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International Journal of clinical pharmacology and therapeutics

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38/5
Mai 2000

Dustri-Verlag
Dr. Karl Feistle
http://www.dustri.de

international journal of
clinical pharmacology and
therapeutics
BML Floor 2
UC San Diego
Received on: 05-19-2000

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This journal is included in the abstracting and indexing coverage of the Bio-Sciences Information Service of Biological Abstracts, and is listed in Current Contents (Life Sciences), INDEX MEDICUS/MEDLINE, International Pharmaceutical Abstracts, EMBASE/Excerpta Medica, Elsevier BIOBASE/Current Awareness in Biological Sciences.

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Managing Editor

Dr. Joyce Mayer, Dustri-Verlag, Dr. Karl Feistle, Bahnhofstr 9, D–82041 Deisenhofen-München, Germany, Tel. +49-89-613861-25
email: dustri-jm@t-online.de

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ISSN 0946-1965

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Volume 38 (12 issues per volume) will be published in 2000.

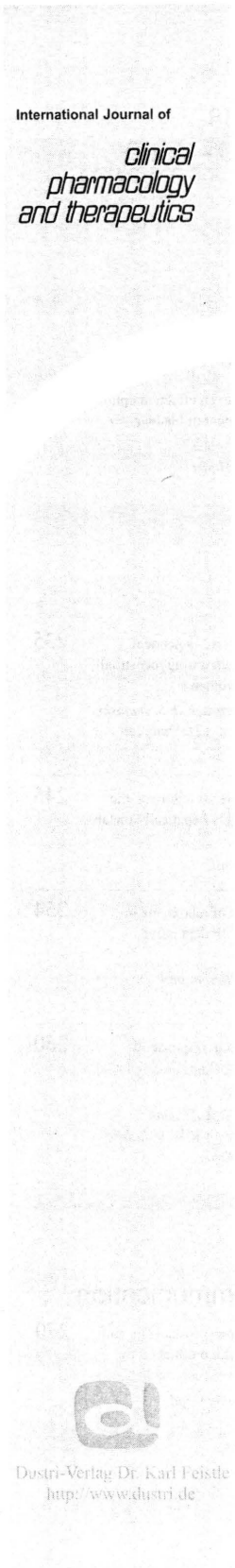
Subscription price for 2000: DM 375.–, US $ 190.– / US $ 230.– Institution plus postage. Single copies: DM 40.–, US $ 25.– plus postage.

Available from all booksellers or directly from the publisher.

Periodical postage paid at Jamaica, NY, U.S.A. Postmaster; Send address changes to **International Journal of Clinical Pharmacology and Therapeutics**, Publications Expediting Inc., 200 Meacham Avenue, Elmont, NY 11003. Air freight and mailing in the U.S. by Publications Expediting, Inc., 200 Meacham Ave., Elmont, NY 11003, USA.

Subscriptions are automatically canceled at the end of the year and recommence only with renewal. Prepayment is required on all orders.

Printed in Germany by A. Butz, Haager Straße 8, D-81671 München, Germany



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International Journal of Clinical Pharmacology and Therapeutics, Vol. 38 – No. 5/2000 (245-253)

Effect of chronic renal failure on the disposition of highly hepatically metabolized drugs

R. Yuan[1] and J. Venitz[2]

[1]CDER-OPS-OCPB-DPE-I, Food and Drug Administration, Rockville, MD, and [2]Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, USA

Key words
renal – impairment – metabolism – binding

Abstract. Objective: The objective of this study was to investigate the effect of renal impairment on the disposition of an extensively metabolized drug, i.e., drug X. Drug X has a hepatic extraction ratio of less than 0.1 and free fraction in plasma of less than 1% in healthy volunteers. Methods: Pharmacokinetic (PK) parameters of drug X were obtained from subjects with normal renal function (I, n = 6), as well as in subjects with mild (II, n = 5), moderate (III, n = 7) and severe renal impairment (IV, n = 5). Disease-PK models were developed to describe the changes of PK parameters with respect to renal function measured by creatinine clearance. While experimentally observed data are presented for drug X, additional simulations were performed for other drugs that are extensively metabolized (extensive metabolism is defined as metabolism that accounts for more than 90% of total drug elimination). The simulated scenarios included drugs that have a low extraction ratio (ER) and with high plasma protein binding (PPB), low ER and with low PPB, high ER and with high PPB, or high ER and with low PPB. Results: Systemic clearance of drug X, a low ER and high PPB drug, in renal patients depended on the simultaneous effects of renal disease on protein binding and intrinsic metabolic clearance. Protein binding of drug X was related to creatinine clearance in an inverse hyperbolic relationship, while the unbound intrinsic metabolic clearance declined linearly with creatinine clearance. Because the disease effects on these two factors offset each other in terms of total systemic clearance, the lowest total systemic clearance was not observed in the severely renal impairment patients, but rather in the moderately impaired group. Additional simulations showed that for low ER drugs that are highly metabolized, the pattern and magnitude of systemic clearance change in renal patients depended on how the disease affected PPB and/or intrinsic metabolic clearance. But the systemic clearance of high ER drugs would not be as susceptible to the effect of renal disease as that of low ER drug. Conclusions: Chronic renal disease should not be considered as an isolated event that affects only renally excreted drugs. Uremia may also modify the disposition of a highly metabolized drug by changes in plasma protein binding and/or hepatic metabolism.

