# Clinical Pharmacology of Intravenous and Intraperitoneal Aminoglycoside Antibiotics in the Prevention of Wound Infections

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**Seventeen patients had intraoperative peritoneal lavage with a solution containing one gram of kanamycin in 200 ml of 0.9% NaCl. The solution was removed by suction at two or five minutes. Venous blood samples were obtained at 15 minute intervals for two hours following lavage. Despite diligent attempts, an average of only 60% of the solution was recovered by suction. The peak concentration of kanamycin in serum correlated directly with the kanamycin dose ($p < 0.025$). In six patients lavaged for five minutes, peak absorption occurred at 15 minutes with serum concentrations of 20.3 ± 2.0 μg/ml. In five patients lavaged for two minutes insignificantly ($p > 0.1$) lower peak serum concentrations (15.3 ± 1.8 μg/ml) occurred at 15 minutes. Six additional patients had peak kanamycin serum concentrations which occurred at 75 minutes and reached 23.2 and 24.0 μg/ml in two patients. In three patients who received intravenous gentamicin prior to surgery, nine paired serum and peritoneal fluid samples obtained during three hours preceding lavage showed no significant differences in gentamicin concentrations ($p > 0.5$). These pharmacokinetic data demonstrate the penetration of parenterally administered aminoglycosides into intraoperative peritoneal fluid. Kanamycin lavage for wound prophylaxis should be used cautiously and should be abandoned in patients who have renal impairment where prolonged toxic serum concentrations could develop.**

IN THE PREVENTION of wound infections following abdominal surgery both parenteral and topical aminoglycosides have been advocated.[2] Whereas the pharmacokinetics of gentamicin in serum have been delineated,[5,11] little is known of the penetration of gentamicin into the peritoneal cavity, particularly at the time of surgery. Knowledge of the pharmacokinetics of intraoperatively administered intraperitoneal kanamycin is scant.[1]

This study was undertaken to define the pharmacokinetics of absorption of intraperitoneally administered kanamycin under controlled conditions which mimic reasonable operative procedure. In addition, the penetration of parenterally administered gentamicin into the peritoneal cavity during operation was assessed in order to compare and to contrast on a purely pharmacokinetic basis these two approaches to the prophylaxis of intraperitoneal infection.

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Submitted for publication: November 10, 1977.

## Patients and Methods

Seventeen patients undergoing abdominal operations at Hermann Hospital, The University of Texas Medical School of Houston, were studied. Informed consent was obtained in all cases, and patients were randomly assigned to a two or five minute period of lavage.

Shortly before closure, the peritoneal cavity of each patient was lavaged with a solution containing 1 g of kanamycin in 200 ml of normal saline at room temperature. The 200 ml was poured rapidly into the peritoneal cavity and the abdominal contents were agitated gently to insure dispersion of the solution. The lavage solution was then removed by suction. The volume obtained was recorded, and aliquots were frozen at −70° for determination of kanamycin concentrations. Venous blood samples were collected at 15 minute intervals following onset of lavage. They were centrifuged immediately and serum was frozen at −70°.

Three patients, who received preoperative intravenous gentamicin, had paired venous blood and peritoneal fluid samples obtained before kanamycin lavage. The peritoneal fluid was obtained from either the right or left abdominal gutter and represented the fluid which accumulated because of bleeding and transudation across the surgical wound. These peritoneal fluid

0003-4932-78-0700-0066-0075 

samples were not preceded by lavage of the peritoneal cavity.

The concentrations of kanamycin and gentamicin were determined by the radioenzymatic method of Smith et al.[13] utilizing the enzyme gentamicin adenyl transferase with $^{14}$C-labeled adenosine 5′-triphosphate as the substrate.[12] The enzyme was obtained from a mutant strain of *E. coli* W677/HJR66 using osmotic disruption. In those patients who had received preoperative gentamicin, kanamycin concentration determinations were corrected for the presence of the gentamicin.

## Results

No significant difference in age, weight, serum concentration of creatinine, or the calculated dose administered across the peritoneum occurred between patients in the five and two minute lavage groups (Table 1). Despire diligent attempts an average of only 60% of the lavage solution was recovered by suction in both groups. Wound infection, respiratory distress in the postanesthetic period, hypotension or oliguria during or after surgery did not occur.

