AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 21, NUMBER 1, OCTOBER 1992

EDITOR: B.O. ONADEKO
ASSISTANT EDITORS:
B.O. OSOTIMEHIN and A.O. UWAIFO

SPECTRUM BOOKS LIMITED
Ibadan • Owerri • Kaduna • Lagos

ISSN 1116–4077

Afr. J. Med. med. (1992) 21, 67 - 72

Pattern of adrenocortical response to the stress of severe illness in Nigerians

O. O. FAMUYIWA, A. O. AKANJI, B. O. OLUTADE, C. E. EZENWAKA*
*Departments of Medicine & *Chem. Pathology, University College Hospital Ibadan, Oyo State Nigeria*

Summary

Twenty-eight severely ill, hospitalized Nigerian patients, 18 males and 10 females with a median age of 41 years (group I) and 20 stable ambulatory patients, 11 males and 9 females with a median age of 42.5 years (group II), had early morning plasma cortisol measurements. Ten healthy young Nigerian males with a mean age of 22.1 years (group III) had plasma cortisol estimations during insulin tolerance test. The mean (± SD) cortisol values for the three groups in nmols/l were as follows: group I – 389.3 (202.4), group II – 267.1 (67.4), group III – 624.5 (81.1). The results for the group III healthy controls represent the peak (60 mins) value during insulin induced hypoglycemic stress. A one way analysis of variance (ANOVA) demonstrated a statistically significant difference between the three mean cortisol values, $P < 0.001$. A pair-wise comparison using the *t*-test also showed significant differences between the groups, $P < 0.05$ in each case. An important observation was the variable pattern of cortisol stress response in different types of illnesses. Cases of stroke appeared to be associated with increased cortisol stress values (Z-score + 5.67) while patients with hypotension (B.P. ≤ 90/60) and those on Rifampicin had reduced cortisol responses (Z-scores – 3.66 and 3.51 respectively). However, no firm recommendations can as yet be made regarding the usefulness of corticosteroids in life-threatening illnesses among Nigerians, other than those for which steroids are known to beneficial.

Résumé

Vingt huit patients Nigérians hospitalisés, 18 masculins et 10 féminins, d'age moyen de 41 ans (groupe I), qui sont gravement malades, et 20 patients ambulants sains, il masculins et 9 féminins d'age moyen de 42.5 ans (groupe II) ont été présentés pour le mesurage de la cortisole du plasma prise au lit avant de se lever. Dix jeunes hommes Nigérians, en bonne santé, d'age moyen de 22.1 ans (groupe III ont subi de estimations de la cortisole du plasma au cours d'une évaluation de leur tolérance d'insuline. Les valeurs moyennes (± SD) de cortisole pour les trois groupes en nmol/L étaient les suivantes: group I – 389.3 (202.4), group II – 267.1 (67.4), groupe III – 624.5 (81.1). Les resultats pour le groupe III, qui comporte les temoins sains, représentent la vaeur pointe (60 min) pendant le stress hypoglycémique provoqué par des doese excessives d'insuline. Une analyse de variance simple (ANOVA) a démontré une différence statistiquement significative entre les trois valeurs moyennes de cortisole, $P < 0.001$. Une comparaison par paires untilisant le *t*-test a aussi montré des différences significatives entre les groupes, $P < 0.05$ dans chaque cas. Une observation importance était la tendance variable de reponse de stress de cortisole dans des maladies différentes. Il parait etre une association etre des cas d'attaques d'apoplexie et les valeurs augmentées du stress de cortisole (Z-score + 5.67) tandis que les patients d'hypotension (BP ≤ 90/60 mmHg) et ceux qui suivent une thérapie de rifampicin avaient des responses diminuées de cortisole (Z-scores – 3.66 et 3.51 respectivement). Pourtant, on ne peut pas encore faire des recommendations décidées au sujet d'utilité des corticostéroids dans les maladies ménacantes qui se trouvent parmi less Nigerians.

Introduction

In the last three decades, corticosteroids have found a place in the treatment of many kinds of disease. Apart from the strictly endocrine use as replacement therapy for adrenocortical insufficiency, they are given for a broad range of disorders that appear to have no common denominator[1]. The main pathologic disorders ameliorated by these compounds are allergic, inflammatory and neoplastic diseases. But there are other conditions such as cerebral edema, myxodema coma and septic shock for which the mechanism of action remains unclear[1].

