Bile Duct-Cannulated Rats in Mass Balance Excretion Studies and Metabolite Profiling

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INTRODUCTION

Bile duct cannulated (BDC) rats are often used in mass balance excretion (AME) studies, and the bile, urine, feces, and sometimes plasma samples are subsequently used for metabolite profiling and identification. The objective of this study was to review 2013 in-house mass balance excretion studies, data from Sprague Dawley (SD) and Wistar Han (WH) rats, to compare the WH vs. SD BDC model based on bile flow and collection volumes. SD BDC rats have been widely used in AME studies, but in recent years there has been a trend toward WH BDC rats. Our initial experience suggested that the WH model is less robust than the SD model with respect to tolerating surgical alteration and requires longer post-surgical recovery time.

MATERIALS AND METHODS

This study compares results from 33 studies (using 95 WH rats in 21 studies and 86 SD rats in 12 studies) performed in a 5-month period. Both WH and SD rats were supplied by a single vendor and were prepared with an indwelling bile duct cannula, which was used for bile sample collections and for infusion of bile salt replacement solution through the duodenal loop.

Animals were housed in wire bottomed plastic metabolism cages throughout the study. Approximately one day prior to dosing rats were lightly anesthetized with isoflurane and the BDC were externalized.

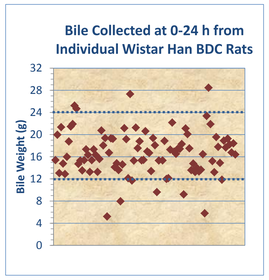
Most animals in this study had a solution of sodium taurocholate (2.3 mg/mL in saline) infused *via* the distal (duodenal) cannula at a rate of 0.9 mL/h, starting on the day of cannula externalization and continuing until the time of euthanasia. Some rats had the distal (duodenal) cannula tied off to seal the cannula and were provided an electrolyte drinking solution instead of being infused with a taurocholate solution.

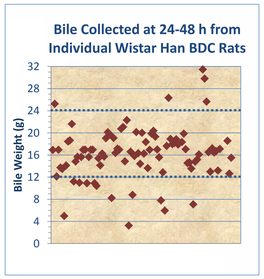
Bile samples were collected from each animal at pre-dose (overnight) and at 2-5 intervals during the first 24 h, and every subsequent 24 h interval post-dose up to 72 h post-dose for WH rats and up to 168 h post-dose for SD rats. All bile specimens were collected over dry ice. The total weight of each bile collection was documented.

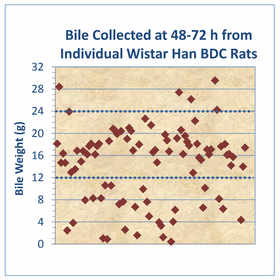
The sample weights of bile, urine, and feces were recorded. All samples were analyzed for radioactivity, with feces being homogenized and oxidized. DEBRA™ v6.0.6.63 LIMS system was used during the in-life and sample and data processing.

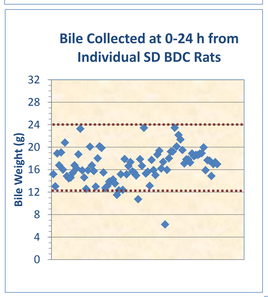
RESULTS

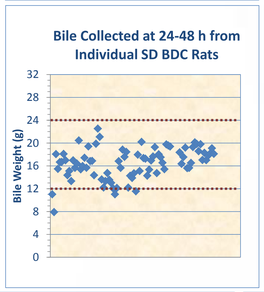
Bile Weights in Each 24 h Collection Period from Individual Rats (◆Wistar Han BDC Rats; ◆ Sprague Dawley BDC Rats)

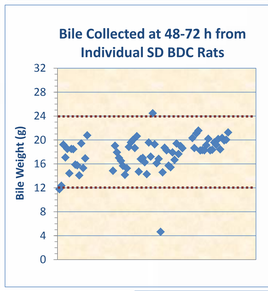


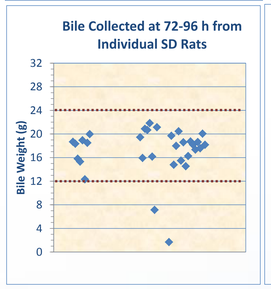


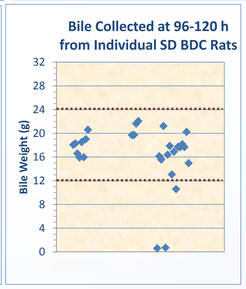


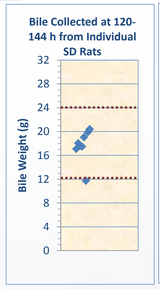


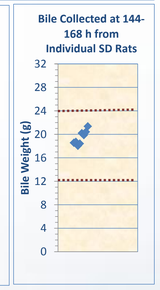












The overall radioactivity recovery from SD rats averaged 92.4%. The overall radioactivity recovery in WH rats averaged 90.9%, with two studies having lower recovery possibly due to the position of the radiolabel.

Mean Bile Weights Collected in 24 h Periods from Wistar Han BDC Rats and Sprague Dawley BDC Rats

Wistar Han BDC Rats							
Collection interval (h)	0-24	24-48	48-72				
Mean Bile Wt (g)	17.1	16.5	14.6				
SD	6.0	5.1	7.2				
%CV	35	31	49				
n	95	91	90				
Sprague Dawley BDC Rats							
Collection interval (h)	0-24	24-48	48-72	72-96	96-120	120-144	144-168
Mean Bile Wt (g)	16.7	16.5	17.7	17.2	16.5	17.7	19.4
SD	2.9	2.7	2.8	4.1	5.1	2.7	1.2
%CV	17	16	16	24	31	15	06
n	86	82	70	32	28	8	8

CONCLUSIONS

- The overall mean volume of 24-h interval bile collection was similar in SD and WH rats: 17.0 g (19% CV) from SD rats and 16.1 g (39% CV) from WH rats.
- This data provides evidence that SD BDC rats are a more robust model with regard to consistency of bile flow and for studies lasting longer than 72 hours.
- For WH BDC rats, because of the observed higher variability, it would be prudent to have spare rats available for mass balance excretion studies.
- Results compiled from approximately 200 BDC studies (over a 3-year period) with both rat strains indicated that for approximately two-thirds of the compounds tested, more than 40% of the recovered radioactivity was eliminated in the bile. Maintenance of physiologic bile flow is therefore a critical component of rodent excretion mass balance and metabolite