PERCUTANEOUS ABSORPTION OF A CORTICOSTEROID (BETAMETHASONE VALERATE) IN COMBINATION WITH AN ANTIBIOTIC (GENTAMICIN)*

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Data have accumulated to show that steroids can be absorbed through the skin; Scoggins has shown that large amounts of corticosteroid creams produce systemic changes under occlusion.[1] Without occlusion, systemically significant amounts of these substances are absorbed only if the dose applied is very large.[2] Gentamicin is a new broad-spectrum antibiotic which has proved useful against Gram-negative and some Gram-positive organisms. Since it comes from the same chemical family as the neomycin, kanamycin, streptomycin series, it could be regarded as potentially nephrotoxic.

Gentamicin is excreted almost entirely in active form by the kidney by glomerular filtration with little or no reabsorption. Since Jao and Jackson[3] have shown that at recommended systemic therapeutic dosage levels, the drug is concentrated by the kidney, urinary levels would provide a very sensitive test for the presence of gentamicin by topical absorption.

To ascertain whether steroid absorption could carry gentamicin with it, and whether this would be nephrotoxic, large amounts of a cream containing betamethasone valerate 0·1%, and gentamicin sulphate 0·1%, were applied to the skin surface of an adult male, and kidney function and gentamicin excretion evaluated. The excretion of 17-hydroxycorticosteroids and 17-ketosteroids was also measured to determine whether there was any adrenal suppression.

*The material was supplied by Scherag (Pty) Limited, as Celestoderm-V (betamethasone valerate) with Garamycin (gentamicin) cream.

MATERIAL AND METHOD

An adult male patient, height 5 ft. 9 in., weight 205 lb. (92 kg.), was admitted to the Chamber of Mines Hospital, Johannesburg, suffering from an acute exudative eczema of both feet extending up to the ankles, and to a minor degree, up to the knees. He was a miner, and had suffered two previous attacks of contact dermatitis, while wearing rubber boots. Seven weeks before admission, he had been treated with oral antibiotics and local hydrocortisone ointment, and the condition had cleared, but recurred, hence his present admission to hospital. He had never received any steroid by mouth.

Pre-admission urinalysis was carried out to determine renal function and freedom from disease (protein, sugar, microscopic examination and bacterial growth).

On each of the first 2 days' stay in hospital (i.e. pre-treatment) urine was examined for protein, sugar and casts. The 17-ketosteroid determination was carried out by the method described by Sheath,[4] 17-hydroxycorticosteroid determination by the method of Moxham and Nabarro[5] and creatinine estimations by the method of Owen *et al.*[6]

TABLE I. LABORATORY INVESTIGATIONS

Tests done	Pre-admission	Pre-treatment		Treatment days			Post-treatment		
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Protein	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	
Sugar	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	
Serum creatinine mg./100 ml.		1·2							4·4
Blood urea nitrogen mg./100 ml.		16·8							23·0
Urinary creatinine mg. 100 ml.		133		140	116	112			
Urinary volume (ml.)		1,500	1,230	1,400	1,800	2,100	1,580	2,130	
Microscopic examination of urine									
Leucocytes/ml.	<500								
Erythrocytes/ml.	<500								
Epithelial cells	Observed								
Bacterial growth	Nil								
Casts	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Urine gentamicin level 4-hour specimens (μg./ml.)		<0·036	<0·036	<0·036	<0·036	<0·036	<0·036	<0·036	<0·036
Urinary 17-ketosteroids (mg./24 hours)		15·1	22	11·7	15	16·2	12·5	12·5	
Urinary 17-hydroxycorticosteroids (mg./24 hours)		19·2	25·2	17·3	27	18	15·5	19·5	

Microbiological assay was carried out on 4-hourly urine specimens for gentamicin content by the serial dilution method, using the Oxford strain of staphylococcus as the test organism. On one of these days blood urea nitrogen and serum creatinine were determined.

Medication

On the third day, treatment was commenced and continued for a total of 3 days. (By this time he had developed a generalized fine papular allergic rash, sparing only his head, neck and upper chest.) Treatment consisted of inunction of 10 G of the combination cream thrice daily (i.e. a daily total administration of 30 mg. gentamicin and 30 mg. betamethasone valerate). On the first day, inunction was applied only to the feet and legs as far as the knees, but on the second and third days of treatment it was applied to the entire rash area. Polythene occlusion was applied during the first night of treatment, but proved so irksome that it was removed next morning, and not repeated. No other medication at all was given during his entire stay in hospital, and the patient had a bath every morning.

During the 3 days of treatment, urines were examined for casts, sugar, protein, creatinine, steroids and gentamicin. For 2 subsequent days, urines were examined for casts, sugar, protein, steroids and gentamicin. On the 8th day in hospital, blood nitrogen and serum creatinine were repeated.

Urine was collected in separate 4-hourly aliquots and 2 ml. withdrawn from each aliquot for gentamicin assay, and microscopic examination of the freshly voided specimen. Aliquots were subsequently pooled to make up 24-hour specimens for steroid, chemical and creatinine determinations.

RESULTS

The results of the laboratory investigations are shown in Table I.

Gentamicin excretion. The minimal inhibitory concentration of gentamicin against the Oxford strain of staphylococcus is 0·036 μg./ml. In this patient no urinary levels above 0·036 μg./ml. were detected.

Renal status. Pre-admission, pre-treatment, treatment and post-treatment urines all showed no impairment of renal function or evidence of infection or disease, and creatinine excretion showed no inaccuracy of urine collection or change of renal function.

Adrenal function. There was no evidence of adrenal suppression.

Two days after treatment stopped, there was great improvement in the patient and the general rash had disappeared. He was discharged on the 8th day after admission, and seen 2 weeks later when his condition was very much improved.

SUMMARY AND CONCLUSIONS

Although the area of denuded epithelium was small, a large amount of corticosteroid (betamethasone valerate 0·1%) was applied in conjunction with an antibiotic (gentamicin sulphate 0·1%) and there was no evidence that any gentamicin was absorbed since the urine did not contain a detectable level. In this patient large amounts of a topical corticosteroid (i.e. 30 G daily of a 0·1% betamethasone valerate cream) without occlusion, did not produce evidence of adrenal suppression, whereas Scoggins[2] did produce adrenal suppression using 90 G of a 0·025% fluocinolone acetonide cream.

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REFERENCES

1. Scoggins, R. B. (1962): J. Invest. Derm., **38**, 473.
2. Scoggins, R. B. and Kliman, B. (1965): New Engl. J. Med., **273**, 16.
3. Jao, R. L. and Jackson, G. G. (1964): J. Amer. Med. Assoc., **189**, 11.
4. Sheath, J. B. (1959): Aust. J. Exp. Biol. Med. Sci., **37**, 133.
5. Moxham, A. and Nabarro, J. D. N. (1956): J. Clin. Path., **9**, 351.
6. Owen, J. A., Iggo, B., Scandrett, F. J. and Stewart, C. P. (1954): Biochem. J., **58**, 426.