Gryglewski, R. J., Korbut, R., Ocetkiewicz, A. (1978) Nature (London) 273: 765–767

Higgs, E. A., Moncada, S., Vane, J. R. (1978a) Prostaglandins 16: 153–162

Higgs, G. A., Moncada, S., Vane, J. R. (1978b) J. Physiol. (London) 275: 30P–31P

Hjemdahl, P., Fredholm, B. B., Malmsten, C., Samuelsson, B. (1978) in: Abstracts, 7th International Congress of Pharmacology, Paris, 1978, Pergamon Press. Oxford p. 344

Moncada, S., Gryglewski, R. J., Bunting, S., Vane, J. R. (1976) Nature (London) 263: 663–665

Moncada, S., Korbut, R., Bunting, S., Vane, J. R. (1978) Ibid. 273: 767–768

Murota, S.-I., Morita, I., Tsurufuji, S., Sato, H., Sugio, K. (1978) Prostaglandins 15: 297–301

Ohuchi, K., Sato, H., Tsurufuji, S. (1977) Biochem. Pharmacol. 26: 2049–2053

Parnham, M. J., Shoshan, S., Bonta, I. L., Neiman-Wollner, S. (1977) Prostaglandins 14: 709–714

Peck, M. J., Williams, T. J. (1978) Br. J. Pharmacol. 62: 464P–465P

Persellin, R. H., Kittinger, G. W., Kendall, J. W. (1972) Am. J. Physiol. 222: 1545–1549

Partition of cinoxacin and nalidixic acid in canine vascular and extravascular compartments

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Cinoxacin, 1-ethyl-1, 4-dihydro-4-oxo-(1,3)-dioxolo-(4,5-g) cinnoline-3-carboxylic acid, belongs to the same class of antimicrobial drugs as nalidixic acid and oxolinic acid, which are used in the treatment of infections of the genito-urinary system. While its antibacterial activity is similar to nalidixic acid and oxolinic acid in vitro, it may be superior in vivo against pyelonephritis in rats (Holmes et al 1974). Numerous antibiotics have been shown to be nephrotoxic. This toxicity has usually been related to high concentrations of the agent present in tissue fluid. Lymph fluid has been shown to be similar to interestitial fluid by Guyton (1963) and Mortillaro & Taylor (1976), therefore sampling lymphatic drainage from the kidney would be a means of determining if toxic concentrations of a drug were present in interestitial fluid when blood concentrations were at clinical values. To determine the relationship between blood and interstitial concentrations of cinoxacin and nalidixic acid, blood, thoracic duct lymph and renal hilar lymph were collected simultaneously over 5 h. Comparisons were made between the two drugs as well as between drug concentrations in various fluid compartments.

Thirty mongrel dogs of either sex, 16 ± 2 (s.e.) kg, were anaesthetized with pentobarbitone (25 mg kg^{-1}), then intubated with endotracheal tubes and ventilated via a Harvard Respirator. The femoral artery and vein were cannulated. The arterial cannula was connected to a Statham strain gauge pressure transducer and arterial blood pressure was recorded on a Beckman type RS Dynograph. The venous cannula was advanced into the inferior vena cava and connected to a saline monitor to measure pressure in the inferior vena cava. The measurements were made every 20 min.

The thoracic duct was exposed in the neck and cannulated as previously described (Szwed et al 1972). The left kidney was exposed and one renal hilar lymphatic identified and cannulated with P.E.-10 tubing for lymph collection. A catheter was placed into the bladder. Baseline fluid samples were collected for 30 min before drug administration. Cinoxacin and nalidixic acid were injected in doses of 5, 10 and 20 mg kg^{-1} as an intravenous bolus to separate groups of five dogs for each dose. No autologous fluid was returned to the animals to preclude reinfusion of antibiotic. A constant intravenous infusion of 0·5 ml min^{-1} of 5% dextrose in 0·9% NaCl saline was continued throughout the study. Blood, thoracic duct, renal lymph and urine samples were collected at 15, 30, 45, 60, 120, 180, 240, and 300 min after injection of the drugs. A fluorometric assay of cinoxacin (sensitivity 0·5 μg ml^{-1}) was carried out by the Eli Lilly Research Laboratories. Nalidixic acid was analysed by liquid chromatography (Schargel et al 1973). Statistical analysis was by analysis of variance for repeat measurements.

