SHORT REPORT

Treatment of accidental high dose intraventricular mezlocillin application by cerebrospinal fluid exchange

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Abstract

An accidental high dose of intraventricular mezlocillin was given during antibiotic treatment for pneumonia in a patient admitted because of severe traumatic brain injury and occlusive hydrocephalus. Because of serial epileptic seizures not responsive to antiepileptic drug treatment, CSF exchange was performed. The CSF was drained through a ventricular catheter, while mock CSF was infused into the lumbar subarachnoid space. The patient soon recovered to her clinical status previous to intraventricular mezlocillin application. Side effects of CSF exchange were not seen. Under continued antiepileptic medication no more seizures occurred. It is concluded that high doses of intraventricular mezlocillin have proconvulsive effects. In this patient CSF exchange was a suitable means of preventing putatively permanent impairment of brain function caused by serial epileptic seizures due to intraventricular mezlocillin application.

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Therapeutic intravenous and intrathecal penicillin application may cause epileptic seizures as a neurotoxic side effect,¹⁻³ whereas therapeutic intravenous mezlocillin application does not.⁴⁻⁵ Penicillin applied experimentally to the cortex regularly leads to the development of an epileptic focus.⁶⁻⁸ To our knowledge there is a single case report of therapeutic intrathecal mezlocillin application, neurotoxic effects not being mentioned.⁹⁻¹⁰ We therefore report this case of an accidental high dose intraventricular mezlocillin application and the management of its neurotoxic effects.

Case report

A 43 year old woman was admitted due to a severe traumatic head injury with an initial Glasgow coma score of 7, and a previously undiagnosed oligosymptomatic occlusive hy-

drocephalus due to aqueductal stenosis. Thirty five years previously she had been operated on and received local radiation because of a left parietooccipital glioma, confirmed later to be an infantile desmoplastic ganglioglioma. There was no epilepsy in her medical history.

At admission cranial CT showed severe brain injury, hydrocephalic enlargement of the lateral and third ventricles and a left parieto-occipital postoperative brain defect, not communicating with the lateral ventricles (fig 1). Ventriculostomy was immediately performed. During the next three weeks her clinical condition improved slightly. Control cranial CT confirmed the contusions and showed normalisation of the ventricle width. Electroencephalography disclosed severe general dysrhythmia with predominant delta waves. A depression of the right hemisphere was noted and the left hemisphere records showed some alpha activity.

At that time mezlocillin treatment was begun because of pneumonia. One night accidentally 4 g mezlocillin dissolved in 50 ml double distilled water were connected to the ventriculostomy catheter, partially delivered into the lateral ventricle, and partially collected directly in the CSF collecting bag. As soon as the antibiotic application terminated, the fault was recognised and during the next nine hours CSF drainage was accelerated by lowering the drainage height of the ventriculostomy device. The CSF and serum mezlocillin concentrations were determined as described elsewhere.¹¹ Because of the occurrence of a series of generalised seizures six hours after the start of intraventricular mezlocillin application, which became resistant to phenytoin treatment, the patient was put on artificial ventilation and clonazepam was administered. A CSF exchange was initiated 12 hours after the start of intraventricular mezlocillin application, to avoid further spread of mezlocillin from the ventricles into the subarachnoid space. The balanced infusion of mock CSF (composition NaCl 9 g/l, glucose 1 g/l, human albumin 0.15 g/l) was started through a newly inserted lumbar drain and native CSF was drained by passive flow out via the ventriculostomy. The CSF replacement was stopped 16 hours later, when a turnover of 450 ml was achieved. During that

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Figure 1 Cranial CT on emergency admission into the hospital after traumatic head injury. Note the left frontotemporo-parietal traumatic subarachnoid haemorrhage, hydrocephalic enlargement of the lateral and the third ventricles due to aqueductal stenosis (no enlargement of the fourth ventricle), and the pre-existing left parieto-occipital brain defect after resection and radiation of a glioma 35 years previously.

time the intraventricular mezlocillin concentration had decreased from 1500 mg/l to 483 mg/l. Seizures had ceased under continued phenytoin medication. Thereafter the EEG was dysrhythmic with predominance of delta and theta waves, but exhibited some multifocal sharp slow wave complexes; a few irregular spikes were superimposed as well. By further passive drainage of 350 ml CSF through the ventriculostomy, 108 hours after the beginning of the intraventricular infusion of mezlocillin, its concentration was lowered to 36 mg/l. Dur-