The mean peak concentration of kanamycin in serum (Table 1) was higher in the five minute lavage group than in the two minute group; however, there was no significant ($p > 0.1$) difference. In the five minute lavage group, five of nine patients had peak serum kanamycin concentrations near or exceeding what we recognize as a potentially toxic level of 20 μg/ml. In the two minute group, 2 of 8 patients had peak levels in this range.

Figure 1 shows the dose of kanamycin delivered in mg/kg compared to the peak serum concentration. By linear regression analysis the peak concentration of kanamycin in serum was directly correlated ($p < 0.025$) with the dose of kanamycin administered.

Figure 2 shows concentrations of kanamycin in serum achieved during a two hour period following lavage. Data was derived from patients 1–6 in the five minute lavage group and patients 9b–13 in the two minute lavage group. Peak serum kanamycin concentrations occurred at 15 minutes. The mean peak of the five minute lavage group reached potentially toxic levels (20.3 ± 4.8). No significant ($p > 0.1$) difference by Student's t test occurred between the peak values of patients in the five and two minute lavage groups.

Three patients each from the five and two minute lavage groups had a pattern of absorption different from the pattern shown in Fig. 2. Figure 3 shows the concentration of kanamycin in serum for the patients (7, 8, 9a) in the five minute lavage group. Each curve shows a delayed peak at 75 minutes. The peak concentration of patient 9a reached the potentially toxic range. Patients 14, 15, and 16 from the two minute lavage group also experience a late peak serum concentra-

TABLE 1. *Patient Data*

| Patient | Surgical Procedure | Age (yrs) | Weight (kg) | Creatinine (mg/dl) | Kanamycin Dose (mg/kg) | Peak Serum Kanamycin Concentration (μg/ml) |
|---|---|---|---|---|---|---|
| Five Minute Lavage | | | | | | |
| 1 | Porto-caval shunt | 45 | 82.3 | 1.0 | 4.3 | 15.8 |
| 2 | Cholecystectomy | 37 | 59.1 | 0.8 | 9.1 | 26.5 |
| 3 | Cholecystectomy | 32 | 70.5 | 1.0 | 4.8 | 15.2 |
| 4 | Cholecystectomy | 24 | 73.6 | 0.9 | 5.0 | 19.6 |
| 5 | Cholecystectomy | 59 | 75.5 | 0.8 | 3.7 | 19.0 |
| 6 | Cholecystectomy | 39 | 82.3 | 1.0 | 3.8 | 25.8 |
| 7 | Whipple procedure | 71 | 90.0 | 1.0 | 3.4 | 8.9 |
| 8 | Small bowel exploration | 61 | 66.4 | 1.1 | 5.7 | 15.4 |
| 9a | Choledoco-jejunostomy | 59 | 56.0 | 1.8 | 11.3 | 23.2 |
| Mean ± SD | | 47 ± 16 | 73 ± 11 | 1.0 ± 0.3 | 5.7 ± 2.7 | 18.8 ± 5.7 |
| Two Minute Lavage | | | | | | |
| 9b | Drainage right subhepatic abscess | 59 | 56.4 | 1.0 | 8.5 | 15.8 |
| 10 | Cholecystectomy | 34 | 94.5 | 0.9 | 2.1 | 13.9 |
| 11 | Cholecystectomy | 27 | 110.9 | 0.9 | 6.1 | 16.9 |
| 12 | Bilateral adrenalectomy | 44 | 83.2 | 0.8 | 6.6 | 22.8 |
| 13 | Small bowel resection | 28 | 72.7 | 1.0 | 5.2 | 7.8 |
| 14 | Resection enterocutaneous fistulae w/enteroenterostomy | 41 | 59.1 | 1.0 | 3.4 | 6.3 |
| 15 | Cholecystectomy | 73 | 77.3 | 1.3 | 4.0 | 15.7 |
| 16 | Colectomy | 71 | 66.4 | 1.7 | 8.4 | 24.0 |
| Mean ± SD | | 47 ± 18 | 78 ± 18 | 1.1 ± 0.3 | 5.5 ± 2.3 | 15.4 ± 6.3 |

