Journal of Critical Care 36 (2016) 116–124

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Antiepileptic dosing for critically ill adult patients receiving renal replacement therapy☆

Keaton S. Smetana, PharmD [a], Aaron M. Cook, PharmD, BCPS [a,b], Melissa L. Thompson Bastin, PharmD, BCPS [a,b], Douglas R. Oyler, PharmD, BCCCP [a,b,*]

[a] University of Kentucky HealthCare, Department of Pharmacy, Lexington, KY
[b] University of Kentucky College of Pharmacy, Department of Pharmacy Practice and Science (UK College of Pharmacy), University of Kentucky, Lexington, KY

ARTICLE INFO

Available online xxxx
Keywords:
Anticonvulsants
Hemodialysis
Continuous renal replacement therapy
Intensive care

ABSTRACT

Objectives: The aim of this review was to evaluate current literature for dosing recommendations for the use of antiepileptic medications in patients receiving renal replacement therapy (RRT).
Data sources: With the assistance of an experienced medical librarian specialized in pharmacy and toxicology, we searched MEDLINE, EMBASE, CINAHL, Web of Science, WorldCat, and Scopus through May 2016.
Study selection and data extraction: Four hundred three articles were screened for inclusion, of which 130 were identified as potentially relevant. Micromedex® DRUGDEX as well as package inserts were used to obtain known pharmacokinetic properties and dosage adjustment recommendations in RRT if known.
Data synthesis: Data regarding antiepileptic drug use in RRT are limited and mostly consist of case reports limiting our proposed dosing recommendations. Known pharmacokinetic parameters should guide dosing, and recommendations are provided where possible.
Conclusion: Additional studies are necessary before specific dosing recommendations can be made for most antiepileptic drugs in critically ill patients receiving RRT, specifically with newer agents.
© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Seizures are a common neurologic complication encountered in the intensive care unit (ICU) and are witnessed in nearly 3.5% of the general medical ICU population [1]. The incidence in critically ill patients has been reported to range from 19% to 34% using continuous electroencephalogram monitoring, with 76% to 92% of patients in non-convulsive status epilepticus [1,2]. Given the recommendation that all patients in status epilepticus receive antiepileptic drug (AED) therapy, it may be common for patients to begin an AED in the ICU. Further, the overall incidence of AED use for seizures in the general population is nearly 1 AED per 100 persons, and these medications are generally continued on admission to the hospital [3].

Acute kidney injury (AKI) develops in up to 25% of patients in the ICU; 6% of ICU patients who develop AKI require renal replacement therapy (RRT) [4]. Approximately half of these patients receive continuous RRT (CRRT), largely owing to improved hemodynamic stability with this modality [5]. Traditional means of RRT may lead to worsening cerebral edema, cerebral hypoxia exacerbated by intracellular acidosis secondary to carbon dioxide diffusion across the blood brain barrier, increased intracranial pressure, and reduced cerebral perfusion pressure from rapid reduction in the effective plasma volume [6]. It is therefore possible that CRRT may be preferred in patients with neurologic injuries. Although the incidence of AED use in CRRT has not been quantified, it is likely significant given the commonality of both CRRT and AED use in the ICU.

The following review discusses the available evidence to provide dosing and monitoring strategies for AED use in critically ill patients receiving CRRT.

2. Methods

With the assistance of an experienced medical librarian specializing in pharmacy and toxicology, the following electronic bibliographic databases were searched: MEDLINE, CINAHL, Web of Science, WorldCat, International Pharmaceutical Abstracts, and Scopus. In addition to specific generic AED names, using the operator function OR amongst search terms, the following core terms were used in the search: (Antiepilep* OR Antiseizur* OR Anticonvuls*) AND (Hemodialys* OR Haemodialys* OR Hemofiltrat* OR Haemofiltrat* OR Renal Replacement). The use of both controlled vocabulary, such as MeSH terminology, as well as text words was used in the search strategy when applicable. A related citation function was also used as available. Only English language

☆ All authors of this study have no direct or indirect conflicts of interest to disclose.

