Amikacin Concentrations in Serum Following Intraoperative Irrigation of the Pleura and Peritoneum

CHARLES W. VAN WAY, M.D.,* GERALD HASSE, M.D.†

Serum concentrations of amikacin following operative wound irrigation were studied in 17 patients having laparotomy and in eight patients having thoracotomy. Irrigation was done with 500 mg of amikacin in 200 ml of saline. The irrigant was reaspirated after 3 minutes. Measurement of amikacin in the irrigant allowed calculation of the retained dose. Serum levels were measured before surgery, and at 30 minutes, 60 minutes, 6 hours, and 12 hours following irrigation. Amikacin was assayed by a microbiological technique. The retained dose after peritoneal irrigation was 350 ± 128 mg, and after pleural irrigation was 100 ± 79 mg. The average maximum serum level in the peritoneal irrigation group was 9.4 ± 6.7 gm/ml; in the thoracotomy group it was 3.5 ± 1.7. Fourteen of the 17 laparotomy patients but only one of the eight thoracotomy patients had measurable plasma levels at 6 hours. Plasma half-life in the laparotomy group was 2.81 ± 1.34 hours, and in the thoracotomy group 1.53 ± 0.83 hours. Interoperative amikacin irrigation, even with immediate aspiration, results in significant absorption in both thoracotomy and laparotomy patients. There was less absorption and a shorter serum half-life in the thoracotomy patients.

LOCAL ANTIBIOTIC IRRIGATION of the operative wound is commonly done in contaminated or infected cases.1–5 It is well-known that aminoglycosides are absorbed from the peritoneal and the pleural cavities.6–7 The present study was done to document the amount of absorption of amikacin, an aminoglycoside antibiotic, following irrigation and aspiration during operation in the pleural and peritoneal cavities. By using a standard amount of amikacin and measuring the amount aspirated, the retained dose was calculated. Serum levels were measured to determine the maximum serum level reached after operation and to allow calculation of the serum half-life.

Significant amikacin absorption was seen following irrigation of either the peritoneal or the pleural cavity. After thoracotomy, the retained dose was much less than after laparotomy. The serum levels were lower and the observed serum half-life was significantly shorter after pleural cavity irrigation.

Materials and Methods

Twenty-five patients were studied. Seventeen had laparotomies. The average age was 47 (±14) years. The average weight was 71 (±12) kg. There were 10 men and 17 women. Six had cholecystectomies, five gastric procedures, two colostomy closures, and four other procedures. Eight patients had thoracotomies. The average age was 38 (±15) years. The average weight was 69.6 (±13.6) kg. There were four wedge resections, two lobectomies, one pleurodesis, and one exploratory thoracotomy. Ten patients had concurrent antibiotic therapy; appropriate adjustments were made to the assay procedure.

Irrigational Protocol

The operative site was irrigated with 200 milliliters of 0.25% amikacin, for a total dose of 500 mg. After removal of all packs and sponges, the amikacin solution was instilled rapidly. The irrigant was left in place for 3 minutes, then aspirated as completely as possible. The volume of aspirate was measured and an aliquot sent for antibiotic levels. The measured amount was subtracted from 500 mg to calculate the retained dose. A control blood sample was obtained at the beginning of the operative procedure. Following irrigation, timed samples were obtained at 30 minutes, 60 minutes, 6 hours, and 12 hours. All samples were centrifuged and serum sent for assay.

* Associate Professor, University of Colorado, School of Medicine, Denver, CO.
† Assistant Clinical Professor, Children’s Hospital, Denver, CO.

Reprints requests: Charles W. Van Way, M.D., Department of Surgery, Denver General Hospital, 777 Bannock Street, Denver, CO 80204-4507.

Submitted for publication: August 30, 1984.