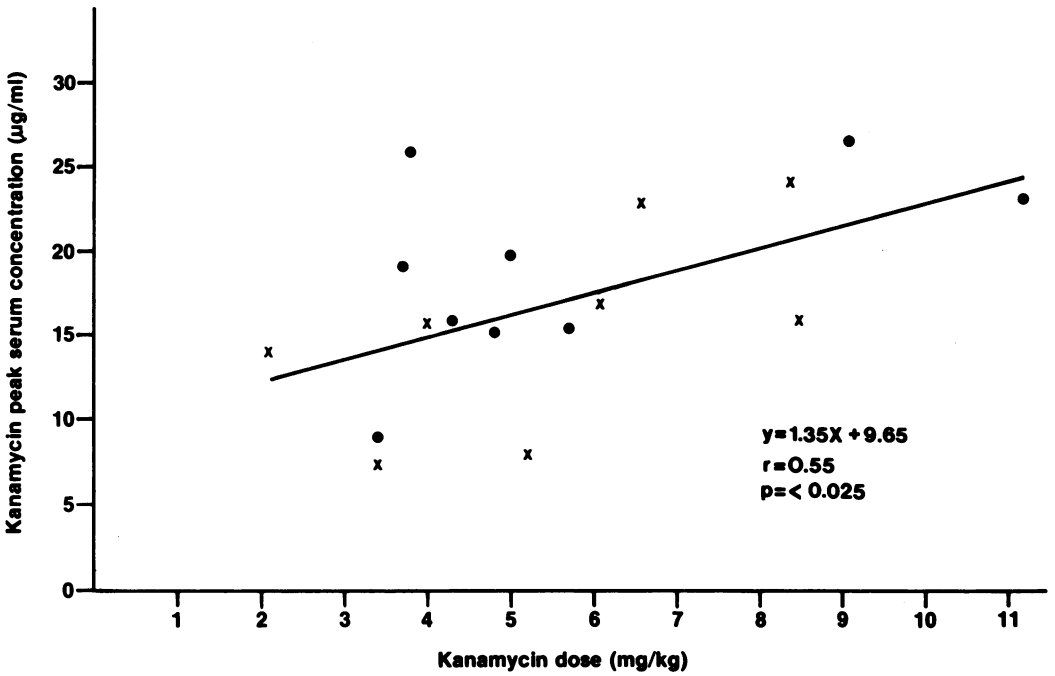


FIG. 1. Comparison of the dose of kanamycin given intraperitoneally with the concentration of kanamycin in serum. Dots and X's indicate patients from the five and two minute lavage group, respectively.

tion and in patient 16 the peak levels were in the potentially toxic range.

Figure 4 shows the comparison of paired serum and peritoneal fluid gentamicin concentrations in three patients who had received preoperative intravenous gentamicin. Also displayed is paired data obtained after one patient underwent copious saline lavage. The concentrations of gentamicin in the peritoneal fluid at operation closely reflected the concomitant concentrations in the serum. The mean difference between paired samples was 0.2 µg/ml. There was no significant difference between paired gentamicin concentrations in serum and peritoneal fluid samples (paired Students t test, $p > 0.5$). Saline lavage lowered both serum and peritoneal fluid gentamicin concentrations in the patient studied.