Received
August 20, 1999:
accepted in revised form
November 22, 1999

Correspondence to
Dr. R. Yuan
Building 1-3C39,
340 Kingsland Street,
Nutley, NJ 07110, USA

Introduction

Liver function as it relates to drug metabolism has generally been assumed to be unchanged in patients with chronic renal failure (CRF) as compared to patients with normal renal function (NRF). Based on this assumption, the disposition of highly metabolized drugs in CRF patients is expected to be similar to that in NRF subjects. This implies that it may not be important to prospectively study new drugs in CRF patients, if they are almost exclusively hepatically metabolized. However, mounting evidence has shown that CRF can change the non-renal clearance (i.e., mainly hepatic metabolism) and thereby cause alterations in the disposition of highly metabolized drugs as well [Lam et al. 1997, Touchette and Slaughter 1991].

CRF is known to cause alterations in plasma protein binding [Matzke and Keane 1989]. In plasma, the unbound fraction (f_u) of a drug can either increase or decrease in CRF patients depending on the physico-chemical properties and binding characteristics of the drug. Acidic drugs that preferentially bind to albumin usually have an increased f_u as a result of a qualitative change in the binding site(s), decreased serum albumin levels due to renal albumin loss, and/or an endogenous binding displacers that accumulate in uremia. The f_u of basic drugs, on the other hand, may

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decrease because of increased serum α_1-acid-glycoprotein levels as the response to a chronic inflammatory disease state [Gibson 1986].

CRF may also result in decreased hepatic metabolic activity for a drug [Gibson 1986, Touchette and Slaughter 1991]. Product inhibition and reverse hydrolysis as a result of acyl-glucuronide migration are the proposed mechanism to explain decreased hepatic metabolism in CRF patients for some drugs [Debord et al. 1994, Fillastre 1994], but they do not offer an explanation for the entire observed reduction in hepatic metabolism in CRF patients. In an ex vivo single-pass perfusion study in rat liver, Terao and Shen [1985] demonstrated the existence of endogenous molecule(s) circulating in the uremic blood that inhibited the intrinsic hepatic metabolic clearance of propranolol. In their study, the normal liver perfused with uremic blood had a lower metabolic activity than the normal liver perfused with normal blood, while the uremic liver perfused with normal blood had the same metabolic activity as normal liver with normal blood. Although the exact nature of the circulating metabolic inhibitor(s) has not been identified, this hypothesis is often cited as the mechanism for the reduced metabolic clearance in CRF patients [Lam et al. 1997, Matzke and Keane 1989, Touchette and Slaughter 1991].

For a highly metabolized drug that has low hepatic extraction ratio (ER), systemic clearance (CL_{tot}) of the drug is determined primarily by f_u and intrinsic hepatic metabolic clearance (CL_{int}) [Wilkinson and Shand 1975]. In this paper, we report a case where the systemic clearance of a drug (drug X) in CRF patients was affected simultaneously by CRF effects on both CL_{int} and f_u, leading to an unusual U-shaped relationship between CL_{tot} and creatinine clearance (CL_{crea}). Under such circumstances, severely renally impaired patients and NRF patients on the two extremes had the same CL_{tot} while only moderately impaired patients had a reduction in CL_{tot}. We developed a disease-PK model and conducted a series of simulations to illustrate different scenarios on how CL_{tot} of highly metabolized drugs may be affected by CRF.

Drug X is a synthetic compound with a small molecular weight (MW ~ 300 Dalton) that is administered therapeutically as a short i.v. infusion. Of the total administered dose, less than 1% is excreted as unchanged drug in urine (fe) and less than 10% in feces. Hepatic glucuronyl conjugation of the parent drug accounts for less than 10% of the dose excreted in urine, whileas the rest are oxidative metabolites formed by different cytochrome (CYP) pathways. The main circulating metabolite is formed by CYP2D6 hydroxylation. Drug X is a low hepatic extraction ratio drug with a total systemic clearance of 8 l/h. In healthy subjects, 99.6% of the parent drug in plasma is protein-bound, mainly to albumin. Linear pharmacokinetics are observed for the parent drug over one half to two times of the proposed therapeutic dose range.

Methods

Data resources

The clinical PK study was part of a new drug application submitted to US Food and Drug Administration (FDA) for review. In this particular clinical study (see below), the sponsor provided the estimates of pharmacokinetic parameters for each individual subject such as f_u, $AUC_{0\text{-}inf}$, CL_{tot} and CL_{crea}, but did not perform the analysis reported here. The only pharmacokinetic estimates extracted from the original submission were the total $AUC_{0\text{-}inf}$, the unbound fraction in plasma f_u, and the amount of parent compound excreted in urine (Ae). These parameters were taken from all subjects who completed the study without any violation of the protocol.

