Taurolidine instillation as therapy for empyema thoracis
A prospective study of 50 patients

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Summary
Fifty patients with chronic empyema thoracis, without bronchopleural fistula, were treated by drainage and twice-daily instillations of 2% taurolidine (Taurolin; Continental Ethicals) for 14 days. No antibiotics were used. Forty-three patients completed the treatment and 7 were withdrawn from the trial because of evidence of bronchopleural fistula and pain during instillation, associated chest-wall cellulitis, an unexplained acute epilepsy-like episode during instillation, and inadvertent administration of antibiotics. All 43 patients who completed the trial showed an excellent clinical response with control of the local and systemic effects of sepsis. A rapid falling-off in the volume and purulence of pleural drainage fluid was noted. Twenty-four of the 43 patients (55.8%) were rendered bacteriologically sterile by the treatment. Instillation of 2% taurolidine was therefore an effective form of monotherapy in cases of chronic empyema thoracis without bronchopleural fistula.

Empyema thoracis (suppuration in the pleural space) remains an important cause of prolonged hospitalization and patient morbidity and mortality.1-4 The high prevalence of inflammatory and suppurrative lung disease among urban Black patients is responsible for the frequent occurrence of empyema.2,3 Infected haemothorax after a penetrating thoracic injury is a further important cause. Standard therapy for empyema includes early adequate closed-tube drainage and administration of broad-spectrum systemic antibiotics. However, all the empyemas treated will not resolve and a significant number progress to a chronic form.

The distinction between acute and chronic empyema is made on pathological and chronological grounds and is somewhat arbitrary. Varkey et al.1 suggested that it is practicable to consider an empyema as chronic when the disease has reached a stage at which obliteration of the pleural space by appropriate antimicrobial therapy and closed-tube drainage is impossible. Chronicity in an empyema usually heralds a prolonged course with ongoing suppuration and with its acute and chronic debilitating effects on health and nutrition.

Since the introduction of antibiotics the mortality and morbidity associated with empyema thoracis have declined.1-4 However, the bacteriological aspect has also changed5-7 and anaerobic infection has assumed a prominent role,8 with serious implications for empyema patients. Many patients become infected with hospital pathogens resistant to antibiotics and, in addition, more than one pathogen may be present. This questions the appropriateness of drug choice and antibiotic therapy for empyema thoracis. A further factor of importance is the effective penetration of antibiotics through the dense empyema wall and their subsequent effectiveness in the presence of pus.

The occurrence of infections by multiple, antibiotic-resistant pathogens in body spaces or cavities (pleura, mediastinum, peritoneum) has led to a renewed interest in broad-spectrum chemotherapeutic substances for local use — the antiseptics.8 Antiseptics in common clinical use fall into two main groups: (i) the organic iodine compounds, e.g. povidone iodine; and (ii) the methylol donors, e.g. noxytiolin and taurolidine (Taurolin; Continental Ethicals). Numerous clinical studies over 2 decades have demonstrated the effectiveness of noxytiolin solution.9 A newer compound is taurolidine, also a methylol donor but supplied as a stable infusion for use. It is formed by the condensation of two molecules of taurine and three molecules of formaldehyde.8-10 The compound has wide bactericidal activity against aerobes and anaerobes at low concentrations. In addition its specific anti-endotoxin property gives it a considerable advantage over antibiotics.8-11

The putative mode of action is the killing of bacteria by the transfer of methylol groups to their capsules. The loose linkage between taurine and the methylol groups ensures their transfer. The endpoint of the process is the liberation of taurine to the amino acid pool. Tagging of the methylol groups with carbon-14 shows 60% excreted as carbon dioxide, 10% by the kidneys and a small amount in the faeces. The half-life of taurolidine is 2/2 hours, and formaldehyde is never present in the free form.8

Favourable reports of the efficacy of taurolidine in peritonitis,8 in wound infection after appendicectomy12 and in empyema thoracis11 suggested an evaluation of its effectiveness in chronic empyema thoracis without bronchopleural fistula. This report is based on such a study, conducted prospectively according to protocol, in 50 patients with empyema thoracis from an urban Black population.

