Prophylactic antibiotics for cardiac pacemaker implantation

A prospective trial

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SUMMARY A prospective trial was conducted to assess the value of prophylactic antibiotic treatment in preventing postoperative infection of permanent transvenous pacemaker systems. Four hundred and thirty-one patients were randomly allocated to treatment (234) or no-treatment (197) groups. Treated patients received systemic benzylpenicillin and flucloxacillin just before operation and one and six hours afterwards.

Nine primary generator pocket infections occurred without evidence of wound dehiscence or skin erosion. Seven infections were in untreated patients and two in treated patients. Antibiotic prophylaxis diminishes the risk of infection after pacemaker implantations.

Pacemaker generator pocket infection has remained a major complication of implantation since the first units were used 25 years ago. Sepsis rates in recent series have varied between 0.3%¹ and 12.6%.²

It is common practice to employ prophylactic antibiotic treatment at the time of implantation in the expectation that the number of infections will be reduced. Some retrospective analyses of uncontrolled series have supported this view³ but Siddons and Nowak⁴ have suggested that the protective effect is small. Furthermore there is no uniformity of practice in the use of antibiotics. In these circumstances there was clearly a need for a prospective trial to evaluate the effectiveness of prophylactic antibiotic treatment at the time of pacemaker implantation.

Subjects

We studied all patients who underwent elective permanent pacemaker implantation (new systems) or generator changes at the Radcliffe Infirmary, Oxford, between July 1976 and December 1978. The data were analysed in October 1979 and the follow-up period therefore ranges between nine and 40 months. Patients were excluded from the study only if they were already being given antibiotic treatment for other reasons, or if wound infection was present at the site of a temporary transvenous pacemaker. All

non-elective reoperations, such as the repositioning of previously implanted electrodes, were studied separately.

Four hundred and thirty-one patients were randomly allocated to treatment or no-treatment groups with the single exception of 13 patients who reported allergy to penicillin and who did not receive antibiotics. The patients were allocated according to the last digit of their hospital record number: odd numbers received treatment and even numbers did not.

The antibiotic regimen was: flucloxacillin 1 g together with benzylpenicillin 600 mg intramuscularly, one hour before operation one hour and six hours after operation.

All operations were carried out under local anaesthesia after premedication with either intravenous diazepam or morphine sulphate and droperidol. All procedures took place in the same operating theatre using standard instrument packs, and aseptic technique. This theatre was used on other occasions for minor surgical procedures. Chlorhexidine 4% was used for hand cleansing. Providone-iodine 10% aqueous solution was used for skin preparation on the night before the operation and on the morning of operation, and was followed by providone-iodine 7.5% with surfactants at the time of operation.⁵ All new systems consisted of standard intravenous electrodes attached to subcutaneous or subfascial generators. Cephalic, percutaneous,

subclavian,⁷ or occasionally external jugular veins were used for insertion of the electrodes. After implantation subcutaneous tissues were sutured with catgut and the skin closed with either interrupted silk sutures or continuous subcuticular polyglycolic acid. Wounds were painted with gentian violet. Drains and local antibiotics or antiseptic solutions were not used. At generator changes, the original pouches were reused.

Patients were discharged three to five days after a successful operation. Implantation sites were routinely inspected after one month and one year at a pacemaker clinic.

DEFINITION OF INFECTION

We concluded that infection was present either (1) if a patient had a raised oral temperature of 37.5°C on two or more occasions on or after the third postoperative day together with evidence of acute inflammation around the generator and of pus or bacteria in the generator pouch, or (2) if frank pus was found in a generator pocket (even in the absence of fever or inflammation). Late infections which followed as a result of primary wound dehiscence or erosion of the generator or electrode through the skin were excluded from the analysis. At the time of analysis, the assessor was aware whether or not the patient had been treated.

DATA ANALYSIS

Student's unpaired *t* test, the χ^2 test, and Fisher's exact test were used for statistical comparisons. Significance was assumed at the value $p < 0.05$.

Results

(1) PATIENTS

Four hundred and forty-five patients fulfilled the criteria for entry to the study and the results of 431 cases (97%) are reported here. Of the remaining 14, eight died within one month of implantation, and the follow up notes of six were inadequate for assessment. There was no evidence of infection in any of these cases, and no reoperations took place. No complications of the antibiotic therapy were reported. The period of follow up varied between nine and 40 months, and the average length of follow up was identical for the treated and untreated groups at 22.8 months.

