Thorax (1971), **26**, 551.

Use of sodium cephalothin in the management of lung gangrene

B. T. le ROUX

Thoracic Surgical Unit and the Department of Surgery, University of Natal

Thirty-one of 256 cases of chronic destructive pneumonia who were judged, by the severity of illness and haemoptysis, to have lung gangrene, were managed with intravenous sodium cephalothin. Five patients died, two in relation to emergency pneumonectomy. In comparison with results of management of this disease in previous, similar patients, the results are encouraging.

There is a group of chronic infective destructive pulmonary lesions which may be difficult to distinguish, on clinical and radiological grounds, from peripheral cavitated pulmonary carcinoma and pulmonary tuberculosis, and which, while resembling precisely acute lung abscess radiographically, do not present as an acute illness of short duration. In the majority of patients the conservative management of chronic destructive pulmonary lesions is more or less satisfactory—in most, although there is bronchographic evidence of permanent residual bronchial damage, the abscess cavities diminish in size and residual symptoms are unusual. In a proportion of patients, however, pulmonary destruction is progressive, molar rather than molecular, and haemoptysis is ingravescent and life-threatening. The surgical management of progressive destructive pneumonia is associated with a complication rate so high that any operation other than drainage should be avoided unless it is judged that death from haemoptysis is otherwise certain.

The bacterial flora of chronic cavitated suppurative pneumonia is often mixed and the causative organisms are difficult to isolate. The source of mixed pulmonary infection, which is the cause of some chronic destructive pneumonias, is probably similar to that which results in acute lung abscess —aspiration during sleep, or in periods of unconsciousness related to drunkenness, anaesthesia, epilepsy, suicidal barbiturate narcosis, electroconvulsive therapy, and aspiration in relation to oesophageal obstruction from whatever cause. There is also no certain evidence that the initial insult is bacterial and not the consequence of pulmonary infarction, although the relative youth of many of the patients and the absence of cause for pulmonary infarction make this unlikely.

The patient with a chronic destructive pneumonia is at risk in many ways—because of the imminent danger of exsanguinating haemoptysis; because of the general and local consequences of a chronic suppurative illness; because the patient may in fact have a carcinoma, treatment of which is delayed for so long that the carcinoma has disseminated; because the patient may be managed as if he had a carcinoma, by pulmonary resection and, in the circumstances outlined, pulmonary resection carries with it an almost prohibitively high rate of postoperative complications; or because the patient has pulmonary tuberculosis. The complications of the surgical management of chronic suppurative pneumonia are pleural and metastatic infection, particularly brain abscess, and the metastatic and pleural infections, like the original lesion, commonly do not respond to available antibiotics. The armamentarium available to the respiratory physician and the thoracic surgeon for the investigation of pulmonary disease fails regularly, in the circumstances outlined, to provide a diagnosis. Clinical history and examination are usually non-contributory; bacteriological examination of the sputum may be consistently unhelpful and demonstrates a variety of organisms not certainly consistently pathogenic; and the appearances at bronchoscopy are normal apart from the presence of pus in the bronchus related to the pulmonary lesion. Serial radiography should be the key to the diagnosis, but an ingravescent lesion does not necessarily mean that the lesion is a carcinoma, and the lesion which appears to diminish does not necessarily exclude the diagnosis of carcinoma. Antibiotic treatment with a variety of drugs, singly or in combination, over a prolonged period, preceding referral for a thoracic surgical

opinion, is commonplace among the group of patients who fall into this category, so that when there is ultimately need to submit the patient to a surgical procedure, appropriate antibiotic cover is no longer available. A large haemoptysis may lend a sense of urgency to management so that, in some instances, an operation is undertaken in exceptionally unfavourable circumstances.

In a previous paper (le Roux, 1970) the value of the exhibition of intramuscular cephaloridine in the management of chronic destructive pneumonia was suggested. Available evidence establishes that treatment with an antibiotic hastens resolution, shortens the period of hospitalization, and aids distinction from peripheral cavitated pulmonary carcinoma, but does not prevent peripheral pulmonary damage. Intramuscular cephaloridine emerges as a safe and satisfactory antibiotic for routine use, since it does not, in the dosage used, carry the risks which may attend use of the effective alternative—chloramphenicol.