Patients and methods
Between November 1982 and May 1983, 50 patients with chronic empyema thoracis without bronchopleural fistula were prospectively studied at the University of the Witwatersrand's thoracic surgery unit based at Leratong Hospital. The patients were entered in the trial and studied according to a protocol in...
which no antibiotics were used and inclusion criteria were as follows: all patients over 18 years of age (of either sex and giving informed consent) who had empyema, without a bronchopleural fistula, which had failed to respond to antibiotics, tube drainage or rib resection. Excluded from the study were those patients with associated bronchopleural fistula, whose empyema was due to tuberculosis or cancer, those with systemic disease impairing immunity (e.g. diabetes, chronic leukaemia, chronic renal failure), patients with renal or hepatic impairment and patients receiving chemotherapy or radiation treatment. Following inclusion in the study routine haematological and biochemical studies and tests of renal and hepatic function were carried out and thereafter repeated weekly. Rib resection and closed-tube drainage of the empyema space was effected and pus thus obtained was sent by hand within a suitable transport medium for culture of aerobes and anaerobes. At the time of initial drainage or tube insertion a pleural biopsy was done.

Twice daily for 14 days 100 ml of 2% taurolidine solution was instilled into the empyema space through the drainage tube, which was clamped for 1 hour and then released. The volume and appearance of the pleural drainage fluid were recorded daily. Pleural fluid culture specimens were taken every 3 days in the early morning prior to instillation of the taurolidine. After 14 days of treatment the results were assessed. Successful therapy was defined as: (i) bacteriological sterility of the empyema space in terms of pathogenic organisms; and (ii) absence of frank pus drainage. The presence of these two conditions allowed progression to (a) drain removal, (b) pulmonary decortication, (c) excision of the empyema cavity, (d) a space reduction procedure, and (e) primary space closure with an antibiotic solution. Failure of therapy was defined as the continuing drainage of frank pus with pathological organisms after 14 days of treatment and, by definition, failure to progress to the above steps.

Of the 50 patients, 48 were males and 2 females. All were from an urban Black population living in poor socio-economic circumstances. Ages ranged from 18 to 70 years; 4 patients were between 18 and 20 years of age, 19 between 20 and 30 years, 9 between 40 and 50 years, 12 between 50 and 60 years, 5 between 60 and 70 years and 1 over 70 years. Twenty-five empyemas were left-sided and 25 were right-sided. Empyema was due to inflammatory or suppurative lung disease in 23 patients, to infected haemothorax following penetrating thoracic injury in 24, to post-pneumonectomy space infection in 2, and to oesophageogpleural fistula after a stab wound in 1. Several organisms were found on bacteriological examination in 35 patients, and single isolates were found in 15. The latter were Staphylococcus aureus in 7 patients, Pseudomonas in 4, Bacillus subtilis in 2, and Staph. pyogenes and Enterobacter in 1 patient each. Twenty-three patients (46%) had anaerobic infections. The bacteriological findings are summarized in Table I.

Seven patients were withdrawn from the trial for the following reasons: bronchopleural fistulas (3 patients, on days 2, 4 and 7); pain following instillation (1 patient); chest-wall cellulitis at entry into the study with withdrawal on day 4 because of its progression (1 patient); and the discovery that antibiotics had been given during the first 7 days of the taurolidine instillation period (1 patient). The remaining patient developed an acute syndrome resembling an epileptic fit during the instillation period on day 10. Although he was found to have an old depressed skull fracture and a previous history of epileptic fits, he was nevertheless withdrawn from the trial. Four patients complained of burning pain on taurolidine instillation but this occurred only within the early part of the trial and was abolished by injecting 1% lignocaine through the tube.

Results

All 43 patients who completed the trial had an excellent clinical response with control of the local and systemic toxic effects of sepsis and a rapid falling-off in the volume and purulence of the pleural drainage fluid. In addition culture was negative in 24 of the 43 patients. A further 4 patients in whom multiple pathogens had been present at the start of the study finished with a marked reduction in numbers of pathogens (reduced from 7 to 2, 5 to 2, 4 to 1, and 2 to 1 respectively). Clinical well-being was apparent in all patients, with freedom from suppuration.

At the end of the study period the volume of pleural drainage fluid was less than 50 ml per day in all 43 patients; the fluid was serous in 25, sero- or mucopurulent in 16, and purulent in 2 patients.

