Prophylactic co-trimoxazole in biliary surgery

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Summary and conclusions

A double-blind study was conducted to test the prophylactic effect of a single dose of co-trimoxazole on the incidence of septic complications after elective cholecystectomy. Forty-eight patients received co-trimoxazole and 47 placebo. Wound sepsis occurred in 10 (21%) of the controls but in only 2 (4%) of the treated group, and the incidences of pulmonary complications were 49% (23 cases) and 19% (9) respectively. These differences were significant.

Wound sepsis after cholecystectomy occurs mostly in patients with infected bile. Co-trimoxazole given by intravenous infusion rapidly achieves a high concentration in the plasma and is effective against most biliary pathogens.

Introduction

Infective complications after biliary surgery are common. Some 30% of patients undergoing cholecystectomy have positive bile cultures^{1,2}; 20% develop a wound infection.^{2,3} There is a close correlation between the presence of bacteria in the bile and wound sepsis.⁴ Patients particularly at risk include the elderly, patients with stones in the common bile duct, and those undergoing emergency surgery.^{5,6} Pulmonary complications are also common after cholecystectomy.^{7,8} Retention of secretions due to hypoventilation, impaired cough reflex, and dehydration may lead to patchy atelectasis, particularly in smokers, the obese, and patients with a history of respiratory disease. Secondary infection may supervene.

We report the results of a double-blind clinical study of the effect of a single dose of co-trimoxazole on septic complications after elective cholecystectomy.

Patients and methods

Consecutive patients admitted for elective cholecystectomy were allocated at random to one of two groups. The treated group received

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10 ml co-trimoxazole (equivalent to 160 mg trimethoprim plus 800 mg sulphamethoxazole) in 250 ml physiological saline by intravenous infusion over 60 minutes before operation. The control group received 250 ml physiological saline only. The choice of abdominal incision, technique of cholecystectomy, and type of drainage used was at the discretion of the surgeon. Patients with obstructive jaundice were not included.

Samples of bile and venous blood were obtained at operation for bacteriological and co-trimoxazole assay. One observer (CM), who was unaware of which treatment the patients received, monitored the wounds daily. Wound sepsis was defined as the presence of pus, either discharging spontaneously or requiring drainage.⁹ Sepsis at drain sites was not included. Wound swabs were obtained when clinically indicated. Antibiotics were given postoperatively at the discretion of the clinician.

In addition, the incidence of pulmonary complications was assessed on the basis of cough, production of purulent sputum, persistently raised temperature, physical signs, and a routine chest radiograph on the third postoperative day.

Bacteriological specimens were cultured aerobically and anaerobically for 48 hours with 10% added carbon dioxide. Culture media used for bile and wound exudates were: 6% horse-blood agar, 6% horse-blood agar incorporating gentamicin sulphate 15 mg/l, MacConkey agar, and Robertson's cooked meat broth. Blood culture specimens were inoculated into brain-heart infusion broth and Robertson's cooked meat broth and subcultured at 48 hours and 10 days. Bacteria were identified by standard procedures.¹⁰

Concentrations of trimethoprim in plasma and bile were measured by a standard bioassay.¹¹ Sulphamethoxazole was assayed with the colorimetric technique of Bratton and Marshall.¹²

Results

Out of 101 patients who entered the study, six were excluded: four were given antibiotics at operation, one had a fatal pulmonary embolus on the sixth postoperative day, and one was found at laparotomy to have unsuspected widespread intra-abdominal carcinomatosis. Of the 95 patients evaluated, 48 received co-trimoxazole and 47 placebo. The two groups were comparable in age, sex, clinical presentation, ease and duration of operation, type of incision, and the incidence of risk factors.⁶ Choledochotomy was performed on three patients in each group; two of the controls and three patients in the treated group underwent appendicectomy. Nine patients in each group had a positive bile culture, coliforms and enterococci predominating (table I).

