BLOOD LEVELS OF PROCAINE AND p-AMINOBENZOIC ACID FOLLOWING THE USE OF INTRAVENOUS PROCAINE HYDROCHLORIDE IN GENERAL ANESTHESIA * †

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THE intravenous use of procaine hydrochloride is well established as an adjunct to general anesthesia. The total amount given has varied from a few milligrams to several grams and the time for injection from minutes to hours. For proper evaluation of clinical procedures, it would seem desirable to know the concentrations of procaine and its products of hydrolysis in the blood after such administration. Only scant information regarding blood levels after known doses of procaine is available.

Dunlop (1) found that about an hour was required for the disappearance of unchanged procaine from the blood of dogs after intravenous doses of 20 mg. per kilogram. The p-aminobenzoic acid formed remained for a much longer time. Shumacker (2) determined "free" and "total" procaine in the heart blood of guinea pigs given lethal doses of procaine. His results indicate, "that after intravenous, intrapleural, intramuscular and subcutaneous injections, although the injected dose varied from 40 to 500 mg. per kilogram of body weight, the average unchanged procaine level was almost identically the same," from 11 to 16 mg. per 100 cc. Allen and Livingstone (3) found traces of "procaine" in the blood of rabbits for as long as 6 hours after subcutaneous injections. Goldberg, Koster and Warshaw (4) found up to 0.016 mg. per 100 cc. unchanged but a total of 0.42 mg. per 100 cc. of procaine in the blood of human subjects a few minutes after a spinal injection of 300 mg. Overgaard (5) found 8 to 11 mg. per 100 cc. of total procaine in the blood of guinea pigs to be acutely fatal, but that 2 mg. per 100 cc. produced no symptoms. After local anesthesia, the amount in the blood of patients was usually too low to determine, although in a few cases concentrations as high as 0.3 mg. per 100 cc. were found. He suggested that such levels might explain toxic reactions. Graubard, Robertazzi and Peterson (6) reported total procaine blood levels of 32 mg. per 100 cc. in rabbits receiving 20 mg. per kilogram of procaine hydrochloride, and as high as 8 mg. per 100 cc.

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in the blood of patients given 200 to 500 mg. total dose intravenously. Brodie, Lief and Poet (7) gave 2 Gm. of procaine hydrochloride intravenously to 5 human subjects and determined the resultant blood levels of procaine, p-aminobenzoic acid and diethylaminoethanol. They found that the plasma level of procaine was always less than 0.35 mg. per liter but that the plasma p-aminobenzoic acid increased to as much as 15 mg. per liter. One hour after the infusion no free procaine was found in the plasma, but considerable p-aminobenzoic acid remained. Burgen and Keele (8) followed the procaine and p-aminobenzoic acid concentrations in the blood of chloralosed cats after intravenous injections. They found that the blood procaine reached maximum levels of 6 to 66 mg. per liter after continuous infusions of 0.5 to 2.5 mg. per kilogram per minute. Constant blood levels of procaine were attained if the infusions were maintained for more than ten minutes. Free procaine disappeared in less than thirty minutes after the injections were stopped, but the p-aminobenzoic acid concentrations fell more slowly.

PROCEDURE

Total procaine and total p-aminobenzoic acid concentrations were determined in the blood of patients receiving intravenous procaine as an adjunct to general anesthesia. In a few patients both free procaine and free p-aminobenzoic acid were also determined. Bloods for analysis were obtained at the time the infusions were stopped and at one and at two hours later. The procaine was extracted from an alkalinized filtrate with chloroform. The method for analysis was a modified

TABLE 1

PROCAINE AND PABA IN VENOUS BLOOD AFTER INFUSION OF PROCAINE HYDROCHLORIDE. NO DISEASE RELATED TO LIVER OR KIDNEYS; BARBITURATES WITH NITROUS OXIDE

