MAJOR SIDE-EFFECTS OF GLUCOCORTICOIDS IN JAPAN

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The present statistical investigation was undertaken in order to establish what is the most significant out of various side-effects of glucocorticoids (GC) in Japan.

From the viewpoint of mortality, side-effects of GC can be classified into two groups: "Major" and "Minor" side-effects. "Minor side-effects" denotes moon-face, obesity, hypertrichosis, anorexia, polyphagia, headache, hypertension, hypercholesterolemia and glucosuria, etc., which by themselves scarcely affect the mortality.

On the other hand, "major side-effects" may contribute to the mortality or tend to leave various severe disturbances. The frequency of major side-effects much lower than that of minor ones, may still reach 5 to 20 % of the patients treated with GC (Smyth *et al.*, 1959; Katsu *et al.*, 1963).

The results of our survey on the side-effect of glucocorticoid by means of questionnaires sent to clinical department in various medical schools in Japan is summarized in the present report.

METHODS

The questionnaires concerning the major side-effects were sent to 344 clinical department of internal medicine, surgery, orthopedics, pediatrics and dermatology, in medical schools all over Japan. The answers were obtained from 102 departments. Among 194 cases thus collected (107 males and 87 females) 15 showed at least one side-effect, giving the total frequency of side-effect of 212. The age distribution ranging from 1 month to 79 years old is shown in Table 1.

Table 1. Age distribution

Age	Case no.
~ 10	12
11 ~ 20	39
21 ~ 30	34
31 ~ 40	23
41 ~ 50	28
51 ~ 60	24
61 ~	23

Cortisone, cortisol, prednisolone, methylprednisolone, triamcinolone, dexamethasone, paramethasone and betamethasone were used, the use of prednisolone and dexamethasone being most frequent, followed by paramethasone and betamethasone, while others were only rarely used. In half of the cases frequent interchange among GC made the separate evaluation of the side effects of various steroids extremely difficult.

RESULTS AND DISCUSSION

1) The frequency of major side-effects

As shown in Figure 1, both severe infections or complications of digestive canals such as peptic ulcer were observed in more than a quarter of all cases. Next came disorders of the central nervous system and shock due to iatrogenic adrenal insufficiency. Thrombophlebitis or embolism, severe diabetes mellitus, pathologic fractures due to severe osteoporosis and bleeding from the urinary tract followed in the order.

Fig. 1. Major side-effects of glucocorticoids in Japan

2) The relationship of major side-effects to the diseases treated with GC

Major side-effects were mainly observed in such diseases as rheumatoid arthritis, acute leukemia or other diseases of blood, nephrotic syndrome, systemic lupus erythematosus (S.L.E.) or other collagen diseases, rheumatic fever and bronchial asthma, etc., in which GC played a major role in the therapy as shown in Table 2. Major side-effects tended to occur especially in such diseases in which massive doses of GC were used as acute leukemia or collagen diseases.

Table 2. Major side-effects: Relations to the diseases subjected to glucocorticoid therapy

(The parenthesized numbers show death-tolls.)

Diseases treated by glucocorticoids	Major side-effects	Severe infectious complications, no.	Complications of digestive canals, no.	Disorders of central nervous system, no.	Shock or adrenal crisis, no.
Rheumatoid arthritis		11 (3)	10 (2)	6 (1)	5 (2)
Blood diseases { leukemia, sarcoma* other blood diseases**		17 (15)	10 (4)	2 (0)	0
		5 (4)	4 (3)	0	1 (0)
Nephrotic syndrome		2 (0)	2 (1)	11 (0)	1 (0)
SLE. and other collagen diseases		10 (8)	4 (2)	2 (0)	2 (2)
Rheumatic fever		5 (1)	3 (2)	8 (3)	3 (1)
Bronchial asthma		0	5 (1)	1 (0)	8 (6)
Diseases of liver		1 (1)	7 (3)	0	0
Diseases of nervous system		4 (3)	4 (3)	2 (0)	0
Diseases of skin		2 (1)	1 (1)	0	1 (1)
Cancer, sarcoma except RES		0	3 (0)	0	1 (0)
Others		1 (0)	3 (0)	0	2 (1)
Total, No. %		58 (36) 27.3 (42.8)	56 (22) 26.4 (26.2)	32 (4) 15.1 (4.8)	24 (13) 11.3 (15.5)

