Prophylaxis of endocarditis

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ABSTRACT

For a long time it has been known that bacteraemias caused by medical or dental procedures may cause endocarditis in patients with specific types of congenital or acquired heart disease. In the 1940s it was thought that the administration of antibiotics before such procedures would prevent endocarditis. However, the beneficial effect of this preventive measure on the incidence of endocarditis did not live up to its expectations. Quite soon it became obvious that prophylaxis was not 100% efficacious in man, although it did prevent endocarditis in animals. A controlled study into the protective effect of prophylaxis in humans has never been carried out. In the last decade it has become clear from case-control studies that endocarditis prophylaxis is not a very effective preventive measure but that it reduces an already small risk even further. In this article the theoretical background of endocarditis prophylaxis and possible explanations for its lack of effect are discussed.

INTRODUCTION

Adjusted for sex and age, the incidence rate of endocarditis is 19 per million persons per year (95% CI: 10.5 to 27.5) in the Netherlands. There is a significant increase in the incidence rate with age. Male sex is also a risk factor. The crude incidence rate ratio is 1.6 for men versus women. Before the introduction of antibacterial chemotherapy, endocarditis was uniformly fatal. To this day the disease leads to a high morbidity and mortality, despite modern antibacterial and surgical treatment. Individuals with specific congenital or acquired heart disease are at an increased risk of developing endocarditis. Prevention of the disease in these patients is a long-cherished desire. As Libman put it in 1925: 'While a remedy for the disease is a great desideratum, it is even more important that it be prevented. Even if we could overcome the infection, there is left the danger of anaemia, nephritis, myocardial insufficiency, splenic disease, embolism and increasing damage to the valves'. Soon after the introduction of chemotherapeutics in the 1930s, prophylaxis for endocarditis was introduced. Unfortunately, the effect of this preventive measure on the incidence of endocarditis has not lived up to its expectations. In this article the theoretical background of endocarditis prophylaxis and possible explanations for its lack of effect will be discussed.

BACKGROUND

Around the turn of the 19th century it had become obvious that invasion of the blood by bacteria was a requisite for the development of endocarditis, and that any factor leading to a bacteraemia might cause onset of the disease. The relevance of antecedent heart disease in the causation of endocarditis was also perceived, as was the temporal association between endocarditis and invasive healthcare procedures. Cases were reported in which surgical intervention in the oral cavity could be related to the development of endocarditis. Furthermore, it was demonstrated that bacteraemia could occur during surgery, particularly of the mouth and throat. Other authors pointed to the genital-urinary tract and to wounds as potential sources of bacteraemia. Over the years almost every conceivable
healthcare procedure was added to the list of culprits. Horder was, in 1909, the first to suggest prophylactic actions. He noted that subacute endocarditis was usually caused by streptococci ‘of the types found in normal faeces and in normal saliva’. He also observed that acute disease caused by more virulent micro-organisms such as Staphylococcus aureus occurred more often in patients with healthy valves. Thus, prophylactic measures would only apply to the subacute cases and he suggested that ‘oral sepsis’ should be treated, and constipation should be avoided in patients known to have heart disease.

In the 1930s chemotherapeutic agents were introduced and used against a variety of infectious diseases. The potential of cure by chemotherapeutics led to speculations on their use, as agents to protect susceptible individuals against endocarditis in situations prone to cause bacteraemia. In 1941 a study on the efficacy of prophylaxis with sulphanilamide for the prevention of rheumatic fever was published. In this study two patients in the control group developed endocarditis versus none of the patients in the sulphanilamide group. These authors also hypothesised in their discussion that sulphanilamide might prevent bacterial endocarditis. This approach seemed self-evident and from the 1940s onwards prophylaxis was recommended in those situations likely to be associated with bacteraemia. In 1945 Clement and Montgomery reported a case in which sulphadiazine prophylaxis failed. Glaser et al. cited five examples of the development of endocarditis after penicillin prophylaxis in 1948. Other reports on prophylaxis failure followed. The problems of prophylaxis were critically discussed in 1954 by Finland, in the New England Journal of Medicine. He stated that no proof existed for the beneficial effect of prophylaxis and that more data were needed before prophylaxis could properly be evaluated. It would take several decades before the beginning of an answer to this critique was formulated.