The administration of parenteral corticosteroids to acutely or terminally ill patients is a common practice in hospital in many developing

Correspondence: Dr. O. O. Famuyiwa, Department of Medicine (38) College of Medicine & King Khalid University Hospital, P. O. Box 2925, Riyadh 11461 Saudi Arabia..

countries. No credible scientific evidence has been provided to justify such a practice and its benefit if any, has not been established. The practice is often dictated by the desperation of the physician to "do something" for a severely ill patient in circumstances where the hospitals often do not have what is needed for acute care, intensive support or resuscitation. The persistence of such a practice over many years at the University College Hospital (UCH), Ibadan, which is a tertiary care facility, prompted our evaluation of the adrenocortical response to the stress of acute, severe illness in hospitalized Nigerians. If the cortisol stress levels could be shown to be adequate, then the use of glucocorticoids in such patients would have to be carefully weighed based on other considerations such as the nature of the underlying disease or previously established efficacy of steroids for the disorder.

There is a pressing need to establish a rational basis for the use of corticosteroids in severely ill patients in developing countries. The measurement of stress levels of plasma cortisol may unmask patients with functional impairement or true organic disorder of the adrenal glands. It would therefore be possible to minimize the current practice of empiric and injudicious administration of corticosteroids to all critically ill patients.

Materials and methods

Three categories of subjects were studied. Group I comprised patients who were admitted into hospital for severe and often life-threatening medical illnesses. There were 28 patients, 18 males and 10 females whose ages ranged from 12 to 74 years with a mean (± SD) of 38 (18.9) years and a median of 41 years.

Group II was composed of 20 patients with relatively stable or completely resolved medical problems who were being seen in the outpatient clinic. Eleven were males and 9 were females and their ages ranged from 16 to 75 years with a mean (± SD) of 47.8 (17.1) years and a median of 42.5 years.

Group III comprised 10 young healthy male volunteers who had an insulin tolerance test performed on them. Their ages ranged from 20 to 27 years with a mean (± SD) of 22.1 (2.4) years.

In groups I and II patients, single blood samples were drawn from each subject between 8.00 and 9.00am for plasma cortisol. Insulin tolerance test (ITT) was performed in the group III subjects after an overnight fast. A 19-gauge butterfly needle was inserted into the ante-cubital vein and this was kept patent with small volumes of normal saline. Baseline blood was drawn for glucose and cortisol; thereafter, soluble insulin was administered intravenously at a dose of 0.1 unit/kg body weight. Blood was subsequently drawn for glucose and cortisol at 15, 30, 60 and 90 mins. after the insulin injection. The plasma was separated from all the cortisol samples immediately the blood was drawn, and this was kept frozen at -20°C until the samples were analyzed. Cortisol was measured by radio-immunoassay using Amerlex Cortisol RIA kit (Amersham, U.K.).

Statistics - The statistical methods included analysis of variance (ANOVA), the *t*-test for unpaired data, chi-square analysis and the *Z*-score.

Results

Table 1 lists the spectrum of medical problems among groups I and II patients. All the patient in group I were severely ill, 17 of them had infective illnesses while 11 had non-infective disorders. Two among them died during the study. One had severe tetanus and the other had hepatic failure. Group II patients on the other hand had stable medical problems or had fully recovered and none was acutely stressed. Table 2 provides the ranges and means of plasma cortisol values for the three groups of subjects. Only the 60 mins cortisol values for group III subjects have been reported because this was the time that the plasma cortisol peaked during the ITT. A one-way analysis of variance (ANOVA) was used to compare the mean values between the three groups. The F-value showed a statistically significant difference between the group ($P < 0.001$). A pairwise comparison using the *t*-test also showed significant differences between group I and group II, group I and group III, and between group II and group III subjects, $P < 0.05$ in each case.

