Antibiotic Prevention of Experimental Staphylococcal Meningitis

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POSTOPERATIVE infection in the neuro-
surgical patient is a serious complication,
often resulting in fatal meningitis or
brain abscess. Further major surgery is often
required. The incidence of infections in neuro-
surgical cases is not much different from that
in general surgery. Coagulase-positive staph-
ylococci are the most common infecting or-
organisms. Burke\(^1\) has shown that antibiotics
prevent soft tissue infections providing the
drug is given within 3 hours of the bacterial
inoculation. If there is a longer delay, the
antibiotic loses its ability to prevent infection
and merely modifies the subsequent course.

These data indicate that if antibiotics are to
prevent an infection, they must be available
to kill the bacteria before a biochemical lesion
has been established. Thus, there is a valuable
period during which prevention of infection
is possible. However, the established duration
of this period in soft tissue infections may be
exceeded by the appreciable time necessary to
establish effective bactericidal concentrations
in the cerebrospinal fluid.

The statement that antibiotics do not pene-
trate the blood brain barrier is only a half
truth since factors of time and concentration
are usually neglected. Radioactively-tagged
penicillin does enter the cerebrospinal fluid
slowly, but high concentrations in the cere-
brospinal fluid are not achieved because the
penicillin is actively removed from the fluid
by a mechanism analogous to secretion.\(^2\)
High blood concentrations do elevate cerebro-
spinal fluid levels. Trauma and inflammatory
changes alter the permeability of vessels and
favor the passage of antibiotics from the
blood to the cerebrospinal fluid.

Since even small traces of antibiotics in-
fluence the growth of bacteria, the efficacy of
antibiotics in the prevention of infection
requires therapeutic trial under optimal con-
ditions. The ideal proof would be protection
against otherwise fatal meningitis. To simu-
late the clinical problem, we have induced
fatal meningitis experimentally by the intra-
thal injection of coagulase-positive staphy-
lococci, and have studied the effect of a suit-
able antibiotic on these animals.

Materials and Methods

A frozen tube of hemolytic *Staph. aureus*,
coaugulate-positive, phage type 75, 53, 54, 47,
previously isolated from a patient with a
wound infection, was thawed at room tempera-
ture. This organism was subcultured over-
night in tryptose soy broth and the sub-
cultured strain used to inoculate two bottles,
each containing 100 ml of this media. These
were incubated at 37° C for 16 hours and
then centrifuged for 15 minutes at 3,000 rpm.
After the supernatant fluid was decanted, the
dedimented bacteria were pooled and re-
suspended in 40 ml of sterile isotonic saline.
Previously-plotted growth curves of this
organism indicated that a 100-ml 16-hour broth
culture yielded concentrations of ap-
proximately 100,000,000 viable bacteria per
ml. The saline bacteria suspension was esti-
mated to contain 500,000,000 viable organisms
per ml. This estimate was checked by further
serial dilutions of aliquots of the saline bac-
teria suspension. Dilutions of 1:1,000,000 and
1:10,000,000 were plated out and counted
in duplicate. The average concentration of
viable organisms was calculated at 585,000,000
per ml.

Twenty-four adult male albino rabbits
weighing approximately 2 ½ kg each were used
in the experiment. The rabbit was chosen be-
cause it is particularly easy to perform a lum-
bar puncture with it. Preliminary work on
rabbits had shown that a subcutaneous inocu-
um of 250,000 organisms produced a small
abscess at the injection site.

Received for publication February 20, 1967.
Revision received August 4, 1967.
Four animals were given 75 mg/kg Nafcillin intramuscularly 24 hours prior to a 1 ml inoculum of the saline suspension of bacteria injected into the lumbar subarachnoid space. Four other animals received the same dose of intramuscular Nafcillin, but at the same time as the bacterial inoculations. Two other groups of four rabbits were similarly treated with the exception that 125 mg/kg of Nafcillin were given intravenously. A fifth group of four rabbits received 125 mg/kg Nafcillin intramuscularly just before spinal injection of 585,000,000 staphylococci.

A control group of four animals were given the same intrathecal bacterial inoculation (1 ml) but received no antibiotics.

Nafcillin was injected intramuscularly twice daily for 1 week at the initial dose level in all surviving animals except those in the control group. Surviving animals were sacrificed 2 weeks after the initiation of the experiment. All dead animals were autopsied and specimens of the meninges, brain, and blood were obtained for culture and histological study.

