Unfortunately, in most cases reported serial plasma calcium levels during treatment are not given. The relevant details in the present three cases, and six others in which the relevant information is available, are shown in Table II. In all but one the plasma calcium concentration had returned to normal within eight weeks of beginning treatment. Thus it would seem reasonable to wait at least this long before considering a second pathological condition to explain concomitant hypercalcaemia.

We wish to thank Dr. R. Bolton and Dr. A. W. W. B. Woods for permission to study patients under their care, and Dr. D. Frizel for help in the laboratory investigations.

REFERENCES

Adams, P. H., *et al.* (1967). *Quarterly Journal of Medicine*, **36**, 1.
Ahuja, M. M. S., and Chopra, I. J. (1968). *Metabolism*, **17**, 854.
Aliapoulios, M. A., Voelkel, E. F., and Munson, P. L. (1966). *Journal of Clinical Endocrinology and Metabolism*, **26**, 897.
Aub, J. C., Bauer, W., Heath, C., and Ropes, M. (1929). *Journal of Clinical Investigation*, **7**, 97.
Baxter, J. D., and Bondy, P. K. (1966). *Annals of Internal Medicine*, **65**, 429.
Breuer, R. L., and McPherson, H. T. (1966). *Archives of Internal Medicine*, **118**, 310.
Buckle, R. M., Mason, A. M. S., and Middleton, J. E. (1969). *Lancet*, **1**, 1128.
David, N. J., Verner, J. R., and Engel, F. L. (1962). *American Journal of Medicine*, **33**, 88.
Epstein, F. H., Freedman, L. R., and Levitin, H. (1958). *New England Journal of Medicine*, **258**, 782.
Follis, R. H., jun. (1953). *Bulletin of the Johns Hopkins Hospital*, **92**, 405.
Frizel, D., Malleson, A., and Marks, V. (1967). *Lancet*, **1**, 1360.
Goldsmith, R. S., and Ingbar, S. H. (1966). *New England Journal of Medicine*, **274**, 1.
Hubble, D. (1958). *Proceedings of the Royal Society of Medicine*, **51**, 475.
Kleeman, C. R., Tuttle, S., and Bassett, S. H. (1958). *Journal of Clinical Endocrinology and Metabolism*, **18**, 477.
Klotz, H. P., Blahos, J., Delorme, M. L., and Kanovitch, D. (1968). *Annales D'endocrinologie*, **29**, 624.
Koenig, M. P., Scholz, D. A., and Salassa, R. M. (1957). *Minnesota Medicine*, **40**, 782.
Krane. S. M., Brownell, G. L., Stanbury, J. B., and Corrigan, H. (1956). *Journal of Clinical Investigation*, **35**, 874.
Lahey, F. H. (1932). *Annals of Internal Medicine*, **5**, 1123.
Miller, E. S., and Evans, L. R. (1942). *New England Journal of Medicine*, **227**, 949.
Nikkilä, E. A., and Pitkänen, E. (1960). *Annales Medicinae Internae Fenniae*, **49**, 293.
Noble, J. F., and Borg, J. F. (1936). *Archives of Internal Medicine*, **58**, 846.
Pribek, R. A., and Meade, R. C. (1957). *Archives of Internal Medicine*, **100**, 994.
Sataline, L. R., Powell. C., and Hamwi, G. J. (1962). *New England Journal of Medicine*, **267**, 646.
Stanley, M. M., and Fazekas, J. (1949). *American Journal of Medicine*, **7**, 262.
von Recklinghausen, F. C. (1891). In *Festschrift Rudolph Virchow*, p. 1. Berlin, Reimer.
Werner, S. C. (editor) (1962). *The Thyroid*, 2nd. ed. New York, Hoeber.
Wijnbladh, H. (1937). *Acta Chirurgica Scandinavica*, **79**, 507.

Clinical and Bacteriological Studies with Clindamycin

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British Medical Journal, 1970, 2, 703–704

Summary: Fifty patients have been treated with clindamycin, a chemical analogue of lincomycin. Forty-four responded satisfactorily to treatment. Gastrointestinal side-effects were rare though five patients developed rashes. Most recently isolated staphylococci are clindamycin-sensitive.

Introduction

Clindamycin (7 (S)-chloro-7-deoxylincomycin) is a derivative of lincomycin obtained by chemical replacement of the 7 (R)-hydroxyl group of lincomycin by a 7-chloro substituent. It is four to eight times more active than lincomycin against most Gram-positive organisms and is better absorbed from the gastrointestinal tract (McGehee *et al.*, 1968). We report the results of treatment with clindamycin of a group of patients known or suspected to be suffering from infections caused by Gram-positive organisms. In-vitro sensitivity studies were also carried out and the results are reported.