(2) ANTIBIOTIC AND NO-ANTIBIOTIC GROUPS

Of the 431 patients who were randomly allocated to treatment, 234 received antibiotics and 197 did not. Two hundred and eighty-six patients had new implantations and 145 generator changes. Retrospective analysis showed that the two groups were well

matched for a large number of variables which we considered might have had a bearing on the outcome of the trial (Table 1) and there were no significant differences between them.

We recorded the nature and prevalence of all diseases which our patients had in addition to their primary diagnosis; they were similar in the two groups (43.2% and 44.2%). Similarly, examination of the factors we thought most likely to favour infection (that is diabetes mellitus, corticosteroid or anti-coagulant therapy, and carcinoma) showed that 25 patients in the no-treatment group had these risk factors (12.7%) compared with 22 in the treated group (9.4%; $p > 0.5$).

The rates of *non-infective* complications after pacemaker implantation were similar ($p = 0.1$). The reoperation rate for complications other than infection was 20.9% (53 patients) in the treatment group and 18.8% (37 patients) in the no treatment group, ($p > 0.05$).

There were two main reasons for this high intervention rate. First, we used a large number of a type of electrode which we subsequently found to have a displacement rate of about 25%. Second, in common with other centres, we had to replace many generators of one particular type because of premature failure.

(3) POSTOPERATIVE FEVER

We chose late postoperative fever to indicate infection since we noted, as have others,⁸ that many patients who have otherwise uncomplicated recoveries from generator implantation demonstrate brisk but short lasting postoperative fever. We studied this phenomenon further in a randomly selected sample of 150 patients from each of the two groups and found that 66% of patients in each group had a postoperative fever, but that only 10 of these 300 had a temperature greater than 37.5°C by the third postoperative day. Only four of these 10 had a further raised temperature, and in all the wound was normal and recovery subsequently uneventful.

Early postoperative fever was more often seen after new system implantations (153/216, 70.8%) than after generator box changes (43/84, 51.2%; $p < 0.002$).

(4) INFECTIONS

Among the 431 patients who were randomly allocated to treatment or no-treatment regimens, nine cases (2.1%) became infected after a single elective operation, and in each case without prior wound dehiscence or erosion (Table 2). Seven infections occurred after new implantations (2.5%) and two after generator changes (1.4%; $p > 0.5$ by exact test).

Six infections occurred early within two months of operation (cases 1 to 6, "early infections") and were accompanied by evidence of acute inflammation

Table 1 Comparison of characteristics of patients and operation details for 431 entrants to prophylactic antibiotic trial

(a) Diagnosis			(b) Age (y)		
	AB+	AB-		AB+	AB-
(1) Congenital	5	2	(1) <20	1	0
(2) Rheumatic	5	5	(2) 21-40	12	12
(3) IHD	27	20	(3) 41-60	28	20
(4) Idiopathic CHB	139	120	(4) 61-80	140	120
(5) Sinoatrial disease	49	44	(5) >80	53	45
(6) Other	10	6			
$\chi^2=8.27$ (p>0.05)			$\chi^2=8.76$ (p>0.05)		
(c) Operators			(d) Operation date (6 monthly periods)		
	AB+	AB-		AB+	AB-
(1)	30	26	(1)	41	34
(2)	46	43	(2)	52	40
(3)	57	35	(3)	37	44
(4)	31	32	(4)	60	36
(5)	60	47	(5)	44	42
(6)	10	14			
$\chi^2=4.77$ (p>0.05)			$\chi^2=5.96$ (p>0.1)		
(e) Generator type			(f) Operation details		
	AB+	AB-		AB+	AB-
(1) Devices	62	60	(1) New implant	155	131
(2) ELA	30	26	(2) Box change	79	66
(3) LEM	58	42	(3) Pectoral box	220	184
(4) Medtronic	26	13	(4) Abdominal box	14	13
(5) Vitatron	20	22	(New implants)		
(6) Teletronics	31	30	(5) Pectoral vein	123	98
(7) Other	7	4	(6) Other veins	32	33
			(7) Right side	73	52
			(8) Left side	82	79
$\chi^2=8.93$ (p>0.1)			p>0.05		

Note: 234 patients received antibiotics (AB+) and 197 did not (AB-). There were no significant differences for any of the variables listed between their distributions in the two groups.

