

Acute Intestinal Iron Intoxication

II. Metabolic, Respiratory and Circulatory Effects of Absorbed Iron Salts

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IN THE PRECEDING PAPER¹ the true absorptive nature of acute intestinal iron poisoning was pointed out. Following oral or rectal administration of toxic doses of dissociable iron salts, it was found that excessive amounts of iron were absorbed through the anatomically intact intestinal mucosa, resulting in extraordinarily high serum iron levels within one hour after ingestion of the iron salts. These findings indicate that the frequently lethal outcome of acute iron poisoning is not the result of a local necrotizing effect of the ingested iron salts in the gut but is rather due to the toxicity of the absorbed iron.

Except for a marked capillary congestion, the autopsy findings in acute experiments did not provide any leads as to the site of action of the absorbed iron. In order to obtain such information, a number of vital functions were, therefore, studied in animals with intestinal iron poisoning.

METHODS

Ferrous sulfate, ferrous gluconate and ferrous chloride were given by stomach or duodenal tube or by enema to dogs and rabbits. General procedures, dosage, and methods of serum iron determination were outlined in the preceding paper.¹ In addition, FeSO₄ was given to two dogs intravenously as a 4 per cent solution mixed with saline in doses listed in table 1.

The blood pH was measured in a Beckman pH meter immediately after the blood had been drawn under anaerobic precautions.

Sodium and potassium serum concentrations were measured in a Perkin-Elmer flame photometer, blood glucose according to Folin and Wu,² serum chloride according to Schales,³ blood lactic acid according to Mendel,⁴ blood pyruvic acid according to Bueding,⁵ and serum citric acid according to Dickman.⁶ Blood oxygen and plasma carbon dioxide content were determined by the manometric Van Slyke method, all blood samples being collected and handled under mineral oil.

Oxygen consumption, CO₂ output, respiratory rate and tidal volume were recorded by a modification of the Donald-Christie method⁷ while the animal was breathing room air. Cardiac output was determined according to the Fick principle, the mixed venous blood sample being obtained through a cardiac catheter placed into the pulmonary artery. Blood pressure in the femoral artery was recorded by means of a Sanborn electromanometer and PolyViso direct writer. Plasma volume was measured with Evan's blue dye. Blood samples were drawn 15, 30, and 45 minutes after injection of the dye, and the spectrophotometrically determined densities were extrapolated to the time of injection. Relative cell volumes were determined in Wintrobe tubes, and a centrifuge correction factor of minus 5 per cent was applied to all hematocrit readings.

To detect possible abnormal hemoglobin derivatives, absorption spectra of the hemolyzed blood in 0.4 per cent ammonia were obtained in several dogs over the range from

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TABLE 1.—Blood pH, Plasma CO₂ and Serum Iron in Iron Intoxication. Fe in Microgram Per Cent, CO₂ in meq. Per Liter

