ing disease was diagnosed. We initiated oral treatment with UFT (600 mg daily in 3 divided doses, combined with 30 mg calcium folinate 3 times daily, days 1-28; days 29-35, pause), which was followed by a partial response and not associated with adverse effects until an episode of minor duodenal bleeding occurred in December 2002. In this situation we decided to pause chemotherapy. Three months later, the patient had increasing pain from the rheumatoid arthritis, and treatment with leflunomide (*N*-[4-(trifluoromethyl)-phenyl] 5-methylisoxazole-4-carboxamide) (Arava; Aventis Pharma, Frankfurt, Germany) was initiated with a starting dose of 100 mg/d for 3 consecutive days followed by a maintenance dose of 20 mg/d. This measure was followed by a good response of polyarthritis, and the patient reported good quality of life. Therefore the locally progressing tumor was again treated with UFT (dosage as described earlier). After completion of 2 cycles, the patient had increasing numbness of both lower extremities in a stocking pattern, which was suggestive of polyneuropathy (PNP). Nerve conduction studies confirmed axonal sensorimotor PNP. In addition, the patient had severe diarrhea and hand-foot syndrome. The latter 2 adverse events were self-limited and manageable in an outpatient setting.

Because (1) there were no further risk factors for the development of PNP, (2) there was no exposure to any other neurotoxic drugs, and (3) the patient had previously tolerated UFT alone well, we believe this to be a case of PNP and gastrointestinal toxicity that was induced by a potential drug interaction between UFT and leflunomide. This is of special interest because leflunomide is currently being investigated—as an inhibitor of platelet-derived growth factor receptor signaling—in ongoing phase I and II studies in combination with cytotoxic agents for the treatment of various cancers.[2]

Both 5-fluorouracil (5-FU) and leflunomide have been reported to cause neurotoxicity on their own,[3,4] but we infer a potential drug interaction as the cause of this unexpected toxicity: Leflunomide's active metabolite A77 1726 inhibits the key enzyme in pyrimidine synthesis, dihydroorotate dehydrogenase.[3] In UFT, uracil is used to increase the bioavailability of the 5-FU prodrug tegafur by inhibiting dihydropyrimidine dehydrogenase, which is the rate-limiting enzyme in 5-FU catabolism.[5] Thus leflunomide may increase 5-FU toxicity either by upstream inhibition of pyrimidine synthesis, thereby increasing conversion of 5-FU to fluorouracil monophosphate (FUMP), or by additional blockade of dihydropyrimidine dehydrogenase (Fig 1).

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Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms

To the Editor:

Recently, Niemi et al[1] reported in the Journal that cytochrome P450 (CYP) *2C9*1/*3* individuals showed significant alterations in glimepiride pharmacokinetics compared with **1/*1* individuals. In individuals heterozygous for the *CYP2C9*3* allele (n = 3), the median total area under the plasma concentration–time curve (AUC) of glimepiride was 267% of the values in subjects with the *CYP2C9*1/*1* genotype. However, only 3 individuals heterozygous for the *CYP2C9*3* allele were involved in this experiment. The concentrations of hydroxy metabolite (M1) and carboxy metabolite (M2) were not measured, and the parameters related to M1 and M2 were not mentioned. Glimepiride is metabolized mostly in the liver to the active M1 metabolite by CYP2C9, which shows genetic polymorphism,[2] with further dehydrogenation to the inactive M2 (carboxy) metabolite.[3] Thus we assessed the pharmacokinetics of oral administration of glimepiride in relation to CYP2C9 genetic polymorphism in healthy Chinese subjects.

The protocol was designed according to Good Clinical Practice principles and approved by the Ethics Committee of the Chinese People Liberation Army General Hospital, Beijing, China. All volunteers were determined to be healthy and signed informed consent forms before participation. CYP2C9 genotype was determined by oligonucleotide microarray as described earlier.[4] Nineteen subjects (9 expressing *CYP2C9*1/*1*, 9 expressing *CYP2C9*1/*3*, and 1 expressing

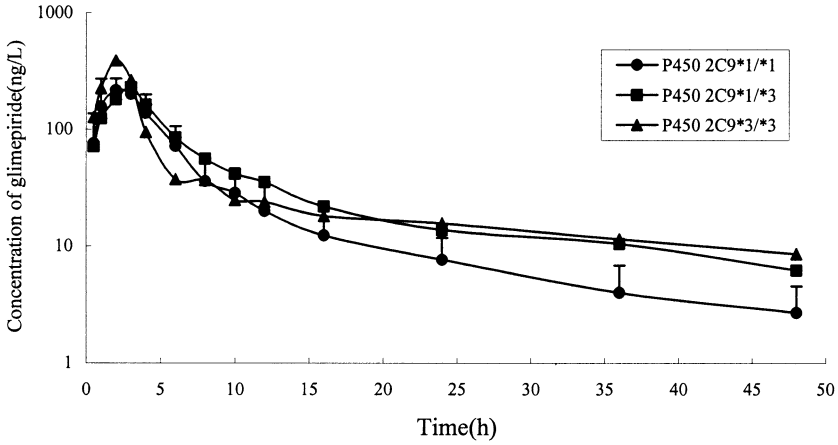

Fig 1. Mean (±SD) plasma concentrations of glimepiride in healthy Chinese volunteers with different CYP2C9 genotypes after single oral 4-mg dose of glimepiride.

