITY FOR MICE OF PROCAINE HYDROCHLORIDE AND INTRACAINE HYDROCHLORIDE WITH AND WITHOUT POTASSIUM SULFATE

Test Conditions: Albino mice housed in air conditioned room, temperature 22–23.5 C. Weight of mice 17–23 grams. Freshly prepared solutions used for injection. Injection of solutions with and without added potassium sulfate paired with respect to time of injection and weight of mice used.

Subcutaneous Injections

Dose 4% Procaine.HCl mg./kg.	Mortality	% Deaths	Dose equivalent read from graph mg/kg.	Dose Procaine.HCl 4% with K_2SO_4 3% mg./kg.	Mortality	% Deaths	Dose equivalent read from graph mg./kg.	Toxicity ratio—Procaine.HCl with K_2SO_4 to Procaine.HCl as unity
800 } 872 900 }	6/15 } 29/54 29/39 }	53.7	902	1100 } 1108 1200 }	16/48 } 18/52 2/4 }	34.6	758	$\frac{758}{902}\times\frac{872}{1108}=0.661\pm5.94\%$
				1300	25/42	59.5	952	$\frac{952}{1071}\times\frac{1111}{1300}=0.760\pm7.44\%$
1100 } 1111 1200 }	24/34 } 27/38 3/4 }	71.1	1071					
1300	4/4	100.0						Wdt. avg. $\overline{0.705\pm4.65\%}$ Solution containing 3% K_2SO_4 is 29.5% ±3.3 less toxic than 4% Procaine.HCl without added K_2SO_4
Dose 4% Intracaine.HCl mg./kg.	**Mortality**	**% Deaths**	**Dose equivalent read from graph mg./kg.**	**Dose 4% Intracaine.HCl with K_2SO_4 3%**	**Mortality**	**% Deaths**	**Dose equivalent read from graph mg./kg.**	**Toxicity ratio—Intracaine.HCl with K_2SO_4 to Intracaine.HCl as unity**
700	8/20	40	713	700	5/20	25.0	662	$\frac{662}{713}\times\frac{700}{700}=0.928\pm4.99\%$
750	19/31	61.3	788	750	17/31	54.8	761	
850 } 882 900 }	5/7 } 12/19 7/12 }	63.2	796	850 } 882 900 }	7/7 } 18/19 11/12 }	94.7	1000	$\frac{761}{788}\times\frac{750}{750}=0.966\pm4.06\%$
1000	7/7	100.0		1000	7/7	100.0		$\frac{1000}{796}\times\frac{882}{882}=1.256\pm6.14\%$ Wdt. avg. $\overline{1.031\pm2.8\%}$ Solution containing 3% K_2SO_4 not significantly different in toxicity from 4% Intracaine. HCl solution without added K_2SO_4

Example of Method of Calculation Used

Subcutaneous dose—Procaine.HCl in 4% solution 872 mg.
No. mice injected 54. Incidence of mortality 53.7%

$$\gamma \text{ of incidence } \sqrt{\frac{53.7\times46.3}{54}}$$

$$\text{P.E. of incidence } \sqrt{\frac{53.7\times46.3}{54}}\times0.6745=4.6$$

	Dose from graph	Deviation
53.7	902	—
53.7 −4.6 = 49.1	868	−34 Avg. 36.5
53.7 +4.6 = 58.3	941	+39

$$\frac{36.5}{902}\times100=4.05\% \text{ of dose}$$

$$\text{Toxicity ratio}\frac{758}{902}\times\frac{872}{1108}=0.661+5.94\%$$

$(4.05)^2=16.4$

$(4.35)^2=\frac{18.92}{35.32}$

$\sqrt{35.3^2}=5.94$ P.E. of ratio

Subcutaneous dose Procaine.HCl in 4% solution +3% K_2SO_4 1108 mg.
No. mice injected 52. Incidence of mortality 34.6%

$$\gamma \text{ of incidence } \sqrt{\frac{34.6\times65.4}{52}}$$

$$\text{P.E. of incidence } \sqrt{\frac{34.6\times65.4}{52}}\times0.6745=4.5$$

	Dose from graph	Deviation
34.6	758	—
34.5 −4.5 = 30.1	725	−33 Avg. 33.
34.6 +4.5 = 39.1	791	+33

$$\frac{33.0}{758}\times100=4.35\% \text{ of dose}$$

tage in using concentrations higher than 1:150,000. It should be pointed out, however, that the necessity for a local vasoconstrictor is not as great in the case of intracaine as it is in the case of procaine for the former has no vasodilatory effect.