Wound sepsis occurred in 10 (21%) of the controls but in only 2 (4%) of the treated group ($P < 0.05$ —table II). Severe wound infections occurred only in the control group. Of the nine controls with positive bile cultures, three developed wound infections; none of the patients in the treated group with a positive bile culture developed wound sepsis. Thirty-four patients in each group had a radiologically functioning gall bladder; of these 10 patients in the control group and none in the treated group developed wound sepsis ($P < 0.005$). Five of the controls and one patient in the treated group developed bacteraemia during operation (table I). Residual intra-abdominal sepsis did not occur in either group.

Postoperative pulmonary complications occurred in 23 (49%)

TABLE I—Bacteriological isolations in control and treatment groups

	Bile		Blood		Wound	
	Control	Co-trimoxazole	Control	Co-trimoxazole	Control	Co-trimoxazole
Coliforms	4	5	1		3	
Streptococci	3	5	3		1	
Staphylococci	4	3		1	11*	
Clostridia	1		1		1	2*

*Includes skin commensals.

TABLE II—Infective complications occurring in control and treatment groups

	Control	Co-trimoxazole
No of patients	47	48
Wound sepsis	10 (21%)	2 (4%)*
Seropurulent	2	2
Purulent	8	9
Pulmonary complications	23 (49%)	9 (19%)†

*P < 0.05.

†P < 0.005.

of the controls but in only 9 (19%) of the treated patients ($P < 0.005$ —table II). Eighteen out of 26 smokers in the control group developed pulmonary complications as opposed to only five out of 20 in the treated group. Nine of the controls and three patients in the treated group received antibiotics postoperatively, mainly for chest infections. The mean duration of stay in hospital of patients who developed either wound or pulmonary complications was $12.2 \pm SE 0.7$ days compared with 10.3 ± 0.4 days for patients with an uncomplicated postoperative course ($P < 0.05$; unpaired Student's t test). Apart from two patients who developed macular rashes, no untoward side effects of co-trimoxazole were noted.

The concentrations of trimethoprim and sulphamethoxazole in plasma and bile are shown in figs 1 and 2. Plasma trimethoprim concentrations were at least twice the minimal inhibitory concentration for all *Escherichia coli* and 90% of *Streptococcus faecalis* strains. There was a striking difference between patients with functioning and non-functioning gall bladders in that patients with functioning gall bladders concentrated trimethoprim in the bile.

Concentrations of plasma sulphamethoxazole were at least twice the minimal inhibitory concentration for *E coli* but not for *Str faecalis*, whose resistance to sulphamethoxazole is well recognised. Sulphamethoxazole was not concentrated in bile.

Discussion

These results show that single-dose prophylactic co-trimoxazole significantly reduces septic complications after elective cholecystectomy. Wound sepsis is more common in

FIG 1—Trimethoprim concentrations in plasma, bile from functioning gall bladder, and bile from non-functioning gall bladder.

*Minimal inhibitory concentration for *Str faecalis*.²²†Minimal inhibitory concentration for *E coli*.²²

FIG 2—Sulphamethoxazole concentrations in plasma, bile from functioning gall bladder, and bile from non-functioning gall bladder.

*Minimal inhibitory concentration for *E coli*.²²

patients with infected bile. The choice of antibiotic for prophylactic use is therefore governed by the organisms found in the biliary tree, predominantly coliforms and streptococci. Fewer than half of these organisms are now sensitive to ampicillin and tetracycline.³ We find that the cephalosporin antibiotics are only marginally more effective. The widespread use of gentamicin as a routine prophylactic antibiotic has theoretical disadvantages. It is not effective against streptococci; while highly effective against coliform bacilli, extensive prophylactic use with attendant dangers of emerging resistance may diminish its usefulness in life-threatening sepsis. In contrast, co-trimoxazole is a safe, non-toxic antibiotic; after intravenous infusion it rapidly achieves high plasma concentrations, which persist for several hours. It is effective against the common biliary pathogens.

