Pharmacodynamics of Lividomycin in Renal Failure

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The sulphate of lividomycin is excreted in high concentration in the urine. We have studied the possible accumulation in the uraemic patient after a 350mg intramuscular injection. The serum half-life of this antibiotic is markedly increased in uraemic patients. The dose of this antibiotic should be adapted according to creatinine clearance ($C_{cr}$). The serum half-life is 1 hour 59 minutes in healthy subjects. $T_{1/2}$ is 8 hours 16 minutes in patients with $C_{cr}$ of 20-80ml/min, 18 hours 16 minutes in patients with $C_{cr}$ of 5-20ml/min, 34 hours 23 minutes in patients with $C_{cr}$ less than 5ml/min and 44 hours 24 minutes in anuric patients.

The sulphate of lividomycin is a new antibiotic isolated from streptomycetes lividus and is actively excreted in high concentration in the urine. It has a broad antibacterial spectrum and is bactericidal for both gram positive and gram negative organisms. It can be administered only intramuscularly. Its possible accumulation in the uraemic patient has not so far been studied.

PATIENTS AND METHODS

Three healthy subjects, aged between 23-27 and studied in the standing position were given 350mg by intramuscular injection. Ten normal subjects, aged between 24 and 63, were studied while recumbent after a 350mg intramuscular injection. In all patients, blood samples were taken 30min, 1, 2, 4, 6 and 8 hours after the injection; the urine was collected after 6 hours.

Forty uraemic patients aged between 22-74 were divided into 4 groups:

- **Group I**: 12 patients with a creatinine clearance ($C_{cr}$) of 20-80ml/min
- **Group II**: 8 patients with a $C_{cr}$ of 5-20ml/min
- **Group III**: 8 patients with a $C_{cr}$ of less than 5ml/min
- **Group IV**: 12 patients on haemodialysis with a $C_{cr}$ of 0-2ml/min

Lividomycin sulphate (350mg) was given to all patients. Blood samples were taken at zero and 30 minutes, then at 1, 2, 4, 6, 8, 24 and 48 hours after
the injection. The urine was collected after 6 hours (U₁), 6-12 hours (U₂), 12-24 hours (U₃). The patients on haemodialysis were studied twice, at two week intervals, both between dialysis sessions and during dialysis.

Coil dialysers (Ultraflo 145) were used with a blood flow rate of 200-250 ml/min.

\( C_{cr} \) was measured using the auto analyser modification of Jaffe’s method. The lividomycin was assayed by agar plate diffusion using bacillus subtilis ATCC 66.33 as the test organism. Incubation at 37°C was carried out for 18 hours and the inhibition zones were read using a Zeiss enlarger. The serum concentrations of lividomycin were plotted on a semilogarithmic scale against time to find the half-life.

RESULTS

In the healthy subjects after 350mg IM lividomycin in the standing position the concentration peak was at 1 hour (15-19mcg/ml). The serum half-life is between 1 hour 30 min and 1 hour 50 min (mean 1 hour 38 min); 85.93% of the injected dose had been excreted in 6 hours. In normal subjects in the recumbent position the concentration peak was at 1 hour (8.6-23mcg/ml). The serum half-life is between 1 hour 24 min and 3 hours 19 min (mean 1 hour 59 min); 63.2% of the injected dose had been excreted in 6 hours.

In the uraemic patients the concentration peak was obtained at the same time but the serum T 1/2 was prolonged:

**Group I:** the average peak serum concentration was 20.3 ± 6.2μg/ml. After 8 and 24 hours, the average serum concentrations were 9.1 ± 4.6μg/ml and 2.10 ± 1.49μg/ml respectively. The serum T 1/2 was 8 hours 16 minutes +

![Figure 1](image-url)

**Table 1**

<table>
<thead>
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</tr>
<tr>
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<table>
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<th>Time (h)</th>
<th>C_Cr (ml/min)</th>
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Figure 2. Urinary elimination of lividomycin sulphate in normal and uraemic patients

1 hour 7 minutes; 61.7% of the injected dose had been excreted in 24 hours.

**Group II**: the average peak serum concentration was $19.6 \pm 5.9 \mu g/ml$. After 8, 24 and 48 hours the average serum concentrations were $11.9 \pm 5.4 \mu g/ml$, $7.61 \pm 2.3$ and $2.18 \pm 1.2 \mu g/ml$ respectively. The serum T 1/2 was 18 hours 16 minutes ± 4 hours 1 minute; 35% of the injected dose had been excreted in 24 hours.

**Group III**: the average peak serum concentration was $21.6 \pm 5.1 \mu g/ml$ at 2 hours. After 8, 24 and 48 hours the average serum concentrations were $15.3 \pm 3.8$, $9.4 \pm 4.4$ and $7.8 \pm 1.6 \mu g/ml$ respectively. The serum T 1/2 was 34 hours 23 minutes ± 5 hours; 16% of the injected dose had been excreted in 24 hours.

**Group IV**: in patients with a very low $C_{cr}$ 0-2ml/min, the average peak serum concentration in the interdialysis studies was $23.2 \pm 7.7 \mu g/ml$ at 2 hours. After 24 and 48 hours the average serum concentrations were high: $13.3 \pm 6.3 \mu g/ml$ and $9.8 \pm 2.4 \mu g/ml$ respectively. The serum T 1/2 was 44 hours 24 minutes ± 4 hours 36 minutes. During dialysis the serum concentrations were always lower, and the T 1/2 calculated on the eight hours being 19 hours 40 minutes before haemodialysis and 6 hours 30 minutes during haemodialysis. The extraction percentage was between 28 and 34% of the administered dose.
COMMENTS

In uraemic patients the serum half-life of lividomycin sulphate is increased so it is necessary to adapt dosage to renal function (Figure 1). The urinary excretion rate of lividomycin is correlated with glomerular filtration (Figure 2).

In normal subjects 350mg lividomycin IM every 8 hours should be given. In patients with a $C_{cr}$ of 20-80ml/min, 350mg should be given every 24 hours. In patients with a $C_{cr}$ of 5-20ml/min 350mg IM every 48 hours. In patients with a $C_{cr}$ of less than 5ml/min 350mg of lividomycin should be given every 72 hours. It is the same dose for anuric patients. This antibiotic had to be avoided by intramuscular route in haemodialysis patients.