Pt.	Sex and Age	Wt., kg.	Total Dose, Gm.	Time in minutes	mg./kg.	Average mg./kg./min.	Blood Levels					
							Zero Time		1 Hour		2 Hours	
							Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.
McI	F 37	75.0	1.80	90	24.0	0.266	0.45	1.03	0.05	0.71	0	0.27
GAN	F 28	43.2	1.75	100	40.5	0.405	0.36	1.70	0.04	0.76	0.02	0.48
THO	F 42	71.8	3.00	150	41.7	0.278	0.56	2.24	0.04	1.36	0	0.58
AST	F 46	80.7	3.50	95	43.2	0.450	0.28	2.56	0.04	1.76	0.04	1.12
STA	F 51	66.4	3.00	135	45.2	0.334	0.95	2.64	—	1.99	0.05	0.99
MOW	M 59	61.8	3.50	120	56.7	0.472	0.20	2.50	0.16	1.36	0.04	0.70
BUR	F 23	81.8	5.00	140	61.8	0.437	0.56	2.00	0.08	1.16	0.04	0.66
KEL	M 47	61.4	4.00	140	65.1	0.465	0.40	1.76	0.12	1.02	0.02	0.48
DOS	F 25	56.8	4.00	80	70.4	0.880	0.80	2.88	0.40	1.36	0.28	0.76
COW	F 25	43.2	3.25	150	75.0	0.501	0.18	2.90	0.09	1.81	0.04	0.52
MIT	F 33	40.4	3.50	150	86.5	0.576	0.30	2.24	0.05	1.15	—	—
WIL	M 44	62.3	7.50	250	120.4	0.483	0.60	2.88	0.08	1.66	0.08	1.10

Bratton-Marshall method for sulfonamides * (9, 10). Readings were made on a photo-electric colorimeter.

Analyses for total procaine and p-aminobenzoic acid were made on one or more blood samples from 54 patients. Of these 54 patients 29 had varying degrees of pathologic change which might affect liver or kidney function or both. Obesity was included in the pathologic series since calculations of dosage were made on a weight basis. Because previous work has shown that the liver is important for the hydrolysis of procaine and that p-aminobenzoic acid is excreted mainly

TABLE 2

PROCAINE AND PABA IN VENOUS BLOOD AFTER INFUSION OF PROCAINE HYDROCHLORIDE. PATHOLOGIC CASES; BARBITURATES WITH NITROUS OXIDE

Pt.	Sex and Age	Wt., kg.	Total Dose, Gm.	Time in minutes	mg./kg.	Average mg./kg./min.	Blood Levels					
							Zero Time		1 Hour		2 Hours	
							Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.
THO	F 68	72.7	1.50	130	11.0	0.084	0.00	1.19	0.00	1.72	—	—
BAU	F 39	114.1	4.00	165	14.4	0.087	0.24	1.52	0.20	1.10	0.12	0.66
JOH	M 84	64.5	1.25	80	19.4	0.243	1.80	4.04	0.70	3.78	0.60	3.78
HOR	F 50	75.9	1.75	105	23.0	0.170	0.15	1.44	0	1.06	0	0.84
ROM	M 24	56.0	1.50	45	26.7	0.594	1.40	0.86	0.12	0.72	0.12	0.44
RIL	F 43	103.0	3.00	150	29.1	0.194	1.60	1.52	0.28	0.76	—	—
SHO	M 57	66.7	2.00	100	30.0	0.500	3.36	1.96	0.36	1.10	0.32	0.72
DEC	F 66	79.5	3.00	145	37.8	0.260	0.08	2.12	0.04	1.20	0.02	1.20
DAV	F 24	87.7	3.75	170	42.4	0.249	2.36	1.24	2.28	0.92	—	—
HEA	F 37	77.3	3.80	150	49.2	0.328	1.10	3.51	0	1.01	0	1.06
SPA	F 48	90.9	5.00	125	55.0	0.440	3.00	3.04	—	—	—	—
HAY	M 48	63.7	3.50	100	55.0	0.550	1.48	2.00	0.12	1.00	0.04	0.52
CON	F 42	60.9	5.00	175	82.5	0.471	2.75	3.27	0.25	2.00	0.10	1.32
JOH	F 33	50.5	5.00	105	99.2	0.944	1.00	4.86	0	3.08	0	1.35

The pertinent findings for the patients were as follows:

THO—pyelitis, hypertension, arteriosclerosis; BAU—obesity; JOH—hydronephrosis with pyuria, NPN 90, auricular fibrillation; HOR—hypertension, obesity; ROM—osteomyelitis; RIL—obesity; SHO—obstruction of ureters, pyuria, albuminuria; DEC—hypertension, obesity; DAY—obesity, pyuria; HEA—Pott's disease, pyuria; SPA—hypertension, obesity, pyuria, palpable liver; HAY—arteriosclerosis, chronic heart diecase; CON—treated with arsenicals for syphilis three years ago; JOH—pyuria.

