

In vivo microdialysis in pharmacological studies of antibacterial agents in the brain

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Editor's key points

- *In vivo* cerebral microdialysis (MD) has been used in neurophysiology and neurochemistry research.
- The penetration of drugs such as antibiotics into brain tissue is poorly quantified.
- Cerebral MD studies of antibiotics show considerable variation in concentrations achieved.
- There is a need for further standardized studies using MD in this important clinical setting.

Summary. Cerebral microdialysis (MD) has proven to be a valuable clinical and research tool in neuroscience. It allows sampling of endogenous and exogenous molecules of interest from the extracellular fluid (ECF) of the brain. MD has also been successfully used to assess drug delivery to the target tissues in pharmacokinetic (PK) studies. There is a concern that due to the blood–brain barrier (BBB), current regimens of commonly used antibiotics might be inadequate. Although PK/pharmacodynamic (PK/PD) studies play an important role in drug evaluation, PK MD studies of antibacterial agents in cerebral tissue are few in number. These studies demonstrate a significant variation in drug penetration in the presence of intracranial pathology. Antibacterial agents from the same chemical group have significantly different PK profiles due to different affinity to the transport proteins of the BBB. Some studies suggest that commonly used antibiotics do not reach a therapeutic concentration range in brain ECF. Studies reviewed in this article are small and performed in different patient populations (brain tumour, head injury, epilepsy) using different methodological approaches to the drug recovery estimation. Nevertheless, they provide interesting and important data on the variability of antibiotic penetration that could be utilized for PK/PD studies and which may have clinical relevance.

Keywords: antibiotics; microdialysis; pharmacokinetics

Over the last 15 yr, the technique of *in vivo* cerebral microdialysis (MD) has become an important research tool in neurophysiology and neurochemistry. It allows direct estimation of various endogenous and exogenous substances in the extracellular fluid (ECF) of the human brain. The interstitial biomarkers of brain ischaemia and other pathological processes, such as glucose, lactate, pyruvate, glycerol, glutamate, and others, have been extensively studied.

More recently, MD has been used as a method of measuring drug delivery to the ECF of different tissues including brain.^{1–4} Owing to the blood–brain barrier (BBB), the penetration of drugs such as antibiotics into brain tissue may be less than that in other organs that do not have such a physiological barrier, and therefore, MD could offer a more objective method of assessing the extracellular concentration of the drug.

Before the development of newer imaging techniques (positron emission tomography scanning, nuclear magnetic resonance spectroscopy) and the technique of MD, pharmacokinetic (PK) studies had to rely on data from plasma, cerebrospinal fluid (CSF), or samples of brain tissue. Such data allowed an estimation of drug concentrations in compartments other than the targeted tissue compartment or an average concentration of drug across a number of compartments.

Brain MD allows for quantification of the concentration of antibacterial agents in the compartment of interest, that is, the cerebral extracellular space.⁵ In recent years, a number of studies using this technique demonstrated that the recommended dosages of some commonly used antibiotics might be inappropriate for treatment of infection in brain tissues.^{6,7} This article outlines the principle of cerebral MD and its use in the estimation of cerebral concentrations of antibacterial agents.

Principles of cerebral MD

Cerebral MD was first described in 1966 and subsequently modified. The initial objective was to introduce an artificial capillary into the brain which would act as a blood vessel and allow sampling of the interstitial fluid. Current MD systems consist of a perfusion pump connected to the MD catheter introduced into the tissue, and a sample collector. The insertion of the catheter is a surgical procedure and carries a low risk of surgical complications. An average rate of haematoma formation of 3% and infection rate of 5% has been reported for a mix of intracerebral monitoring devices, including MD catheter, brain tissue oxygen, and cerebral blood flow monitoring devices.⁸

