the patients had hypertension (diastolic blood pressure >95 mm Hg), ischaemic heart disease, asthma, respiratory failure, or thyrotoxicosis or was alcoholic. All patients yielded normal results to liver function tests. All gave informed written consent to the study, which was approved by the hospital research committee.

Before endoscopy respiratory rate and blood pressure were recorded and expired minute ventilation measured with a Wright's respirometer attached to a closely fitting anaesthetic face mask. The orientation and cognitive function of each patient were tested by standardised questions regarding place and time, and simple mental arithmetic; the patient's overall state of alertness was evaluated and recorded on a 10 cm horizontal visual analogue scale ranging from totally unresponsive (0 cm) to fully alert (10 cm). All evaluations were made by the same physician and sealed in separate envelopes to prevent comparisons during the study.

Another physician administered diazepam by slow intravenous injection until sedation and relaxation were produced as indicated by drooping of the patient's eyelids, dysarthria, generalised muscle relaxation, and ability to swallow the gastroscope. After endoscopy measurements of alertness, ventilation, and blood pressure were repeated. Each patient was then randomly assigned to receive by bolus intravenous injection either 100 mg doxapram or an identical placebo; assessments were repeated five, 60, and 120 minutes later.

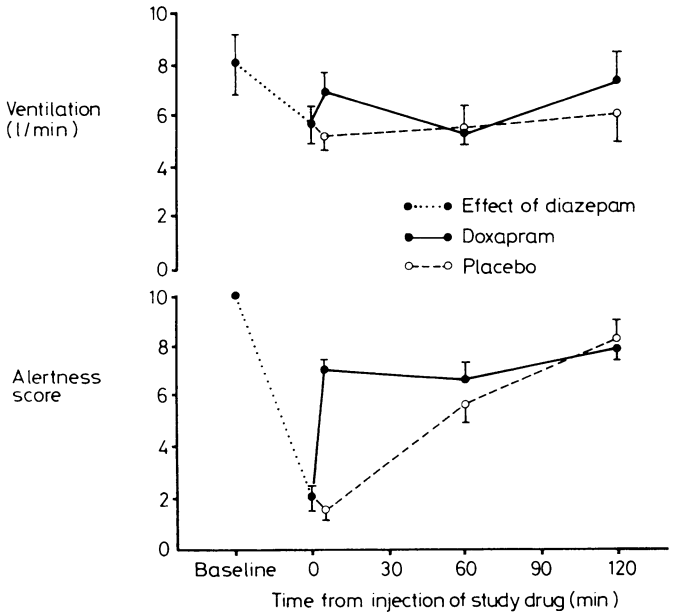
Data were analysed by paired t test, χ^2 test, or Fisher's exact test.

Before diazepam all 115 patients were orientated and 113 could make a satisfactory attempt at mental arithmetic. After diazepam 24 became unexpectedly heavily sedated (visual analogue scale < 5 cm). There were no significant differences in dose of diazepam (mean 26·0 mg), age, weight, height, liver function, or concurrent medication between patients who became heavily or lightly sedated.

Of the 24 heavily sedated patients, 13 received doxapram and 11 placebo. There was a highly significant improvement compared with placebo five minutes after doxapram was given: the number of patients orientated increased from three to nine ($p < 0{\cdot}0001$), the number able to attempt mental arithmetic from three to 10 ($p < 0{\cdot}0001$), and the mean visual analogue score from 2 to 7 cm ($p < 0{\cdot}001$). None of the measurements after placebo changed. A mean increase in ventilation of 1·7 l/min ($p < 0{\cdot}001$) occurred in patients who received doxapram, but there was no change in ventilation in those given placebo.

Sixty minutes after injection of doxapram ventilation had fallen to values seen before injection and was similar in heavily sedated patients who had received doxapram and those who had received placebo. However, the level of alertness of the heavily sedated patients who had received doxapram did not fall (figure); the proportion orientated, the number able to do arithmetic, and the mean visual analogue score were the same as at five minutes. During the elapsed time the alertness of the placebo-treated patients had increased, so the difference between the two groups was not significant. After 120 minutes there were no differences.

No potentially serious side effects occurred. All patients who received doxapram showed a small rise in systolic blood pressure (mean rise 24 mm Hg) but no change in heart rate. Eight patients complained of feeling hot and sweaty; they were all lightly sedated. In no patient did doxapram interfere with the short term memory loss produced by intravenous diazepam or induce convulsions.



Effect of doxapram on alertness and ventilation of patients heavily sedated with diazepam (mean ± SEM). Baseline measurements were taken before endoscopy and administration of diazepam. Time 0 was after endoscopy, showing effect of diazepam immediately before patient received study drug (doxapram or placebo).