by the kidney (1, 3, 8, 11, 14) the cases in which functional involvement of liver or kidney was not found were called nonpathologic. These patients, however, cannot be considered normal. The conditions included coarctation of the aorta, mild and severe diabetes and inactive rheumatic heart disease. The patients were divided into four groups. The first group, shown in table 1, had no disease relative to kidney or liver. These patients received either thiopental sodium or seconal sodium with nitrous oxide. Group 2, shown in table 2, had the same

* By the method of analysis employed, it was possible to determine 0.02 mg. per cent of procaine, or 0.01 mg. per cent of p-aminobenzoic acid in blood, and to detect differences of this order of magnitude.

anesthesia but all were pathologic cases which might show functional involvement of either liver or kidney or both. The third group, shown in table 3, were similar to the cases shown in table 1 except for the anesthesia. These patients received ether or cyclopropane or a combination of the two. Group 4, shown in table 4, received the same anesthesia as group 3 but they were composed of patients who had pathologic conditions.

RESULTS

Comparing the patients in tables 1 and 2, similar doses of procaine on either a per kilogram basis or a per kilogram per minute basis, the blood procaines were higher in the pathologic series except in 3 cases, THO, HOR, and DEC. These were all cases of hypertension with some

TABLE 3

PROCAINE AND PABA IN VENOUS BLOOD AFTER INFUSION OF PROCAINE HYDROCHLORIDE. NO DISEASE RELATED TO LIVER OR KIDNEYS; ETHER AND CYCLOPROPANE OR BOTH

Pt.	Sex and Age	Wt., kg.	Total Dose, Gm.	Time in minutes	mg./kg.	Average mg./kg./min.	Blood Levels					
							Zero Time		1 Hour		2 Hours	
							Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.
NOR	F 60	61.4	0.50	60	8.1	0.135	0.10	0	—	—	—	—
MIL	F 51	65.9	1.25	135	19.1	0.141	—	—	0	0.83	0	0.79
ROB	F 13	58.4	1.25	135	21.4	0.158	0.08	0.76	0.16	0.64	0.04	0.32
BRU	F 16	54.5	2.00	85	36.8	0.254	0	1.60	0.40	1.12	0.13	0.87
WHI	F 20	68.2	3.50	150	51.3	0.342	0.07	2.93	—	—	0	0.94
FRE	M 48	76.8	4.50	175	58.9	0.337	—	—	0.32	1.56	—	—
ALL	M 51	47.3	3.00	130	63.4	0.488	0.36	1.76	0.32	1.36	0	0.80
STR	F 28	49.0	3.20	250	65.3	0.261	0.45	1.44	0.20	1.16	0.20	0.64
SIM	F 15	54.5	4.00	150	73.3	0.495	0.15	1.39	0	0.58	—	—
DEN	F 28	66.4	5.00	200	75.3	0.377	0.15	1.90	0.05	1.18	0	0.48
FLI	F 31	50.0	4.00	160	80.0	0.500	0.03	1.35	0.05	1.11	0	0.12
TER	M 17	65.8	5.50	215	83.7	0.389	0.40	2.24	0.20	1.24	0.20	1.04
SPA	M 54	51.8	5.00	145	96.1	0.663	0	0.96	0	1.20	0	1.20

obesity. The p-aminobenzoic acid levels are compared only on a milligram per kilogram basis because that has been shown to be the most important factor in dogs (15). The p-aminobenzoic acid levels were higher in the pathologic series than in the normal except for ROM, DAV, and HAY. These included osteomyelitis, pyuria with obesity and arteriosclerosis.

Comparing tables 3 and 4, the procaine levels were higher in group 4 except for LAM, WHI, GRI, and OWE. These included pyuria, bronchiectasis and albuminuria. The p-aminobenzoic acid levels were higher in group 4 except for DEL, WIL, BOG, LAM, and WHI. These included pyuria, albuminuria, obesity and heart disease. It will be noted that there was more irregularity in the ether and cyclopropane

TABLE 4

PROCAINE AND PABA IN VENOUS BLOOD AFTER INFUSION OF PROCAINE HYDROCHLORIDE. PATHOLOGIC CASES; ETHER AND CYCLOPROPANE OR BOTH

