Results of the First-in-Human Clinical Trial for MB-102, a Novel Fluorescent Tracer Agent for Real-Time Measurement of Glomerular Filtration Rate

Richard B. Dorshow*, Martin P. Debreczeny, and Thomas C. Dowling#

MediBeacon, LLC, 1100 Corporate Square Drive, St. Louis, Missouri 63132, USA
#Ferris State University, Grand Rapids, Michigan 49503, USA

ABSTRACT

The fluorescent tracer agent 2,5-bis[N-(1-carboxy-2-hydroxy)]carbamoyl-3,6-diaminopyrazine, designated MB-102, has been developed with properties and attributes necessary for use as a direct measure of glomerular filtration rate (GFR). Comparison to known standard exogenous GFR agents in animal models has demonstrated an excellent correlation. A clinical trial to demonstrate this same correlation in humans is in progress. This clinical trial is the first in a series of trials necessary to obtain regulatory clearance from the FDA. We report herein the comparison of plasma pharmacokinetics between MB-102 and the known standard exogenous GFR agent Iohexol in healthy subjects with normal renal function. Post simultaneous administration of both agents, blood samples over a period of 12 hours were collected from each subject to assess pharmacokinetic parameters including GFR. Urine samples were collected over this same period to assess percent injected dose recovered in the urine. Results indicate MB-102 is a GFR agent in humans from the comparison to the standard agent.

- **Keywords**: Clinical trial, GFR, renal function, pyrazine, fluorescence, optical monitoring, renal clearance, fluorescent tracer agent, plasma pharmacokinetics

1. INTRODUCTION

Measurement of glomerular filtration rate (GFR) is widely accepted as the most reliable measure of renal function.[1] As a result there is a growing medical need for determining accurate real-time GFR for minimizing the risk of kidney injury due to acute and chronic conditions. The optimum measure of GFR is by the use of exogenous tracer agents. However all current methods are not amenable to portable bedside use, and are therefore used mainly for research purposes. The current clinical standard, measurement of serum creatinine and its use in any of the estimated GFR equations, is a time-delayed measurement. An injury or insult to the kidney would be noted only after 24 to 48 to 72 hours. The serum creatinine measurement is also rather insensitive in that a patient could lose half their kidney function before a measured serum creatinine value reaches an abnormal level. In addition, factors not related to renal function affect serum creatinine, so the measurement itself is often inherently inaccurate as well.

To overcome the deficiencies of the research GFR tracer agents and the current clinical standard, we have synthesized MB-102, a fluorescent tracer that has exhibited characteristics essential for accurate real-time measurement of GFR.[2, 3] In rodents, this compound is freely filtered by the kidneys, is not secreted by the renal tubules, nor has demonstrated any significant metabolism *in vivo*. In dogs, MB-102 has demonstrated similar clearance curves when compared to known exogenous GFR tracer agents such as iohexol and iothalamate, suggesting that MB-102 will provide a similar GFR value and accurate status of overall kidney function in humans.

A formal battery of safety and toxicity studies *(in vitro* and *in vivo*) were completed to gauge overall toxicity and toxicokinetics of MB-102 in both rodents and dogs necessary to proceed to first-in-human clinical evaluation of this compound. Overall the *in vitro* assays indicated no toxicity relating to CYP-450, cloned hERG channels, bacterial reverse mutation or chromosomal alteration assays. Additionally, the compound was totally compatible with human blood and plasma samples. *In vivo*, the compound exhibited no potential toxicity in a series of CNS, respiratory or cardiovascular studies in either rodents or dogs. The results of these studies thus allowed continuation to perform the clinical trial.

*Corresponding author. Tel.: 314 269 5808; E-mail: rbdorshow@medibeacon.com

Reporters, Markers, Dyes, Nanoparticles, and Molecular Probes for Biomedical Applications VII, edited by Samuel Achilefu, Ramesh Raghavachari, Proc. of SPIE Vol. 9339, 933906 · © 2015 SPIE ·
CCC code: 1605-7422/15/$18 · doi: 10.1117/12.2078346

2. MATERIALS AND METHODS

2.1. Fluorescent Tracer Agent.

MB-102 is a fluorescent compound belonging to the general class of compounds known as pyrazines. The chemical structure is shown in Figure 1. The chemical name of MB-102 is 3,6-diamino-2,5-bis{N-[(1R)-1-carboxy-2-hydroxyethyl]carbamoyl}pyrazine. MB-102 has a molecular weight of 372.3, with light absorption and emission maxima at 445 nm and 560 nm, respectively.[2] MB-102 has no structural relationship to other molecules that are known to be carcinogenic or raise other toxicity safety issues.