Thrombo-angitis, embolism, no.	Severe diabetes mellitus, no.†	Pathologic fractures due to osteoporosis no.	Severe disturbances of electrolyte metabolism no.	Bleeding from urinary-tract, no.	Others, no.	Total, no.
4 (3)	1 (0)	3 (0)	1 (0)	1 (0)	1 (0)	42 (11)
0	1 (0)	0	0	0	1 (0)	31 (19) 12 (7) } 43 (26)
0	2 (0)	0	0	0	0	
3 (1)	1 (0)	1 (0)	1 (1)	0	1 (0)	23 (3)
1 (1)	1 (0)	1 (0)	0	0	1 (0)	22 (13)
0	0	0	0	1 (0)	1 (0)	21 (7)
1 (1)	1 (0)	0	0	1 (0)	0	17 (8)
0	3 (0)	0	1 (1)	0	0	12 (7)
0	0	0	0	1 (1)	0	11 (7)
1 (0)	0	2 (0)	0	0	0	7 (3)
0	0	0	0	0	0	4 (0)
0	0	0	3 (0)	0	0	9 (1)
10 (6) 4.8 (7.1)	10 (0) 4.8 (0)	7 (0) 3.3 (0)	6 (2) 2.8 (2.4)	4 (1) 1.9 (1.2)	5 (0) 2.3 (0)	212 (84) 100 (100)

† Including only patients who showed glucosuria more than 100 g per day or blood sugar more than 200 mg/dl before breakfast

* Including acute and chronic leukemia, lymphosarcoma, Reticulum cell sarcoma and Hodgkin's disease, etc.

** Including purpura, agranulocytosis, hypoplastic anemia, pernicious anemia, etc.

3) *The relationship of major side-effects to the duration of GC therapy*

Although previous reports have shown that the incidence of side-effects paralleled with the duration of the GC therapy (Smyth *et al.*, 1959; Ito, 1962), many side-effects and death-tolls were seen in a short term-treatment as shown in Figure 2, as far as major side-effects were concerned. Most of them occurred less than three months after therapy, it could be explained by the massive dose of GC since the beginning of therapy. Especially a half of the complications of digestive canals such as steroid ulcer were observed within only one month after the therapy.

Fig. 2. The relationship of major side-effects to the duration of GC therapy

4) *Major side-effects*

a) *Severe infectious complications:* GC does not only act as an anti-inflammatory agent but also inhibit antibody-formation resulting in a weakened biological defence mechanisms in some cases.

There have been many reports concerning the occurrence of severe infections during GC therapy (Page, 1954; Allenby, 1957).

Table 2 shows that the severe infectious complications consisting mainly of tuberculosis and mycosis are the most frequent among the major side-effects, giving a high mortality rate of 59 % (34/58 cases).

Infectious complications were often observed in cases of blood diseases or collagen diseases treated with a considerably high dose of GC.

An antigranulomatous action and inhibition of fibroblastogenesis by GC apparently interfere with the localization of tuberculosis, encouraging to disseminate hematogenously, resulting in miliary tuberculosis (Hill and Kirshbaum, 1956).

Mycosis, one of the most serious complications during GC therapy, in variably caused death in our series. Mycosis was observed in 8 patients with acute leukemia and 4 patients with S.L.E. In so far as causative fungi were concerned, candida, aspergillus and cryptococcus were found in almost same frequency. It is suggested

that the excessive administration of antibiotics in order to prevent bacilli-infections may cause the exacerbation of fungi-infections. The fact that most of them were found only at autopsies indicates the difficulty of proving mycotic infection before death.

