The effect of topical application of antibiotics on the cerebral cortex

An experimental update

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A common complication of intrathecal sepsis is the development of clinical seizure activity. However, some of the newer, commonly used antibiotics may have epileptogenic and electrocortical depressant effects when applied topically to the cerebral cortex. Epileptogenic characteristics of these antibiotics may be masked by the known tendency for intracranial sepsis to produce both early and late clinical seizure problems. In this experimental study, electrocortical spike activity was produced by penicillin, methicillin, cephalothin, carbenicillin, colistimethate, and neomycin, and electrocortical depression was caused by tobramycin and gentamicin. A mixed picture was found with neomycin and carbenicillin.

Key Words: antibiotics • epilepsy • ventriculitis • shunt tract infection • meningitis

Several of the newer broad-spectrum, potent antibiotics are currently being used for the treatment of meningitis,1,2,6,7 ventriculitis,8,9 and shunt-tract infections.10 The risk of complications following intrathecal administration of some of these newer antibiotics varies considerably. Possible complications of immediate or delayed seizure, cortical electrical depression,6 radiculopathy, transverse myelopathy, and arachnoiditis4 after intrathecal or intraventricular administration must be weighed against the potential value of this route. These risks may influence the therapeutic management of a specific clinical situation.

Earlier studies8,4,6,11 have defined the effect of some of the well known older chemotherapeutic and antibiotic agents on electrocortical activity. An experimental update is indicated to evaluate electrocortical activity of several newer antibiotics currently in use. We studied the effect of carbenicillin, cephalothin, colistimethate, gentamicin, methicillin, amikacin, tobramycin, and neomycin, and used penicillin for purposes of standardization.

Materials and Methods

Acute experiments were carried out on 20 adult cats. An additional six cats were used for chronic histopathological study. The cats were anesthetized with intravenously administered pentobarbital sodium (Nembutal) in the dose of 20 mg/kg of body weight, with additional doses given intravenously as needed to abolish movement. The cats were allowed to breathe spontaneously throughout the experiment. After being placed in a Kopf stereotaxic headholder* for head immobilization, each cat underwent bilateral craniectomies with dural removal over the anterior aspect of both hemispheres.

Electrocortical recording was obtained by four ball-tipped cortical electrodes, 1 mm in diameter, applied to each hemisphere over the sensorimotor cortex of each animal. The electrode tips were placed 5 mm

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*Kopf Stereotaxic Headholder manufactured by the David Kopf Company, Tujunga, California.
Action of antibiotics upon cerebral cortex

FIG. 1. Electroorticograms of the central cortex of a cat before and 26 minutes after the topical application of cephalothin, 50 mg/cc. There is extensive high-voltage spike activity on the right side. LAS: left anterior sensorimotor cortex; the control phase demonstrates normal sleep spindles; RAS: right anterior sensorimotor cortex; LPS: left posterior sensorimotor cortex; RPS: right posterior sensorimotor cortex.

Results

Penicillin, which has a well recognized epileptogenic effect when applied to the cerebral cortex, was used to standardize and ensure the reliability of our experimental model. Three minutes after topical administration of potassium penicillin (50,000 units/cc), electrocortical spike activity was noted over the right hemisphere. During the next minute, the cortical EEG became extremely dysrhythmic with continuous high amplitude spike activity. Five minutes after the application of penicillin, very low amplitude epileptiform potentials were noted in the contralateral hemisphere, probably representing transcallosal transmission of discharge impulses. Precautions were taken to avoid antibiotic spillage onto the left cerebral cortex.

Gentamicin has been studied in two series. In the initial phase of this study in 1972, gentamicin effected identical results in three acute preparations as follows: 1) 0.2 mg/cc produced ipsilateral electrocortical depression throughout the 40-minute period of observation; 2) 0.4 mg/cc produced electrocortical depression with occasional spike activity appearing toward the end of the 40-minute run; and 3) 1 mg/cc resulted in immediate marked electrocortical depression with late spike activity. The gentamicin study was recently repeated and the profound electrocortical depression observed previously did not appear with gentamicin concentrations up to 10 mg/cc. The manufacturers are not aware of any change in preparation or packaging of gentamicin during the intervening period.