Cerebral MD catheters are made of polyurethane and equipped with a gold tip which makes it visible on a CT scan. The catheter consists of two concentric tubes, connected at the tip (Fig. 1). The outer wall of the thicker tube is a polyamide semi-permeable membrane 0.5 mm [CMA71 (CMA Microdialysis, Solna, Sweden)] or 0.6 mm [CMA70 (CMA Microdialysis)] in diameter. Commercially available catheters offer a choice of higher or lower 'cut off' membranes with pores sized 100 000 Da for bigger molecules (cytokines, free fraction of drugs) or 20 000 Da for smaller molecules (lactate, glucose, pyruvate, urea).^{9–10} The exchange of the molecules occurs across the membrane due to simple diffusion down a concentration gradient. The catheter is perfused with an isotonic saline or colloid solution at a constant rate in the range of 0.1–5 $\mu\text{l min}^{-1}$. The concentration of the molecule to be studied in the collected dialysate is proportional to the concentration in the ECF. Although lower flow rates allow more time for diffusion and result in a higher proportion of the target substance in dialysate, it also restricts how often the samples for analysis can be collected. More frequent sampling is possible with higher flow rates,¹¹ but the concentration in the collected dialysate becomes lower and for some molecules of interest, is undetectable. This is important when choosing flow rate, sampling interval, and analytical method.

As with any other technique, brain MD has limitations. It provides information only about local changes in the area around the catheter. The process of dialysis itself can deplete the surrounding tissue of the solutes able to penetrate the membrane. Some of the dialysate fluid can escape into the tissue, thus artificially increasing the concentration of the studied substance in the collected fluid. Volume loss and relative recovery of the larger molecules

can both be improved by perfusing the MD catheter with colloid solution^{10–12} which will exert additional oncotic pressure.

Penetration through the membrane thus depends on a number of factors, including the properties of the membrane itself, properties of the dialysate fluid, and integrity of surrounding tissue after the insertion.^{13–14} It is also affected by the presence of inflammation, tumour, brain injury, or haematoma formation after the insertion. As a result, a regional variation in recovery values may be seen in normal and injured brain.¹⁵

Relative recovery and its quantification

The ratio between the dialysate and the interstitial concentrations of studied substance is defined as relative recovery.¹⁶ When studying endogenous metabolites, it is not critical to be able to measure the actual concentration in the tissue as it is often compared with the baseline value. However, when studying the distribution of exogenous compounds, it is important to quantify their actual concentrations. The *in vivo* relative recovery estimation allows evaluation of this proportion on an individual basis to minimize the effect of variability.¹⁷ As comparative studies between *in vivo* and *in vitro* techniques do not show a significant correlation,^{2–18} *in vivo* techniques remain the main method of quantification.

The main principles of *in vivo* recovery are:

- (1) *No-net-flux method*, based on calculating the difference between the concentration of a substance in perfusate (fluid going in) and dialysate (fluid coming out). When the difference becomes zero, the concentration is considered to be that of the ECF.¹⁷ This method is considered to be the 'gold standard', but requires a number of repeat samples at steady state and therefore is not suitable for dynamic studies.
- (2) *The extrapolation-to-zero-flow method* involves measuring the concentration in dialysate at different perfusion rates and extrapolating it to zero flow, when full equilibration with ECF occurs. Unfortunately, this approach has the problem of very long lag times between sampling and is not practical in PK studies.
- (3) *Retrodialysis* is a technique that involves an MD catheter being perfused with the reference substance (C_{in}) until it equilibrates. Relative recovery is calculated from a concentration loss (C_{out}) of the studied substance in perfusate and expressed as a percentage (Fig. 1).

$$\text{Relative recovery} = \frac{C_{in} - C_{out}}{C_{out}} \times 100\%$$

This retrodialysis-by-drug (where the reference substance is the substance being studied) is widely used in PK studies, but has to be performed either before the PK study or when the steady state has been achieved.