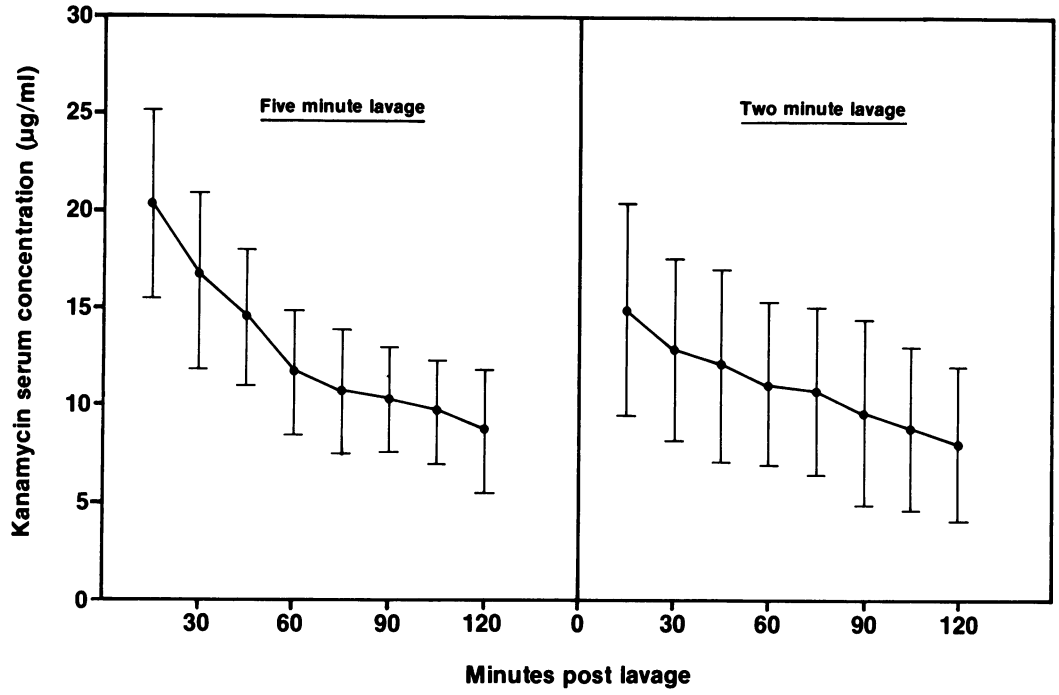


FIG. 2. Comparison of the concentrations of kanamycin in serum during two hours following kanamycin lavage in the five and two minute lavage groups. Brackets indicate ± one standard deviation.

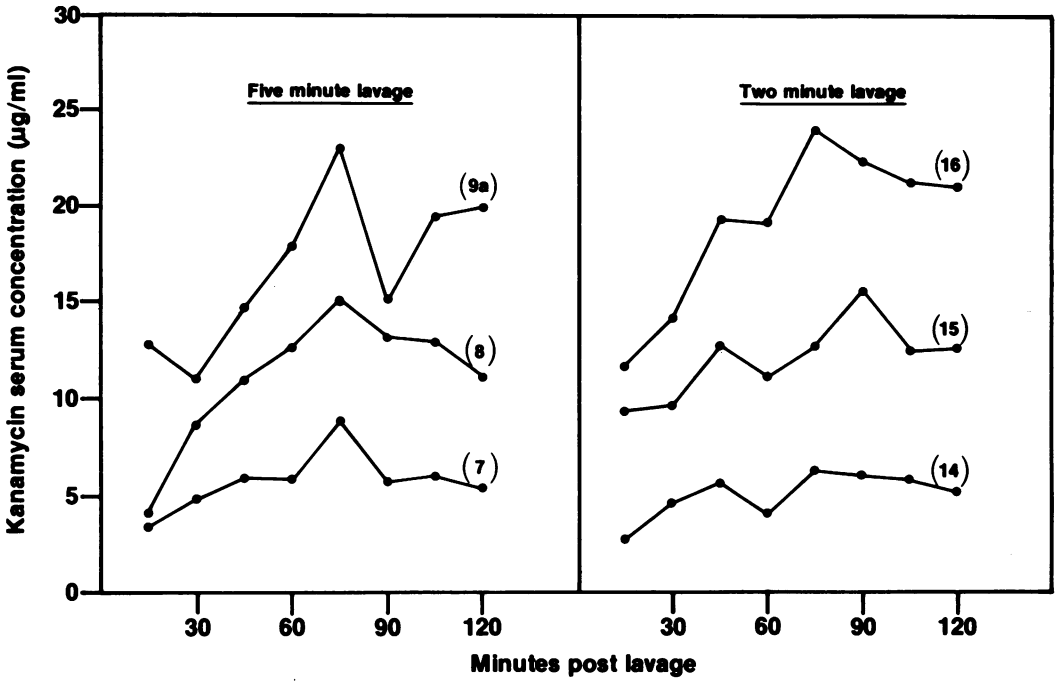


FIG. 3. The anomalous patterns of absorption of kanamycin over two hours following kanamycin lavage. Numbers in parenthesis indicate patient studied.

## Discussion

No effort has been made in this study to evaluate the efficacy of either parenteral or topical antibiotics in the prophylaxis of wound infections.