Dog no.	Amount mg. Fe/Kg. given	Route, iron salt		Be-fore	Hours after iron administration											
					$\frac{1}{2}$	1	2	3	4	5	6	8	10	24		
C19	150	Rectal FeSO ₄	Fe μ g. %	82			2720		3280		2520	2360	2160			
			pH	7.33		7.23		7.22		7.16	7.07	7.10				
			CO ₂ meq.	22		19.0		17.5		11.5	10.9	8.6				
C11	200	Rectal FeSO ₄	Fe μ g. %	98	1100	1540	1830	1570		1360						
			pH	7.31	7.28	7.23	7.16	7.05		7.15						
			CO ₂ meq.	28	25.7	25.2	21.4	15.6		14.2						
C22	235	Rect. Gluc.	Fe μ g. %	70		700	1740	5780	8320	10280						
			pH	7.38		7.32	7.21		7.14	7.06						
			CO ₂ meq.	24		14.1		11.1	7.6							
LC3	10	I.V. FeSO ₄	Fe μ g. %	116		7230	6170	4180	3310	2680	2200			372		
			pH	7.36		7.14	7.10	7.16	7.21	2.21	7.22			7.33		
			CO ₂ meq.	24.5		20.3	19.5	16.8	16.2	18.2	20.5			26.5		
C4	4 \times 2.5 60' interval	I.V. FeSO ₄	Fe μ g. %	111	1050	865	2780	5076	6280	4976	3860		1460			
			pH	7.36		7.26	7.22	7.22	7.14	7.04	6.93		6.85			
			CO ₂ meq.	29.9		12.5	17.5	16.5	14.5	14.2	13.2		14.9			
318	150	Duod. FeSO ₄	Fe μ g. %	132		1564			961		904			248		
			pH	7.34		7.30			7.16		7.26			7.29		
			CO ₂ meq.	25.1		22.1			16.0		14.7			21.8		
C7	250	Duod. FeSO ₄	Fe μ g. %	116	1100	4560	7200	6600	6260		5820					
			pH	7.30	7.29	7.26	7.24	7.08	7.09		7.13					
			CO ₂ meq.	22.2	19.5	17.8	17.8	13.5	11.0		11.2					
C5	250	Duod. FeSO ₄	Fe μ g. %	152	1150	5020	6400	4260		3460						
			pH	7.32	7.09	7.05	7.05	6.96		7.04						
			CO ₂ meq.	21.4	19.0	18.5	16.2	16.0		14.8						

650 to 400 μ in a Beckman spectrophotometer. Heilmeyer's⁸ quotient 576/590 μ was used as a quantitative index of methemoglobin.

RESULTS AND DISCUSSION

(1) Metabolic Effects

In all animals a very marked hyperventilation developed within the first hour following ingestion of iron salts. This hyperventilation was found to be caused by a profound metabolic acidosis that developed rapidly and regardless of whether the iron was given by stomach tube, rectally, or intravenously* (tables 1, 2, 4).

The conversion of ferrous salts to ferric iron appears to be mainly responsible for the acidosis. Iron is, very likely, absorbed in the ferrous form, but when its plasma concentration exceeds the iron binding capacity of the plasma it is rapidly converted in the blood into the ferric form with formation of ferric hydroxide. Due to the insolubility of the latter and its tendency to form complexes, an increase in hydrogen ion concentration is to be expected. Such an effect was

* The acidotic effect of intravenous injection of iron salts was observed in 1880 by Meyer and Williams (Boston), working in Schmiedeberg's laboratory. They found a marked lowering of the blood CO₂ content following intravenous injection of iron tartrate. (Arch. Exper. Path. Pharmak. 3: 70, 1880.).

demonstrated in vitro when FeSO_4 was added to blood kept in equilibrium with 5 per cent CO_2 in 95 per cent O_2 . Blood pH and plasma CO_2 were determined before and sixth minutes after adding the iron, allowing this time interval for a conversion of Fe^{++} to Fe^{+++} . The following results were obtained:

	pH	CO_2 meq./L.	Fe $\mu\text{g.}/100 \text{ cc.}$
Before adding Fe	7.36	24.4	118
After adding 10 mg% Fe^{++}	7.25	23.0	10,367
After adding 20 mg% Fe^{++}	7.14	18.8	19,920

In these in vitro experiments the CO_2 tension was kept constant. In vivo the pH change which can be expected from an increment of 10 mg. per cent in serum iron will be smaller because of a compensatory hyperventilation with increased dissipation of CO_2 and removal of carbonic acid. Yet it will be noted in table 1 that in the iron poisoned animal much greater pH changes occurred and at serum iron levels which were considerable lower than those in the in vitro experiments. It has been pointed out already, that the serum iron level in these animals is not a criterion of the total amount of iron absorbed because iron is constantly transferred from the blood into the extravascular compartment. As the conversion of this iron from the ferrous into the ferric form takes place in the blood, the acid liberated in this process will progressively titrate the plasma buffers and this accumulative effect cannot be judged from the serum iron values.

