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Tissue Distribution of [^{14}C]-Lefamulin in the Urogenital Tract in Rats

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INTRODUCTION & PURPOSE

- The World Health Organization estimates that 1 million sexually transmitted infections (STIs) are acquired each day worldwide[1]
- The incidence rates and causes of STIs vary by geographic region; however, in the United States, the most common bacterial causes of STIs are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, and incidence rates appear to be increasing[2]
- Left untreated, STIs may cause serious health problems[3-5]
  - In women, gonorrhea and chlamydia can lead to pelvic inflammatory disease, which can result in chronic pelvic pain, ectopic pregnancy, and infertility
  - *Mycoplasma genitalium*, another STI-associated pathogen, causes urethritis in men and cervicitis in women
- Although there are treatment options for STIs, antibiotic resistance, especially for *N. gonorrhoeae*, is a persistent and rising problem. The Centers for Disease Control and Prevention estimates that 30% of *N. gonorrhoeae* isolates are antibiotic resistant[2,6]
- Lefamulin is a novel semisynthetic pleuromutilin antibiotic that just completed a phase 3 trial for the treatment of community-acquired bacterial pneumonia. Lefamulin inhibits protein synthesis by binding selectively and specifically to the A- and P-sites of the peptidyl transferase center of the 50S ribosomal subunit[7]
- Lefamulin shows potent *in vitro* activity against a variety of pathogens, including those commonly associated with STIs such as *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium*, and its activity is unaffected by an organism's resistance to other antibiotic classes[8,9]
- Lefamulin rapidly and predictably distributes into plasma, skeletal muscle tissue, subcutaneous adipose tissue, and the epithelial lining fluid of the lungs[10]
- The purpose of this study was to investigate the distribution of lefamulin in tissue structures of the urogenital tract in rats

METHODS

- [^{14}C]-lefamulin was administered to nonpigmented male (n=3) and female (n=3) rats as a single, intravenous, 30-mg/kg dose
- At 0.5, 6, and 24 hours postdose, 1 male and 1 female rat were killed at each time point to investigate the tissue distribution by quantitative whole-body autoradiography (QWBA) and tape-transfer micro-autoradiography of sagittal planes
- Distribution of radioactivity ([^{14}C]-lefamulin) was determined using a storage phosphor image analyzing system
  - The interpretation of micro-autoradiography results was qualitative
- Selected samples were prepared for quantitative radiochemical analysis by liquid scintillation counting, and data were expressed as microgram equivalents per gram of original sample weight

RESULTS

Lefamulin Distribution in the Male Urogenital Tract

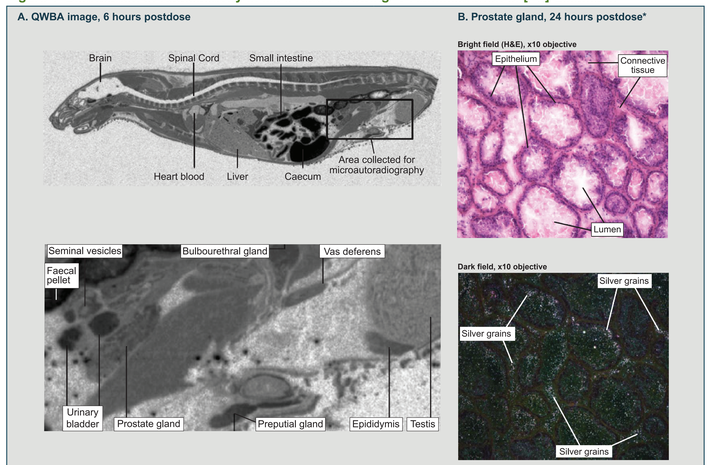
- High concentrations of [^{14}C]-lefamulin were observed in certain glandular tissues (eg, preputial, bulbourethral), with notable concentrations also observed in the urethra **(Table 1)**
- Micro-autoradiographs of the seminal vesicles and prostate gland showed higher concentrations of radioactivity associated with the walls (epithelium and mucosa) vs the lumen **(Figure 1)**
- Concentrations in several urogenital tract tissues at 24 hours after administration were similar to those observed in the lung at that time **(Table 1)**

Table 1. Concentration of [^{14}C]-Lefamulin in the Urogenital Tract of Male Rats at 0.5, 6, and 24 Hours After Administration

