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Penetration of vancomycin into human lung tissue

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Vancomycin penetration into lung tissue was evaluated in thirty patients following the administration of 1 g of vancomycin as a 1 h iv infusion. Mean concentrations (range) of vancomycin in lung tissue were 9.6 (6.3–12.1) mg/kg at 1 h, 5.7 (4.7–7.4) mg/kg at 2 h, 4.2 (0.8–6.5) mg/kg at 3–4 h, 2.4 (1.4–4.7) mg/kg at 6 h, and 2.8 (0.9–7.8) mg/kg at 12 h after the end of infusion. Ratios of lung tissue to serum concentration ranged 0.24 to 0.41 at 1 and 12 h, respectively. One of six patients observed at 6 h, and 3 of 7 patients at 12 h did not have detectable levels of vancomycin in lung tissue. A 1 h iv infusion of a 1 g dose of vancomycin does not achieve sustained lung concentrations above the MIC for susceptible staphylococci over a dosing interval of 12 h. Therefore, a more appropriate modality of administration, such as continuous infusion, should be considered.

Introduction

Vancomycin is a glycopeptide antibiotic used worldwide to treat infections caused by staphylococci and enterococci. Staphylococci are frequently involved in the aetiology of nosocomial pneumonia. Successful treatment of deep-seated infections is dependent on penetration of the therapeutic agent into the site of infection. Drug concentration monitoring in the lung can be performed at several sites, namely, lung tissue, pleural fluid, bronchial secretions, bronchial mucosa, alveolar epithelium lining fluid, and alveolar macrophages. Evaluation of drug concentration in each of these tissues and fluids presents some technical and interpretation drawbacks (Baldwin, Honeybourne & Wise, 1992*a*,*b*). However, the comparison of drug pharmacokinetics at different sites of the respiratory tract may allow a more accurate prediction of therapeutic outcome. To date vancomycin penetration in the respiratory tract has been evaluated in pleural fluid, lung lymph of sheep, and alveolar epithelium lining fluid (Geraci *et al.*, 1956; May *et al.*, 1987; Lamer *et al.*, 1993). A single concentration of vancomycin in lung tissue has been reported in one patient observed post-mortem (Torres, Sanders & Lewis,

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1979). We investigated the penetration of vancomycin into lung tissue of thirty patients undergoing lung resection.

Patients and methods

Thirty patients (23 males, age 62.1 ± 11.2 years; weight, 77.7 ± 14.3 kg (mean ± S.D.)) were enrolled in the study after giving written informed consent. The study was approved by the internal Committee for Human Research. Twenty eight patients underwent thoracotomy because of lung carcinoma, one patient because of relapsing pneumothorax, and one patient because of tubercular abscess. All patients had normal kidney and liver function.

Vancomycin was administered as a single 1 g dose infused iv over 1 h. At the time of lung resection samples of healthy lung tissue and venous blood were obtained concomitantly for determination of vancomycin concentrations. Vancomycin administration and surgery were planned in order to allow taking of blood and tissue samples at discrete times in the interval 1–12 h after the end of vancomycin infusion. Blood was placed on ice, allowed to clot, centrifuged, and serum was stored at −20°C until assayed. The samples of lung tissue were rinsed three times in 0.9% sodium chloride solution, dried with sterile blotting paper, weighed, and homogenized in approximately five volumes of saline. The homogenates were centrifuged at 1950 **g** at room temperature. The supernatant was harvested and stored at −20°C until assayed.

Vancomycin was separated from biological matrices by means of a liquid-solid extraction using C18 cartridges (LC-18 SPE purification column, Supelco, Bellefonte, PA, USA). Cartridges were previously washed with 3 mL of methanol and 1 mL of water. One-millilitre of sample was loaded onto the column and washed with 1 mL of water. Vancomycin was eluted with 0.5 mL of a methanol-water (1:1) mixture; the eluate was then centrifuged at 15,300 **g** and 50 μL were injected into a high performance liquid chromatography (HPLC) column. The HPLC system was equipped with a binary pump LC 250 (Shimadzu, Tokyo, Japan), an UV detector LC 95 (Shimadzu, Tokyo, Japan) operating at 230 nm, and an autosampler model ISS 200 (Perkin Elmer, Norwalk, CT). The elution was carried out on Aquapore RP 300, 7 μm column (100 × 4.6 mm) (Perkin Elmer), in gradient mode, using 20 mM phosphate buffer (pH 5.5) and acetonitrile according to the following profile: from 0 to 7 min, isocratic with phosphate buffer: acetonitrile (97:3); then, from 7 to 10 min, gradient up to phosphate buffer: acetonitrile (75:25). The flow rate was 1.5 mL/min.

The calibration curve in serum was linear in the range 0.2–50 mg/L. The calibration curve for determination of vancomycin concentrations in lung tissue was prepared by spiking an appropriate amount in antibiotic-free lung tissue homogenate. The calibration curve for lung tissue homogenates was linear in the range 0.5–50 mg/kg. The coefficient of variation calculated at the concentrations of 5, 20, 30 and 40 mg/L (mg/kg) ($n = 7$ for each concentration both in serum and lung tissue homogenate) was below 8%. Accuracy, calculated at concentrations 2, 10 and 20 mg/L (mg/kg) was 99.1%, 100.1% and 100.9% in serum standards and 98.9%, 97.1 and 100.4% in lung tissue. Recoveries from serum and lung tissue homogenates, evaluated at the concentration of 2 and 40 mg/L (mg/kg) were >95%. The lower limits of quantitation

were 0.2 mg/L in serum and 0.5 mg/kg in lung tissue homogenate. Haemoglobin concentration in lung tissue was used for correction of blood contamination (Plaue *et al.*, 1980).