Patients and Methods

Fifty patients (29 female and 21 male) aged 9 months to 82 years were selected for treatment with clindamycin; 25 were children. Thirteen presented with bone or joint infection (Table I), 17 had a variety of infections caused by penicillin-resistant *Staphylococcus aureus* species, and 20 suffered from pneumonia. The 17 miscellaneous staphylococcol infections were: cellulitis 4, wound infection 5, suppurative lymphadenopathy 3, chronic bronchitis 2, breast abscess 1, and skin infection 2.

The antibiotic was administered in capsules at six-hourly intervals as clindamycin hydrochloride hydrate (Dalacin C). The six-hourly dose was 300 mg. for adults, 150 mg. for children under 12 years, and 75 mg. for babies, who were given the antibiotic in powder form in milk. Parenteral preparations of clindamycin are not available at present, and four patients who were judged on clinical grounds to be septicaemic were given intramuscular lincomycin for the first three to four days of their illness. Septicaemia was subsequently confirmed in all four patients. The duration of clindamycin therapy ranged from 7 to 187 days, depending on the severity and chronicity of the infection. Liver function tests, full haematology, urine analysis and measurement of serum urea and electrolytes were performed at least once during treatment in all adults and most children. The patients were observed for clinical evidence of possible untoward reactions to the drug.

Before treatment was started appropriate specimens were taken for bacteriological examination. The clindamycin sensitivity of all organisms cultured was determined with a 2-μg. disc. The disc sensitivities to clindamycin of 500 *Staph. aureus* and 100 *Haemophilus influenzae* isolates were also recorded. The minimum inhibitory concentrations for 34 *Staph. aureus* strains were determined by the tube dilution technique.

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Results

Of the 50 patients, 44 were successfully treated with clindamycin. Two developed extensive rashes during treatment and clindamycin was therefore discontinued, though the infections had been responding to the antibiotic. A young woman presented with pneumonia which did not respond to clindamycin. She was subsequently found to be tuberculous. The remaining three patients were considered to have failed treatment. One was a young man with long-standing osteomyelitis complicating a compound fracture of tibia and fibula in whom amputation was eventually performed for non-union of infected bone. The other two treatment failures were in cases of pneumonia.

While receiving clindamycin five patients developed rashes, which were extensive in two instances. The eruptions were maculopapular and pruritic and usually appeared at the end of the first or during the second week of therapy. In two cases the rash was severe and clindamycin was therefore stopped before the course had been completed. Two patients developed the rash on the last day of treatment. The fifth rash was not severe and clindamycin was continued with spontaneous resolution of the eruption. Four of the five patients with rashes were also being given drugs for night sedation. The only other possible side-effects of clindamycin therapy were diarrhoea in one patient and dyspepsia in two patients. No significant abnormalities were noted in biochemical tests of liver or renal function, or of blood count, even in those patients who received the antibiotic for prolonged periods.

Staph. aureus was isolated from pretreatment cultures in 26 patients, *Streptococcus pyogenes* in two, and *H. influenzae* in one. Twenty-one of the staphylococcal infections were resistant to benzylpenicillin but all were initially sensitive to clindamycin. A clindamycin-resistant *Staph. aureus* (minimum inhibitory concentration>40 μg./ml.) was, however, cultured from the sputum of one of the treatment failures on the tenth day of therapy. In 21 patients it was not possible to culture an organism before treatment was started—16 (including 12 children) suffered from pneumonia and 5 from closed bone or joint infection. A positive blood culture was obtained from four patients suffering from bone or joint infection (Table I).

Four hundred and seventy-five out of 500 *Staph. aureus* and 78 out of 100 *H. influenzae* isolates were sensitive to 2 μg. or less of clindamycin. The minimum inhibitory concentration of most staphylococcal isolates tested was 0·2 μg. or less (Table II).