Pt.	Sex and Age	Wt., kg.	Total Dose, Gm.	Time in minutes	mg./kg.	Average mg./kg./min.	Blood Levels					
							Zero Time		1 Hour		2 Hours	
							Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.	Procaine mg. per 100 cc.	PABA mg. per 100 cc.
THA	F 45	57.3	0.10	32	1.7	0.053	0.40	1.44	—	—	—	—
KER	F 63	86.4	1.50	100	17.4	0.174	2.20	0.96	1.20	0.84	0.60	0.44
WED	F 42	75.0	2.50	45	33.3	0.741	0.32	2.32	0.08	1.48	0.04	0.92
DEL	M 35	65.8	2.25	150	34.2	0.227	1.92	1.24	0.08	0.82	0.04	0.58
TRA	M 43	68.2	2.50	95	36.7	0.387	0.12	3.78	0.08	3.24	0.04	3.14
BEL	M 37	59.1	2.25	90	38.1	0.254	0.13	3.13	0.05	2.84	0.05	1.83
WIL	F 38	86.4	4.25	155	49.2	0.317	0.28	2.72	0.12	1.70	0.02	0.98
BOG	F 45	73.6	4.00	120	54.3	0.453	0.95	1.92	—	—	0.02	0.75
LAM	M 53	78.6	5.00	270	63.6	0.236	0.12	1.60	—	—	—	—
FEL	M 55	92.4	6.00	225	65.0	0.289	1.36	3.34	0.52	1.86	0.48	1.34
KYL	F 23	45.0	3.00	125	66.7	0.534	—	—	0.12	2.24	0.08	0.98
WHI	M 17	52.2	5.00	265	95.8	0.361	0.28	2.08	0.20	1.44	0.12	0.80
BAK	F 14	45.5	4.50	255	99.0	0.388	1.95	—	0.87	1.25	0.20	0.81
GRI	F 34	49.5	5.00	180	100.9	0.561	0.02	2.80	0	1.80	0	1.02
OWE	F 32	45.5	5.00	280	109.9	0.393	0.40	3.14	—	—	—	—

The pertinent findings for the patients were as follows:

THA—essential hypertension, pyuria; KER—metastatic Carcinoma in the liver; WEB—bowel obstruction, obesity, pyuria, urinary casts; DEL—pyuria, hematuria, bleeding peptic ulcer; TRA—Pott's disease; BEL—albuminuria; WIL—obesity; BOG—heart disease, compensated; LAM—anemia, pyuria; FEL—hypertension, pyuria, gastric ulcers; KYL—bronchiectasis; WHI—albuminuria, pyuria; BAK—neurofibroma of the mediastinum, pyuria; GRI—bronchiectasis; OWE—albuminuria.

TABLE 5

PERCENTAGE OF PABA REMAINING IN THE BLOOD ONE HOUR AFTER THE PREVIOUS DETERMINATION

	No. of Pts.	Range	Median	Mean	S.E.$_m$
Barbiturate Anesthesia					
Nonpathologic 0–1 hour	12	44.7– 75.3	57.9	58.9	± 8.6
Nonpathologic 1–2 hours	11	28.7– 63.7	51.6	51.2	±11.3
Pathologic 0–1 hour	12	50.0– 93.7	62.1	64.8	±18.1
Pathologic 1–2 hours	9	52.0–105.0	66.0	74.2	±21.4
Cyclopropane and Ether					
Nonpathologic 0–1 hour	9	41.7–125.0	77.2	75.5	±21.8
Nonpathologic 1–2 hours	9	10.8–100.0	58.7	63.6	±26.8
Pathologic 0–1 hour	10	55.7– 90.7	65.1	70.1	±12.6
Pathologic 1–2 hours	12	43.8– 97.0	64.5	65.8	±13.2

series than in the barbiturate series. In general, the p-aminobenzoic acid levels were higher for the same dose of procaine with barbiturates as anesthetics than with ether and cyclopropane. These results are in agreement with those found in dogs (14). The procaine level seemed also to be a little lower in the ether series than in the barbiturate series. This was the opposite of our findings in dogs (14).

TABLE 6

PERCENTAGE OF PABA FREE IN BLOOD

Pt.	Sex and Age	Zero Time	1 Hour	2 Hours
Nonpathologic Barbiturates				
STA	F 51	76	50	38
MIT	F 31	14	50	—
KEL	M 47	67	46	31
McI	F 37	—	27	11
Pathologic Barbiturates				
THO	F 68	58	26	26
HEA	F 37	57	24	45
JOH	F 33	94	—	—
HOR	F 50	45	27	39
Nonpathologic Ether and Cyclopropane				
FLI	F 31	36	43	42
NOR	F 60	42	—	—
DEN	F 28	73	19	31
WHI	F 20	74	—	—
SIM	F 15	52	17	—
STR	F 28	42	12	22
ALL	M 51	64	33	13
MIL	F 51	—	22	23
Pathologic Ether and Cyclopropane				
KER	F 63	49	39	48
BOG	F 45	62	—	37
BEL	M 37	52	41	51
CON	F 42	65	62	51
THA	F 45	60	—	—
TRA	M 43	77	75	85
BAK	F 14	—	27	35