An increase in organic acids was found as an additional factor in the greater in vivo acidotic effect of iron salts. Lactic and citric acid increased progressively in the blood of the iron poisoned animal as seen in table 2, which is a representative example of several experiments. Muscular activity or convulsions could be ruled out as the cause of the increase in lactic acid. The role of the capillary dilatation and congestion in the development of the acidosis is difficult to evaluate. From respiratory and circulatory data (vide infra), it appears that the accumulation of organic acids occurred earlier than the circulatory and respiratory failure and that circulatory anoxia was not a decisive factor in the development of the acidosis, at least not during the first hours following iron administration. It is, therefore, suspected that in iron poisoning the catabolism of the organic acids is interfered with, possibly by an effect of iron ions upon enzymes in the Krebs cycle. Such intracellular toxic effect of iron found support in the results

TABLE 2.—Dog C17, 350 mg. Fe/Kg. Body Weight by Rectum as FeSO_4

Time in hours	Serum iron, gamma %	Blood pH	Plasma CO_2 , meq./L	Blood glucose, mg. %	Blood lactic acid, mg. %	Blood pyruvic acid, mg. %	Serum citric acid, mg. %	Serum Na, meq./L	Serum K, meq./L	Serum Cl, meq./L
Before	150	7.29	24.9	111	16.0	2.23	3.33	144	4.5	104
1	10,120	7.09	17.5	153	23.0	2.02	7.78	141	4.9	110
2				136	32.0	1.81				
3	10,700	7.06	12.0	170	28.5	2.46	9.16	142	5.1	110
4				258	36.0	2.10				
5	10,320	7.02	8.5	204	39.5	2.76	16.89	145	5.3	114

of several experiments where in vivo administration of sodium bicarbonate failed to prevent the fatal outcome of iron poisoning.

As the acidosis occurred invariably both in dogs and in rabbits, it seems reasonable to assume that it was likewise present in children with iron intoxication, although it apparently escaped observation in the reported cases. While a rapid respiration is commonly mentioned in the case histories, we could only find one CO₂ determination (15 meq.)⁹ in the reports.

When the animal survived the acute phase of iron intoxication, the pH returned to normal values within 24 hours. As these animals did not excrete significant amounts of iron during this time, these findings suggest that the iron ions must be neutralized or bound somewhere in the tissues and that normal metabolic cell functions are restored.

(2) Circulatory and Respiratory Effects

The hemocentration suggested by the increase in hematocrit values was confirmed by the determination of the plasma volume by means of the dye method. As seen in table 3, the plasma volume decreased from 577 cc. before, to 439 cc. two hours after, and to 401 cc. four hours after iron had been administered. A similar trend was seen in two other dogs. As the urinary output was less than 50 cc. and the amount of fluid usually seen in the intestinal lumen after iron poisoning was not excessive, the most likely explanation of the decrease in plasma volume is a shift of fluid from the vascular compartment into the interstitial and possibly into the intracellular compartment. The increase in total cell volume probably is not real because the cell volume was not measured directly but was derived from the plasma volume and the venous hematocrit, and it is likely that in the state of marked capillary congestion, the relation between venous hematocrit and body hematocrit was markedly altered.

In spite of the reduced plasma volume, a normal blood pressure was maintained for several hours until the final collapse occurred, as seen in table 4. The cardiac output dropped progressively and the heart rate increased markedly, resulting in very marked changes in the stroke volume which dropped from 10 cc. to 3.3 cc. This decrease in cardiac output is probably not so much a direct effect of the iron ions upon the heart muscle but rather is secondary to a diminished venous return. The latter is due to congestion in the capillaries and venules and partly due to the reduction in plasma volume. A marked capillary congestion and increased capillary permeability throughout the body was found at autopsy in all animals. It could not be decided whether this capillary dilation