Table 2 Infections after pacemaker implantation

Case No.	age (y)	Opn	AB	Interval (d)	Inflam.	Abnormal fever		Swab microsc.	Swab culture	WCC ($\times 10^9/\mu\text{l}$)	Comment
						First week	Late				
1	49	BC	No	7	+	+	N/A	Pus, G+cocci	<i>S. albus</i>	13.0	PI 29%; Pen. sens.
2	63	New	No	10	+	0	+	Pus, G+cocci	<i>S. aureus</i>	8.8	Pen. sens.
3	83	New	No	13	+	0	+	Pus, G+cocci	<i>S. aureus</i>	10.0	Diabetic; Pen. sens.
4	88	New	No	14	+	0	+	Pus	-ve	9.9	
5	62	New	No	30	+	0	+	Pus	<i>S. aureus</i>	10.3	
6	64	New	No	45	+	0	+	Pus, G+cocci	<i>S. aureus</i>	9.7	
				Interval (mth)							
7	62	BC	Yes	5	0	0	0	Pus, G+cocci	-ve	9.5	
8	66	New	Yes	8	+	0	+	Pus, G+cocci	-ve	N/D	
9	70	New	No	23	0	0	0	Pus	-ve	7.0	

Abbreviations: Opn, type of operation; BC, generator box change; New, new system implantation; Interval, time from operation to diagnosis of infection; Inflam., presence of inflammation around generator; Swab microsc. and swab culture, results of examination of bacteriological samples from generator pouch; P/S, P/R, organism penicillin sensitive (S) or resistant (R); N/A, not applicable; N/D, not done; PI, prothrombin index for patient on anticoagulants; Pen. sens., patient reported penicillin sensitivity. G+ = Gram positive. Note that antibiotics were given to only two of these nine patients.

around the generator pouch. Three cases presented later (cases 7 to 9) and without local inflammation. In seven cases abnormal fever was present, but in only one (case 1) was this in the first postoperative week.

In all cases swabs or aspirates from the generator pouches were purulent, and in six, Gram positive cocci were seen on microscopy. Swab cultures were positive in five instances (despite the concurrent administration of antibiotics), the organism being *Staphylococcus aureus* in four and *Staphylococcus albus* in one. Three patients were allergic to penicillin, and one of these was being treated with anticoagulants. Another patient was a diabetic on oral hypoglycaemic drugs.

Two of the patients whose systems became infected had received antibiotics, and seven had not. This represents a significant difference between the overall outcome of the treated and untreated groups (2/232 vs. 7/190, one-tailed $p=0.04$ by exact test).

Discussion

(1) ROLE OF ANTIBIOTIC PROPHYLAXIS IN REDUCING PACEMAKER INFECTIONS

Pacemaker generator pocket infection represents a serious complication of pacemaker insertion especially since it usually necessitates removal of the whole system and reinsertion of a new one. Rettig *et al.*⁹ have reported a 25% mortality from infected electrodes in 21 patients from an original group of 1734. Infections can arise in a number of ways (Table 3), and it is evident that some of these, especially deep infections after wound dehiscence or erosion of either the electrode or generator through the skin, will not

be affected by antibiotic treatment. It is also clear that this treatment will not prevent infection occurring in a system because of persistent bacteraemia from another source. Thus, the rationale of prophylactic therapy in this context is that it might reduce the chance of infection occurring as a result of wound contamination at surgery.

The problem of preventing both early and late infection in hip prostheses is similar to that presented by pacemakers. Infection rates of about 5% were reported in early series using the Charnley prosthesis,¹⁰ but more recent work has shown firstly that sterile theatre air systems can reduce this to about 1%, and secondly that prophylactic antibiotics given systemically before and just after operations can reduce the infection rate to about the same level.¹¹

The use of preoperative as well as postoperative treatment receives additional support from the animal model work of Burke¹² who has shown the superiority of antibiotic pretreatment compared with postoperative treatment in limiting experimentally induced staphylococcal wound infections. These were the organisms found to cause infection in our series, and are the commonest pathogens in others.^{13 14}

(2) PREVIOUS SURVEYS OF PACEMAKER INFECTION

Earlier retrospective surveys of pacemaker implantation series indicated that the total surgical complication rate, including erosions and wound infections, was about 5%.^{4 14} We have reviewed 18 other series published between 1973 and 1979.^{3 4 13-28}

In eight reports the data allowed exclusion of generator induced skin erosion. We found that the mean infection rate for 9739 procedures (including some non-elective reoperations) was 2.9%. The seven series in this review in which antibiotics were always used seemed to have a lower infection rate (106 in 4579 procedures, 2.31%), than the six in which they were never used (71/2190, 3.24%; $p<0.05$). In only three large series, however,^{4 13 22} are there data on the infection rates with and without antibiotics from the same unit, and the mean rates are then nearly identical (36/1366, 2.75% and 20/724, 2.73%; $p<0.6$). Retrospective comparisons such as this, however, cannot be used confidently as evidence for or against antibiotic prophylaxis, particularly as the reports contain few data about the populations studied.