* Corresponding author at: Department of Pharmacy Services, H110, University of Kentucky HealthCare, 800 Rose Street, Lexington, KY, 40536-0293, USA. Tel.: +1 859 323 6962; fax: +1 859 323 2049.
E-mail addresses: ksmetana0427@gmail.com (K.S. Smetana), amcook0@uky.edu (A.M. Cook), mlthompson@uky.edu (M.L.T. Bastin), doug.oyler@uky.edu (D.R. Oyler).

http://dx.doi.org/10.1016/j.jcrc.2016.06.023
0883-9441/© 2016 Elsevier Inc. All rights reserved.

studies performed in adult humans and published in the peer-reviewed literature were eligible for inclusion. The full search strategy, combination of terms, and limits are provided in Fig. 1. No date restriction was imposed on the search strategy, which completed on May 25, 2016. References from included articles were reviewed for additional materials, and the Clinical Trials website (http://clinicaltrials.gov/) was also reviewed. Additionally, Google Scholar was searched for publications not indexed in core databases. In total, 403 articles were screened for inclusion, of which 130 were identified as potentially relevant.

3. Pharmacokinetic principles in RRT

The understanding of solute and medication removal via RRT has evolved over the years. A complete review detailing the intricacies of solute removal is beyond the scope of this article; however, in order to apply the concepts of solute removal to dosing recommendations, one must have a baseline understanding of solute clearance as well as the physiochemical and pharmacokinetic properties of the medications in question.

In anuric patients receiving RRT, solute clearance occurs through three possible mechanisms: diffusion, convection, and adsorption. Diffusion—the passive movement of solute across a semipermeable membrane driven by counter-current flow—is the primary removal modality of intermittent hemodialysis (IHD) and continuous venovenous hemodialysis (CVVHD). This solute clearance has been characterized as slow, and removal is time dependent. CVVHD utilizes dialysate fluid, the components of which will be individualized to the degree of electrolyte and metabolic derangement being treated [5]. Diffusion is a highly efficient method for removal of small solutes with molecular weight (MW) <300 Daltons (Da), such as urea or creatinine [7].

Convection is the primary solute removal modality utilized in continuous venovenous hemofiltration (CVVH). Solute elimination occurs during transport across a semi-permeable membrane due to increased trans-membrane pressure and resulting solute drag. Water and electrolytes lost are corrected with a replacement fluid, and the net water lost is termed the ultrafiltrate [7]. Ultrafiltration can occur during any modality of RRT and will vary with the individual prescription. The rate of solute removal during convection is proportional to the replacement fluid rate: if a faster replacement fluid rate is utilized, greater solute removal should be expected. Ultrafiltration rates of 3 to 4 L/h are associated with greater solute removal and may warrant more aggressive dosing of susceptible medications, including AEDs. As most patients will receive convection doses ≥25 mL/kg/h, it may be possible to anticipate which patients receive a higher intensity regimen for dosing optimization [8]. The types of solutes that are removed by convection are completely dependent on the pore size of the filter. Many contemporary CRRT machines utilize high-flux filters that will remove solutes with a MW ≤50 000 Da. For susceptible molecules, increasing ultrafiltration rates proportionally increases clearance. A small pharmacokinetic study in critically ill patients demonstrated that CRRT ultrafiltration flow rates of 2.5 L/h resulted in creatinine clearance of 40 mL/min; for each 500 mL/h incremental increase in flow, the clearance of creatinine increased by 10 mL/min [9].