TABLE 3.—*Plasma Volume in Dog CO6 before and after Administration of 200 mg. Fe per Kg. Body Weight by Duodenal Tube. Weight of Dog 11.80 Kg.*

Time after Fe administration	Serum Fe, gamma %	Blood pH	Plasma CO ₂ meq./L	Hemato- crit corrected	Plasma volume, cc.	Cell volume, cc.	Blood volume, cc.
1 day before.....	112	7.27	24.2	46.0	577	491	1068
2 hours after.....	2350	7.17	21.0	55.5	439	559	998
4 hours after.....	3200	7.15	16.2	58.3	401	560	961
24 hours after.....	462	7.34	18.7	54.5	467	559	1026

TABLE 4.—*Circulatory and Respiratory Function in Acute Iron Poisoning, 11.6 Kg. Dog, Nembutal Anesthesia, 400 mg. Fe/Kg. Body Weight by Enema*

Time after Fe admin.	Serum Fe	pH	Hemogl. Gm. %	Heart rate/min.	Arter. pressure		Cardiac output, L/min.	Stroke volume, cc.	Breathing volume, L/min.	O ₂ consumpt., cc/min.	CO ₂ output, cc/min.	Respir. rate/min.	O ₂ saturation, %		CO ₂ content, vol. %	
					mm. Hg, syst./diast.	Mean							Art.	Vein*	Art.	Vein*
Before	165	7.29	12.6	120	170/105	115	1.21	10	1.89	64	56	9	95	63	44.8	49.6
1 ^h	9,757	7.13		195	150/110	120			3.30	68	78	12				
2 ^h	10,437	7.09	14.9	200	150/110	120	1.18	5.9	5.00	73	80	16	93	57	24.5	31.1
3 ^h	10,297	7.07		203	145/115	125			5.70	72	76	19				
4 ^h	10,097	7.09	16.4	230	135/110	125	0.76	3.3	5.20	67	71	20	92	53	19.6	28.9
5 ^h	10,141	7.03		218	130/105	110			5.04	62	62	24				
6 ^h	10,022	6.72		95	75/42	58			Animal dying							

* Mixed venous blood obtained by catheter from pulmonary artery.

was the result of the acidosis and its underlying disturbance in cell metabolism, or whether the high serum iron concentration directly affected the capillary system.

The greatly increased breathing volume (from 1.89 L to 5.7 L per minute) reflects the acidotic stimulation of the respiratory center. The CO₂ output rose markedly as a result of the accumulation of the organic acid and the RQ of greater than 1 reflects the increased CO₂ elimination rather than the CO₂ production. The O₂ consumption rose slightly above the baseline level in spite of the described interference with the oxidative breakdown of the organic acids. This slight rise is probably due to the greater energy expenditure in the increased ventilatory efforts and indicates that at least during the first four hours no significant degree of anoxia was present. The arterial O₂ saturation decreased from 95 to 92.5 which can be entirely accounted for by the effect of the lowered pH upon the O₂ dissociation curve of the hemoglobin (shift to the right).

A possible formation of methemoglobin in the blood of children with iron poisoning has been discussed¹⁰ but not demonstrated. The blood in eight experiments and at various stages of iron intoxication was examined spectrophotometrically. No deviations from a normal oxyhemoglobin spectrum were found, and in all instances Heilmeyer's quotient 576/590 was found to be above 3.6, indicating that no significant amounts of methemoglobin were present.

In the experiment presented in table 4, the dog suddenly stopped breathing at six hours after Fe administration. Blood pressure and heart rate dropped rapidly, and the dog died in respiratory failure, which was the direct cause of death in most experiments.

SUMMARY

Following oral or rectal administration of toxic doses of dissociable iron salts in dogs and rabbits, the rapidly and excessively absorbed iron produced a profound metabolic acidosis with blood pH values as low as 6.7. The acidosis was mainly due to the hydrolysing effect of ferric ions and partly due to an increase in lactic and citric acid. The latter findings suggest a possible interference of the absorbed iron with enzymes in the Krebs cycle.