(3) DIAGNOSIS OF INFECTION

Analysis of the temperature charts on uninfected cases showed that raised body temperature was a common occurrence at implantation (day 0) and for two days afterwards.

Fever beyond the second postoperative day was seen in seven out of nine infected cases in this series

Table 3 Causes of pacemaker pocket infections

Cause	Affected by
(1) Wound contamination at surgery	Skin preparation Equipment preoperative technique Fluid around generator
(2) Blood borne pathogens	Sepsis elsewhere Old systems Temporary pacing electrodes
(3) Wound breakdown	Tissue healing Operative technique
(4) System erosion	Method of insertion Tissue healing Body build Generator size
(5) Diminished antimicrobial defences	Any of 1 to 4

and inflammation around the generator was seen in all of these.

In two cases, we diagnosed infection because of pus in the generator pocket (cases 7 and 9), albeit without fever or inflammation. This finding was unexpected, and occurred in each case some months after the original operation. We felt that the presence of pus and organisms was evidence of generator pocket infection rather than a "foreign body" reaction and accordingly have included them in the analysis. Other authors¹⁶ have reported the frequent presence of sterile effusions found at box change, but there have been fewer reports of purulent fluid indicating prior or active infection in the pouch.²⁰

(4) PENICILLIN HYPERSENSITIVITY

Thirteen patients (2.6%) reported penicillin allergy. None received antibiotics. Three became infected and, in addition to these, two more had delayed wound healing. It is possible that the allergy to penicillin and therefore putative atopy is associated with a predisposition to react abnormally to the foreign body of the implant and therefore to increase the likelihood of infection. We have, however, no evidence to support this speculation, and prick tests were not performed. There were no instances where the box sites were surrounded by abnormal erythema and there was no difference between the temperature profile of the 10 patients who were allergic to penicillin and did not develop infection and the whole untreated group.

(5) HIGH RISK PATIENTS

We supposed that the presence of "intercurrent" disease in addition to the primary pathology which needed treatment by pacing would adversely affect the postoperative healing in some cases. When all additional diagnoses were considered there was inconclusive evidence that this was so. Though 67% (6) of the infected patients had another disease, there was no significant difference between the infection rate in patients with another disease (6/186: 3.2%), and the others (3/245, 1.2%; $\chi^2=1.21$; $p>0.5$).

Particular factors which we thought would be even more strongly associated with adverse predisposition were diabetes mellitus, carcinoma, steroid therapy, and anticoagulant therapy. Forty-seven patients had these factors and two systems were infected. This incidence of 4.2% compares with 7/384 (1.8%) among patients without these factors – again indicating a slightly, but not significantly increased infection risk ($p>0.4$; exact test).

(6) EFFECT OF PROPHYLACTIC ANTIBIOTICS

The results of this study in which seven infections occurred in untreated patients compared with two in

treated patients support the conclusion that prophylactic antibiotics reduce the incidence of infection in pacemaker generator pockets. It is noticeable, however, that whereas of the six "early infections" occurring within two months of operation, and accompanied by acute inflammation, none was in treated patients ($p=0.01$), of the three infections which presented later, two were in treated patients (NS). It thus appears that the principal effect of antibiotic treatment is to reduce the number of acute early infections. It is possible then to argue that prophylactic antibiotics may just delay the presentation of some preoperative infections and not prevent them altogether, and that this is an undesirable effect of treatment. Our data, however, do not show a substantial excess of treated patients in the late infections group, and because there are significantly less infections overall in treated patients, we conclude that the administration of prophylactic antibiotics at the time of pacemaker implantation is beneficial.

Currently the first procedure infection rate at Oxford is less than 0.5%. This compares favourably with the infection rate in the years before the trial of 3.8%.²⁹ From our data we calculate that if prophylactic antibiotics are given to all patients in our unit, we should reduce the number of infections by three per 100 operations, compared with a non-antibiotic policy. If we treated only "high-risk" patients, we should still have an additional two infections per 100 operations, compared with the expected numbers if all patients were treated.

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