Table 3 indicates the proportions of patients among acutely ill and ambulatory patients with low cortisol values, where 276 nmols/l (10μg/dl) has been used to define this level. Healthy volunteers have not been included because none of them had a value less than 500 nmols/l. A chi-square analysis showed no significant difference in proportions of patients with low values of cortisol among group 1 and II patients. After elimination of the 3 patients in the acutely ill group who were on Rifampicin, a drug known to lower plasma cortisol by accelerating its metabolism, an almost significant difference at the 5% level in the pro-

portion of patients with low cortisol values was observed among the ambulatory patients.

Table 4 present the cortisol values in groups I patients based on the type of illness and other clinical parameters including the level of blood pressure. A Z-score of more than 2 may be interpreted as a significantly different value from the average for the entire patient population. However, the extremely small numbers of patients in the various categories indicate that caution should be exercised in the generalization of the findings especially as pertains to patients with tuberculosis and those with low blood pressure. Patients with cerebrovascular accident had a significantly higher mean value and their response is strikingly different from those with central nervous system infections.

Discussion

There have been several reports on the hypothalamic-pituitary-adrenal response to the stress of surgery [2-4]. Moreover, different types of anaesthesia [5-8] or surgery [5,9] are known to have varying effects on the pattern of response. Regarding the adrenocortical response to the stress of medical illnesses, some studies have reported the expected rise in plasma cortisol [10,11] while a few have highlighted the striking variability in the pattern of cortisol response [11,12].

In the present study, severely ill, hospitalized Nigerians with a variety of medical problems had a significantly higher mean plasma cortisol level than non-hospitalized ambulatory control patients. However, these stress levels of plasma cortisol were significantly lower than the mean value for a group of healthy volunteers who had insulin-induced hypoglycemic stress. The cortisol values in our severely ill patients were also lower than values reported for similar patients in other studies [10,11]. Adadevoh [13], has previously observed that Nigerians had only moderate cortisol response to insulin induced hypoglycemia compared to other populations.

Table 1. Medical disorders in hospitalized and ambulatory patients.

Group I - Severely ill hospitalized patients		
	n	%
Stroke syndrome	5	17.8
Meningitis/meningo-encephalitis/brain abscess	5	17.8
Tuberculosis (pulmonary 2, meningitis, generalised)	4	14.2
Amoebic liver abscess	2	7.1
Tetanus	2	7.1
Septicemia	2	7.1
Others (1 each)	8	28.5
Typhoid, bronchopneumonia, mesothelioma, lymphoproliferative disease, encephalopathy, hepatocellullar carcinoma, accelerated hypertension with renal insufficiency, respiratory failure.		
Total	28	100
Group II - Stable ambulatory patients		
Hypertension	5	25
Chronic duodenal ulcer	4	20
Epilepsy	3	15
Recovered typhoid fever	2	10
Recovered tetanus	2	10
Asymptomatic rheumatic valvular heart disease	2	10
Haemoglobin SC disease	1	5
Achondroplasia	1	5
Total	20	100

Table 2. Plasma cortisol levels in severely ill patients, ambulatory patients and healthy controls.

Group	N	Plasma Range	Cortisol (nmols/l) Mean(+SD)	*t* -value	*P* -value
Severe ill patients	28	149-878	389.3(202.4)	2.506	< 0.05+
Ambulatory patients	20	179-428	267.1(67.4)	6.101	0.008#
Healthy controls	10	512-801*	624.5 (81.1)	4.104	0.024**

* 60 mins, values during stress of insulin hypoglycemia.
Analysis of variance (ANOVA) F value between groups, 18.638, $P < 0.0001$
Student's *t*-test
+ severely ill patients compared with ambulatory patients
# ambulatory patients compared with healthy controls
** severely ill patients compared with healthy controls.

Table 3. Proportions of patients with low cortisol levels among severely ill and ambulatory patients

Group	*N*	Plasma < 276nmols/l	Cortisol level > 276 nmols/l	X^2_1**	*P*-value
Severely ill patients	28	11 (39.3)	17 (60.7)	2.142	0.139
Ambulatory patients	25*	8* (32)	17 (68)	3.626	0.054
	20	13 (65)	7 (35)		

( ) Percentage
* Minus the 3 patients who were on Rifampicin
** Chi square analysis - Comparison of severely ill patients with ambulatory patients.