In a group of 31 patients, whose relevant clinical data are given in the Table, it was judged necessary to manage ingravescent pulmonary destruction by intravenous chemotherapy in large dosage if death was to be avoided. All had large abscess cavities. At the time of referral for a thoracic surgical opinion, all had been gravely ill for more than a month—seven for more than two months. All had haemoptysis. The extent of pulmonary destruction made likely the diagnosis of lung gangrene, and in five, in whom drainage of the abscess cavity was undertaken, a large lung slough was found in the cavity. Eight other patients coughed up large pieces of gangrenous lung.

The youngest patients were 22 and 23 years, respectively, and the oldest 77—one of the only three females. Twenty-eight patients were men, two-thirds in the age range 30–50, precisely the age range of bronchial carcinoma in Bantu males, and a decade younger than the peak incidence of bronchial carcinoma in Caucasian males in the same area.

Two-thirds of the chronic lung abscesses were right-sided and two-thirds were upper lobar. In half, sputum examination failed to demonstrate any organisms, despite the fact that sputum was grossly purulent and in many heavily bloodstained. The normal range of blood urea estimation in the laboratory in which this investigation was made is accepted as 20–40 mg/100 ml; in 14 of the 31 patients the blood urea was elevated, in three grossly so, and these three patients died. All had extensive tubular necrosis at necropsy, and two

TABLE

Age/Sex	Race	Site	Diabetic	Blood Urea (mg %)	Sputum Culture	Cephalothin			Subsequent Lobectomy for Bronchiectasis
						Only	+Open Drainage	Pneumonectomy	
32 M	B	RU				+			
47 M	B	RU		35	Coliforms	+			
45 M	B	LU	+	48	Staphylococci		+		
50 M	B	RU	+	60		+			
60 M	A	RL	+	190	Coliforms			Died	
59 M	B	RU		52			+		
40 M	B	LU	+	90	Klebsiella	+			+
29 M	B	RM				+++			
36 M	B	LL			Staphylococci	+			
32 M	B	RL			Staphylococci	+			+
49 M	B	RU		80			+		
70 M	B	LU		200		Died			
22 F	B	RL			Klebsiella	+			+
77 F	C	LL	+	120	Klebsiella	Died			
46 M	A	RU	+	50	Coliforms		+		
46 M	B	RL						Empyema	
48 M	A	LL	+	90	Klebsiella	+			
37 M	B	RM		30	Coliforms		+		
32 M	B	RU				+			
31 M	B	RU		45	Coliforms	+			+
40 M	B	LU		40		+			
27 M	C	LL		89	Klebsiella	Died			
36 M	B	RL			Staphylococci	+			
29 M	B	RU	+	36		+			
23 M	B	RU			Coliforms	+			
58 M	B	LU		30				Died	
50 M	B	RU		90		+			
46 M	B	RU			Klebsiella	+			
41 M	B	RU		60		+			+
40 M	B	RU				+			
37 F	C	LU		40	Coliforms			+	

A=Asiatic; B=Bantu; C=Caucasian. L, R=Left, Right; U=Upper; L=Lower; M=Middle.

were anuric at the time of death. In 10 patients, none gravely ill, and all of whom recovered, blood urea was not estimated.

The purpose of intravenous therapy as opposed to the oral or intramuscular route was to ensure continued high dosage of the drug selected. The purpose of the use of massive doses was to flood the abscess cavity with the antibiotic in the hope that organisms which continued to thrive in gangrenous lung, and which were therefore not accessible to circulating antibiotics in conventional intramuscular dosage, would be reached by diffusion of large concentrations of the antibiotic into the cavity.

The drug selected was sodium cephalothin (Keflin) and the dosage used was 8 to 12 g a day by continuous intravenous infusion. The drug was used without reference to *in vitro* sensitivity estimations since these were not available at the time of institution of therapy. When sensitivity tests became available, resistance to sodium cephalothin was never convincingly demonstrated, but organisms were not always isolated.

