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Potential γ-Hydroxybutyric acid (GHB) Drug Interactions Through Blood–Brain Barrier Transport Inhibition: A Pharmacokinetic Simulation-Based Evaluation

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Recreational abuse or overdose of γ-hydroxybutyric acid (GHB) results in dose-dependent central nervous system (CNS) effects including death. As GHB undergoes monocarboxylic acid transporter (MCT)-mediated transport across the blood–brain barrier (BBB), one possible strategy for the management of GHB toxicity/overdose involves inhibition of GHB BBB transport. To test this strategy, interactions between GHB and MCT substrates (salicylic acid or probenecid) were simulated. Competitive, noncompetitive and uncompetitive inhibition mechanisms were incorporated into the GHB–MCT substrate interaction model for inhibitor dosing either pre-, concurrent or post-GHB administration. Simulations suggested that salicylic acid was the better candidate to limit GHB accumulation in the CNS. A time window of effect (>10% change) was observed for salicylic acid pre- and post-administration, with maximal transport inhibition occurring within 12 hr of pre- and 2 hr of post-administration. Consistent with the prediction that reduced GHB brain concentrations could translate to decreased pharmacodynamic effects, a pilot study in rats showed that the pronounced GHB sedative/hypnotic effects (24.0 ± 6.51 min; $n = 4$) in the control group (1.58 mmol/kg GHB plus saline) were significantly ($p < 0.05$) abrogated by salicylic acid (1.25 mmol/kg) coadministration.

KEY WORDS: γ-hydroxybutyric acid; nonlinear pharmacokinetics; pharmacokinetic simulations; pharmacokinetics; drug interaction; salicylic acid.

INTRODUCTION

γ-Hydroxybutyric acid (sodium oxybate, GHB) is an endogenous compound (1) present in brain and peripheral tissues such as liver, heart,

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muscles and brown fat (2). GHB, while approved for the treatment of narcolepsy, is widely abused as an anabolic agent, euphoriant and date rape drug. Recreational abuse or overdose of GHB (or precursors) results in dose-dependent central nervous system (CNS) effects (respiratory depression, unconsciousness, coma, death) as well as tolerance and withdrawal (3,4). Currently the treatment of GHB overdose includes empirical interventions and symptomatic treatments. Although naloxone and physostigmine have been tried as antidotes, their use is controversial (5,6). In addition, treatment of GHB toxicity is complicated by nonlinear pharmacokinetics (7).

There are multiple transport systems at the blood–brain barrier (BBB) which are responsible for influx or efflux of molecules from the CNS and form the basis of many possible drug–drug interactions (8–10). Using an *in situ* brain perfusion technique, we demonstrated that GHB undergoes carrier-mediated transport at the BBB, likely by an isoform of the monocarboxylic acid transporter (MCT1) (11). Competition for carrier-mediated transport may lead to GHB–drug interactions. However, competition for carrier-mediated transport might be exploited to develop a strategy for treatment of GHB intoxication. Theoretically, administration of a transport inhibitor would diminish additional brain accumulation of GHB during overdose conditions and potentially shorten the duration of associated toxic effects.

From our *in situ* experiments, MCT substrates (salicylic acid, valproic acid, and probenecid) significantly inhibited GHB brain influx (11), suggesting that MCT substrates may be potential transport inhibitor candidates for GHB toxicity. Each of these drugs is therapeutically used in humans and therefore may potentially cause a GHB–drug interaction. Salicylic acid is a primary active metabolite of aspirin, a common over-the-counter analgesic. Probenecid is administered in conjunction with antibiotics in the treatment of bacterial sexually transmitted disease such as gonorrhea (12) and syphilis (13,14), diseases that are commonly found in populations of drug abusers (15,16). Valproic acid is prescribed for epileptic seizures (absence, partial, myoclonic, and tonic-clonic), bipolar disorder, and migraine prophylaxis. Physicians may also prescribe valproic acid for non-FDA approved indications for severe behavioral disturbances (e.g., agitation, aggression, explosive temper) which may occur secondary to severe head injuries, Alzheimer's dementia and behavioral disorders (attention-deficit hyperactivity, oppositional defiant and conduct) (17,18).

Probenecid and salicylic acid appear to be reasonable candidates for the management of GHB toxicity via inhibition of GHB transport across the BBB. Valproic acid's psychoactive profile diminishes its

utility as a potential transport inhibitor. However, it was not clear which drug, salicylic acid or probenecid, would be pharmacokinetically optimal for the management of GHB toxicity. Hence, we wished to utilize pharmacokinetic modeling to better appreciate salicylate–GHB and probenecid–GHB drug interactions. Our objectives were to (A) model and simulate GHB plasma and brain concentrations in rats, (B) identify a dose of an inhibitor that will produce therapeutic concentrations of the inhibitor, (C) test whether a potential interaction is possible between GHB and each inhibitor using inhibitor concentrations within the inhibitor's therapeutic window and (D) understand the effect of pre-, concurrent or post-administration of the inhibitor in relationship to GHB administration.

MATERIALS AND METHODS

Pharmacokinetic Models

All computer modeling and simulations were performed using WinNonlin (WinNonlin Pro version 4.1, Pharsight Corp, Cary, NC). Literature data were extracted by Graph Digitizer (Graph Digitizer, version 2.0, internally validated). Criteria for judging the quality of the model fit to the literature data were: visual inspections, square residual plots and weighted sum of residuals. Akaike and Schwartz criteria were used to discriminate between different models used to fit the GHB, salicylic acid or probenecid data.

