Letters to the Editor:

Pharmacokinetics of Tolbutamide in Acute Renal Failure Induced by Glycerol: Speculative Thoughts and Perspectives

Nuggehally R. Srinivas*
Suramus Biopharm, 77, 10th Cross, 29th Main, J.P. Nagar I Phase, Bangalore, India

Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

To the Editor:

Izuwa et al.1 recently performed and reported a comparative study of altered quinidine pharmacokinetics in rats for two different acute renal failure (ARF) models, namely glycerol-induced ARF and cisplatin-induced ARF.1) The selection of quinidine was an important consideration, since only 3% of the administered dose of healthy rats was renally eliminated, and the choice of two different ARF models was good to tease out pharmacokinetic differences between the two approaches for a drug that undergoes elimination by non-renal mechanisms.1) Also, since the pathogenesis appeared to be different between glycerol-induced ARF and cisplatin-induced ARF, this particular study attains a greater significance for understanding the underlying cause of the differences from a mechanism point of view.1) The experimental protocol, data generation, and data interpretation of quinidine pharmacokinetics in the two different ARF models were performed with rigor using all available literature information for appropriate corroboration of the observed findings. The increased alpha-acid glycoprotein expression during glycerol-induced ARF is a significant finding, since it may have relevance for many highly protein bound compounds. Interestingly, another substrate, tolbutamide, was also evaluated in the glycerol-induced ARF model in this study.1) Although there was a decreased exposure of tolbutamide in ARF rats relative to control rats, the authors did not comment on the likely reasons for the decreased exposure, which was the exact opposite to what was observed for the quinidine substrate in both ARF rat models. The intent of this communication is to provide some perspectives and speculative comments to possibly explain the decreased exposure of tolbutamide in ARF rats.1)

Interestingly, tolbutamide has been previously studied in a folate-induced ARF model in rabbits. In this model, tolbutamide plasma concentrations were significantly elevated in both mild ARF and moderate ARF relative to control rabbits (for instance, the reported AUC values for control, mild-ARF, and moderate-ARF rabbits were 2295, 2906, and 4074 µg/mL/h, respectively).2) Also, the urinary excretion of tolbutamide was significantly retarded in the ARF model (approximately twofold lower urinary recovery in ARF relative to control rabbits). The overall elimination rate constant in ARF rabbits was approximately 61% lowering of elimination rate constant in ARF rats relative to control rabbits.2) It was concluded that depressed metabolism of the drug was the main contributor to increased levels during ARF.2) Therefore, the reported decreased exposure in tolbutamide, albeit in a different type/species of ARF model, was somewhat unexpected, but was an interesting observation.1)

In the literature on sulfonylureas, which include tolbutamide, there has been a report of increased biliary glutathione stimulation by these agents.3) Also, it has been suggested that the formation of an in vivo metabolite of tolbutamide, namely formyltolbutamide, may have primarily contributed to the formation of labile glutathione conjugates which were rapidly excreted in the bile.3) Hence, biliary excretion of tolbutamide and/or its primary metabolite such as formyltolbutamide may have contributed to the observed lower exposure of tolbutamide in the glycerol-induced ARF model.1) In this context, there have been reports of enhanced biliary excretion of substrates, perhaps as a compensatory mechanism, during ARF.5,6) Moreover, in an interesting study of radio-labeled warfarin, it was found that administration of either tolbutamide or phenylbutazone 60 min after warfarin dosing hastened the biliary excretion of warfarin due to increased biliary flow rate.6)

The contribution of ARF to increased cytochrome P450 (CYP) enzymatic expression has been reported.7,8) Therefore, it is conceivable that there could have been a mild to moderate increase in CYP2C expression in rats during ARF, leading to a greater formation of the formyltolbutamide metabolite. As suggested earlier, the presence of formyltolbutamide may have hastened biliary excretion by forming labile conjugates with glutathione.5,7)
Tolbutamide is a poorly water soluble compound, and some research has been carried out to improve the oral bioavailability of tolbutamide using self-emulsifying microemulsion systems. Similar to the issues found with oral cyclosporine during glycerol-induced ARF, it is conceivable that the oral absorption of tolbutamide may have been diminished due to either a decreased rate of absorption or delayed gastric emptying, resulting in a reduced exposure to the drug in the rat ARF model.

Lastly, as a result of renal impairment, there may be altered protein binding of acidic compounds, since nephrotoxic substances may compete and/or inhibit the serum albumin binding potential of such acidic compounds. Therefore, an increased unbound fraction of acidic compounds such as tolbutamide may contribute to lowered blood/plasma concentrations due to an increased apparent volume of distribution.

Overall, it may be reasonable to speculate that multiple pathways such as enhanced biliary excretion, increased hepatic CYP expression, increased volume of distribution, and/or retarded oral absorption of tolbutamide may have contributed to the observed lower exposure of tolbutamide in the glycerol-induced ARF rat model.

References