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Short-term adverse effects of antibiotic prophylaxis for open-heart surgery

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ABSTRACT A study was made of the incidence of postoperative endocarditis and of septicaemia in early convalescence in 814 consecutive patients undergoing open-heart surgery. The results were related to the prophylactic antibiotic given to "cover" the operation. A subgroup of 150 patients was studied more intensively and the bacterial flora of the tracheal aspirates and catheter tips from these patients have been related to the antibiotics used. The results demonstrate that the use of a narrow spectrum agent (flucloxacillin) is associated with a modest change in bacterial flora at the two sites sampled, but that much more pronounced shifts in flora are found with a more broad spectrum agent (cephradine). The changes in flora have been related to the incidence of septicaemia in early convalescence, which was higher (7·7%) in the cephradine group than in the flucloxacillin group (0·9%). Since the overall incidence of prosthetic infection using flucloxacillin was acceptably low (0·49% of perfusions; 0·56% of valve insertions), it is concluded that narrow spectrum prophylaxis offers the better overall choice, at least until more objective comparisons are made.

The use of prophylactic antibiotics in open-heart surgery is now established practice, although formal demonstrations of the efficacy of this technique are remarkably few. Indeed, one comparison which included a control group receiving no antibiotic concluded that the problems resulting from the drugs might outweigh their theoretical benefits[1]. Even less evidence exists for the relative merits of the many different regimens advocated by different units, although limited comparisons have been made. One recent review concluded that large doses of iso-oxazolyl penicillins—for instance, oxacillin, methicillin, or cloxacillin—or cephalothin, given immediately before and for a short time after operation would satisfy the needs currently identified.[2] More recently a regimen consisting of penicillin, flucloxacillin, and gentamicin has been advocated, although no formal comparisons with other regimens were made.[3]

One approach to this problem, short of conducting a proper clinical trial to look for differences in the eventual incidence of postoperative endocarditis, is to examine the impact of the prophylaxis on the reservoirs from which it is thought the endocarditis arises. An incidental comparison of flucloxacillin and cephradine has been made during a study on the microbiology of perfusion blood,[4] although it was also concluded in that study that perfusion blood might not be the most important of the reservoirs attendant on cardiac surgery. This present report concerns the impact of the same two drugs on the isolation rates of bacteria, especially coagulase-negative staphylococci and diphtheroids, from the tips of intravenous and intra-arterial catheters, a source commonly accepted as important in the genesis of postoperative endocarditis. Another very relevant point regarding chemoprophylaxis is the incidental effects of the drugs used. Thus, if the antibiotic to be used produces unacceptable pharmacological or microbiological side-effects in the short term, its possible benefits against endocarditis in the long term might be outweighed. Accordingly, in this study, the alterations in tracheal aspirate flora produced by the two antibiotics have been studied, and the incidence of both early prosthetic valve endocarditis and postoperative septicaemia have been related to the regimen employed.

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Methods

The patients studied form a subpopulation of the 814 patients undergoing open-heart surgery in Freeman Hospital between April 1978 and December 1979. The incidence of early endocarditis was ascertained for the total series (814) and was defined as infection of the intracardiac operative site presenting within three months of operation. The incidence of postoperative septicaemia (occurring between the date of operation and the date of hospital discharge) was also assessed, only cases proven by blood culture being recorded. Within the total series (814 patients), 150 consecutive patients were studied on an intensive basis. Of the 150 patients, 90 received flucloxacillin as prophylaxis, given as 2 g iv at induction of anaesthesia to cover the operation, and continued thereafter as 500 mg iv six hourly. Forty-six patients received cephradine, given as 1 g iv at induction of anaesthesia and 500 mg iv six hourly thereafter. Proportionately lower doses were given in children. The patients receiving flucloxacillin prophylaxis comprised 65 adults mean age 51·2 years; range 20–70 years) and 25 children (mean age 3·42; range 7 months–14 years). Of the 90 operative procedures, 59 were for valve replacement. All of the 46 patients receiving cephradine prophylaxis were adult (mean age 54·6 years; range 41–66 years) and of the 46 operations performed, 12 were for valve replacement. Allocation to these two groups depended purely upon routine referral within the hospital and surrounding area, it being the custom of two cardiac surgeons to use flucloxacillin prophylaxis, and the custom of a third to use cephradine. Eleven patients were already receiving antibiotics for the treatment of bacterial endocarditis (none of them postoperative endocarditis) and the details of these are seen in table 1. Finally, three patients began routine prophylaxis with flucloxacillin, but immediately after operation developed liver dysfunction and as part of the treatment instituted for this complication received oral neomycin (up to 4 g per day).

Tracheal suction specimens were obtained at the end of a session of physiotherapy, and were collected into a suction trap before being sent to the laboratory. The resultant specimens were there cultured in a routine manner. Organisms isolated were classified into *Haemophilus species* (speciation into *Haemophilus influenzae, Haemophilus parainfluenzae* and so on was also performed), "coliforms" (a collective term embracing such organisms as *Proteus, Klebsiella, Pseudomonas, Escherichia coli*, and so on) and yeasts. No more than one tracheal suction specimen was obtained per day, and, for the majority of patients, this meant that only one specimen was received. In the small number of patients requiring prolonged intensive care further specimens were taken daily.

