Pharmacological Reports 69 (2017) 340–349

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Short communication

Population pharmacokinetic modelling of valproic acid and its selected metabolites in acute VPA poisoning

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ARTICLE INFO

Article history:
Received 21 December 2015
Received in revised form 18 November 2016
Accepted 8 December 2016
Available online 6 January 2017

Keywords:
Valproic acid
Population pharmacokinetics
Acute poisoning
Metabolic pathway
Monolix

ABSTRACT

Background: Valproic acid (VPA) is a first-line antiepileptic drug. It is used in the treatment of many different types of partial and generalized epileptic seizures. Though the clinical pharmacokinetics of VPA has been well defined, information about pharmacokinetics after overdoses is rare.
The aim of this study was to try to build a population pharmacokinetic model that would describe the time course of VPA and its selected metabolites when the drug is ingested in an overdose situation.
Methods: Blood samples were collected during admission to the hospital and several times during treatment for poisoning (10 men and 10 women). The concentration of VPA and its metabolites were determined by liquid chromatography coupled with mass spectrometry. For population pharmacokinetic evaluation of VPA and its metabolites, the two-compartment-model was applied.
Results: The estimated doses of VPA taken ranged from 6 to 65 g, while the time after ingestion ranged from 1 to 30 h. Results showed that the β-oxidation process exhibited Michaelis-Menten kinetics becoming saturated during acute intoxication. The same could not be said for the desaturation route. VPA therapy increased the Vmax for β-oxidation by 59% while decontamination appeared to be of moderate efficacy lowering the F value by 34% on the average.
Conclusions: None of the models perfectly described the experimental data. Important factors like the variable degree of protein binding by VPA could not be included in the models. The small number of subjects used in the study made the analysis of more covariates impossible.

Introduction

Valproic acid (VPA) is a first-line antiepileptic drug. It is used in the treatment of many different types of partial and generalized epileptic seizure [1,2]. It is also used in the treatment of psychiatric diseases (bipolar and schizoaffective disorders, social phobias and neuropathic pain). Overdosing on this drug is often treated and reported to poison centers [3]. Serious VPA overdose is associated with significant central nervous system depression, respiratory insufficiency, and severe complications such as hemorrhagic pancreatitis or cerebral edema [4]. The metabolic pathway of VPA is very complex [1,5,6]. It includes, among others, the following main routes: desaturation, ω-, ω1-, ω2- hydroxylation, β-oxidation, and conjugation with glucuronic acid. β-oxidation leads to the formation of pharmacologically active 2-ene-VPA (2VPA). Desaturation, in turn, leads to the formation of reactive 4-ene-VPA (4VPA).

The clinical pharmacokinetics of VPA have been well defined [7]. Non-enteric-coated preparations of VPA are rapidly and nearly completely absorbed from the gastrointestinal tract and the maximum plasma concentration is observed 4–5 h after therapeutic doses [8], although after an overdose this time is highly variable and ranges from 5 to 20 h [9]. The half-life time of elimination *via* metabolism by the liver *via* glucuronic acid conjugation, mitochondrial and cytosolic β-oxidation (59%) and excretion (3%) of unchanged VPA [10] ranges from 5 to 20 h, although following an

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http://dx.doi.org/10.1016/j.pharep.2016.12.003
1734-1140/

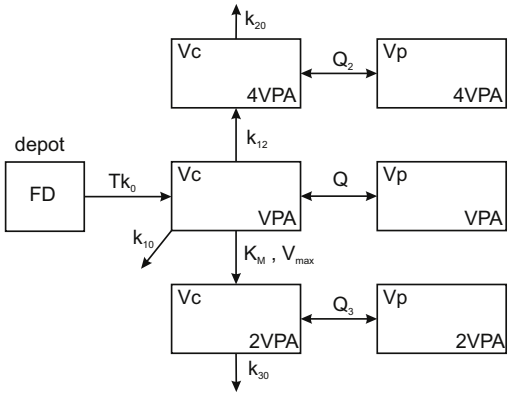

Fig. 1. The two-compartment pharmacokinetic model for VPA and its selected metabolites.

overdose the half-life may be prolonged for as long as 30 h [11]. In our previous study with a limited number of cases, we also observed a highly variable rate of elimination of VPA in poisoned patients [12].

There are a number of population pharmacokinetic (PPK) studies of VPA using therapeutic doses [13–15]. While a few simple pharmacokinetic analyses were also done with overdoses [16–18] (mostly as case studies), to our knowledge, no attempt to conduct a PPK study of VPA ingested in toxic doses has been reported. In this study, we built a population pharmacokinetic model to describe the time course of VPA and its selected metabolites when the drug is ingested in an overdose situation.

Materials and methods

Subjects and data collection

Blood specimens were obtained from 20 patients with acute VPA poisoning. They were hospitalized at the Chair of Toxicology

```
write "A model for VPA/VPA-4-ene/VPA-2-ene drug-metabolites system"$

load Daisy$

% B_ is the variable vector

B_:={R,CVPA,CVPA4,CVPA2,AcVPA,AcVPA4,AcVPA2,ApVPA,ApVPA4,ApVPA2}$

% R is an input function; it equals R=k0=FD/Tk0 for time tau and, then, it is 0.
% Tk0 is not included in identifiability analysis, because it can be determined
% from discontinuity in derivative of CVPA in time.

for each el_ IN b_ DO DEPEND el_,t$

%B1_ is the unknown parameter vector

B1_:={KM,Vmax,k10,k20,k30,k12,Vc,Vp,Q1,Q2,Q3}$


% Number of inputs
NU_:=1$
% Number of outputs
NY_:=3$
% Number opf states
NX_:=6$

% Model equations

C_:= {
 df(AcVPA,t) = -(k10+k12+Q1/Vc)*AcVPA + Q1/Vp*ApVPA + R -
Vmax*AcVPA/(KM+AcVPA/Vc),
 df(ApVPA,t) = Q1/Vc*AcVPA - Q1/Vp*ApVPA,
 df(AcVPA4,t) = -(k20+Q2/Vc)*AcVPA4 + Q2/Vp*ApVPA4 +
Vmax*AcVPA/(KM+AcVPA/Vc),
 df(ApVPA4,t) = Q2/Vc*AcVPA4 - Q2/Vp*ApVPA4,
 df(AcVPA2,t) = -(k30+Q3/Vc)*AcVPA4 + Q3/Vp*ApVPA2 + k12*AcVPA,
 df(ApVPA2,t) = Q3/Vc*AcVPA2 - Q3/Vp*ApVPA2,
 CVPA=AcVPA/Vc,
 CVPA4=AcVPA4/Vc,
 CVPA2=AcVPA2/Vc
 }$

seed_:=1321$

Daisy()$

end$
```

Fig. 2. The input to the Daisy program for the identifiability of the model from Fig. 1.