The pattern of absorption of kanamycin after peritoneal lavage is unpredictable. Although peak kanamycin concentration in serum did correlate directly with dose, some patients demonstrated rapid absorption with peak serum concentrations at 15 minutes; whereas, other patients demonstrated peaks at 75 minutes. In both the five and two minute lavage groups several patients had peak concentrations in serum greater than 20 μg/ml.

These data are at variance with the study of Pissiotis et al.[9] in which 500 mg of kanamycin in 20 ml of saline was administered postoperatively as a bolus into the peritoneal cavity. Peak serum concentrations occurred at one hour. In the present study, in which a special effort was extended to expose the full surface of the peritoneum, the majority of peak concentrations occurred at 15 minutes. In those cases in which peak absorption occurred at 75 minutes, unrecognized pooling of the lavage solution probably occurred.

In the present study seven of 17 patients experienced peak serum kanamycin concentrations in the potentially toxic range. Kanamycin lavage has been used for years with practically no overt toxicity.[8] There have been occasional reports of neurotoxicity[4] and respiratory depression,[7,10] which did not correlate with the amount of antibiotic or the route of administration.[6] Theoretically, subclinical damage to renal or auditory function might occur. However, even after prolonged therapy with aminoglycosides, renal lesions are generally reversible after discontinuation of the drug. Pharmacokinetic data indicate that kanamycin concentrations develop in endolymph and perilymph after the administration of a single parenteral dose.[15] Most studies, however, stress the oto-toxic potential of prolonged therapy with aminoglycosides.[3]

A major concern is a patient who has renal impairment or who suffers renal shutdown shortly after lavage. Potentially toxic concentrations of kanamycin in serum could persist and might cause toxicity.

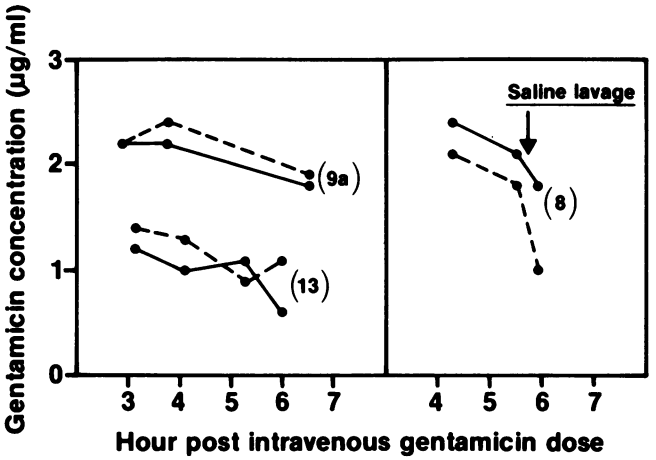


FIG. 4. Comparison of paired concentrations of gentamicin in serum (● —— ●) and peritoneal fluid (● - - - ●) following intravenous administration of gentamicin. Numbers in parenthesis indicate patient studied.

Kanamycin lavage might be entertained when other aminoglycosides are being administered parenterally. This situation should be avoided since the present data predicts that potentially toxic serum concentration of aminoglycosides might occur after combined peritoneal and parenteral administration.

If one subscribes to the use of parenterally administered antibiotics in the prevention of intraperitoneal infection, then the present pharmacokinetic data supports this usage. Differences between gentamicin concentrations in paired serum and peritoneal fluid samples averaged only 0.2 μg/ml. One precaution should be noted. Copious saline lavage will lower the serum and peritoneal fluid concentrations slightly. Since copious saline lavage is often used at closure, the prophylactic parenteral dose of aminoglycoside should be administered within one or two hours before closure to ensure adequate concentrations.

If intraperitoneal lavage with kanamycin is used, then from the data in this study certain precautions can be recommended. To avoid potentially toxic concentrations in serum, the total amount of kanamycin in the lavage solution should not exceed 1 g. The optimal amount of kanamycin may be less, but cannot be determined from these data. The duration of lavage should be short since lavage for two minutes produced potentially toxic concentrations of kanamycin in serum. An effort should be made to recover the lavage solution by suctioning. If a patient has abnormal renal function or an unstable operative course such as hypotension or oliguria, then peritoneal lavage with kanamycin solutions should be avoided.

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