TABLE II.—*Minimum Inhibitory Concentration of 34 Staph. aureus Isolates*

M.I.C. (μg./ml.)	0·025	0·05	0·1	0·2	0·4	0·8	1·6	3·2
No. of isolates	1	3	10	15	2	1	0	2

Discussion

This study has confirmed the safety and efficacy of clindamycin in the treatment of respiratory tract, bone, joint, and soft-tissue infections. Clindamycin appears to be particularly suitable for prolonged therapy, such as is necessary in bone and joint infection, in view of the low incidence of gastrointestinal side-effects. Whereas 8 out of 65 patients in one reported series treated with lincomycin had diarrhoea (Geddes *et al.*, 1967), only one patient in the present study developed this symptom. The reduced incidence of diarrhoea with clindamycin is probably related to improved absorption as compared with lincomycin. As a result of the good absorption, very satisfactory serum levels of clindamycin have been obtained following oral administration of the antibiotic, peak levels averaging 6 μg./ml. being achieved one to two hours after a dose (Geddes *et al.*, 1970). Serum levels of clindamycin are at least twice as high as those following an equivalent dose of lincomycin, and whereas the absorption of lincomycin is decreased by the presence of food in the stomach, clindamycin absorption is virtually unaffected (McGehee *et al.*, 1968).

While gastrointestinal side-effects have been uncommon in this study, 10% of patients treated with clindamycin developed rashes. These were similar to the rashes seen in patients receiving ampicillin, which have been attributed to residual impurities from the biosynthetic manufacturing process (Shapiro *et al.*, 1969). Though clindamycin is a "semisynthetic" antibiotic, it is produced from lincomycin by chemical manipulation, and biological impurities are therefore unlikely. Further studies of this problem are indicated. A parenteral preparation of clindamycin would be an advantage for the initial treatment of seriously ill patients, but until this is available lincomycin hydrochloride is a satisfactory alternative.

In this hospital most recently isolated staphylococci were sensitive to clindamycin. Almost 80% of *H. influenzae* isolates have also been found to be clindamycin-sensitive, which is rather unexpected as most *Haemophilus* strains are lincomycin-resistant (Garrod and O'Grady, 1968), and studies are in progress to assess the value of clindamycin in the treatment of exacerbations of chronic bronchitis.

We wish to thank Dr. R. G. Jacomb, of Upjohn Ltd., for his interest and advice, and are grateful to surgical and medical colleagues for allowing us to treat patients under their care.

REFERENCES

Garrod, L. P., and O'Grady, F. (1968). *Antibiotic and Chemotherapy*, 2nd edn. Edinburgh, Livingstone.

Geddes, A. M., Bridgwater, F. A. J., Grimshaw, G. J., and Williams, D. N. (1970). In *Proceedings of the 6th International Congress of Chemotherapy, Tokyo*. In press.

Geddes, A. M., Munro, J. F., Murdoch, J. McC., Begg, K. J., and Burns, B. A. (1967). In *Proceedings of the 5th International Congress of Chemotherapy, Vienna*, vol. 1, ed. K. H. Spitzy and H. Haschek, p.361. Vienna, Wiener Medizinischen Akademie.

McGehee, R. F., Smith, C. B., Wilcox, C., and Finland, M. (1968). *American Journal of the Medical Sciences*, **256**, 279.

Shapiro, S., Slone, D., Siskind, V., Lewis, G. P., and Jick, H. (1969). *Lancet*, **2**, 969.

TABLE I.—*Bone and Joint Infections Treated with Clindamycin*

Age in Years	Affected Bone/joint	Acute/chronic Infection	Surgical Drainage	Organism	Duration of Therapy (Days)	Result of Treatment	Comment
47	Sacroiliac	Acute	—	Nil	132	Successful	
13	Tibia	Chronic	—	*Staph. aureus* (bone)	187	Successful	
20	Tibia	Chronic	—	*Staph. aureus* (bone)	118	Failed	Amputation for non-union
12	Humerus	Acute	—	Nil	51	Successful	
47	Wrist	Acute	Yes	*Staph. aureus* (joint)	92	Successful	
11	Fibula	Acute	—	Nil	40	Successful	
22	Rib	Acute	Yes	*Staph. aureus* (bone)	53	Successful	
6	Femur	Acute	—	*Str. pyogenes* (blood)	44	Successful	Lincomycin for 4 days
13	Ankle	Acute	Yes	*Staph. aureus* (blood and bone)	92	Successful	Lincomycin for 4 days
12	Femur	Acute	Yes	*Staph. aureus* (blood and bone)	104	Successful	Lincomycin for 4 days
9	Tibia	Acute on chronic	—	Nil	82	Successful	
19	Clavicle	Acute	Yes	Nil	73	Successful	
34	Humerus	Acute	—	*Str. pyogenes* (blood)	6	Failed	Rash. Lincomycin for 3 days