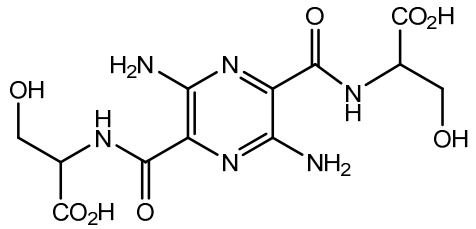


Figure 1. Structure of 3,6-diamino-2,5-bis{N-[(1R)-1-carboxy-2-hydroxyethyl]carbamoyl}pyrazine (MB-102)

2.2. Iohexol.

A known standard GFR tracer agent is the x-ray contrast agent iohexol, marketed under the name Omnipaque[4]. A standard dose for a GFR measurement is 5mL of Omnipaque 300.

2.3. Procedure.

The first-in-human clinical trial consists of administration of the fluorescent tracer agent simultaneously with a known standard (non-fluorescent) GFR tracer agent. Fifteen blood draws over 12 hours post-administration along with collection of urine was completed on 16 subjects with normal renal function as determined by a SCr measurement. The blood samples were spun and concentrations of MB-102 and Iohexol were determined from the plasma samples. Standard pharmacokinetic software (Phoenix WinNonlin) was employed to determine clearance (and hence GFR) from the concentration vs. time data for each agent.

3. RESULTS

3.1 Plasma disappearance of MB-102

Subjects in this clinical study received a dose of 1μmole/kg. The plasma disappearance curve of MB-102 for a representative subject is shown in Figure 2. The circles are the measured concentration of MB-102 at each time point and the line is a fit to this data using a two compartment pharmacokinetic model.

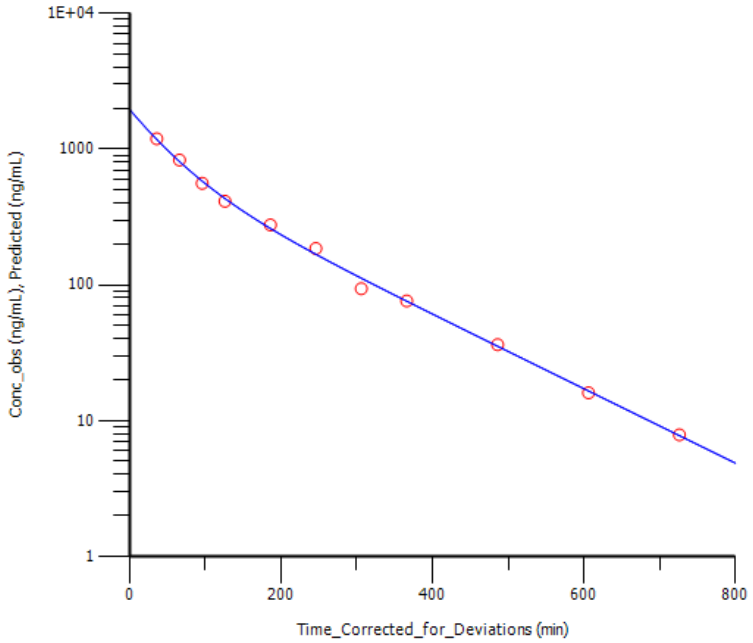


Figure 2. Plasma disappearance, circles are the measured agent concentrations from blood draws and the line is a fit to a standard two-compartment pharmacokinetic model