**Results**

All four animals that did not receive Nafcillin died within 48 hours, three within 24 hours. None of the 12 animals receiving Nafcillin simultaneously with the bacterial inoculum survived more than 72 hours. Six of these animals succumbed within 24 hours and five within 48 hours. Neither the route of antibiotic administration nor the size of the dose had any statistically significant effect on survival time. All of the animals that died during the course of the experiment showed symptoms as well as gross pus in all parts of the neuraxis. Even the meninges of the brain showed evidence of inflammation. Cultures of tissues in all these cases were bacteriologically positive for *Staph. aureus*. Microscopic examination of the tissue confirmed the presence of a suppurative meningitis. The blood cultures of these animals were uniformly negative.

All eight animals that were given Nafcillin 24 hours prior to the bacterial inoculation into the spinal subarachnoid space survived and were completely asymptomatic for the 2-week experimental period. These animals were sacrificed after 2 weeks. The gross and microscopic appearances of the brains and spinal cords were normal. Cultures of the cord, meninges, and brain were sterile.

Although we did not make quantitative measurements of drug concentration in the cerebrospinal fluid, we assume that the achievement of effective levels across the blood brain barrier explain the uniform survival in groups that received Nafcillin prior to the bacterial inoculation. From 3 to 5 times the recommended dosage of Nafcillin was used in all animals.

**Discussion**

Wright has reported that 5.7% of the intracranial procedures at the Massachusetts General Hospital from 1952 to 1963 developed wound sepsis. Most of these infections were caused by coagulase-producing staphylococci.

In Cairn's series at Oxford, 8.5% of the patients became infected and all died as a result of this sepsis. Generally speaking, the mortality following neurosurgical infections has been high. A conservative estimate based on the study of published material indicates that 20% of infected cases succumb as a direct result of infection. Up to the present time, the systemic use of antibiotics postoperatively has not been effective. The prophylactic (preoperative) use of antibiotics deserves more serious consideration.

It is essential that all coagulase-producing staphylococci be susceptible to the antibiotic used. Unfortunately, penicillin levels are not easily achieved in the cerebrospinal fluid. Experimental studies with radioactively-tagged penicillin confirm the fact that there is diminished entry into the cerebrospinal fluid and demonstrate that there is active removal from the cerebrospinal fluid comparable to that observed in the renal tubules. Probenecid effectively raised the level of penicillin in the cerebrospinal fluid but reduced it in the brain tissue. The extra-cellular position of penicillin is the only concern in wound prophylaxis. Moreover, high plasm levels exceed the ability of the transport system to remove penicillin, and this can result in effective penicillin levels in the cerebrospinal fluid.

In our experiments, Nafcillin was chosen as an effective penicillinase-resistant penicillin. Sustained high blood levels may not be achieved after oral administration; therefore, the antibiotic must be administered by the parenteral route.

Our study confirms that animals can be protected from otherwise fatal staphylococcal infections of the central nervous system if an
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Effective blood level has been maintained for 24 hours before the introduction of the organisms. It implies that prophylactic antibiotics may effectively prevent human postoperative infections if used in a similar fashion. Prophylactic antibiotic administration has been found to prevent soft tissue infections if administered soon enough. Fatal endocarditis in vascular surgery has been virtually eliminated with preoperative and postoperative penicillinase-resistant penicillins.5,6

In neurological cases it is important to realize that the crucial period during which protection can be achieved starts appreciably before the introduction of the organisms into the cerebrospinal fluid. This is in the truest sense a precious or "golden" period. Unlike the simpler problem with soft tissue infections, the intravenous administration of an antibiotic at the time of the introduction of bacteria into the cerebrospinal fluid does not prevent infection.

Although there is some risk associated with the preventive use of antibiotics, the chance of a serious reaction is exceedingly small. In none of the series where penicillinase-resistant penicillin was used was an antibiotic death reported.5,6 and there was a striking reduction in fatal sepsis. The dangers of superinfection, drug reaction, and sensitivity have been overrated. When one considers the fact that penicillin has been used for a great many years in millions of people, it is surprising that so few staphylococci are resistant to penicillinase-resistant penicillin. The possibility that resistant strains may evolve from occasional prophylactic use seems remote. One of the objections raised to the prophylactic use of antibiotics concerns the apprehension that it will lead to relaxation of rigid and basic operating room techniques. Yet, the precaution seems to us to be analogous to the accepted preoperative procedure of preparing the skin with a germicide.

We are not advocating the prophylactic use of antibiotics merely on the basis of these animal experiments, but believe they indicate the need for a related, critical, clinical study utilizing the double blind technique.

Summary

The intramuscular administration of penicillinase-resistant penicillin 24 hours prior to experimental intrathecal bacterial inoculation prevents an otherwise fatal meningitis in rabbits.

References