**EFFICACY OF PROPHYLAXIS IN ANIMALS**

In 1970 Garrison and Freedman developed a comparatively simple model to produce endocarditis in rabbits. Durack and Petersdorf modified their procedure so that the time of onset of infection could be accurately defined. This model proved that antibiotics could prevent endocarditis in animals. Basically, three mechanisms of action have been proposed for prophylaxis. Firstly, kill the bacteria in the circulation before adherence to the damaged valve takes place. Secondly, damage the bacteria and thus prevent implantation of bacteria on an endocardial focus. Finally, eliminate the bacteria after they have lodged on the valve. In rabbits, the seeding of previously induced sterile endocardial vegetations appeared to occur within minutes after bacteria were introduced into the circulation. It proved to be remarkably difficult to prevent the bacteria from lodging on the experimental endocardial lesion. Therefore, it was concluded that all effective antibiotics had to be capable of killing the bacteria after they had lodged on the valve. However, in these experiments rabbits were inoculated with very high numbers of bacteria. Studies in which rabbits were exposed to lower bacterial inocula revealed that mechanisms of protection other than bacterial killing exist. The results suggested that antibiotics exert their protective effect by impairing the adherence of the bacteria to the vegetation rather than through bactericidal activity. When the animals were challenged with higher inocula (>1D₉₀) endocarditis could be prevented only when a prolonged level of antibiotics was maintained, such as that achieved with multiple doses or a long-acting agent. Malinverni induced endocarditis by dental extraction in rats with periodontal disease. He showed that amoxicillin prophylaxis did not influence either the degree of the post-extraction bacteraemia or the rate of bacterial clearance. Thus, neither the magnitude nor the duration of the bacteraemia is significantly influenced by prophylaxis. Rather, the adherence of the bacteria to the endocardial lesion and their subsequent multiplication are impaired.

**EFFICACY OF PROPHYLAXIS IN HUMANS**

No controlled studies to demonstrate the protective effect of prophylaxis have ever been done. Such a trial would require a very large number of patients because of the rarity of the disease after a single bacteraemic episode in a patient at risk. Also, such an approach is considered unethical today.

A retrospective cohort study by Horstkotte and colleagues indicated a beneficial effect of prophylaxis in patients with prosthetic heart valves. In a period of 15 months these investigators selected 229 patients with prosthetic heart valves, in whom 287 diagnostic or therapeutic interventions were performed for which endocarditis prophylaxis was indicated. Prophylaxis, similar to that recommended by the American Heart Association, was used in all cases. None of these patients developed prosthetic valve endocarditis. During the same period, 1898 potential control patients were retrospectively questioned about procedures they had undergone. In 409 of these patients (22%) no
reliable information was obtained, **1102 patients did not undergo a procedure, and inadequate prophylaxis was given to 73 patients.** The remaining 304 patients had undergone a total of 390 procedures without any prophylaxis. In this group six patients developed prosthetic valve endocarditis within 14 days after the intervention. However, this study had several important limitations. In a retrospective cohort study or non-concurrent prospective study subjects are selected on the basis of their exposure status. The exposed group must be selected in such a manner that an appropriate unexposed comparison group can be identified. Selection of the subjects requires careful attention and reasonably accurate data on the presence or absence of exposure of individual cohort members should be available. Underascertainment of disease occurrence can diminish the precision in estimating exposure disease associations. Varying lengths of observation in exposed and unexposed groups can occur and should be accounted for. The distribution of confounding variables among exposed and unexposed patients should be compared. The study by Horstkotte and colleagues did not do at all well on these criteria. It was neither clear from which population the exposed group was derived nor how the unexposed comparison group was selected. Patient characteristics were not reported. Scant information was given about the way in which the data on exposure were obtained; in exposed patients the data seemed to have been collected prospectively, whereas the data on unexposed patients were apparently based on recall. Whether the information was obtained through direct interview or mail questionnaire was not mentioned. The way in which endocarditis was ascertained was not described and possible confounding variables were not stated.

Four case-control studies on the protective efficacy of prophylaxis against native-valve endocarditis have been performed. The first, by Imperiale, found a protective efficacy of 91%. However, this study was limited by the retrospective recruitment of cases (n=8) over six years. This might have made it difficult to assess the time relation between procedures and the onset of symptoms. Misclassification of a single subject would have reversed the conclusion of this study. Our findings from a case-control analysis were not reported. Scant information was given about the way in which the data on exposure were obtained; in exposed patients the data seemed to have been collected prospectively, whereas the data on unexposed patients were apparently based on recall. Whether the information was obtained through direct interview or mail questionnaire was not mentioned. The way in which endocarditis was ascertained was not described and possible confounding variables were not stated.

In our study, based on a large survey of 438 patients with endocarditis, prophylaxis was not effective. When the analysis was limited to the patients in whom endocarditis occurred within 30 days after a procedure, the protective efficacy was 49% (not statistically significant). In a French case-control study of 171 patients, no increased risk of endocarditis was found for dental procedures. A 46% protective efficacy of prophylaxis (not statistically significant) was calculated for dental procedures. In 1998 Strom and colleagues published another case-control study of 273 patients, in which no link was found between endocarditis and dental procedures. In an accompanying editorial it was pointed out that six of the 273 patients had had tooth extractions, compared with none of the 273 controls and that a type II error with regard to extractions might exist. In comparison: in our study 12 of 438 patients had had tooth extractions compared with 7 of 200 controls.