The respiratory changes were those seen in metabolic acidosis: greatly in-

creased respiratory rate and minute volume, lowering of the blood CO₂, excessive CO₂ output. The cardiac output decreased progressively due to diminished venous return, but a normal blood pressure was maintained by arteriolar constriction until the final collapse occurred, which was preceded by respiratory failure.

A marked capillary congestion and increased capillary permeability were noted, the latter possibly being the result of a direct action of the high non-protein bound serum iron upon the capillary wall. The increased capillary permeability caused a reduction in plasma volume and hemoconcentration.

No abnormal hemoglobin derivatives were found.

SUMMARIO IN INTERLINGUA

Post administration oral or rectal de toxic doses de dissociabile sales de ferro in canes e conillos, le rapide e excessive absorption de ferro resultava in un forte acidosis con valores del pH sanguinee abassate usque a 6,7. Le acidosis esseva debite in parte al effecto hydrolysante de iones ferric e in parte al augmento de acido lactic e citric. Iste ultime constatationes suggere le possibilitate de un interferentia del ferro absorbite con enzymas del cyclo de Krebs.

Le cambiamentos respiratori esseva illos observate in acidosis metabolic: forte augmento del rapiditate e del volumine-minuta de respiration, reduction del CO₂ sanguinee, excesso de descarga de CO₂. Le rendimento cardiac decreseva progressivamente in consequentia del reduceite retorno venose, sed un pression sanguinee normal esseva mantenite per constriction arteriolar usque al occurrentia del colapso final. Isto esseva precedite per syncope respiratori.

Un alte grado de congestion capillar e un augmento del permeabilitate capillar esseva observate. Iste ultime esseva possibilmente le resultado de un action directe super le parietes capillar per le alte contento de ferro seral non ligate a proteina. Le augmentate permeabilitate capillar causava un reduction del volumine plasmatic e del hemoconcentration.

Esseva observate nulle abnormalitates in derivatos hemoglobinic.

REFERENCES

- ¹ REISSMANN, K. R., COLEMAN, T. J., BUDAI, B. S., AND MORIARTY, L. R.: Acute intestinal iron intoxication. I. Iron absorption, serum iron and autopsy findings. *Blood*, this issue.
- ² FOLIN, O. AND WU, H.: A system of blood analysis. *J. Biol. Chem.* **38**: 81, 1919.
- ³ SCHALES, O. AND SCHALES, S.: A simple and accurate method for the determination of choride in biological fluids. *J. Biol. Chem.* **140**: 879, 1941.
- ⁴ MENDEL, B.: Zur Methode der kolorimetrischen Milchsäurebestimmung. *Biochem. Ztschr.* **202**: 390, 1928.
- ⁵ BÜDING, E. AND WORTIS, H.: Stabilization and determination of pyruvic acid in blood. *J. Biol. Chem.* **133**: 585-591, 1940.
- ⁶ DICKMAN, S. R. AND CLOUTIER, A. A.: Factors affecting the activity of aconitase. *J. Biol. Chem.* **188**: 379-388, 1951.
- ⁷ DONALD, K. W. AND CHRISTIE, R. V.: A new method of clinical spirometry. *Clin. Sc.* **8**: 20, 1949.
- ⁸ HEILMEYER, L.: *Medizinische Spektrophotometrie*. Jena, G. Fischer, 1933.
- ⁹ SWIFT, S. C., CEFALU, V., AND RUBELL, E. B.: Ferrous sulfate poisoning. *J. Pediat.* **40**: 6, 1952.
- ¹⁰ SMITH, R. P., JONES, C. W., AND COCHRAN, W. E.: Ferrous sulfate toxicity: Report of a fatal case. *New England J. Med.* **243**: 641, 1950.