Sepsis, pulmonary abscess and staphylococcal and pneumococcal pneumonia were observed in a few cases respectively.

Table 3. Severe infectious complications of glucocorticoids

Infectious complications		Case no. (Death-toll no.)		
Tuberculosis	Miliary tuberculosis	6 (4)	} 14 (5)	
	Pulmonary tuberculosis	7 (0)		
	Intestinal tuberculosis	1 (1)		
Mycosis	Candidasis	5 (5)	} 15 (15)	
	Cryptococcosis	5 (5)		
	Aspergillosis	4 (4)		
	Mucor mycosis	1 (1)		
Suppurative germs	Sepsis	8 (7)		
	Pulmonary abscess and pneumonia	8 (4)		
	Other purulent diseases	Severe abscess (whole body)	7 (2)	} 13 (3)
		Purulent arthritis	2 (0)	
		Pyothorax	1 (0)	
Others		3 (1)		
Total		58 (34)		

b) Complications of the digestive canals: Much attention should be paid to these side-effects as well as severe infections. So called "steroid ulcer", (Bollet *et al.*, 1955; Boland, 1956; Stefanini and Martino, 1956; Bunim, 1957), was found in 56 cases in our series and 22 of them died of these side-effects in which the mortality was 39.3 %.

Except such slight gastrointestinal symptoms as anorexia, nausea or polyphagia, only those cases which had shown some objective signs such as niche on X-ray pictures, positive occult blood or hematemesis were analyzed.

These side-effects were often evident in liver diseases.

The affected regions extended to all over the digestive canals—from the oesophagus to the rectum (Table 4). The most frequently affected regions were the stomach and duodenum. Ulcers or disseminated petechial bleedings in small or large bowel, sometimes extending over the whole digestive canals, were found in some cases.

Peptic ulcer was most frequent among these complications. Simple ulcer without bleeding nor perforation was relatively rare (12/42), while perforation,

Table 4. Affected regions of digestive canals as the side-effects of glucocorticoids

Affected regions of digestive canals	Case no. (Death-toll no.)
Stomach	26 (8)
Duodenum	7 (1)
Stomach and duodenum	2 (0)
Jejunum, ileum and colon	7 (6)
Oesophagus	2 (1)
Whole digestive canals	6 (5)
Unknown	3 (0)
Total	53 (21)

hematemesis and melena occurred frequently (30/42) and death often ensued (Table 5).

Bleeding and perforation occurred so suddenly that they were hardly predicted. Besides peptic ulcers, disseminated petechial bleeding on the mucosa throughout the whole gastrointestinal tracts was detected mainly on autopsy.

Table 5. The kind of complications of digestive canals

Kind of complications	Case no. (Death-toll no.)
Peptic ulcer 42 (15)	<div style="display: flex; align-items: center;"> <div style="font-size: 3em; margin-right: 10px;">{</div> <div> Perforation Hematemesis Melena Simple peptic ulcer </div> <div style="margin-left: 20px;"> 10 (7) 15 (6) 5 (2) 12 (0) </div> </div>
Disseminated petechial bleedings on mucosa	5 (4)
Bleeding from varices	4 (2)
Unknown	2 (0)
Total	53 (21)

According to the report by Hirshowitz *et al.* (1955), these side-effects appear at a comparatively early period. About a half of them reported here occurred within only one month in agreement with his report (Fig. 2).

The characteristics of "steroid ulcer" characteristically had a sharp edge and deep, fragile pit, a rather poor healing with little fibroblast-proliferations and very

little inflammatory changes around ulcer. Steroid ulcer often grows without any symptom and penetrates into other organs, perforates suddenly or invades into vessels resulting in massive bleedings (Spiro and Millers, 1960). Disseminated petechial bleedings on the mucosa may also occur with little organic changes. Most of the severe gastrointestinal complications were first found accidentally as shown in Table 6, suggesting a difficulty in detecting them. The occult blood test is regarded as the best means to find some of the complications in the digestive canals.