Case

The clinical study included subjects with various degree of renal function stratified by severity of CRF, based on the observed CL_{crea}. Data included in our analysis were from 6 subjects with NRF (group I, CL_{crea} > 80 ml/min), 5 with mild (group II, CL_{crea} = 50 – 79 ml/min), 6 with moderate (group III, CL_{crea} = 20 – 49 ml/min) and 5 with severe chronic renal impairment (group IV, CL_{crea} < 19 ml/min). All subjects received a short intravenous infusion of the drug. Creatinine clearance for each individual was determined

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from two 24-hour urine collections, and the plasma protein binding of the drug was examined by equilibrium dialysis of the pre-dose plasma samples fortified with radiolabeled drug. The plasma and urine concentrations of the drug were determined using a validated HPLC method with UV detection. The detection limit for the parent drug was 2 ng/ml in plasma and in urine.

Pharmacokinetic analysis

Total plasma clearance of the drug (CL_{tot}) was estimated by non-compartmental analysis:

$$CL_{tot} = dose/AUC_{0\text{-}inf} \quad \text{(Eq. 1).}$$

The unbound plasma clearance of the drug was derived from normalizing CL_{tot} by f_u:

$$CL_{tot}^{u} = CL_{tot}/f_u \quad \text{(Eq 2).}$$

The fraction of the drug excreted in the urine (fe) was obtained as fe = Ae/dose. Ae is the amount of drug excreted in urine. Hepatic clearance of total drug (CL_{hep}^{tot}) was calculated as:

$$CL_{hep}^{tot} = CL_{tot} \times (1 - fe) \quad \text{(Eq 3).}$$

Using the well-stirred hepatic clearance model developed by Wilkinson and Shand [1975], the unbound intrinsic metabolic clearance (CL_{int}) was calculated as:

$$CL_{int} = CL_{hep} \times Q_{hep}/(Q_{hep} \times f_u - CL_{hep} \times f_u) \quad \text{(Eq 4)}$$

where Q_{hep} is the hepatic plasma flow and is assumed to be unaffected by CRF [Leblanc et al. 1996]; f_u is the unbound fraction in the plasma.

After reviewing the data obtained for drug X, the following empirical disease-PK model was used to relate f_u to creatinine clearance (CL_{crea}):

$$f_u = f_u^{max} - (f_u^{max} - f_u^{min}) \times CL_{crea}/(CL_{crea} + RF_{50}) \quad \text{(Eq 5).}$$

This relationship postulates an inverse hyperbolic relationship between f_u and CL_{crea}, where f_u^{max} was the maximum unbound fraction of the drug in the plasma at the lowest renal function, f_u^{min} was the minimum unbound fraction of the drug in the plasma achieved in NRF, and RF_{50} was the creatinine clearance at which f_u was decreased to 50% of ($f_u^{max} - f_u^{min}$, see also Figure 1d).

The following empirical disease-PK model was used to relate CL_{int} to CL_{crea}:

$$CL_{int} = CL_{int}^{0} + S_{int} \times CL_{crea} \quad \text{(Eq 6)}$$

where CL_{int}^{0} (intercept) is the intrinsic clearance in severe CRF patients who have virtually no residual renal function, and S_{int} (the slope) is the increment in CL_{int} with increase in CL_{crea}.

Because of the common practice of using the values from healthy volunteers (NRF) as baseline condition when PK of a drug in renal patients are evaluated, the model can be reparameterized to:

$$CL_{int} = CL_{int}^{N} - S'_{int} \times \%\ of\ \Delta CL_{crea} \quad \text{(Eq 7)}$$

which assumes a decline in CL_{int} that is proportional to the decline in CL_{crea}. CL_{int}^{N} is the intrinsic clearance in NRF and S'_{int} (the slope) is the decrement in CL_{int} with each percent decrease in CL_{crea}. Note that the most severe CRF patients, who have 100% decrease of creatinine clearance, would have a $CL_{int} = CL_{int}^{N} - S'_{int} \times 100$.

For drug X, after calculations of the pertinent variables from the clinical PK data, i.e., CL_{int} (CL_{crea}) and f_u (CL_{crea}), the following parameters were estimated in order to describe the effect of CRF on the pharmacokinetic parameters: f_u^{max}, f_u^{min}, RF_{50}, CL_{int}^{0}, S_{int}, as well as CL_{int}^{N} and S'_{int}.

Pharmacokinetic simulations

With the parameters obtained from modeling f_u and CL_{int} of drug X (see above), the following three cases were simulated for drugs with similar pharmacokinetic characteristics as drug X:

- renal impairment affects only f_u, but to different degrees by altering RF_{50} from 0.5 to 50 l/h,
- renal impairment affects only CL_{int}, but to different degrees by altering S_{int} from 30 to 900, and
- renal impairment affects both f_u and CL_{int} by setting RF_{50} at 1 l/h and S_{int} at 300.

These three cases described a scenario where the CRF affects PK of a drug with high

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