Comment

Doxapram is both a peripheral chemoreceptor agonist and central neuronal stimulant[1 2]; it speeds recovery from general anaesthesia[3 4] and reverses opiate induced ventilatory depression.[5]

Roughly one fifth of patients in this study who received intravenous diazepam became unexpectedly and unpredictably heavily sedated; this randomised controlled trial shows that doxapram effectively and safely reverses this heavy sedation.

We thank Sister Joy Banks and the staff of the diagnostic unit; Mr C Jones for providing doxapram, placebo, and the statistical analysis; and Dr M Craven for editorial help.

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Trimethoprim resistance in Gram negative urinary pathogens

Trimethoprim has been available for use alone in Great Britain since 1979. As there is in vitro evidence that the presence of a sulphonamide inhibits the development of resistance to this agent[1] it is important that observations on the level of resistance in clinical isolates should be made. We have kept figures for the normally susceptible Gram negative urinary pathogens isolated in our laboratory during the month of October for the past five years.

Methods and results

Sensitivity testing, whether primary or secondary, was performed by a modified Stokes method, using *Escherichia coli* NCTC 10418 as the control organism. Discs containing 100 μg sulphafurazole and 25 μg co-trimoxazole (23·5 μg sulphamethoxazole, 1·5 μg trimethoprim) were included in the agents tested. Zones not more than 3 mm smaller than the control were interpreted as sensitive, those of at least 3 mm radius but more than 3 mm smaller than the control as moderately resistant, and those of less than 3 mm radius as resistant. Tests giving equivocal results or "clouded" zones (especially those with too heavy an inoculum) were repeated; since 1979 organisms showing borderline zones with co-trimoxazole have been retested with a 2·5 μg trimethoprim disc. All organisms found to be sensitive to sulphonamide but apparently resistant to co-trimoxazole have also been retested with a trimethoprim disc. There has been no change in this methodology over the study period.

Sensitivity tests were performed only when the isolates were considered to be clinically relevant; thus the figures do not include isolates from bag specimens from babies, or, except rarely, mixed isolates or isolates from patients with long term indwelling catheters.

Moderately resistant and resistant isolates were not separated in the records before 1981; the figures were kept separately for 1981 and 1982. In 1981 and 1982 the figures for hospital (inpatient and outpatient) and general practitioner patients were also analysed separately.

The table shows the percentage of isolates considered to be resistant to trimethoprim over the study period.

None of the organisms that were retested with a trimethoprim disc were found to be sensitive. During 1981 only four of 100 resistant isolates and during 1982 only 22 of 169 resistant isolates were moderately resistant.

All isolates resistant to trimethoprim before 1980 were also resistant to sulphonamide. Since then we have isolated an increasing number of strains resistant to trimethoprim and sensitive to sulphonamide; six during 1980, 11 during 1981, and 30 during 1982. Most (27) were isolated from general practice.

Comment

It is essential, when considering the prevalence of resistance, to compare like with like; only normally susceptible Gram negative urinary pathogens were included in this survey, the laboratory techniques were unchanged, the same period was studied each year, and there were no outbreaks of hospital cross infection during the study periods. Inevitably such figures, especially those for hospital patients, must include more than one isolation from some patients, but this factor is not likely to vary from year to year.

Percentage of normally susceptible Gram negative urinary pathogens resistant to trimethoprim. Figures in parentheses are numbers of isolates tested

	1978	1979	1980	1981	1982
Hospital (inpatient and outpatient)	NA	NA	NA	19 (326)	24 (381)
General practice	NA	NA	NA	7 (521)	15 (507)
Total	9 (709)	12 (821)	13 (794)	12 (847)	19 (888)

NA = Figure not available: hospital and general practice records analysed separately only in 1981 and 1982.

It appears that a plateau of resistance had been reached by 1979 (before trimethoprim was available alone). Our figure of 12% is in broad agreement with those from other centres in Great Britain at that time,[2 3] and suggests that the routine laboratory method used provides reasonably accurate results. In any case the method has not changed, and therefore the change in the findings is likely to be a true one.

One must wonder whether this sharp rise in resistance is related to the increasing use of trimethoprim alone. As a result of our experience with the emergence of *Staphylococcus epidermidis* infection in patients with catheters who were treated with trimethoprim[4] we have encouraged the use of co-trimoxazole in hospital. (Figures from this hospital pharmacy show that the ratio of the use of co-trimoxazole to trimethoprim is 16:1.) Trimethoprim has been widely promoted in general practice, however, where the level of resistance has more than doubled during the past year. Clearly in those hospitals which serve a local population there must be some overlap between hospital and general practice patients, and the rise in hospital resistance, after a plateau for three years, may be related to the use of trimethoprim in general practice. Furthermore, most of the increasing number of isolates resistant to trimethoprim but sensitive to sulphonamide came from general practice.