From the Department of Surgery,* Denver General Hospital, and Children’s Hospital, † Denver, Colorado

333
TABLE 1. Retained Dose and Maximum Serum Levels Following
Amikacin Irrigation of the Chest and Abdomen

<table>
<thead>
<tr>
<th></th>
<th>Retained Dose (Mean ± S.D.)</th>
<th>Maximum Serum Level (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal cavity</td>
<td>350 ± 128 mg</td>
<td>9.4 ± 6.74</td>
</tr>
<tr>
<td>(n = 17)</td>
<td></td>
<td>Range: 2.6-2.7</td>
</tr>
<tr>
<td>Pleural cavity</td>
<td>100 ± 79 mg</td>
<td>3.5 ± 1.67</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td>Range: 1.7-6.5</td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>(Student’s t-test)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assay of Antibiotics

Assays were done using an agar plate bioassay method. The test organism was *Bacillus subtilis* ATCC-6633. Pour plates were inoculated with a suspension containing approximately $5 \times 10^3$ viable spores per milliliter. Standard culture media were used. The serum and urine samples were diluted with a phosphate buffer and adjusted to pH 7.9 to 8.1. Serial dilutions of the test serum and urine were made. Colony counts were compared to those of standard plates prepared with known concentrations of amikacin in the 0.2 to 1.0 microgram per milliliter range.

Data Analysis

Data were analyzed using Student’s t-test for unpaired samples. For each patient, the half-life of disappearance was calculated using an exponential regression analysis. A one-compartment model with first order elimination was assumed. The half-lives thus obtained were combined with standard statistical techniques and the two groups compared using Student’s t-test.

Patient Consent

All patients participating in this study were fully informed of the risks of the study, and all signed patient consent forms. The study was approved by the Human Experimental Committee of University Hospital, the Denver VA Hospital, and the Denver General Hospital.

Results

Table 1 shows the principal differences observed in the study. The retained dose in the peritoneal cavity was much greater than in the pleural cavity. While the range was large, the average retained dose was 350 mg, 70% of the amount instilled. In the pleural cavity, the retained dose was only 20% of the amount instilled. The mean maximum serum level for peritoneal irrigation was 9.4 mcg/ml and for pleural irrigation 3.5 mcg/ml. The range for peritoneal irrigation was 2.6 to 27 mcg/ml and for pleural irrigation 1.7 to 6.5 mcg/ml. Two patients in the study had maximum amikacin concentrations exceeding the normal therapeutic range of 8 to 16 mcg/ml. Both were in the peritoneal irrigation group.

Figure 1 shows the serum levels and the half-time of disappearance. While the range of serum levels was large, there was a clear difference between the two groups. In the pleural irrigation group, the 30-minute serum value was higher than the 60-minute in seven out of eight cases. In the peritoneal irrigation group, the 60-minute sample was higher in 12 out of 17 cases. The plasma levels were significantly different (p < 0.2) at 60 minutes and at 12 hours.

Regression analysis showed a weakly positive correlation between the dose (in mg/kg) and the maximum serum level (in mcg/ml).

level = 3.58 + 1.0 (dose) \( r = 0.16 \)

The half-time of disappearance for the peritoneal irrigation group was 2.81 ± 1.34 hours. For the pleural irrigation group, it was 1.53 ± 0.83 hours. This difference was significant (p < 0.01).

Discussion

Amikacin is an aminoglycoside antibiotic, a semisynthetic derivative of kanamycin. It has the usual spectrum of activity of the aminoglycosides but is protected from several of the bacterial enzymes which can degrade aminoglycosides. It is therefore especially useful in bacterial populations that have a high incidence of kanamycin resistance. The pharmacokinetics are quite similar to the other aminoglycosides, especially to kanamycin. Therapeutic plasma levels are 8 to 16 micrograms per milliliter. After intramuscular injection of 7.5 mg per kg, a peak level of 20 mcg/ml is reached in 30 to 60 minutes. The half-life of disappearance is usually 2 to 3 hours. Virtually all of the drug is excreted unchanged in the urine.8