Cephalothin, in a concentration of 50 mg/cc, produced spike activity over the ipsilateral hemisphere apart. Baseline electrocorticograms were recorded for at least 5 minutes, or until a steady state was obtained. If equal amplitudes on electroencephalography (EEG) on both sides were not obtained, the animal was eliminated from the study. The EEG was obtained by a 4-channel Grass recorder.

A piece of absorbable gelatin sponge (Gelfoam) 1 × 1 cm in size, soaked in 0.9% normal saline solution was placed over the left control hemisphere, covering the exposed sensorimotor cortex so as to cover all four electrocortical probes. Over the right cerebral hemisphere a similar Gelfoam strip, 1 × 1 cm in size, soaked in antibiotic solution of known concentration, was placed also so as to cover the electrocortical probes. The Gelfoam pledgets were in direct contact with the cerebral cortex throughout its surface area. A low, therapeutically effective antibiotic concentration was used as the initial test dose. Electrocorticograms were monitored for 40 minutes after application of the topical antibiotic. If electrocorticographic alterations did not appear with the initial antibiotic concentration used, a higher dosage was subsequently used over the same area of cerebral cortex. The animals were sacrificed with an overdose of intravenous pentobarbital.

For histopathological study, specimens of cortex from the control group and the group exposed to the antibiotic were obtained from the chronic preparations 10 to 14 days after application of the antibiotic.

†Four-channel Grass recorder manufactured by Grass Instrument Company, Quincy, Massachusetts.
LAS

RAS

LPS

RPS

Control

2 sec.

60 min. after application

Fig. 2. Electrocorticogram of the cerebral cortex of cat before and 60 minutes after the topical application of methicillin 10 mg/cc showing spike activity on the right side. Abbreviations as in Fig. 1.

LAS

RAS

LPS

RPS

Control

2 sec.

4.5 min. after application

Carbenicillin in concentrations of 10 and 500 mg/cc produced mild electrocortical depression in the lower dose range, and a marked ipsilateral depression of the electrocorticogram with occasional epileptiform spike activity with the higher dose.

Colistimethate (7 mg/cc) produced gradual appearance of ipsilateral low-amplitude spike activity over the first 30 minutes of observation, with slight amelioration of the epileptiform potentials over the subsequent 15 minutes.

Neomycin (10 mg/cc) produced initial depression and then progressively increasing ipsilateral spike activity during the later portion of the run.

Amikacin (100 mg/cc) produced no electrocortical depression nor epileptiform spike abnormality;

Methicillin, in a concentration of 10 mg/cc, resulted in low amplitude spike activity 10 minutes after topical administration. Five minutes later both amplitude and frequency had increased, and remained unaltered until the end of the observation period (Fig. 2). In a concentration of 25 mg/cc, methicillin produced rapid-frequency high-voltage spike activity within 4½ minutes after application, with sustained active epileptiform abnormality throughout the observation period (Fig. 3).

15 minutes after topical administration. Spike activity continued for the duration of the 40-minute period of observation. There was no evidence of transcallosal transmission of electrical impulses to the contralateral hemisphere (Fig. 1).

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however, an interesting alteration in electrocortical rhythm did occur. Five minutes after application, the cortex underlying the amikacin-soaked Gelfoam had become hyperemic (Fig. 4). The EEG pattern lost its normal rhythm and became pulse synchronous, corresponding precisely with the electrocardiographic (EKG) frequency. Thus, the drug appears to have a pial vasodilatory effect, presumably caused by a temporary loss of vascular autoregulation. Thirty-five minutes after the topical application of amikacin, the pulse-synchronous EEG configuration had assumed a more normal pattern (Fig. 5).

Tobramycin (2 and 4 mg/cc) produced no effect on electrocortical activity. In an 8-mg/cc concentration, electrocortical depression which persisted throughout the 40-minute period of observation was noted.

Kanamycin in concentrations of 5, 10, and 40 mg/cc did not produce either cortical depression or epileptiform electrocortical activity over the observation period of 40 minutes.