Figure 2 Half logarithmic plot of intraventricular mezlocillin concentration over 108 hours after the beginning of accidental mezlocillin application. The elimination follows a first degree evasion kinetic, implying a decay proportional to the actual drug concentration. Periods of passive CSF drainage (I,III) and active CSF exchange (II) are indicated. The regression lines of the mezlocillin concentration show a steeper decay during active CSF exchange ($t_{1/2} = 10.7$ hours) than passive drainage ($t_{1/2} = 18.7$ hours).

ing that time mezlocillin was never detectable in the serum. A cellular meningeal reaction due to mezlocillin infusion did not occur as assessed by daily determinations of CSF pleocytosis and global protein content. Meanwhile the patient recovered to the clinical state before intraventricular mezlocillin application. One week after the event, the EEG showed less sharp components.

During the next eight weeks there was little improvement of the patient's clinical condition: She became contactable and was able to speak a few words, but still needed full time nursing. With continued antiepileptic medication she remained seizure free. The EEG continuously showed dysrhythmia, but sharp components disappeared. The insertion of a CSF shunting system became necessary. Eight months later the patient had made a good recovery, being able to take care of herself at home.

Discussion

When intravenously applied, penicillin and its semisynthetic acylamino derivate mezlocillin pass the blood-brain barrier, especially when the meninges are inflamed.¹²⁻¹⁵ Penicillin can occasionally induce epileptic seizures when given in therapeutic doses intravenously or intrathecally.¹⁻³ When applied directly into or on the cortex, it regularly causes seizures, often being used as an experimental epileptogenic agent.⁶⁻⁸ Mezlocillin seems to be less epileptogenic when given intravenously in therapeutic doses, seizures not having been described as adverse effects in large studies.^{4,5} To our knowledge, there is a single reported case of therapeutic intraventricular (and simultaneous intravenous) application of mezlocillin in an infant with therapy resistant ventriculitis.^{9,10} The average intraventricular concentration of mezlocillin achieved in the mentioned case was 60 mg/l (range 52–90 mg/l). No worsening of the pre-existing epilepsy was noted. The peak CSF concentration of mezlocillin in the case reported here exceeded the value mentioned above by more than 25-fold.

Being aware of the deleterious course in a case of intraventricular cefotiam application (unpublished data) and because of the occurrence of seizures resistant to antiepileptic medication, CSF was exchanged via lumbar infusion and ventricular drainage to avoid the advance of mezlocillin from the ventricles to the subarachnoid space in the period of extremely high mezlocillin concentration, putatively minimising its epileptogenicity. It is known that intrathecally applied substances hardly pass into the ventricular lumen,¹⁶⁻¹⁸ whereas substances injected into a lateral ventricle lead to high concentrations at the ependymal and cortical surfaces in contact with CSF.^{17,19} When considering the incomplete obstructive hydrocephalus being also present in this case, a penetration of mock CSF to the ventricles after lumbar infusion seems rather unlikely.

A half logarithmic plot of the mezlocillin concentration in CSF suggests that mezlocillin clearance was almost twice as fast during active CSF exchange than during the following

period of passive drainage (fig 2). This assumption is supported by the higher rate of CSF drainage through the ventriculostomy catheter during lumbar infusion of mock CSF compared with the period of solely passive drainage. This effect may be due to a block of flow out of ventricular CSF towards the subarachnoid space, as supported by the lack of the antibiotic in the serum. Thus dilution and drainage through the ventriculostomy catheter seem to be the only way of mezlocillin elimination, which could be enforced by intrathecal mock CSF infusion.

To our knowledge there is one previous report of a massive intrathecal methotrexate overdose treated successfully by CSF replacement via ventriculolumbar perfusion with normal saline.²⁰ Due to the lumbar intrathecal location of drug overdose in the case cited above, direction of CSF replacement was opposite to the direction which had to be used in the case reported here.

It is beyond question that the epileptic seizures were caused by the high intraventricular mezlocillin concentrations. It remains a matter of discussion to what extent the severe traumatic brain injury, the previous operation and radiation of a glioma, and the occlusive hydrocephalus facilitated the occurrence of seizures. This is supported by the EEG before the intraventricular mezlocillin application, already showing a focus over the right hemisphere. The further alteration of the EEG after drug application reversed without normalisation, some time after mezlocillin elimination. Further epileptic events were not seen under continued antiepileptic medication with phenytoin.

Because of the patient's pre-existing severe brain damage the possibility of eventual additional damage due to mezlocillin detectable by CT cannot be assessed. However, it seems unlikely, because after mezlocillin application a rise in CSF pleocytosis or global protein content was not registered.

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