Table 4. Relationship of clinical category to plasma cortisol level among severely ill patients.

Patient category	*N*	Plasma cortisol (nmols/1) Mean (±SE)	Z-score**
All patients	28	389.3 (37.5)	0
All non-infective illnesses	11	458.4 (65.8)	+ 1.84
Cerebro-vascular accidents	5	601.8 (80.5)	+ 5.67
Others	6	339.0 (69.4)	- 1.34
All infective illnesses	17	355.2 (42.2)	- 0.91
Central nervous system infections	5	350.0 (110.5)	- 1.05
Tuberculosis	4*	257.7 (5.7)	- 3.51
Tetanus	2	400.0 (58.6)	+ 0.28
Other infections	6	320.3 (71.0)	- 1.84
Blood pressure status			
≤B.P. 90/60	3	252.0 (78.9)	- 3.66
> B.P. 90/60 but ≤ 160/100	19	397.3 (48.2)	+ 0.21
> B.P. 160/100	6	463.0 (67.8)	+ 1.97

* 3 of these patients were on Rifampicin.
** A score higher than ± 2 is considered significant.

It has been suggested that, if in a critically ill patient the plasma cortisol is less than 10µg/dl (276nmols/l), acute adrenal failure should be strongly suspected [14]. Using this value as a cut-off, 11 out of the 28 severely ill patients (39.3%) or 8 out of 25 (32%), if the three patients on Rifampicin were excluded, had inappropriately low cortisol values. These proportions are not significantly different from those in ambulatory non-stressed patients (Table 3). However, without a Cortrosyn stimulation test, it is not possible to determine whether these patients had true adrenocortical insufficiency. Sibbold *et al* [12] made similar observations among 19% of patients with severe sepsis and they also demonstrated an inadequate response to cortrosyn in the subjects. They speculated on the potential usefulness of glucocorticoid therapy in patients with severe sepsis who fail to respond to appropriate fluid and antibiotic therapy.

Table 4 underscores the variable pattern of adreno-cortical response to different types of illnesses. Only in patients with cerebro-vascular accident was there a significant increase in plasma cortisol compared to the group mean. However, Feibel *et al* [15] have shown that other factors such as the presence or absence of raised intracranial pressure and the integrity of brain stem function affect the pattern of hypothalamic-pituitary-adrenal response to acute brain injury. These parameters were not measured in our patients.

The patients with tuberculosis had low plasma cortisol levels but 3 of them were on Rifampicin, a drug which is known to accelerate glucocorticoid metabolism [16]. A small number of hypotensive patients also had low cortisol values. However, other studies have not found a consistent relationship between plasma cortisol response and severe illness with hypotension [12].

Drucker and Shandling [11] have also commented on the variable adrenal function in acute medical illnesses. With the reported dissociation between plasma cortisol and adrenocorticotrophic hormone (ACTH) levels in patients with acute brain injury [15], attention has been focused on the role of endorphins in adrenocortical response to surgical and medical stress [17,18].

The present unclear picture regarding adrenocortical response to acute medical illnesses makes it difficult to make any recommendations on the use of glucocorticoids in such situations. Moreover, the results of recent controlled trials of high dose steroids in severe sepsis [19,20] and dexamethasone in primary supratentorial hemorrhage [21] did not show any benefit from such treatment. These important well-designed studies put to rest at least for now, the long-standing controversy regarding the usefulness of steroids in severe sepsis and hemorrhagic stroke. It would be best therefore, if practioners in developing countries stopped the frequent and arbitrary practice of administering glucocorticoids to severely or terminally ill patients until further studies establish which patients may benefit from such therapy. It should be remembered that pharmacologic therapy with steroids is not without potential serious side effects which include susceptibility to infection, osteoporosis, gastro-intestinal bleeding, carbohydrate intolerance, electrolyte disturbance, psychosis, Cushing's syndrome and suppression of the pituitary-adrenal axis with the danger of acute adrenal insufficiency.

Acknowledgements

The authors are grateful to Dr. E. A. Bamgboye for assistance with the statistical analysis. Ms. Bennie Campos typed the manuscript.