Definitions of the mathematical symbols are provided in Appendix. Simulations were performed assuming a standard rat weight (300 g) or the literature reported weight when fitting the model to literature data.

Model 1: GHB Pharmacokinetics

One of the objectives of our simulations was to provide insight into the brain concentrations of GHB in presence or absence of transport inhibitors. This necessitated development of a pharmacokinetic model that would simulate GHB brain concentration–time course data.

We developed a one-compartment model with nonlinear elimination using published GHB plasma time course data and limited brain concentration data (7). Equation 1 was used to refit published plasma data using all data points, since the published pharmacokinetic analysis excluded early sampling times ($t < 0.5$ hr). Published parameter estimates (7) were used as initial estimates. (Symbols are defined in Appendix.)

The next step was to develop a model that would simulate brain concentrations of GHB after intravenous dosing. The plasma profile generated by Eq. 1 was used as a forcing function to generate GHB brain concentrations, using an expanded model (inclusion of Eq. 2) that incorporated GHB carrier-mediated uptake parameters determined by *in situ* brain perfusion (11). Limited published data on GHB brain concentrations (7) was used to develop this model, as described in detail in the next paragraph. A schematic representation of the complete model is provided in Fig. 1 (Model 1).

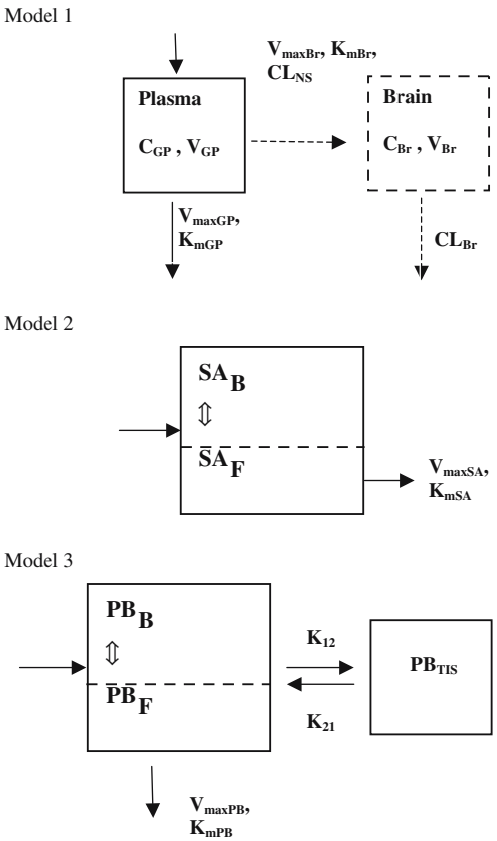

Fig. 1. Schematic diagrams of pharmacokinetic mathematical models. Model 1: GHB; Model 2: Salicylic acid; Model 3: Probenecid.

$$\frac{V_P * dC_{PGHB}}{dt} = -\frac{V_{maxGP} * C_{PGHB}}{(K_{mGP} + C_{PGHB})} \quad (1^1)$$

$$\frac{V_{Br} * dC_{BrGHB}}{dt} = \frac{V_{maxGBr} * C_{PGHB}}{(K_{mGBr} + C_{PGHB})} + CL_{NS} * C_{PGHB} - CL_{Br} * C_{BrGHB} \quad (2)$$

The initial conditions were $C_{PGHB(0)} = \frac{Dose}{V_P}$, $C_{BrGHB(0)} = 0$.

Published whole brain concentrations of GHB at return of righting reflex following intravenous GHB (7) were used for model development. These concentrations, corrected for cerebrovascularly entrapped blood, were fitted using Eq. 2 to obtain estimates of CL_{Br} and V_{Br}. Simultaneous estimation of CL_{Br} and V_{Br} led to high CV% values as these parameters are correlated. Therefore, CL_{Br} was estimated and V_{Br} was fixed at 1.00 ml, assuming GHB distribution into body water, a rat brain weight of 7.2 g/kg and a rat body weight of 0.3 kg (19,20).

Model 2: Salicylic Acid Pharmacokinetics

Another of our objectives was to identify a dose of an inhibitor that will produce inhibitor plasma concentrations within its therapeutic window. A one compartmental model with nonlinear elimination of free drug (Eq. 3) (21) was used to fit the published salicylic acid plasma concentrations (22) (Fig. 1—Model 2). Published data for salicylic acid plasma protein binding (22) was used to estimate protein binding parameters (B_{maxSA}, K_{DSA}, K_{nsSA}). These salicylic acid protein binding parameters were then fixed in Eq. 4 to fit total salicylic acid concentrations. Salicylic acid free concentrations were simultaneously fitted as the product of free fraction and total concentration of salicylic acid. Initial estimates of V_{maxSA} and K_{mSA} for Eq. 3 were obtained from the published plasma profiles (22). Since salicylic acid volume of distribution is dose-dependent, a different volume of distribution was estimated per dose (23,24).

$$\frac{dSA_T}{dt} = -K_{el} * SA_F = -K_{el} * F_{UP(SA)} * SA_T = -\frac{V_{maxSA} * F_{UP(SA)} * SA_T}{V_{SA}(K_{mSA} + F_{UP(SA)} * SA_T)} \quad (3)$$

[1] When fitting our equations to published data, the units for volume were ml and were later converted to ml/kg for unit balancing. This conversion was followed throughout this work.

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