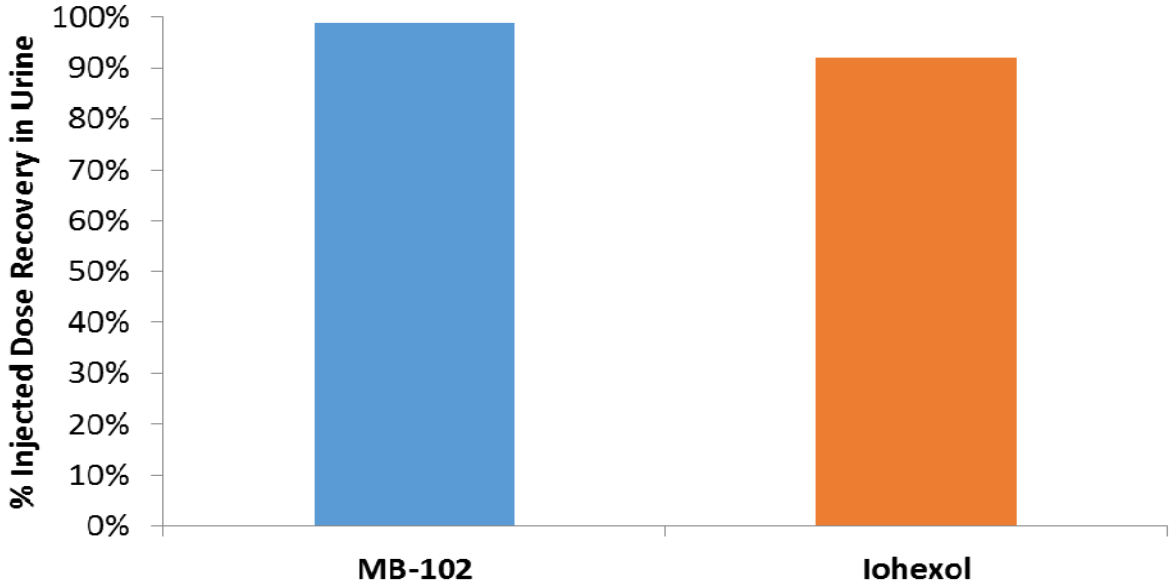
The data for all the subjects fit a two-compartment model with the first compartment being the vascular-to-tissue distribution and equilibrium occurring upon administration of each agent, and the second compartment is the elimination phase resulting from renal excretion. The terminal (second compartment) half-life is approximately 110 minutes and the clearance (GFR) is 134 mL/min.

A similar graph was obtained on the same subject for the Iohexol concentration vs time.

3.2 Injected dose recovery in urine

Collection of all the urine was obtained as best as could be done in a non-catheterized setting for the 12 hour period post-dosing of the agents for 23 subjects in the clinical study. The results are shown in Figure 3.

Figure 3. Percent injected dose recovered in urine (error approximately +/- 7%)



The % injected dose of MB-102 recovered in the urine over this 12 hour time interval post-administration matched that of Iohexol, which is the agreed upon GFR tracer agent standard. Furthermore, the % injected dose of MB-102 recovered in the urine for these human clinical studies match values found in the animal model previously published (J. Med. Chem 2011 **54**, pages 5048-5058, see Table 2, compound **2d**).

4. DISCUSSION

As we found in the previous in vivo animal studies, the plasma pharmacokinetics of fluorescent tracer agent MB-102 matched that of a standard GFR tracer agent in humans with normal renal function. In addition, the amount of the injected dose recovered in the urine matched that of the same standard GFR tracer agent. Clinical trials involving subjects with impaired renal function are scheduled for the near future.

ACKNOWLEDGMENTS

The staff at the General Clinical Research Center at the University of Maryland Medical System in Baltimore were invaluable in conducting the clinical trial, as well as Dr. Jeffrey Fink of the Department of Nephrology, University of Maryland. Dr. J.J. Shieh and Dr. Raghavan Rajagopalan were extremely helpful for their many contributions and discussions.

REFERENCES

[1] Ekanoyan, G.; Levin, N. W., [Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification (K/DOQI)], National Kidney Foundation: Washington, D.C., 1–22 (2002).

[2] Rajagopalan, R., Neumann, W. L.; Poreddy, A. R.; Fitch, R. M., Freskos, J. N., Asmelash, B., Gaston, K. R., Galen K. P., Shieh, J. J., Dorshow R. B., "Hydrophilic pyrazine dyes as exogenous fluorescent tracer agents for real-time point-of-care measurement of glomerular filtration rate" J. Med. Chem. 54, 5048–5058 (2011).

[3] Poreddy, A. R., Neumann, W. L., Freskos, J. N., Rajagopalan, R., Asmelash, B., Gaston, K. R., Fitch, R. M.; Galen K. P., Shieh J. J., Dorshow R. B., "Exogenous fluorescent tracer agents based on pegylated pyrazine dyes for real-time point-of-care measurement of glomerular filtration rate" Bio. Med. Chem. 20, 2490–2497 (2012).

[4] Omnipaque package insert, http://medlibrary.org/lib/rx/meds/omnipaque-1.