References

1. Christy NP. Principles of corticosteroid therapy innon-endocrine disease. In: Current therapy in endocrinology 1983-1984. Eds. Krieger, DI, Bardin, CW. B.C. Decker Inc., Burtington, Ontario, 1983-1984; 318-328.
2. Aun F, McIntosh TK, Lee A, Egdahl RH. The effects of surgery on the circadian rhythms of cortisol. Int Surg. 1984; 69: 101-105.
3. Akinyemi OO, Magbagbeola JAO. Metabolic response to anaesthesia and prostatectomy in Nigerians, Afr J Med med Sci 1982; 11:47-51.
4. Mannelli M, Gheri RG, Selli C, Turini D, Pampanini A, Giusti G, Serio M. A study on human adrenal secretion. Measurement of epinephrine, norepinephrine, dopamine and cortisol in peripheral and adrenal venous blood under surgical stress. J. Endocrinol Invest 1982; 5: 91-95.
5. Tsuji H. Shirasaka C, Asoh, T. Takenchi Y. Influences of splanchnic nerve blockade on endocrine -- metabolic responses to upper abdominal surgery. Brit J Surg 1983; 70: 437-439.
6. Miller IW, Hjorts E, Krantz T, Wandall E, Kehlet H. The modifying effect of spinal anaesthesia on intra- and post-operative adrenocortical and hyperglycemic response to surgery. Acta Anaesthesiol Scand 1984; 266-269.
7. Lehtinen AM, Fyhrquist F, Kivalco I. The effect of fentanyl on arginine vasopressin and cortisol secretion during anaesthesia Anaesth Analg 1984; 63: 25-30.
8. Abdulla YM, Giesecke AH, Tillman-Hein HA, Cordes U. A comparison of the activity of the sympatho adre-

nal and adrenocortical system under inhalation anaesthesia techniques. Acta Anaesthesiol Belg. 1983; 34: 257-264.

9. Magbagbeola JAO, Adedevoh BK. Metabolic response to anaesthesia and upper abdominal surgery in Nigerians : Changes in plasma cortisol, insulin and blood sugar. Brit J. Anaesth 1974; 46: 942-946
10. Sainsbury JR, Stoddart JC, Watson MJ. Plasma cortisol levels. A comparison between sick patients and volunteers given intravenous cortisol. Anaesthesia 1981; 36: 16-21.
11. Drucker D, Shandling M. Variable adrenocortical function in acute medical illness. Critical Care Medicine 1985; 13: 477-479.
12. Sibbald WJ, Short A, Cohen MP. Wilson RF. Variations in adrenocortical responsiveness during severe bacterial infections. Ann Surg 1977; 186: 29-33.
13. Adadevoh BK. Adrenocortical activity of the African. J. Trop Med &Hyg 1968; 71: 259-263.
14. Wingert TD, Mulrow PJ. Adrenocortical insufficiency. In: Krieger DI, Bardin CW, eds. Current therapy in Endocrinology 1983-1984, Philadelphia: B.C. Decker, Inc. 1983; 115-118.
15. Feibel J, Kelly M, Lee L, Woolf P. Loss of adrenocortical suppression after acute brain injury: Role of increased intracranial pressure and brain stem function. J. Clin Endocrinol Metab 1983; 57: 1245-1250.
16. McAllister WAC, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. Br Med J 1983; 1: 923-925.
17. Rees M, Bowen JC, Payne JD, MacPhee AA. PlasmaB-endorphin immunoreactivity in dogs during anaesthesia, surgery, *Escherichia coli* sepsis and naloxone therapy. Surgery 1983; 93: 386-390.
18. Porro CA, Facchinetti F, Bertellini E, *et al*. Beta lipotropin is the major component of the plasma opiod response to surgical stress in humans. Life Sci 1987; 4: 2581-2588.
19. The Veterans Administration Systematic Sepsis Cooperative Study Group. Effect of high dose glucocorticoid Therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 1987; 317: 659-665.
20. Bone RG, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA and the Methylprednisolone Severe Sepsis Study Group. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis And septic shock. N Engl J Med 1987; 317: 653-658.
21. Poungvarin N, Bhoopat W, Viriyavejakul A, *et al* Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. N Engl J Med 1987; 316: 1229-1233.

(*Accepted* 6 *June* 1990)