Tissue	0.5 h	6 h	24 h
Blood	3.4	0.7	BLQ
Bulbourethral gland	53.4	13.4	NS
Lung	26.5	20.5	0.4
Preputial gland	NS	15.4	9.8
Prostate gland, whole	11.0	8.4	0.5
Prostate gland, lumen	4.6	6.5	0.3
Prostate gland, wall	14.4	12.5	0.7
Seminal vesicles, whole	8.3	7.6	0.5
Seminal vesicles, lumen	2.7	4.2	0.3
Seminal vesicles, wall	16.7	10.7	0.6
Testis	1.3	2.3	2.0
Urethra	22.3	24.0	0.8
Urinary bladder, whole	19.5	20.4	0.6
Urinary bladder, contents	24.2	35.0	0.8
Urinary bladder, wall	8.2	3.4	0.1

All data are µg equivalents of lefamulin per gram tissue
BLQ=below limit of accurate quantification (<0.062 µg equivalents/g);
NS=no sample, tissue not sectioned.

Figure 1. Distribution of Radioactivity in Male Rats Following IV Administration of [^{14}C]-Lefamulin



IV=intravenous; QWBA=quantitative whole-body autoradiography.
*Under bright field conditions, radioactive areas (silver grains) show as small particles and the tissue histology can be viewed. Under dark field conditions, silver grains show up bright white against a dark, false-color background.

RESULTS (continued)

Lefamulin Distribution in Female Urogenital Tract

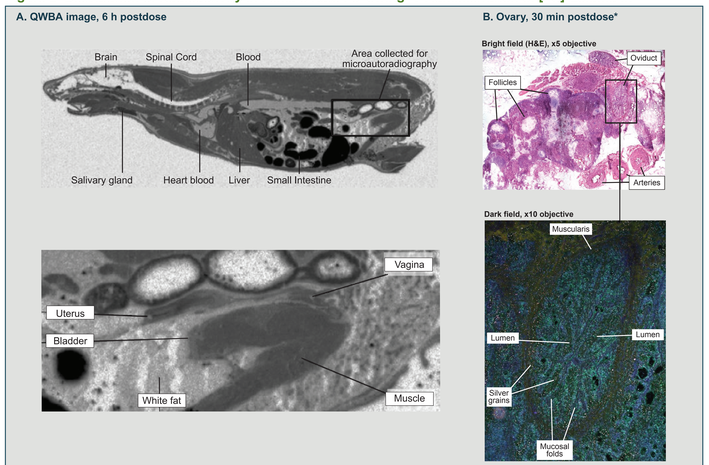
- [^{14}C]-lefamulin was observed in the clitoral glands, the uterus, and the urethra **(Table 2)**
- At 6 and 24 hours postdose, the internal uterine mucosa (endometrium) had higher concentrations of [^{14}C]-lefamulin than the rest of the uterus **(Table 2)**
- The [^{14}C]-lefamulin detected in the ovary was mainly associated with the follicular lumen **(Figure 2)**
- At 24 hours postdose, the clitoral gland showed the greatest accumulation of [^{14}C]-lefamulin, with levels 3-fold greater than those in the lung at that time **(Table 2)**
  - At 6 hours postdose, the radioactivity was most concentrated in the ducts surrounding the acini rather than within these structures
- In the vagina, [^{14}C]-lefamulin distribution was homogenous across the lumen, epithelium, and smooth muscle wall

Table 2. Concentration of [^{14}C]-Lefamulin in the Urogenital Tract of Female Rats at 0.5, 6, and 24 Hours After Administration

Tissue	0.5 h	6 h	24 h
Blood	5.6	1.1	BLQ
Clitoral gland	81.3	NS	2.4
Lung	39.5	22.4	0.8
Ovary	27.3	9.8	0.5
Urethra	32.0	NS	NS
Uterus, whole	31.9	8.4	0.6
Endometrium	30.6	13.4	0.8
Vagina	20.8	8.3	NS

All data are µg equivalents of lefamulin per gram tissue
BLQ=below limit of accurate quantification (<0.062 µg equivalents/g);
NS=no sample, tissue not sectioned.

Figure 2. Distribution of Radioactivity in Female Rats Following IV Administration of [^{14}C]-Lefamulin



IV=intravenous; QWBA=quantitative whole-body autoradiography.
*Under bright field conditions, radioactive areas (silver grains) show as small particles and the tissue histology can be viewed. Under dark field conditions, silver grains show up bright white against a dark, false-colored background.

CONCLUSIONS

- [^{14}C]-lefamulin showed rapid distribution into urogenital tract tissues in rats, corresponding to organs affected by STIs. Concentrations in several urogenital tract tissues were similar to those observed in the lung
- Lefamulin's penetration into relevant urogenital tissues and its *in vitro* activity against susceptible and multidrug resistant STI-associated pathogens support the further assessment of lefamulin as a treatment for STIs

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