Development and Validation of Limited-Sampling Models for the Antiretroviral Agent Zidovudine


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Summary

Limited-sampling strategies for zidovudine were studied in order to estimate the area under the concentration-time curve (AUC), the maximum plasma concentration (C_{max}) and the plasma elimination half-life (t_{1/2}) values of this antiretroviral agent. Six models, using 1 to 4 timepoints, were developed from a test data set of 42 patients. One model, consisting of 2 timepoints, t = 30 and t = 180 minutes after ingestion of zidovudine, and the zidovudine dose as an extra variable, appeared to be the best model for predicting AUC and C_{max} values in a validation data set of another 41 patients. The proposed equations are:

\[
AUC (\text{mg/L} \cdot \text{h}) = 0.0022 (\text{h/L}) \cdot \text{dose (mg)} + 5.24 (\text{h}) \cdot C_{180} (\text{mg/L}) + 0.39 (\text{h}) \cdot C_{30} (\text{mg/L});
\]

and:

\[
C_{\text{max}} (\text{mg/L}) = 0.0022 (\text{L/mg}) \cdot \text{dose (mg)} + 2.11 \cdot C_{180} (\text{mg/L}) + 0.93 \cdot C_{30} (\text{mg/L}).
\]

In contrast, t_{1/2} values could not be predicted with acceptable confidence by any one of the models. However, during the terminal elimination phase, reliable t_{1/2} values could be obtained using only 2 timepoints (t = 120 and t = 180 minutes) to determine the zidovudine concentration. The proposed limited-sampling models can be of great value to obtain more insight into the relationships between the pharmacokinetic and pharmacodynamic properties of zidovudine, which are still poorly understood.

Relationships between pharmacokinetic and pharmacodynamic parameters have been thoroughly studied for only a limited number of drugs. Therapeutic drug monitoring of anticonvulsants, theophylline, digoxin and aminoglycosides are examples in which plasma steady-state or peak-trough concentrations are determined and utilised in order to optimise pharmacotherapy (Spector et al. 1988). Furthermore, determination of the area under the concentration vs time curve (AUC) has been proven to be of value in predicting the clinical response and toxicity of several anticancer agents (Collins et al. 1990; Egorin 1992; Moore & Erlichman 1987).

Only limited investigations on antiretroviral drugs with regard to the relationship between the pharmacokinetic and pharmacodynamic properties have been performed. This is probably due to the rapid introduction and short period of clinical research of the currently available agents, such as zidovudine, didanosine and zalcitabine. Furthermore, pharmacodynamic effects of antiretroviral
agents are mostly measured by ‘surrogate markers’ (CD4+ lymphocyte counts, p24 antigenaemia, vi­raemia) in the absence of other, readily available clinical response criteria. Moreover, the active form of all dideoxynucleosides, including zidovudine, is an intracellular triphosphate-metabolite, which can only be measured after the administration of radiolabelled drug (Stretcher 1991).

Despite these restrictions, some attempts have been made by Balis et al. (1989, 1992) to correlate the pharmacokinetics and pharmacodynamics of antiretroviral agents in 2 investigations with HIV-infected children. In the first study (Balis et al. 1989), they found a correlation between steady-state plasma concentrations of zidovudine after continuous infusion and the development of neutro­penia, but not between plasma or cerebrospinal fluid (CSF) concentrations of zidovudine and neu­ropsychological improvement. Significant relationships between pharmacokinetic parameters (e.g. the AUC) of orally administered didanosine and clinical response, measured as a decrease in p24 antigenaemia and neuropsychological improvement, were found in a subsequent study (Balis et al. 1992).

For zidovudine, the most widely used agent in HIV disease, relationships between pharmacokinetic and pharmacodynamic parameters after oral administration are not known. Measurement of single plasma concentrations is not meaningful in this respect as no steady-state plateau of zidovudine concentrations is reached (Collins & Unadkat 1989). Furthermore, peak levels show great variability, while trough levels are often undetectable. A detailed pharmacokinetic analysis of 10 or more timed plasma concentrations would give much more information but would be inconvenient, laborious and expensive. A more efficient strategy for the estimation of individual patient pharmacokinetic parameters is the application of a limited-sampling model. This strategy has been successfully applied to several anticancer agents, including amonafide (Ratain et al. 1988), carboplatin (Sorensen et al. 1993), cyclophosphamide (Egorin et al. 1989), doxorubicin (Ratain et al. 1991), piri­trexim (Adamson et al. 1992), thiotepa (Ackland et al. 1988), and vinblastine (Ratain & Vogelzang 1987).

The aim of this study was to develop and validate a limited-sampling model for zidovudine in order to provide an efficient basis for future pharmacokinetic-pharmacodynamic investigations in our hospital.

Patients and Methods

Patients

Data were used from 83 pharmacokinetic curves derived from 62 patients, who participated in a population-oriented pharmacokinetic study of zidovudine from 1989 to 1992. Inclusion of more than one curve per subject was allowed, as interpatient variability in zidovudine pharmacokinetics was considered to be as large as interpatient variability. The study was approved by the hospital’s Scientific and Ethics Committees.

Pharmacokinetic Study

After an overnight fast, the participants ingested their usual morning dose of zidovudine at the pharmacokinetic unit of the hospital. No food or drinks were allowed until 90 minutes after ingestion of the zidovudine capsules. Blood samples were collected in heparinised tubes just before and 10, 20, 30, 45, 60, 90, 120, 150 and 180 minutes after drug ingestion. The samples were immediately centrifuged and the plasma was separated and stored at -30°C until analysis. Zidovudine levels were determined by a high performance liquid chromatographic (HPLC) method, as described previously (Underberg et al. 1989). From September 1992, zidovudine was measured in plasma using a commercially available radioimmunoassay (RIA) kit (Incstar Co., Stillwater, MN, USA) [Tadepalli et al. 1990]. Results from both assays were comparable (Tadepalli et al. 1990). The assays proved to be sensitive [lower limit of quantification 20 μg/L (HPLC) and 10 μg/L (RIA)] and reproducible (assay variation coefficient less than 15%).

The following pharmacokinetic parameters were investigated: the maximum observed plasma con-