In 43 patients it was possible to calculate the fall of p-aminobenzoic acid from the cessation of administration to one hour. In 41 it was possible to calculate the fall of p-aminobenzoic acid from one to two hours. Table 5 gives a comparison between the p-aminobenzoic acid in the blood at the cessation of administration to one hour and at one hour to two hours. In those patients who received a barbiturate the

results were fairly consistent for the nonpathologic series, but extremely variable in the pathologic group. In those patients who received ether and cyclopropane, there was no difference between the pathologic and nonpathologic series. It seemed that when ether and cyclopropane were used as anesthetics, the anesthesia itself introduced variations which were as great as the influence of the diseases studied on the fall of p-aminobenzoic acid.

TABLE 7

PERCENTAGE OF PROCAINE FREE IN BLOOD

Pt.	Sex and Age	Zero Time	1 Hour	2 Hours
Nonpathologic Barbiturates				
STA	F 51	92	—	100
MIT	F 33	100	—	—
KEL	M 47	80	33	100
McI	F 37	—	60	—
Pathologic Barbiturates				
HEA	F 37	104	—	—
JOH	F 33	95	—	—
CON	F 42	80	60	30
Nonpathologic Ether and Cyclopropane				
NOR	F 60	50	—	—
DEN	F 28	100	—	—
WHI	F 20	43	—	—
SIM	F 15	100	—	—
STR	F 28	67	60	40
ALL	M 51	53	62	—
Pathologic Ether and Cyclopropane				
KER	F 63	84	100	—
BEL	M 37	54	60	—
TRA	M 43	60	67	33
BAK	F 14	—	75	—
BOG	F 45	—	—	71

Table 6 shows 23 bloods on which free and total determination of p-aminobenzoic acid were made. There were too few cases in any group to draw general conclusions The free p-aminobenzoic acid appeared to represent a rather variable percentage of the total. A larger percentage was free at the cessation of administration than at one and two hours later. The one hour values were the most consistent.

Table 7 shows 18 bloods on which both free and total determinations

of procaine were made. Under barbiturate anesthesia at the cessation of administration of procaine, the free procaine represented 80 per cent or more of the total. With ether or cyclopropane as an anesthetic, the free was at times as low as 40 to 60 per cent of the total. At one and at two hours there were not enough analyses to draw conclusions.

TABLE 8

DATA FROM KEL, MAN, 45 YEARS, WEIGHT 77.3, RECEIVING PROCAINE HYDROCHLORIDE BY VEIN AT VARIOUS INTERVALS

Date	Total Dose, Gm.	Time, min.	After Infusion Time of Blood Sample, minutes	mg. per 100 cc. in Blood	
				Procaine	PABA
1- 7-49	4	240	0	0.12	0.82
			95	0.00	0.32
1- 8-49	5	405	0	0.36	1.32
1-11-49	5	150	0	0.28	2.32
1-10-49	5	120	0	1.20	3.12
			90	0.38	0.98

Table 8 shows the results on one unanesthetized patient who received procaine hydrochloride on four different days. The dose on three days was the same but the time for administration varied. With dogs, over a wider range of time, the p-aminobenzoic acid in the blood was proportional to the dose of procaine hydrochloride in milligrams per kilogram (15). This obviously was not true in this subject.

SUMMARY

Hypertension with kidney involvement produced high p-aminobenzoic acid levels in the blood.

Severe infections, liver disease and marked obesity tended to give high levels of procaine in the blood.

Pyuria may be without effect on either procaine or p-aminobenzoic acid.

p-Aminobenzoic acid disappeared slowly from the blood. The fall was most consistent with nonpathologic patients receiving barbiturates. Pathologic patients receiving barbiturates and nonpathologic and pathologic patients receiving cyclopropane or ether gave inconsistent results, in general falling even more slowly.

The rate of fall of blood procaine was rapid in all four groups.

The percentage of free p-aminobenzoic acid was variable but never reached 100 per cent of the total.

The percentage of procaine which was free approached 100 with barbiturates at the cessation of administration of procaine. In other cases it was more variable and lower.

Levels of p-aminobenzoic acid in the blood of the human subject were not predictable from the intake of procaine hydrochloride.

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