Tips of intravenous and intra-arterial catheters were obtained and cultured as described previously.[5]

Results

In table 1 the results of the tracheal secretion studies are presented. It is seen that in the groups receiving flucloxacillin alone or cephradine alone a short stay in intensive care was the rule (91 specimens from 90 patients and 49 from 46 patients respectively) whereas in patients receiving additional antibiotics a longer stay is implied since the ratio of specimens to patients is higher. This reflects the underlying conditions (pre-existing endocarditis and so on) from which these latter

Table 1 *Incidence of isolation of various organisms from cultures of tracheal secretion in patients undergoing open-heart surgery, related to the antibiotic being administered (apparent discrepancies in totals are the result of more than one organism being isolated from one specimen).*

Antibiotic	*Number of patients*	*Number of specimens*	*No growth*	*Haemophilus species**	*Coliforms†*	*Yeasts*
Fluclox	90	91	57 (63%)	30 (33%)	5 (5·5%)	—
Cephradine	46	49	26 (53%)	13 (27%)	11 (22%)	—
Fluclox+neomycin	3	15	4	1	11	—
Fluclox+ampicillin	3	8	1	—	7	—
Ampicillin	2	16	4	—	11	1
Fluclox+gentamicin	1	2	1	—	1	—
Ampicillin+gentamicin	1	2	2	—	—	—
Ampicillin+gentamicin+ fluclox	4	7	4	2	2	2
Totals	150	190	99	46 (24%)	48 (25%)	3 (1·6%)

*Of the 46 Haemophilus species isolated 36 (78%) were *Haemophilus parainfluenzae*, the remainder being *Haemophilus influenzae*.
†The term 'coliform' is used as a collective name for facultatively anaerobic Gram negative bacilli—for example, *Escherichia coli, Proteus, Klebsiella, Pseudomonas*, and so on.

patients suffered. It is further seen that with flucloxacillin alone the disturbance to the tracheal flora is minimal. The only organisms commonly isolated were *Haemophilus species*. An interesting point is that the majority of these isolates proved on further investigation to be *Haemophilus parainfluenzae*. Coliform organisms were found in only 5·5% of tracheal specimens from patients receiving flucloxacillin alone.

With an increasingly broad spectrum of antibiotic the incidence of resistant organisms (coliforms and yeasts) rises progressively, being 22% with cephradine, and possibly higher with the mixtures of antibiotics given to some other patients.

In table 2 the catheter tip culture results show that the overall isolation rate for patients receiving flucloxacillin or cephradine is very similar (12·6% and 14·4%, respectively), but that coliform organisms were more commonly found in the cephradine group. Coagulase-negative staphylococci were found in 10·9% of the flucloxacillin group and 8·7% of the cephradine group. Yeasts were found only once in a catheter tip culture, being isolated from a patient given ampicillin, gentamicin, and flucloxacillin.

Table 3 shows the incidence of "postoperative endocarditis" in all 814 patients undergoing bypass between April 1978 and December 1979. The incidence is 0·49%. When related to valve insertion the incidence is 0·56%. In contrast, the incidence of septicaemia in patients given flucloxacillin prophylaxis is 0·9%, whereas in those given cephradine the incidence is 7·69%.

Table 3 *Incidence of postoperative endocarditis and septicaemia of convalescence in 814 consecutive patients, related to the prophylactic antibiotic used.*

Number of perfusions	*Number of valve replacements*	*Number of infections of prosthetic material*	*Number of prosthetic valve infections*
814	353	4 (0·49% of perfusions)	2 (0·56% of valve replacements)
*Patients given flucloxacillin**	*Number with septicaemia*	*Patients given cephradine*	*Number with septicaemia*
762	7 (0·9%)	52	4 (7·7%)
Organisms (A) *H parainfluenzae* (A+2C) *E coli* (3) (A) *P mirabilis* (C) *K aerogenes* (A) *P aeruginosa*		*Organisms* (2A) *P aeruginosa* (2) (A) *K aerogenes* (A) *P morgani*	

* In 11 instances in which penicillin allergy was encountered lincomycin was substituted.
(A)=adult, (C)=child

Discussion

The results of this study exemplify the points raised in the introductory section of this paper. It is clear that when the two groups studied intensively (90 receiving flucloxacillin, 46 receiving cephradine) are compared with respect to the tracheal aspirate flora, a shift of flora towards antibiotic-resistant organisms of "'coliform" type is found in the cephradine group. This colonisation of the patients receiving broad-spectrum prophylaxis may well be found elsewhere in the body, for instance in the gut and on the skin. That this may be so is suggested by the finding that coliform bacilli were found more commonly in the catheter tip cultures of the cephradine group than the flucloxacillin group. Finally, the higher incidence of postoperative Gram negative septicaemia in the patients receiving cephradine would suggest that this colonisation may ultimately be expressed as clinical sepsis. In addition, it should be noted that of the seven organisms isolated from septicaemias in the flucloxacillin group, three were *Escherichia coli* whereas this organism did not