Table 6. Clue to discover the complications of digestive canals

Clue of discovery	Case no.	Death-toll no.
Ulcer was already found by routine examinations, e.g. X-ray pictures, during glucocorticoid therapy.	14	2
Hematemesis was the first symptom.	17	8
Melena was the first symptoms.	8	2
Sudden abdominal pain (perforation) was the first symptom.	7	5
Died of the other or unknown causes and the complication was first found by autopsy.	6	3*
Total	52	20

* In 3 cases out of 6, perforation or large bleeding was assumed to be the direct cause of death.

c) *Disorders of central nervous system:* It is well known that GC have some action on the central nervous system causing various psychopathic symptoms (Clark *et al.*, 1952; Hench and Ward, 1954; Katsu *et al.*, 1963; Nakae *et al.*, 1963).

Thirty-nine cases with various symptoms of the central nervous system due to GC were found in the present study (Table 7). The most frequent psychopathic symptoms were depression and schizophrenic reactions. Four patients with depression committed suicide. Neither hereditary factor nor particular inducement appeared to be responsible for these symptoms except GC administration. Most patients with schizophrenic reaction had illusions or delusions, closely resembling genuine schizophrenia.

Many children showed various symptoms simulating the intracranial tumor such as headache, convulsions, vomiting, visual disturbances or choked papillae. Elevation of the cerebrospinal fluid pressure above 500 mm H₂O was seen in three.

As shown in Table 8, about 80 % of these side-effects occurred in patients before the age of 30.

Table 9 shows that dexamethasone was the most common inducer of the disorders of the central nervous system among the GC preparations. These side-effects

Table 7. Disorders of the central nervous system as the side-effects of glucocorticoids

Symptom	Case no.
Depression	9*
Mania	5
Schizophrenic symptoms	9
Cerebral tumor-like symptoms	9**
Disturbance of consciousness	4
Others	1
Total	37

* Four of them died from suicide.

** Three of them showed elevation of cerebrospinal fluid pressure.

Table 8. Age-distribution of central nervous system disorders

Age	Case no.
~ 10	6
11 ~ 20	7
21 ~ 30	11
31 ~	5
Total	29

Table 9. The kind of glucocorticoid preparations as an inducer of disorders of central nervous system

Kind of GC preparations	Case no.
Dexamethasone	18
Prednisolone	8
Methylprednisolone	1
Paramethasone	1
Hydrocortisone	1
Betamethasone	1

were mainly observed in patients with nephrotic syndrome and rheumatic fever.

Most of the disorders of the central nervous system disappeared by withdrawing GC and administering such drugs as chlorpromazine, and they rarely became the direct cause of death.

d) Shock or acute adrenal crisis due to iatrogenic adrenal insufficiency: There have been reported many cases of iatrogenic adrenal insufficiency caused by GC (Sallasa *et al.*, 1953; Rukes *et al.*, 1954; Hench and Ward, 1954; Nicholas *et al.*, 1955; Stevens, 1960).

As shown in Table 2, many cases of shock occurred in patients with bronchial asthma. In some cases, violent asthmatic attacks themselves were regarded as stress to cause shock (Table 10). Most cases of shock caused by asthmatic attacks occurred immediately after the withdrawing GC therapy.

Table 10. Proximate causes of shock due to iatrogenic adrenal insufficiency

Proximate cause			Case no. (Death-toll no.)
Asthmatic attack			5 (5)
Injection or infusion	{ ACTH (i.m.) Transfusions Cortisone (i.m.)	{ 4 (1) 2 (0) 1 (0)	7 (1)
Infections			3 (0)
Operations			2 (2)
Unknown or none			2 (2)
Others			1 (0)
Total			20 (10)

Not only asthmatic attacks but also injections or infusions were regarded as possible causes of shock. Especially the injection of ACTH preparations, for the treatment of iatrogenic adrenal insufficiency or the examination of adrenal function, caused shock in a few patients. Injections of the other drugs may also play the roll of a trigger of acute adrenal crisis.

The mortality of this side-effect was considerably high, and in almost all cases, atrophy of adrenal glands were proved on autopsy.

