Toxicity of Sulfonamides especially antidiabetic Medicine for internal Use

(Study of Heinz-body: Report XXII)

By

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We published these data at the 4th general meeting of the western branch of Japan Endocrinological Society (Folia Endocrinologica Japonica Vol. 32, No. 9, 756, 1956).

Since the outbreak of an accident of penicillin shock, penicillin has been refused by doctors and patients. So sulfonamides are expected to be resorted to again. On the other hand, BZ55, D860, Crebon and other sulfonamides have appeared as an antidiabetic medicine for internal use. The toxicity of sulfonamides on blood, kidney and liver has long been noticed. But it is easily supposed that the use of these sulfonamides for diabetes mellitus may take a long time.

Already, in 1944, one of us, Yoshida, published the study on toxicity of sulfonamides by Heinz-body as Table I, (Journal of Kyoto Prefectural Medical University Vol. 41, No. 4, 811,

1944). And now we have observed the toxicity of new sulfonamides, especially, antidiabetic medicine for internal use,—on blood by Heinz-body and on liver and kidney by tissue respiration.

Method

We used white mice of 15–20 g. We gave the medicine per os with small kneading rice-balls. After these mice have taken the medicine, we gave them more rice and vegetables. Every day we weighed the mice.

We take a little drop of blood from a tail of mouse and mix with a little drop of an 1% brillantcresylblue–0.6% salt solution, which is covered with a cover glass. We observe 1000 erythrocytes and count the % of erythrocytes, which have each Heinz-body in themselves, and thus we count reticulocytes, too.

After 6 daily 0.01g per os medicated days, we killed mice and measured tissue respiration on 38°C with Warburg's apparatus and decided QO_2 of dry weight 1 mg.

Result

The promille of erythrocyte with Heinz-body in blood of mice, which had been given

Table 1. The % of erythrocyte with Heinz-body in blood of mice, which had been given sulfonamides (by H. Yoshida 1944)

Medicine	Daily dose per os (g)	Medicated days	Date Cases	1	2	3	4	5	6	7	8	9
Sulfamine	0.01	1–9	6	2	14	169	454	550	631	769	750	772
Albucid	0.01	1–6	5	1	9	8	6	34	39	52	51	72
	0.03	7–9										
Disulfamine	0.01	1–6	5	0		2	3	4	8	15	15	26
	0.5	7–9										
Sulfapyridine	0.01	1–6	28	0	20	180	375	550	630	670	700	680
Sulfathiazole	0.01	1–6	12	1	2	1	0	0	1	0	0	1
	0.02	1–6										
	0.03	1–6										

Table 2. The % of erythrocyte with Heinz-body in blood of mice, which had been given new sulfonamides

Medicine	Daily dose per os (g)	Medicated days	Date Cases	1	2	3	4	5	6	7	8	9
Irgafen	0.01	1–6	9	7	13	36	140	295	486	540		
Domian	0.01	1–6	5	2	4	6	9	7		15	14	22
	0.03	7–9										
Thiasin	0.01	1–6	13	4	5	18	15	14	15	16	21	27
	0.03	7–9										
Supronal	0.01	1–6	8	8	11	45	167	223	298	676	803	785
Sulfadiazine	0.01	1–6	6	5	17	25	42	38	51	76	92	60
	0.03	7–9										
(TB–1)	0.01	1–6	9	7	8	24	73	127	180			
BZ55	0.01	1–6	13	7	8	10	11	11	18	29	30	
D860	0.01	1–6	24	4	5	4	5	7	3	3	7	
Crebon	0.01	1–6	12	3	7	11	15	21	22	26	37	

daily 0.01 g sulfonamide per os six days long, is shown as Table 2.

Domian and Thiasin increase only a few Heinz-bodies and show very little toxicity on erythrocyte. Sulfadiazine also shows result like these, Supronal and Irgafen increase over 500% Heinz-bodies, and show very strong toxicity on erythrocyte.

BZ55 and Crebon show, after one week, about 30% Heinz-body and have far less toxicity than sulfamine, sulfapyridine, Supronal or Irgafen, and have less toxicity than sulfadiazine or Albucid, too. BZ55 and Crebon show less toxicity than Thiasine, but it is a little stronger than sulfathiazole, disulfamine or Domian.

D860 has less toxicity than BZ55.

Tissue respiration of mice, which had been given daily 0.01 g sulfonamides per os 6 days long, is shown as Table 3.

Tissue respiration of mice, which had been given Irgafen, BZ55, D860 or Crebon, is quite equal to the control. And these sulfonamides are not poisonous for liver or kidney from the viewpoint of tissue respiration.

On the first or second medicated day, reticulocytes increase a little and, after about 5 days, they become very few.

Table 3. Tissue respiration of mice (QO_2 of dry weight 1 mg)

A Control			B Irgafen			C BZ55		
Case number	Liver	Kidney	Case number	Liver	Kidney	Case number	Liver	Kidney
1		20.38	1	11.53	17.80	1	13.13	20.23
2	11.26	17.83	2	13.63	23.02	2	9.53	17.19
3	12.14	17.45	3	12.33	18.47	3	14.19	19.54
4	12.61	20.57	4	13.13	21.38	4	16.88	19.67
5	13.25		5	11.83	18.74	5	13.92	18.95
6	14.01		Average	12.49	19.88	Average	13.53	19.11
7	12.46							
8	9.86	18.52						
9	16.87	20.20						
10	13.70	21.03						
11	12.80							
12	13.24	20.68						
Average	12.92	19.58						

D D860			E Crebon		
Case number	Liver	Kidney	Case number	Liver	Kidney
1	12.32	21.03	1	12.00	17.19
2	12.69	20.50	2	12.31	16.00
3	14.82	22.21	3	15.08	22.36
4	10.58	19.97	4	15.69	20.48
5	14.21	19.83	5	13.27	18.58
Average	12.92	20.70	Average	13.67	18.92

Summary

1. From the viewpoint of Heinz-body, Domian, Thiasin and sulfadiazine have little toxicity, while Supronal and Irgafen show very strong toxicity. But this toxicity may come from slow separation, and the effect is another problem.

2. Even Irgafen which has very strong toxicity from the viewpoint of Heinz-body, shows no toxicity for liver and kidney viewed from the point of tissue respiration.

3. BZ55, D860 and Crebon have a little toxicity from the viewpoint of Heinz-body, and show no toxicity for liver and kidney viewed from the point of tissue respiration.