Forty-one patients progressed to appropriate further treatment consisting of drain removal (16 cases), pulmonary decortication (13), open tube drainage only (9) and open-window thoracostomy (3); the other 2 refused further treatment.

Discussion

Pleural suppuration is always a secondary event.\textsuperscript{1-4} Infection reaches the pleural space, usually from the adjacent lung but occasionally from the mediastinum or the subdiaphragmatic area or as a result of penetrating thoracic injury\textsuperscript{5,8} or recent thoracic surgery.\textsuperscript{1-4} The bacteriological picture of empyema thoracis has changed dramatically several times during recent decades\textsuperscript{5-7}. Before the antibiotic era Staph. pneumoniae and haemolytic streptococci were the common pathogens\textsuperscript{5,7}. The introduction of penicillin resulted in their virtual disappearance, which led to the emergence of Staph. aureus as the dominant pathogen.\textsuperscript{1} Following the introduction of ß-lactamase-resistant antistaphylococcal

| TABLE I. ORGANISMS GROWN ON PLEURAL PUS CULTURE FROM 50 PATIENTS WITH EMPYEMA THORACIS |
|---------------------------------|-----|-----------------|
| No.                             |     | No.             |
| Staph. aureus                   | 30  | Diplococcus pneumoniae | 3   |
| Pseudomonas                     | 14  | Strept. pyogenes  | 3   |
| Klebsiella                      | 9   | Diphtheroids      | 3   |
| Streptococcus faecalis          | 9   | Serratia marcescens | 2   |
| Strept. viridans                | 9   | Salmonella        | 1   |
| Enterobacter                    | 8   | Bacteroides fragilis | 1     |
| B. subtilis                     | 7   | Strept. pneumoniae | 1   |
| Proteus                         | 6   | Bact. melaninogenicus | 1     |
| Escherichia coli                | 5   | Peptostreptococcus | 1   |
| Clostridium                     | 5   |                 |     |
antibiotics the incidence of empyema due to staphylococci decreased, but a rise in the number of Gram-negative organisms was noted. More recently the increasing isolation of anaerobic organisms has caused concern. The incidence reported varies from 5% to 55%, but several series quote 40%. In the present study the incidence was 46%. The variability between studies can be explained by differences in methods of harvesting, transportation and processing of empyema pus specimens for anaerobic culture. However, there is no doubt that the incidence of empyema due to anaerobic organisms has increased markedly during the 1970s, with serious implications for empyema sufferers.

The efficacy of antibiotic therapy in chronic empyema thoracis is largely unknown. The primary therapy of empyema is surgical drainage, and antibiotics are used mainly empirically to protect against the local and systemic effects of sepsis. The absorption of bacterial toxins from infected and suppurating culture. However, there is no doubt that the incidence of empyema due to anaerobic organisms has increased markedly during the 1970s, with serious implications for empyema sufferers.

The role of antiseptics in the management of chronic empyema thoracis can best be defined by a prospective study comparing

empyemas treated by systemic antibiotics, surgical drainage and saline instillations with empyemas managed by drainage and instillations of a specific antiseptic.

This preliminary study suggests that 2% taurolidine is a valuable local compound with excellent chemotherapeutic properties and good patient tolerance. It has been found to be an effective form of monotherapy in patients with chronic empyema without bronchopleural fistula.

REFERENCES


Geographical distribution of lung and stomach cancers in South Africa, 1968-1972

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Summary

The geographical distribution of lung and stomach cancer among three races in South Africa (Whites, Coloureds and Asians) has been investigated for the years 1968-1972, and the patterns of the occurrence of cases of cancer have been tested stochastically and mapped both separately and together. Information was not available for the Black population.

Distinct differences in the distribution of lung and stomach cancer were found. Possible explanations for these differences are discussed.

Our principal aim is to provide a comparative geographical definition of mortality from lung and stomach cancer among three racial groups in South Africa, both for each group separately and for all three taken together as a fourth group. As a secondary objective, age- and sex-specific comparisons are also examined.

The spatial distribution of lung and stomach cancers in the four groups is examined to determine whether any common denominators as regards environment can be found among the groups and between the sexes. A high rate of lung cancer occurs among both Coloured and White males (over 40/100,000), and this is increasing in conformance with the situation in Europe.