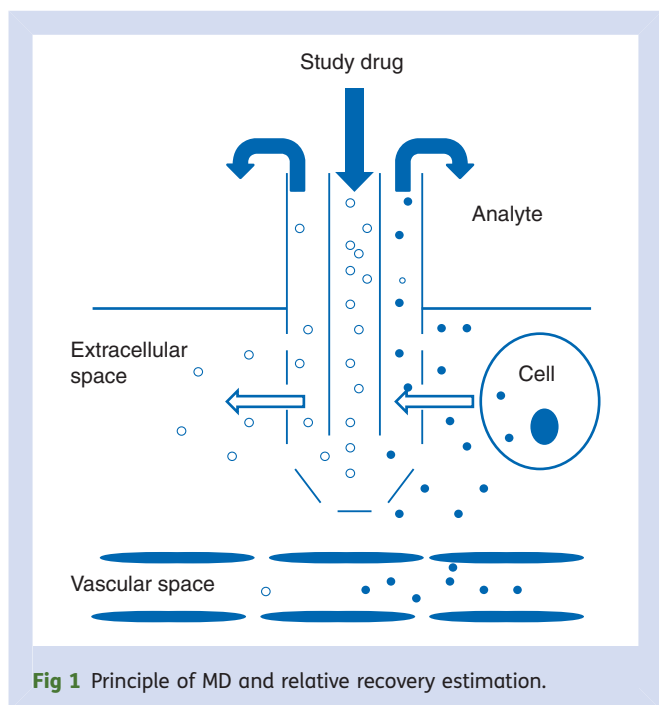


Fig 1 Principle of MD and relative recovery estimation.

Factors influencing antibacterial concentration in the central nervous system

Currently, optimal doses for many antibacterial agents are poorly defined as the majority of the studies are based on plasma concentrations. However, it is understood that only free (unbound) drug concentrations in the ECF at the target site are responsible for the antibacterial effect.¹⁹ This may be more relevant in predicting therapeutic efficacy than plasma concentrations.²⁰ The ECF concentration of a drug will depend on its unbound fraction in plasma, protein binding in the interstitial space, and intracellular distribution of the drug itself. Other characteristics of a drug that will influence brain tissue penetration are molecular size, lipophilicity, and degree of ionization.

Penetration from plasma into the extracellular space is limited by the BBB. Active transport in and out of cerebral intracellular space such as those mediated by P-glycoprotein may lead to complex relationships between concentrations in plasma, ECF, and ventricular and lumbar CSF.^{21–22} The function of this transport could also be altered by the presence of inflammation or acute brain injury, which disrupts the BBB.^{1–23}

PK/pharmacodynamic approach to antibacterial agents

PK/pharmacodynamic (PK/PD) studies play an important role in drug development and drug evaluation. To assess PK/PD of an antibacterial drug, various approaches are used.

Early *in vitro* studies exposed bacteria to a constant antibacterial drug concentration to define minimum inhibitory concentration (MIC), the lowest antibacterial concentration that inhibits bacterial growth after incubation for 18–24 h. The main advantage of this is high level of standardization and reproducibility. However, MIC may not reflect the *in vivo* situation where the concentration of antibacterial agents fluctuates depending on the antibacterial regime and the clinical scenario. In the clinical setting, the concentration of the drug will vary significantly over time due to metabolism and elimination.²⁴

In an attempt to address these issues, *in vitro* experiments simulating *in vivo* fluctuation were developed. The investigators based their data on animal infection models and on healthy humans. Although these studies may more closely reflect the situation in clinical practice, the problem is of the high variability of PK in animals, healthy humans, and infected patients.²⁵ Ideally, the most accurate PK data are from *in vivo* studies of infected patients. Unfortunately, there are drawbacks with this approach. First, it is difficult to quantify bacterial load and the clinical response, and secondly, the population studied will naturally be heterogeneous and difficult to standardize.

In order to quantify dynamic antimicrobial drug effect, PK/PD indices were introduced. In *in vivo* and *in vitro*, studies that use fluctuating concentrations enabled various

parameters to be identified that correlate with antimicrobial effect. These parameters include area under the time–concentration curve (AUC), the duration of time that the serum concentration exceeds MIC ($T > \text{MIC}$), maximum concentration (C_{max}), and minimum concentration (C_{min}). To quantify antimicrobial effect, these measures are divided by MIC and presented as indices. The effectiveness of different antibacterial groups is better described by different indices. They are generally divided into time-dependent (based on $T > \text{MIC}$, C_{min}) and concentration-dependent (based on AUC, C_{max}).²⁶

Time-dependent indices with $T > \text{MIC}$ or C_{min} measures were found to be significant in predicting the effectiveness of penicillins, cephalosporins, and carbapenems. The ratio between C_{max} and MIC ($C_{\text{max}}/\text{MIC}$) seems to be a good predictor for the efficacy for aminoglycosides. AUC/MIC is useful in assessing fluoroquinolones.²⁴

A more recent method of estimating antimicrobial drug effect is mechanism-based mathematical modelling. It is an innovative technique that takes into account mathematical prediction of microorganism replication and the mechanism of antimicrobial effect of the studied drug. Mechanism-based modelling allows for simulation and extrapolation, predicting the effect of altered dosing regimens and profoundly altered PK (e.g. patients with renal failure).²⁷

MD studies of the PK of antibacterial agents

MD studies of antibacterial agents have been conducted extensively in the last two decades. These have mainly focused on penetration of commonly used antibiotics into soft tissues, including lungs, adipose tissue, and muscle.^{4–28–30} There are fewer PK MD studies of antibacterial agents in cerebral tissue, especially human studies, due to the invasiveness of the technique.