**CONTROVERSIES**

Endocarditis prophylaxis has not resulted in a decreased incidence of the disease. This lack of effect might partly be explained by the small number of patients in whom endocarditis can be prevented. Only patients with known pre-existing cardiac valve abnormalities are eligible for prophylaxis. These account for approximately 50% of all patients with endocarditis. Among this group of patients it is only the cases that are temporarily related to a healthcare procedure that might have been prevented by prophylaxis. The proportion of cases that can be related to such a procedure is small. In 1930, Rushton reported four cases out of a series of 40 in which the onset dated from the extraction of a tooth. Weiss retrospectively analysed 364 patients: there were only ten cases (3%) in which a tonsillectomy or tooth extraction preceded the onset of symptoms. Other authors also stated that in the majority of cases no obvious portal of entry could be identified. In a prospective study in the Netherlands only 25 of 197 patients (12.6%) with native-valve endocarditis and a known cardiac valve abnormality had undergone a procedure for which prophylaxis was indicated. Of these 25 procedures, 23 were dental. In a study in Philadelphia only 12 of 104 patients (11.5%) with native-valve endocarditis and a known cardiac valve abnormality had had dental therapy one month before the onset of disease.

The low percentage of patients in whom endocarditis develops after a procedure cannot be ascribed to good compliance with prophylaxis. In practice, prophylaxis is infrequently given, and most patients with a high-risk cardiac lesion undergo high-risk procedures without the use of antibiotics. Yet, only few of them develop endocarditis. The risk of contracting endocarditis from a bacteraemia following a procedure must be small. Irrespective of prophylaxis, the odds are that a patient will not develop endocarditis as the consequence of a procedure. Moreover, the actual number of cases that might have been prevented by prophylaxis is even smaller: a chronological relation between a dental or medical procedure and the development of endocarditis does not prove a causal relation. Transient invasion of the bloodstream by bacteria, especially *Streptococcus viridans*, occurs frequently. Obviously, this type of bacteraemia will also occur when there is an endodontic infection. Thus, these bacteraemias are in addition to the bacteraemia originating from the inflamed
area. When a patient is then treated by a dentist and subsequently develops endocarditis, it is difficult to determine whether the disease was due to a bacteraemia caused by the procedure. It might also have been caused by a bacteraemia from the inamed area or from everyday procedures such as tooth brushing or from bowel movements. Finally, even adequate prophylaxis can never guarantee a 100% protection.

**COST-BENEFIT OF PROPHYLAXIS**

To expose sick people to certain risks associated with medical interventions is one thing, it is quite another matter to subject presumably healthy people to such risks. In the case of endocarditis, prophylaxis is justifiable if the benefit exceeds the potential harm done by the antibiotics. Whether this is the case is not known. Probably it does, since serious adverse effects from the antibiotics used for prophylaxis are rare. However, analysis of the benefit and risks of prophylaxis for patients with mitral valve prolapse without regurgitation indicated that no prophylaxis and prophylaxis with penicillin would result in a similar number of deaths. Parenteral penicillin might even cause serious adverse effects from the antibiotics used for prophylaxis for patients with mitral valve prolapse without regurgitation indicated that no prophylaxis and prophylaxis with penicillin would result in a similar number of deaths. Parenteral penicillin might even cause a net loss of life. In another study oral amoxicillin prophylaxis for all mitral prolapse patients was calculated to prevent 32 cases of endocarditis per million dental procedures at approximate costs of $119,000 per prevented case and $21,000 per year of life saved. Limiting prophylaxis to patients with mitral murmurs would prevent 80% of cases of endocarditis per million procedures at costs of about $19,000 per prevented case and $3,000 per year of life saved. Erythromycin prophylaxis was slightly less expensive than amoxicillin per benefit because of lower cost and lack of drug anaphylaxis, whereas intravenous ampicillin use might cause net loss of life. In this other antibiotic use might cause net loss of life. Since serious adverse effects from the antibiotics used for prophylaxis are rare. However, analysis of the benefit and risks of prophylaxis for patients with mitral valve prolapse without regurgitation indicated that no prophylaxis and prophylaxis with penicillin would result in a similar number of deaths. Parenteral penicillin might even cause a net loss of life. In another study oral amoxicillin prophylaxis for all mitral prolapse patients was calculated to prevent 32 cases of endocarditis per million dental procedures at approximate costs of $119,000 per prevented case and $21,000 per year of life saved. Limiting prophylaxis to patients with mitral murmurs would prevent 80% of cases of endocarditis per million procedures at costs of about $19,000 per prevented case and $3,000 per year of life saved. Erythromycin prophylaxis was slightly less expensive than amoxicillin per benefit because of lower cost and lack of drug anaphylaxis, whereas intravenous ampicillin use might cause net loss of life. Estimates of risks for other cardiac abnormalities are hampered by the lack of prevalence figures for these lesions, which makes it impossible to obtain a reliable denominator.

**CONCLUSION**

Most patients with endocarditis on a known cardiac lesion did not get the disease as a consequence of a bacteraemia related to a healthcare procedure. This cannot be ascribed to good compliance with prophylaxis. In practice, prophylaxis is administered infrequently and most patients undergo high-risk procedures without the use of prophylaxis. Thus, risk of endocarditis as a consequence of a medical or dental procedure must be very small. Antibiotic prophylaxis reduces this risk further and has a protective efficacy of about 50%. This may be worthwhile for an individual patient but is negligible on the scale of a whole population. In the case of mitral valve prolapse without regurgitation, prophylaxis is not worthwhile. Lack of data prohibits risk-benefit analysis for other cardiac lesions. In this case prophylaxis is given the benefit of the doubt.

**NOTE**

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**REFERENCES**