A study of the gross and histological effects on the cerebral cortex following topically administered antibiotics in six chronic experiments using methicillin, carbenicillin, cephalothin, colistimethate, gentamicin,
and neomycin was also carried out. No change in neurons, glia, and cortical vessels, and only minimal thickening of the arachnoid was noted.

**Discussion**

Intrathecal and intraventricular administration of antibiotics have been used for management of meningitis, ventriculitis, and shunt infections for many years. This study makes no attempt to evaluate the efficacy of antibiotics in infectious processes of the central nervous system. Early experience demonstrated the epileptogenicity of penicillin when it came in contact with the cerebral cortex by intrathecal administration into the lumbar subarachnoid space or direct administration into a cerebral abscess cavity. Laboratory studies have confirmed this seizure-producing effect of penicillin. Radiculopathy and myelitis have also resulted from the injection of antibiotics into the subarachnoid space. Keener and Perot commented on the relative safety of chloramphenicol, sulfamethoxypyridazine, and bacitracin. Hanbery and Ajmone-Marsan confirmed the safety of chloramphenicol, and the convulsant effect of penicillin and streptomycin, but believed that bacitracin was also epileptogenic.

Jasper, et al., displayed the danger of sulfathiazole and sulfapyridine in the production of cortical excitations and convulsions when placed directly on the cerebral cortex of monkeys. They stressed that antibiotics act as foreign bodies to the brain and should be used with circumspection. Little information has since been available concerning the electrocortical effect of the newer antibiotics, in spite of their being used with increasing frequency in neurosurgical practice, particularly for Gram-negative meningitis and shunt-tract infections.

Antibiotics are rarely applied directly on the cerebral cortex. However, they may reach it along the normal routes of cerebrospinal fluid (CSF) circulation when administered into the lumbar subarachnoid space. Only low concentrations would be expected to reach the cerebral cortex by this route and, under normal circumstances, none would enter into the ventricular system. Furthermore, intrathecal administration of antibiotics may attenuate their concentration by the dilutional effect of CSF, transport of the drug from CSF, and inactivation of the drug. However, if antibiotics are instilled directly into the ventricular system or abscess cavity through a metallic or silicone rubber cannula, retrograde seepage may occur along the cannula tract to reach the cerebral cortex in significant concentrations. The profound epileptogenic effect of penicillin should preclude its instillation into the ventricular system or abscess cavity. Methicillin, a semisynthetic penicillin, likewise has well-recognized epileptogenic activity. Thus, the risk of inducing seizures should be carefully weighed against the potential therapeutic benefits of its intraventricular or intrathecal administration. Cephalothin, carbenicillin, colistimethate, and neomycin have a lesser degree of epileptogenic activity. Amikacin was the only antibiotic in which recognizable hyperemia in the region of topical antibiotic administration was noted. This was a transient effect, being completely reversed in 1 hour. Tobramycin, a new broad-spectrum antibiotic of the aminoglycoside group, causes significant electrocortical depression when concentrations greater than 4 mg/cc are applied.

Gentamicin, when evaluated during the initial phase of our investigation in 1972, produced marked electrocortical depression in low-dose ranges of 0.2 to 0.4 mg/cc, superimposed on minimal electrocortical spike activity at a concentration of 1 mg/cc. Repeat studies with currently available gentamicin at the same and higher concentrations of up to 10 mg/cc have failed to produce either cortical depression or electrocortical seizure activity.

It is possible that some of the electrographic changes are secondary to the preservatives found in the antibiotics. Even though these are present in minute concentrations, they conceivably may cause further alterations to an already sensitive cerebral cortex. Ideally, drugs should be 1) free of diluents and preservatives, and 2) administered in low concentrations for the treatment of central nervous system infections. Various commercial forms of pure crystalline penicillin have been carefully studied, and the seizure activity was felt to be related to the antibiotic rather than to the preservatives.

Thoughtful consideration should be given concerning the possible early and long-term complications of potential epileptogenicity of some of these antibiotics when used intrathecally or intraventricularly for central nervous system sepsis.

**References**

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This paper was presented at the Annual Meeting of the American Association of Neurological Surgeons, in New Orleans, Louisiana, April 23–27, 1978.

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