Under normal physiological circumstances, the BBB restricts penetration of drugs into the intracellular compartment. The distribution of norfloxacin at a convulsant dose and its epileptogenic effect was studied in rat brains using MD.³¹ This showed significantly reduced concentrations of the unbound drug in the ECF of the brain with an almost 10-fold difference between brain and plasma AUC. Target-site concentration peaked relatively early and concentration vs time profiles in plasma and ECF were almost parallel. Another animal study in rats looked at the penetration of amoxicillin into the brain tissue and demonstrated an almost 20-fold difference between blood and brain concentrations of amoxicillin (Table 1).³²

A study in rats with MD catheters inserted into two different regions of the brain investigated the PK of two cephalosporin antibiotics commonly used for the treatment of bacterial meningitis.³³ Antibiotics were administered i.v. until steady state was achieved. MD catheters were inserted in the corpus striatum and left lateral ventricle sampling ECF and CSF simultaneously. The concentrations of ceftriaxone were similar in ECF and CSF and were ~0.1% of the plasma concentration. The half-life of ceftriaxone in the brain was

Table 1 Pharmacological studies of antibacterial agents in the brain using MD

Study	Antibiotic	Subjects	Tissue studied	Study outcome
Chenel and colleagues ³¹	Norfloxacin	Rats	Brain ECF	AUC blood 10 times higher than AUC brain
Tsai ³²	Amoxicillin	Rats	Brain ECF	AUC blood 20 times higher than AUC brain
Granero and colleagues ³³	Ceftriaxone; ceftazidime	Rats	Brain ECF and CSF	Ceftriaxone—similar levels in brain ECF and CSF; ceftazidime—brain ECF concentration lower than CSF concentration
Wang and colleagues ³⁶	Vancomycin 1 g single i.v. injection	19 postoperative neurosurgical patients	CSF	Easily penetrates into CSF. Concentration above MIC ₉₀ for MRSA maintained for more than 14 h
Caricato and colleagues ⁶	Vancomycin 500 mg every 6 h	4 patients with traumatic brain injury	Peri-contusional brain tissue; subcutaneous tissue	Brain concentration below MIC for <i>Staphylococcus</i> , but subcutaneous concentrations sufficient for clinical use
Mindermann and colleagues ⁵	Rifampicin 600 mg single dose	8 patients with brain tumour	Tissue concentration of brain tumour, perifocal brain, and normal brain, ECF of normal brain	Highest concentration in the tumour followed by the tissue from perifocal area, ECF, and the normal brain tissue
Dahyot-Fizelier and colleagues ²³	Meropenem 1 g every 8 h	2 patients with traumatic brain injury	Brain ECF	Delayed distribution into ECF brain; AUC brain/AUC serum 0.14, 0.78

similar to that in plasma. The PK of ceftazidime, however, was different. The concentration of ceftazidime in the ECF of the brain was significantly lower than that in the CSF (mean value of $2.1 \mu\text{g ml}^{-1}$ in the corpus striatum vs $3.8 \mu\text{g ml}^{-1}$ in the ventricles), and its half-life in brain tissue was prolonged compared with the plasma half-life (mean 88.5 vs 24.4 min). These differences in PK between drugs of the same chemical group may be explained by different affinity for the influx and efflux transporters in the BBB and blood–CSF barriers.^{34–35} The results of this study suggest that the PK and PD of drugs even from the same chemical group may have to be studied individually in order to define appropriate therapeutic regimes.