Aminoglycoside antibiotics have long been known to be absorbed through the peritoneum and the pleura.5-7 Pissotis, Nichols, and Condon noted maximum serum concentrations at 1 hour following intraperitoneal instillation of kanamycin of 24 micrograms per milliliter.6 Ericsson et al. lavaged the peritoneal cavity with 1 gram of kanamycin, aspirating it at 2 to 5 minutes. The total kanamycin dose was 5.5 ± 2.3 following the 2-minute lavage and 5.7 ± 2.7 mcg/kg following the 5-minute lavage. Peak serum kanamycin concentrations were 15.4
and 18.8 mcg/ml, respectively. There was a statistically significant correlation between the peak serum concentration and the kanamycin dose, but the rapidity of absorption was unpredictable. Thys et al. instilled 7.5 mg/kg of amikacin into the pleural cavity in 15 postoperative patients. Amikacin was left in the pleural cavity for 30 minutes and then allowed to drain out through the chest tube in 12 of the 17 patients. It was left in the chest in five patients. Serum concentrations reached 14.1 ± 4.7 mcg/ml.7

Aminoglycoside absorption during operation is of special significance because of the well-recognized problem of neuromuscular blockade.8-10 The danger of aminoglycoside irrigation during operation is that muscle relaxants may greatly potentiate the tendency to produce neuromuscular paralysis.11 Amikacin is probably the least potent of all the aminoglycosides in producing this side effect.8

The present study confirms that plasma levels of amikacin in the therapeutic range are routinely achieved following interperitoneal irrigation with amikacin. Even with care being taken to aspirate the amikacin from the peritoneal cavity, two-thirds of the administered dose is absorbed. The magnitude of the maximum plasma levels and the half-time of disappearance of amikacin appears to be very similar to intramuscular injection.

Pleural irrigation is somewhat different. Serum levels were considerably lower and were in the subtherapeutic range. Toxicity does not appear to be a major problem.

The pharmacokinetics were quite different. Pleural irrigation of amikacin was associated with a plasma half-life of 1.53 ± 0.83 hours, while peritoneal irrigation was associated with a more “normal” half-life of 2.81 ± 1.31 hours. The difference is significance at the one per cent level.

This effect may be due to a difference in pleural absorption. The half-time of amikacin disappearance from the plasma in Thys’s study after pleural absorption was approximately 1.8 hours, which is similar to the present study.7 Zaske et al. reported a group of nine burn patients in whom the amikacin half-life was 1.4 hours.12 Pissiotis et al.’s instillation into the peritoneal cavity of kanamycin of 500 mg showed a half-life of 2.25 hours. The administration of 250 mg of kanamycin showed a half-life of 1.5 hours.

The present experiment is not especially well-designed to calculate the half-time of disappearance. It would have been well to include samples at 2, 3, and 4 hours in order to accurately determine the half-time of disappearance in the range of 1 to 3 hours. But it does appear that irrigation of the chest with amikacin solution may be associated with a lower half-time of disappearance than either intraperitoneal instillation or intramuscular injection. Whether this is related to a lower retained dosage or to some other characteristics of interpleural absorption remains to be determined by further research.

The patients in this study were all either clean or clean contaminated cases. Extrapolation to the infected case should be done with caution. The inflammatory response in either the pleura or the peritoneum may influence absorption.

### Conclusions

The principal difference between intraperitoneal and intrapleural instillation of amikacin appears to be in the amount of drug that is retained by the patient. A much greater proportion of the irrigant can be recovered from the chest than from the abdomen. There is a definite positive correlation between the dose retained by the patient and the peak serum level.

Amikacin appears to behave very much like kanamycin. It is rapidly absorbed from both the peritoneal
and pleural cavities. If it is used for irrigation, a total dose of no more than 7.5 mg/kg should be used, and the irrigating solution should be aspirated quickly.

Acknowledgments

This study was supported by a grant from Bristol Laboratories. Their support and assistance are gratefully acknowledged.

References