Table I. Measures of glimepiride pharmacokinetics and metabolism by CYP2C9 genotype

	*CYP2C9*1/*1*	*CYP2C9*1/*3*	*CYP2C9*3/*3*
$t_{½}$ (h)	11.4 ± 4.3	18.6 ± 6.1†	38.2
$AUC_{0\text{-}48}$ ($\mu g \cdot L^{-1} \cdot h$)	1355.4 ± 314.0	1707.5 ± 500.2	1893.5
$AUC_{0\text{-}\infty}$ ($\mu g \cdot L^{-1} \cdot h$)	1461.9 ± 341.9	1877.8 ± 508.7†	2247.5
t_{max} (h)	2.1 ± 0.6	2.6 ± 0.5	2
C_{max} ($\mu g \cdot L^{-1}$)	260.3 ± 81.5	272.9 ± 86.6	391.6
CL_o ($L \cdot h^{-1}$)	3.0 ± 0.6	2.3 ± 0.4†	1.8
CL_{form} ($L \cdot h^{-1}$)	1.3 ± 0.3	0.8 ± 0.2†	1.1

$t_{½}$, Half-life; $AUC_{0\text{-}48}$, area under plasma concentration–time curve from 0 to 48 hours; $AUC_{0\text{-}\infty}$, area under plasma concentration–time curve from time 0 to infinity; t_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; CL_o, oral clearance; CL_{form}, formation clearance.
†$P < .05$ for *CYP2C9*1/*3* versus *CYP2C9*1/*1* (Dunnett test).

*CYP2C9*3/*3*) were invited to participate in the phenotype phase of the study. Blood and urine samples were collected after 4 mg glimepiride was administered orally. Plasma glimepiride and urine M1 and M2 concentrations were determined by HPLC.[5]

CYP2C9 genotype significantly affected the pharmacokinetics of glimepiride. The concentration-time profiles of glimepiride for each of the genotyped groups are illustrated in Fig 1, and the pharmacokinetic data are presented in Table I. The AUC from time 0 to infinity ($AUC_{0\text{-}\infty}$) was significantly greater in the *CYP2C9*1/*3* subjects than in **1* homozygotes ($P < .05$), with the **1/*3* and **3/*3* individuals demonstrating 1.3- and 1.4-fold increases in mean glimepiride $AUC_{0\text{-}\infty}$, respectively. In subjects with the *CYP2C9*1/*3* allele, the half-life ($t_{½}$) of glimepiride was 163% of the values in subjects expressing *CYP2C9*1/*1* ($P < .05$). Glimepiride oral clearance (CL_o) was significantly reduced in *CYP2C9*1/*3* individuals to 75% of that in **1* homozygotes ($P < .05$), suggesting that significant differences in glimepiride elimination exist among individuals expressing different genotypes. Glimepiride formation clearance (CL_{form}) to its M1 and M2 metabolites was also significantly reduced in *CYP2C9*1/*3* individuals (65%, $P < .05$), as compared with subjects expressing **1/*1*. However, no significant differences were found in the AUC from 0 to 48 hours ($AUC_{0\text{-}48}$), amount of M1 and M2 secreted in urine, and blood glucose variables of glimepiride between the subjects with different genotypes. In clinical diabetes therapeutics, glimepiride is always administered at a dosage of 2 to 4 mg/d for several months, whereas the volunteers in our study were given a single administration of 4 mg glimepiride orally. The relationship of CYP2C9 genetic polymorphisms to pharmacokinetics and pharmacodynamics of glimepiride may be more clear after multiple administrations or 8 mg glimepiride. The results will be more useful to clinical therapeutics after multiple administrations. These preliminary observations suggest that the CYP2C9 genotype should be evaluated with regard to drug interactions or individualized therapy.

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The authors have declared no conflicts of interest associated with this work.

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Traditional Chinese medicine information database

To the Editor:

Recently, De Smet[1] discussed the health risks of herbal remedies. He pointed out the importance of comprehensive, reliable, and easily accessible reference sources for disseminating and evaluating the risks, as well as therapeutic effects, of herbs. Because of increased use of traditional medicines, there is also a need for resources that provide comprehensive information about these medicines, which are otherwise not easily accessible and are sometimes not retrievable from the conventional literature resources. The ability to evaluate the beneficial and risk effects of herbs can be enhanced if information about herbal constituents is also provided.

An initiative for collecting and evaluating toxicologic data about traditional Chinese medicine (TCM) has recently been launched.[2] More comprehensive data about TCM are needed for fully assessing the beneficial and risk effects[1,3] and for facilitating scientific and clinical study of TCM.[4,5] The TCM Information Database (TCM-ID) (http://tcm.cz3.nus.edu.sg/group/tcm-id/tcmid.asp) has been introduced as a Web resource to provide free-of-charge information about all aspects of TCM including prescriptions, constituent herbs, and herbal ingredients, as well as their respective therapeutic effects and clinical indications and applications. The structure and functional properties of active ingredients are also provided.

Data were obtained from reputable Chinese TCM books and relevant Western and Chinese journals including the *Journal of Ethnopharmacology*, *Planta Medica*, *Journal of Pharmaceutical Sciences*, *Phytochemistry*, *Complementary Therapies in Medicine*, *Journal of Alternative and Complementary Medicine*, *The American Journal of Chinese Medicine*, *Chinese Traditional Herbs and Drugs*, *Acta Pharmacologica Sinica*, *Journal of Chinese Medicine Mat*, and *Chinese Journal of Medicine and Chemistry*. TCM-ID currently contains 1197 TCM prescriptions covering 4111 disease conditions, 1104 herbs, and 9862 ingredients (4500 of these with 3-dimensional structure provided). Each prescription/herb/ingredient can be retrieved through multiple methods including prescription name, herb name in 3 languages (Latin, English, and Chinese), name of herbal ingredient, therapeutic effect, and symptom.

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