Table 2 *The isolation rate of various organisms from catheter tips in 150 patients, related to the antibiotic being administered.*

Antibiotic	*Number of patients*	*Number of specimens**	*CNS*	*Streps*	*Coliforms*	*Yeasts*
Fluclox	90	229	25 (10·9%)	3 (1·3%)	1 (0·4%)	—
Cephradine	46	138	12 (8·7%)	4 (2·9%)	4 (2·9%)†	—
Fluclox+neomycin	3	8	2	1	1	—
Fluclox+ampicillin	3	5	1	—	—	—
Ampicillin	2	4	1	—	—	—
Fluclox+gentamicin	1	—	—	—	—	—
Ampicillin+gentamicin	1	—	—	—	—	—
Ampicillin+gentamicin+ fluclox	4	9	1	—	—	1
Totals	150	393	42 (10·7%)	8 (2%)	6 (0·5%)	1 (0·25%)

CNS=Coagulase-negative staphylococci; coliforms=facultatively anaerobic Gram negative bacilli—for example, E coli, Proteus and so on).
*Number of specimens is greater than number of patients since each patient yielded several catheters (eg. left atrial line, right atrial line etc). However, no patient yielded more than one specimen of each.
†The four isolates are from four different patients.

figure at all in the isolates from the cephradine group. In terms of antibiotic resistance the organisms found can be placed in the rank order—*E coli, Proteus mirabilis, Proteus morgani, Klebsiella aerogenes, Pseudomonas aeruginosa*—this order reflecting an increasing degree of antibiotic resistance. Thus, not only is the incidence of coliform septicaemia less in the flucloxacillin group, but the strains isolated from that group are of types more sensitive to antibiotics.

However, before this important conclusion can be drawn, it is pertinent to examine some of the shortcomings of this study. Firstly, in the intensively investigated groups, 90 patients were compared with 46. Clearly, patients were not randomly allocated to the two groups by a conscious mechanism, and, indeed, the flucloxacillin group is in fact two groups—adults and children. It is, therefore, important to question the results on this basis. Similarly, the emphasis on the types of procedure performed on the two groups of patients was different—in the flucloxacillin valve replacements outnumbered non-valve procedures, whereas in the cephradine group the reverse was true.

There is no reason to suppose within the referral system by which the patients came to be in the different groups an unfair bias on infection towards the cephradine group. Indeed, since the flucloxacillin group contains all the children, it could be argued that the reverse is so, children (particularly infants) being more susceptible to coliform infections than adolescents and adults. Correcting for this factor would actually enhance the difference between the two groups. Even if all the colonisation and infection by coliforms were restricted to the adults in the flucloxacillin group (which it is not), a considerable discrepancy would still remain.

It might be argued that postoperative care differs, either in content or duration. In fact both groups underwent postoperative care under identical circumstances, the management being largely standardised, and since non-valve surgery predominated in the cephradine group, it is unlikely that the duration of intensive care was longer than in the flucloxacillin group. It is already clear that in the adult members of the two groups the mean age is not markedly against the cephradine group.

Thus, while it must be admitted that this study, being incidental, is not in any way offering proof that broad-spectrum prophylaxis for open-heart surgery may cause an increased morbidity and mortality in the immediate postoperative period caused by coliform bacilli promoted by the prophylaxis, it does appear that this is a strong possibility. The true answer can only be derived from a properly conducted trial. In the meantime, however, it would seem prudent to caution those advocates of broad-spectrum chemoprophylaxis that evaluation of such regimens must include an assessment of the number and types of infections arising in the first month after surgery as well as the incidence of prosthetic infection. If the former figure is rising more than the latter figure is falling, such prophylaxis may be inadvisable.

Finally, the results of this study also compare the incidence of isolation of coagulase-negative staphylococci from catheter tips in patients given cephradine or flucloxacillin. There is little difference in the isolation rate of coagulase-negative staphylococci from catheter tips in the two groups, but what difference does exist is in favour of cephradine (8·7% compared with 10·9%). It may be that this could ultimately be expressed as a lower incidence of prosthetic endocarditis—indeed, none of the 52 patients given cephradine prophylaxis in this hospital has developed the condition—but the numbers in this series are too small to assess this realistically. However, the figure derived from the total series for the incidence of early prosthetic endocarditis using routine flucloxacillin prophylaxis (0·49%) is valid, being derived from data on 762 patients over nearly two years. This figure is acceptably low. It is, therefore, suggested that advocates of broad-spectrum antibiotic prophylaxis report not only the long-term incidence of endocarditis but also the incidence and types of infection occurring within one month of operation. Finally, it is hoped that at some stage a properly controlled trial of broad-spectrum versus narrow-spectrum chemoprophylaxis will be conducted in which both long-term and short-term effects will be documented.

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