Our results show that adequate plasma concentrations of trimethoprim and sulphamethoxazole were achieved. Keighley argued that plasma concentrations are more important than bile concentrations in that gentamicin, which achieves good plasma concentrations but is poorly excreted in bile, reduces wound sepsis.¹³ Rifamide on the other hand can reach high concentrations in bile, but if plasma concentrations are not adequate this antibiotic is ineffective.¹⁴ Our studies have shown that trimethoprim but not sulphamethoxazole was concentrated in the bile of patients with radiologically functioning gall bladders, thereby altering the ratio of one part trimethoprim to 20 parts sulphamethoxazole in plasma to a 1:1 ratio. The significance of this in vivo is not clear, but it was in this group that the greatest fall in wound sepsis occurred. There may therefore be merit in using an antimicrobial agent that attains therapeutic concentrations in both plasma and bile.

The concept of short-term antibiotic prophylaxis is attractive. Indiscriminate prophylactic antibiotic administration over a prolonged period may encourage antibiotic-resistant organisms, superinfection, or toxicity.¹⁵ An adequate plasma concentration of antibiotic at surgery is critical¹⁶; antibiotics given solely after operation are ineffective.¹⁷ Short-term prophylaxis reduces wound sepsis in gastrointestinal surgery,¹⁸⁻²⁰ and a single dose of cephazolin is as effective as a five-day course in patients undergoing biliary surgery.²¹

In our study co-trimoxazole also reduced the incidence of pulmonary complications after cholecystectomy. Indeed, it appears to have an effect on postoperative chest complications

somewhat similar to that on wound infection. *Haemophilus influenzae* and *Str pneumoniae* are the common pathogens involved. Both are highly sensitive to co-trimoxazole and, interestingly, a single dose of co-trimoxazole appeared to provide clinical benefit. This finding is particularly relevant for patients with chronic respiratory disease and warrants further investigation.

The reduction in wound sepsis achieved with co-trimoxazole was significant. Only patients liable to have pathogenic bacteria in their bile at operation have been thought to require antibiotic cover.²⁻⁷ Several methods have been described whereby such patients might be recognised. These include identifying risk factors, using duodenal intubation, and intraoperative Gram staining.² Few centres, however, have time and resources for these measures. A single dose of co-trimoxazole covering the operative period provides a practical alternative. This reduces not only wound sepsis but also pulmonary complications.

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Epidemiology of adverse drug reactions to phenformin and metformin

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Summary and conclusions

Adverse drug reactions (ADRs) to phenformin and metformin reported to the Swedish Adverse Drug Reaction Committee during 1965-77 were analysed in relation to sales and prescription data. The biguanides accounted for 0.6% of all reported adverse drug reactions but for 6% of the fatal cases (all phenformin). Sixty-four ADRs to phenformin and eight to metformin were classified as causal relation "probable" or "not excluded." Fifty-one of these reactions (71%) were lactic acidosis, all but one being reactions to phenformin. After 1973 phenformin was prescribed less in Sweden and metformin became predominant. A nationwide prescription survey during 1975-6 disclosed no differences in age and sex between patients receiving phenformin and metformin. The mean daily doses prescribed in 1976 were 74 mg of phenformin and 1.5 g of metformin.

The numbers of ADRs to the two drugs reported during

1975-7 were related to use. The relative incidences of ADRs reported for phenformin and metformin did not differ. Significantly more cases of lactic acidosis and deaths were reported for phenformin.

Introduction

Biguanides affect lactate metabolism,¹ and several¹⁻³ but not all⁴ workers have found that phenformin is more potent than metformin. In most reported cases of lactic acidosis the patients had been treated with phenformin; few had received metformin or buformin.¹ This may reflect differences in the use of the drugs rather than true pharmacological differences. A sixfold variation was found in the total use of biguanides in seven European countries.⁴ Phenformin was the most-prescribed biguanide in five of these.

In our study, carried out in Sweden, we attempted to relate reports of adverse reactions (ADRs) to phenformin and metformin (the two biguanides sold in Sweden) to sales and prescription data.

Materials and methods

All reports sent to the Swedish Adverse Drug Reaction Committee are scrutinised by a medical officer, discussed by a working party, and settled by the full committee.⁵ In severe cases the complete medical record is obtained. The following classification is used by the committee: causal relation "probable," "not excluded," or "unlikely," or insufficient information available. Only one adverse reaction per person (the most severe) was included in this study. In 1975 it became obligatory to report suspicions of ADRs to drugs that were fatal or

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