Samples of cinoxacin and nalidixic acid were similar in all body fluids at all times after the 5 and 10 mg kg^{-1} doses. With the 20 mg kg^{-1} dose, nalidixic acid concentrations in serum, thoracic duct lymph, and urine exceeded those of cinoxacin at all times ($P < 0·01$) (Fig. 1A-C). Renal hilar lymph concentrations of nalidixic acid exceeded those for cinoxacin at 45, 60, and 300 min post injection ($P < 0·05$) otherwise there were no differences (Fig. 1D). The serum concentrations of both drugs accurately reflected the concentration of the antibiotics in the renal hilar lymphatic tissue, i.e., renal interstitial fluid. Except for a difference in drug values after the 5 and 20 mg kg^{-1} doses of nalidixic acid during the vascular-extravascular 'mixing phase' occuring during the first 60 min after drug injection, all values for serum and renal hilar lymph were statistically identical (cf Fig. 1A and D). No significant changes in mean arterial blood pressures and inferior vena cava pressures were observed at anytime.

Interstitial fluid and lymphatic fluid are similar in

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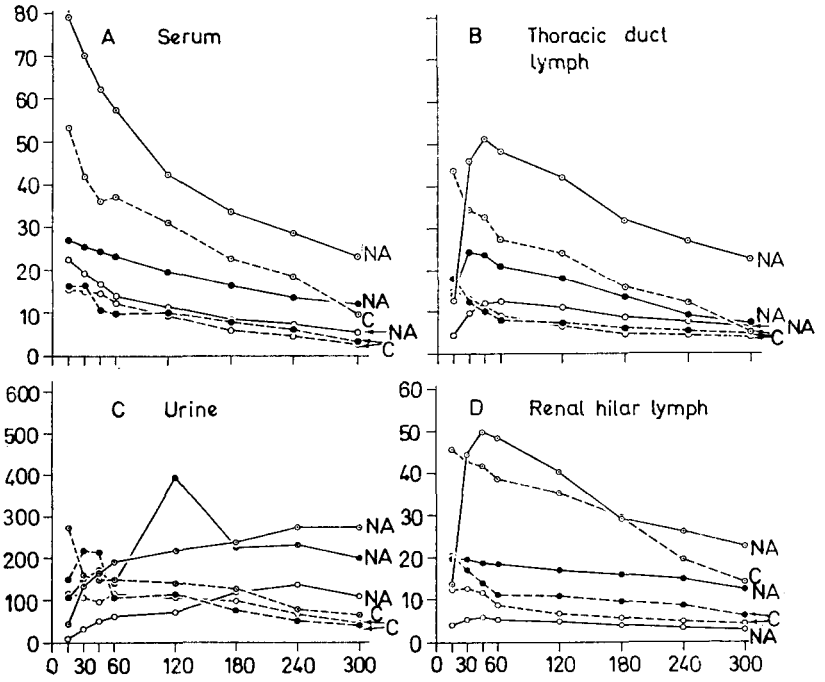

FIG. 1. Concentrations of cinoxacin (C) and nalidixic acid (NA) in (A) serum, (B) thoracic duct lymph, (C) urine, (D) renal hilar lymph of dogs over 300 min, after injections of 5 (○), 10 (●), or 20 mg kg^{-1} of (⊙) ether antibiotic.

protein content and general chemical composition (Mortillaro & Taylor 1976; Taylor & Gibson 1973). Since pyelonephritis begins in the interstital space of the kidney, it is important that an antibiotic reaches effective non-toxic interstitial concentrations. If serum drug concentrations correlate with renal lymph drug values, it would be possible to monitor tissue concentrations with serum concentrations. In this study serum values of both cinoxacin and nalidixic acid closely approximate renal hilar lymph values.

At the 20 mg kg^{-1} dose, nalidixic acid exceeded cinoxacin drug concentrations in serum, thoracic duct lymph and urine at all times. We conclude that serum concentrations of cinoxacin and nalidixic acid accurately reflected their renal interstitial values, that the concentrations of both drugs in the renal interstitial substance were substantial so the drugs would probably be effective antibiotics for pyelonephritis and that their renal toxicity should be low when serum values are at accepted clinical concentrations.

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REFERENCES

Guyton, A. C. (1963) Circulation Res. 12: 319–329

Holmes, D. H., Enswinger, P. W., Gordee, R. S. (1974) Antimicrobial Agents and Chemotherapy 6: 432–436

Mortillaro, N. A., Taylor, A. E. (1976) Circ. Res. 39: 348–358

Schargel, L., Koss, R. F., Crain, A. V. R., Boyle, V. J. (1973) J. Pharm. Sci. 62–73

Szwed, J. J., Kleit, S., Hamburger, R. (1972) J. Lab. Clin. Med. 79: 5, 693–700.

Taylor, A. E., Gibson, H. A. (1973) Lymphology 8: 43–49