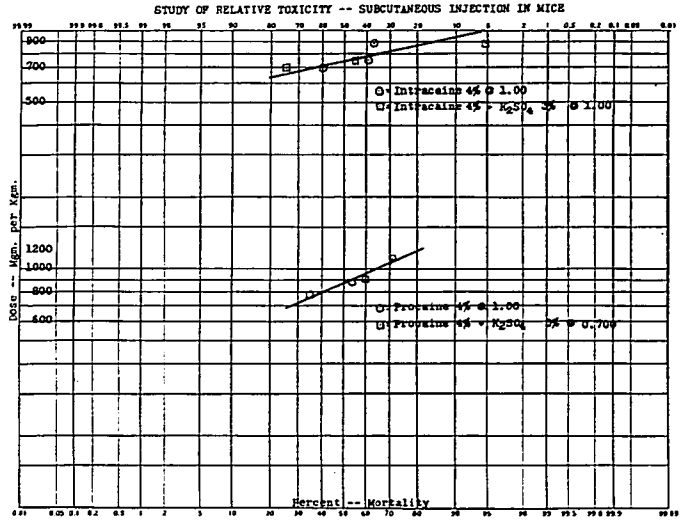

FIGURE 1.

The question of a synergistic potentiation of one drug by another has long been a strongly and a hotly debated question. This is primarily due to the fact that the claims of such synergistic activity were often based on subjective interpretation of clinical data rather than on objective and experimental evidence. The action of inorganic potassium salts on nerve conductivity is a well established physiologic fact. As early as 1912, Menten found that when nerves were immersed in dilute solutions of potassium salts, a loss of conductivity in isolated nerves was caused. Sodium and lithium salts did not produce such an effect. Kochmann and his co-workers (8, 9, 10, 11) applied this observation to pragmatic therapeutics by incorporating potassium sulfate with their local anesthetic solutions. The intracutaneous injection of procaine together with potassium sulfate increased and prolonged the local anesthetic action of procaine almost twofold.

Loeb and Beutner (12, 13) showed that potassium salts not only possess a certain amount of anesthetic action but also that they dimin-

ish the potential (muscle, brain and frog skin) much more than do the sodium salts. Additional data pertinent to this local action of potassium salt were presented by MacDonald (14), Sollmann (15) and Tainter (16).

Their data were sufficiently suggestive to instigate an intensive investigation whose purpose was the objective demonstration of such activity.

It is apparent that increased pharmacologic activity must not be accomplished by a comparable increase in the toxicity of the agent. Hoffman and Kochmann (9) were able to show that mixtures of potassium sulfate and local anesthetics had a lower intravenous toxicity for guinea pigs than did the amount of the local anesthetic, which produced the equivalent effect in man when administered intradermally. This work has been extended to include procaine and intracaine using subcutaneous administration in the mouse as the method for determining toxicities. Average toxicity ratios and their probable error were calculated from the log dose-probability integral correlation graphs. Intracaine hydrochloride, 4 per cent in water with 3 per cent potassium sulfate, calculated to be 3.1 per cent + or — 2.9 more toxic than intracaine hydrochloride, 4 per cent in water. This difference is not statistically significant.

Procaine hydrochloride, 4 per cent in water with 3 per cent potassium sulfate, calculated to be 29.5 per cent + or — 3.3 per cent *less toxic than procaine hydrochloride 4 per cent in water.* This is a statistically significant difference.

These results demonstrate that whatever role potassium may play in the increased local anesthetic activity of these agents, it is not the result of increased toxicity.

It can be demonstrated, however, that this summation of anesthetic effects may be based on the quantitative interruption of action potentials in isolated mammalian nerve. The experimental data on which this statement is based will be presented in detail in the future.

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