Three of the 31 patients died from exsanguinating haemoptysis during treatment, one after four days, and two after nine days. In five the abscess cavity continued to increase in size, and drainage by rib resection was undertaken. In four, increasing haemoptysis prompted management by pulmonary resection—in all, by pneumonectomy. Two of these patients died in the early postoperative period from contralateral pulmonary infection, presumably the consequence of intraoperative spill into the opposite bronchial tree. Another patient submitted to pneumonectomy developed an empyema, in the management of which an extensive thoracoplasty was ultimately required. In 18 of the remaining 19 patients improvement in clinical state became recognizable within 72 hours of the beginning of intravenous therapy with cephalothin; haemoptysis and the volume of purulent sputum produced diminished and sputum became mucoid; there was radiographic evidence of diminution in size of the abscess cavity. In all, a stage was reached when the patient's clinical state justified bronchography and in all there was bronchographic evidence of residual bronchiectasis, in most gross and in some more than lobar. In five of these 19 patients, symptoms recurred during a period of observation and management has been by lobectomy; from this procedure all have convalesced uneventfully.

Of the 31 patients, eight (seven Asiatics and one of Caucasian stock) were diabetic and in them pulmonary infection made control of diabetes difficult. Of these eight patients six had proteinuria and in all creatinine clearance was impaired. In the remaining 23 patients there was proteinuria in 10, and in six of these creatinine clearance was also impaired. The reputed dose-dependent nephrotoxicity of cephaloridine prompted the use of sodium cephalothin since it was the aim of therapy to use high dosage, for the reasons previously indicated. The antibacterial spectrum of the two antibiotics is similar. Serum protein binding of cephalothin is considerably greater than of cephaloridine, but the degree of protein binding of cephalothin must be easily reversed since most is rapidly excreted via the kidneys within six hours (Barber and Waterworth, 1964).

The serum half-life of cephaloridine in patients with normal renal function (1½ hours) is approximately three times that of cephalothin. Available evidence (Kabins and Cohen, 1965; Kunin and Atuk, 1966; and Ruedy, 1967) suggests that, with cephaloridine, impaired renal function, as shown by decreased creatinine clearance, prolongs the serum half-life of the drug, exponentially as the creatinine clearance decreases, and azotaemia necessitates caution in the use of cephaloridine. The short serum half-life of cephalothin is an indication for continuous intravenous therapy. The renal excretion of cephalothin is by both tubular secretion and glomerular filtration and cephalothin is rapidly inactivated by the liver, whereas cephaloridine is not appreciably metabolized within the body. In the presence of impaired renal function, continuous intravenous administration in high dosage of a drug metabolism of which is rapid is probably safer than the use of smaller doses of an equally effective drug the intramuscular administration of which is uncomfortable (a disadvantage obviated by intravenous administration), which is not appreciably metabolized within the body, and the satisactory excretion of which depends upon intact renal function. The value of an effective antibiotic in doses high enough to flood extravascular spaces and to reach organisms cloistered in slough or vegetations is confirmed by the success of cephalothin in the management of bacterial endocarditis (Merrill, Davis, Smolens, and Finegold, 1966; Rahal, Meyers, and Weinstein, 1968).

The 31 patients selected for treatment with intravenous sodium cephalothin reported in this series were from a group of 256 patients with chronic destructive pneumonia treated over a period of three years. The 31 selected were so gravely ill that it was judged that all were in danger of death. That only five died represents an improvement in the result of management of this variety of pulmonary lesions beyond all expectation. While it

is not possible precisely to compare one case with another, from previous extensive experience with greater or lesser degrees of lung gangrene a mortality of at least 50% in patients so gravely ill and with haemoptysis would have been anticipated.

REFERENCES

Barber, M., and Waterworth, P. M. (1964). Penicillinase-resistant penicillins and cephalosporins. *Brit. med. J.*, **2**, 344.

Kabins, S. A., and Cohen, S. (1965). Cephaloridine therapy as related to renal function. *Antimicrobial Agents and Chemotherapy—1965*, p. 922.

Kunin, C. M., and Atuk, N. (1966). Excretion of cephaloridine and cephalothin in patients with renal impairment. *New Engl. J. Med.*, **274**, 654.

le Roux, B. T. (1970). The management of chronic destructive pneumonia with ceporan. *Postgrad. med. J.*, in press.

Merrill, S. L., Davis, A., Smolens, B., and Finegold, S. M. (1966). Cephalothin in serious bacterial infection. *Ann. intern. Med.*, **64**, 1.

Rahal, J. J., Meyers, B. R., and Weinstein, L. (1968). Treatment of bacterial endocarditis with cephalothin. *New Engl. J. Med.*, **279**, 1305.

Ruedy, J. (1967). The use of cephaloridine in adult patients with renal failure. *Postgrad. med. J.*, **43**, Suppl. (Aug.): *Cephaloridine*, p. 87.