Consequently it is most important to prevent adrenal insufficiency by all means. But withdrawal of GC administration should be made with the greatest care, when the iatrogenic adrenal insufficiency is suggested.

e) Miscellaneous major side-effects: Thrombosis and thrombophlebitis were most common in the extremities and embolism was noted in the lung, brain and kidney. They were mainly observed in patients with nephrotic syndrome and collagen disease. It was suggested that nephrotics had a tendency for increased blood

viscosity (Aldersberg, 1955) and that phlebitis often occurred in rheumatoid arthritis or collagen diseases (Kemper and Bagganstoss, 1957; Rotstein and Good, 1957; Charles *et al.*, 1957).

Excluding the slight one (refer to the foot-note of Table 2), severe diabetes mellitus was mainly observed in patients subjected to a long term GC therapy, and often continued even after the withdrawal of GC. It was noted that this side-effect often appeared in liver diseases.

All pathologic fractures due to severe osteoporosis occurred at least after one and half years of GC treatment. It was found that they occurred in multiple sites, especially in the vertebral bodies from lower thoracic to upper lumbar area, ribs and femur. Main initial symptoms were lumbago or lameness.

Severe disorders of electrolyte metabolism, mainly consisting of potassium and calcium imbalances, some caused coma, cramp or arrhythmia in some cases.

In a few cases bleeding from urinary tract was caused by GC.

Cataract found in only one patient with thrombocytopenic purpura (male, 10 years old) appeared to be rare as compared with the data in Europe and the United States.

SUMMARY

Major side-effects of glucocorticoids (GC) in Japan were investigated statistically.

1. Severe infectious complications, severe complications of digestive canals, disorders of the central nervous system, shock or acute adrenal crisis due to iatrogenic adrenal insufficiency, thrombophlebitis or embolism, diabetes mellitus (excluding slight steroid glucosuria) and pathologic fractures due to severe osteoporosis, etc. were major side-effects with GC.

2. Among 212 cases of these major side-effects, severe infections and gastrointestinal complications occupied the overwhelming majority and high mortality. Shock due to iatrogenic adrenal insufficiency also resulted in a high mortality. Disorders of the central nervous system were observed frequently, but their mortality was low.

3. These major side-effects were mainly observed in such diseases as rheumatoid arthritis, blood diseases, nephrotic syndrome, systemic lupus erythematosus (S.L.E.), rheumatic fever and bronchial asthma in which GC therapy played a major role. Especially these side-effects tended to occur in such diseases that were treated with massive dose of GC, e.g. acute leukemia and S.L.E.

4. Severe infectious complications mainly consisted of mycosis, tuberculosis, sepsis and pulmonary abscess. Almost all cases of mycosis, miliary tuberculosis and sepsis were fatal. It should be always kept in mind that fungi-infections can be caused by long-term treatments with GC and antibiotics.

5. Complications of digestive canals mainly consisted of steroid ulcer, which tended to cause a sudden massive bleeding or perforation. Disseminated petechial bleedings on the mucosa, as well as steroid ulcer, were also seen. It was observed that these complications of digestive canals occurred at a rather early period of GC administration.

6. Among various disorders of the central nervous system, depression, mania, schizophrenic symptoms, pseud-cranial tumor symptoms were frequently observed. These side-effects were mainly observed in younger subjects.

7. Shock due to iatrogenic adrenal insufficiency often occurred immediately after the withdrawal of the GC in patients who had been treated for a long time. The shock was frequently observed in patients with bronchial asthma.

8. These results seem to be almost agree well with those in Europe and the United States, except for the lower frequency of cataract in Japan due to some unknown reasons.

9. In most cases of these major side-effects, the continuation of GC therapy becomes impossible and some treatment should be made immediately.

It was therefore suggested that major side-effects should be definitely distinguished from minor ones in which further administration of GC can be continued.

10. It is believed that the present report can give an outline of the major side-effects of GC and contributes to the adequate clinical application of GC.

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