Unlike the BBB, the blood–CSF barrier is more permeable to various substances, and therefore, classic PK models based on the distribution of drugs in CSF may be of limited value.²¹ In support of this hypothesis, vancomycin can easily penetrate into CSF and reach therapeutic levels in the perioperative period after neurological surgery after a single i.v. bolus.³⁶ On the other hand, the distribution of vancomycin in cerebral tissue achieved inadequate concentrations after routine treatment in four patients who underwent evacuation of intracerebral haematoma.⁶ MD catheters were inserted in the pericontusional area of the brain and in the subcutaneous tissue of the same patient. Ratios between the mean serum and the mean target concentrations were compared.⁶ Target concentration of vancomycin in the pericontusional area was significantly lower than that in the subcutaneous tissue (max. of $1.2 \mu\text{g ml}^{-1}$ in the brain) and never reached MIC for methicillin-resistant *Staphylococcus* ($3 \mu\text{g ml}^{-1}$),³⁷ while concentration in peripheral tissue reached levels above MIC after the second i.v. dose. These results may be questioned as the authors did

not calculate the relative recovery and their conclusions were based only on ratios between the mean concentrations.

The integrity of the BBB and hence the distribution of the drugs across it in patients with brain tumours was investigated by measuring rifampicin concentration in tissues that were obtained intraoperatively during resection.⁵ Three areas of the human brain were sampled: brain tumour, perifocal area, and normal brain. Additionally, an MD catheter was inserted distal to the resection area into normal brain tissue. Rifampicin concentration was highest in the tumour tissue, followed by the perifocal area tissue with the lowest penetration observed in the normal brain. The concentration in the normal cerebral ECF measured by MD was slightly higher than that in the normal brain tissue (mean 0.32 vs $0.29 \mu\text{g ml}^{-1}$). The latter represents the average across all compartments of the normal brain. The authors also commented on the relative consistency of rifampicin concentration in ECF compared with tumour and perifocal area where concentrations were highly variable due to differences in BBB impairment. Although the concentration of rifampicin seen in ECF was above MIC for streptococcal and staphylococcal infections, it did not reach MIC for some of the mycobacterial strains.

The unbound concentration of meropenem was measured in brain tissue of two patients with traumatic brain injury in whom MD catheters were inserted as part of routine clinical monitoring and meropenem was given as a treatment for hospital-acquired pneumonia.²³ The level of free brain concentration and AUCs were considerably reduced in brain ECF compared with the serum. The curves describing free cerebral concentration were shifted to the right compared with the serum curves signifying delayed distribution in the extracellular compartment of the brain.

Discussion

The introduction of *in vivo* MD has allowed intermittent sampling of unbound drugs in targeted compartments. For antibacterial therapy to be effective, it is crucial that it achieves a therapeutic concentration of free drug in the interstitial fluid. The BBB restricts distribution of antibacterial agents into the cerebral tissue, but pathological processes affecting its integrity can lead to increased penetration into the cerebral ECF.

PK studies of antibiotics using MD techniques would be an ideal way to determine the effectiveness of antibacterial drugs in cerebral tissues, as they allow measurement of the absolute amount of drug penetrating into cerebral ECF. Unfortunately, the practicalities of such studies present a significant challenge.

Studies in healthy volunteers are unethical and as a result, the majority of human studies are based on small numbers and a variety of pathological changes. Animal studies are useful in determining the proportion of a drug reaching ECF from plasma, rather than measuring a true ECF concentration. Although it is known that the BBB is disrupted in head injury, infective processes, and intracerebral tumours, the degree of this disruption is highly variable and hard to quantify. In these patients, MD is used for clinical monitoring rather than as a pure research tool, and therefore the antibiotic studied will reflect clinical guidelines. There are significantly different methodologies for MD techniques, including the estimation of drug recovery, potentially resulting in different ECF drug concentration estimation.

Cerebral MD is becoming more commonly used as a monitoring tool in neurointensive care units. Small, high-quality studies of the PK of widely used antibiotics can provide invaluable data that could be used for PK/PD mechanism-based mathematical modelling. Currently, treatment of cerebral tissue infection is still a challenge. Based on the current data, there is a concern that some of the dosages of antibacterial drugs may be inadequate for more resistant bacteria, despite an effective plasma concentration. Further MD studies with common methodology and PK/PD mechanism-based modelling that allow prediction of the effectiveness of the altered drug regimens will form the basis of more accurate dosage regimens for patients with central nervous system infection.

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