In general, low MW substances (<300 Da) are best cleared by diffusion, whereas middle (300-5000 Da) and large MW (5000-50 000 Da) substances are best cleared by convection. Sieving coefficients, defined as the ratio of the concentration of drug in the spent effluent to the concentration of drug in the serum, are available for many medications and may be helpful with assessing removal through convection. The sieving coefficient ranges from zero to one, with the later indicating complete passage of the drug through the membrane filter [7]. To estimate a drug's sieving coefficient, the percent protein-bound (PPB) found in the package insert can be subtracted from 100% (e.g., a drug that is 30% protein-bound will have a sieving coefficient of 0.7) [10]. It is important to remember than PPB of many medications may be altered in critical illness [11]. Additionally, the applicability of sieving coefficients to drug dosing is derived from the type of filter set utilized during the original evaluation [10]. With the evolving technology of CRRT and high efficiency filter development, previously established sieving coefficients and estimations based on PPB may not be relevant to the machines utilized today.

Continuous venovenous hemodiafiltration (CVVHDF) is another modality of CRRT combining convection and diffusion. The CVVHDF prescription may denote the intensity of convection vs diffusion and include ultrafiltration. As a general rule, CVVHDF is the most effective means of solute removal, followed by CVVH, CVVHD, and finally IHD [5].

Adsorption is the final and typically least significant modality of solute removal during CRRT. Newer filters are constructed with a neutral charge in order to reduce protein adsorption to the filter. It is possible that some molecules may still adhere to the surface or interior of the membrane; some filters are designed to exploit this property in order to reduce circulating cytokine exposure [12]. Filter brands and nursing protocols regarding changing filters and sets at institutions may vary, further limiting the external validity of published data. It is also important to remember that residual renal function will increase the clearance of renally eliminated medications and may result in underdosing if not taken into consideration.

Residual renal function, physiochemical properties of medication, and dialysis characteristics are the main determinants of solute removal in RRT. Medications with a volume of distribution (V_D) >3.5 L/kg are generally highly concentrated in tissue and unlikely to be removed through convection or diffusion. These medications may still be at risk for adsorption. Medications that are >80% protein-bound are also unlikely to be effectively removed through convection or diffusion. Medications with MW 300 to 50 000 Da will not be highly removed through diffusion, although extracorporeal removal will likely increase if convection is utilized. Molecules >50 000 Da are not likely to be removed through convection but may adsorb to some filters [7].

In summary, the ideal medication to be removed through RRT will have a V_D < 1 L/kg, PPB <80%, and MW ≤50 000 Da; most AEDs fit these criteria. Given the pharmacokinetic alterations in RRT, there is a possibility that medications utilized in critically ill patients requiring RRT may be underdosed, and it has been recommended that therapeutic drug monitoring (TDM) should be done when possible [5].

(((((((phenytoin OR fosphenytoin OR phenobarbital OR valproic valproate OR divalproex OR levetiracetam OR lacosamide OR topiramate OR carbamazepine OR felbamate OR vigabatrin OR zonisamide OR lamotrigine OR gabapentin OR pregabalin OR clobazam OR perampanel OR primidone OR rufinamide OR tiagabine OR eslicarbazepine OR phenylethylmalonamide OR oxcarbazepine OR ethosuximide OR ezogabine OR retigabine) OR (("Anticonvulsants"[Mesh] OR "Anticonvulsants"[Pharmacological Action]) OR ("Epilepsy/drug effects"[Mesh] OR "Epilepsy/drug therapy"[Mesh]))) OR Antiepilep* OR Antiseizur* OR Anticonvuls*)))) AND Humans[Mesh] AND English[lang] AND adult[MeSH] AND ((((("Renal Replacement Therapy"[Mesh]) OR "Hemofiltration"[Mesh]) OR ("Renal Dialysis"[Mesh] OR "Hemodialysis Solutions"[Mesh])) OR ("Dialysis"[Mesh] OR "Dialysis Solutions"[Mesh]) OR (Hemodialys* OR Haemodialys* OR Hemofiltrat* OR Haemofiltrat* OR "Renal Replacement")))

Fig. 1. Search strategy (completed May 25, 2016).

Download English Version:

https://daneshyari.com/en/article/2764370

Download Persian Version:

https://daneshyari.com/article/2764370

Daneshyari.com