Lacey has recently reported no change in the level of resistance of *E coli* to trimethoprim in the hospitals of the King's Lynn Health District, where co-trimoxazole was completely replaced by trimethoprim in 1980.[5] His study concluded in January 1982 and did not include Gram negative pathogens other than *E coli*. His figures are therefore not comparable with the figures reported here.

Co-trimoxazole has been a highly effective agent for treatment of urinary infection for the past 14 years; if the use of trimethoprim alone is now resulting in increased resistance it is important that this should be recognised.

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Hypothermia during chemotherapy for Hodgkin's disease

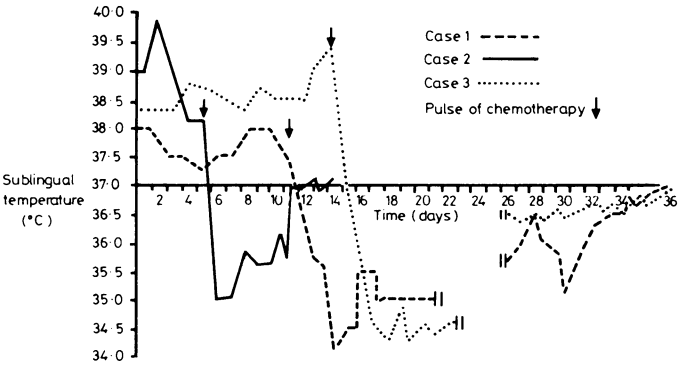
Fever is common in advanced Hodgkin's disease. We describe three patients with advanced Hodgkin's disease and fever who developed hypothermia during chemotherapy.

Case reports

Case 1—A 75 year old woman presented with stage IVB mixed cellularity Hodgkin's disease affecting the liver and a fever of 38°C. Bacteriological investigations gave negative results and chemotherapy was started with 10 mg vinblastine intravenously on day 1 followed by 14 days of chlorambucil 10 mg daily, prednisolone 40 mg daily, and procarbazine 50 mg thrice daily. On day 2 her temperature fell from 38°C to 35°C and on day 3 her rectal temperature was 34°C and remained low for 10 days (figure). Further chemotherapy with vinblastine and prednisolone was not associated with hypothermia.

Case 2—A 36 year old man presented with stage IVB mixed cellularity Hodgkin's disease in relapse. He had received outpatient chemotherapy with the same regimen as case 1, but relapsed one month after completing treatment, with sustained fever, lymphadenopathy, and liver enlargement. Chemotherapy was restarted with intravenous infusion of 30 mg doxorubicin, 10 mg bleomycin, 8 mg vinblastine, and methotrexate 250 mg/m² on day 1, with prednisolone 50 mg daily. His temperature, 38·5°C on admission, fell to 34°C and remained low for four days (figure). Unfortunately, six weeks after chemotherapy, he developed chickenpox and died with disseminated varicella infection. Necropsy showed hepatic Hodgkin's disease.

Case 3—A 34 year old woman presented with nodular sclerosing Hodgkin's disease in relapse. She had first been seen 15 months previously with clinical stage IA disease and had received mantle radiotherapy. Eight months later she relapsed with para-aortic node enlargement, which was treated with radiotherapy. At second relapse she had widespread disease affecting bone marrow, liver, and spleen. Chemotherapy was started using the regimen described for case 1. Within 24 hours her temperature fell from 38°C to 35°C and remained low for a week (figure). One week later she developed a right



Effect of chemotherapy on sublingual temperature of three patients with Hodgkin's disease.

hemiplegia and became drowsy. Computed tomography showed a contrast-enhancing lesion deep in the left hemisphere suggestive of intracerebral Hodgkin's disease. Radiotherapy produced no improvement and she died one month later.

Comment

Spontaneous hypothermia in Hodgkin's disease is rare.[1] Some patients with Hodgkin's disease develop hypothermia after administration of salicylates,[2] but none of our patients received these. There is one report of hypothermia in Hodgkin's disease after chemotherapy with mustine and vinblastine,[3] but the cytotoxics used here differed slightly and only vinblastine and prednisolone were common to all patients: hypothermia is not a recognised side effect of any of these drugs. Case 3 was later found to have intracerebral Hodgkin's disease, which could have affected hypothalamic function, but she was otherwise similar to the other patients.

The cause of fever in Hodgkin's disease in the absence of infection is unknown. Experiments have shown that a substance, "endogenous pyrogen," is produced by Kupffer's cells in rabbits in response to endotoxin. This is also produced in vitro by lymphoid tissue from