Results

Vancomycin concentrations in serum, lung tissue and the ratios of lung tissue to serum concentrations are given in the Table. Concentrations of vancomycin in lung tissue were undetectable in one of six patients who underwent lung tissue sampling at 6 h, and in three of seven patients at 12 h. The figure shows that there was a significant relationship between lung tissue and serum concentrations.

Table. Vancomycin concentrations in lung tissue and serum

Time (h)		Vancomycin concentration serum (mg/L)	lung (mg/kg)	Ratio (lung/serum)
1		34.77	10.94	0.31
		46.50	9.62	0.21
		43.90	12.12	0.28
		37.64	6.35	0.17
		40.11	9.03	0.23
	mean	40.58	9.61	0.24
2		19.46	7.38	0.38
		17.07	5.32	0.31
		25.21	4.68	0.19
		21.54	5.62	0.26
		16.92	5.54	0.33
	mean	20.04	5.71	0.29
3–4		14.47	6.44	0.45
		15.90	5.56	0.35
		8.52	1.34	0.16
		17.45	5.63	0.32
		13.94	2.91	0.21
		7.21	6.47	0.90
		8.61	0.83	0.10
	mean	12.30	4.17	0.35
6[a]		6.78	4.67	0.69
		5.65	1.15	0.20
		8.64	1.92	0.22
		7.21	1.43	0.20
		6.08	3.02	0.50
	mean	6.87	2.44	0.36
12[a]		6.87	7.67	1.12
		7.28	0.98	0.13
		8.68	1.57	0.18
		4.11	0.85	0.21
	mean	6.74	2.77	0.41

[a]Only patients with detectable vancomycin in lung tissue are reported. One of six patients at 6 h and three of seven at 12 h did not have detectable antibiotic in lung tissue. The corresponding vancomycin concentrations in plasma were 4.66 mg/L for the patient at 6 h, and 4.99, 2.31 and 4.85 mg/L for the three patients at 12 h.

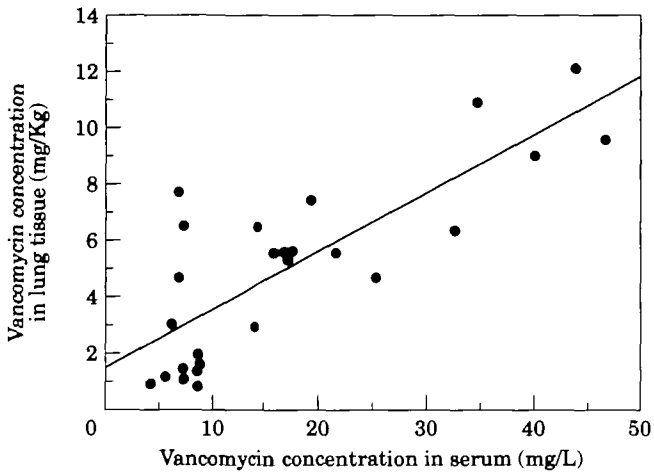

Figure. Relationship between vancomycin concentrations in serum and lung tissue ($r = 0.81$, $P = 0.0001$).

Discussion

Only a few studies have addressed the issue of vancomycin penetration in the respiratory tree. Concentrations of vancomycin in pleural fluid were reported approximately forty years ago (Geraci *et al.*, 1957), and ranged 0–8.1 mg/L at 1–3 h following administration, with pleural fluid: serum antibiotic concentration ratios ranging 0–0.9. Recently, the penetration of vancomycin in lung lymph of sheep has been investigated, with the assumption that lung lymph is identical in composition to the interstitial fluid, and that data obtained from sheep may be applied to humans (May *et al.*, 1987). Concentrations in lung lymph were 80% of those found in plasma 30 min after the end of vancomycin infusion. The concentration of vancomycin was recently measured in alveolar epithelium lining fluid (ELF) obtained by bronchoalveolar lavage (BAL) in 14 patients (Lamer *et al.*, 1993). BAL was performed 8–50 h following ≥ 5 days of vancomycin administered as a 2 h iv infusion. ELF: plasma vancomycin concentration ratio was 0.15. We found that vancomycin concentrations in whole lung tissue homogenate were slightly higher than those reported in ELF (Lamer *et al.*, 1993). Overall, lung tissue:serum antibiotic concentration ratio, determined with the same approach used in the ELF study (Lamer *et al.*, 1993), i.e., as slope of the lung tissue versus serum vancomycin concentration, yielded a value of 0.21 (Figure). The volume of distribution of vancomycin has been reported in the range 0.5–0.9 L/kg (Matzke, 1992), suggesting that vancomycin is widely distributed throughout the body. However, vancomycin penetration in the lung appears to be relatively poor, on the basis of our data and those of others (Lamer *et al.*, 1993). A reason for this may be that vancomycin, a polar compound, partially ionized at physiological pH, and with high molecular weight, does not readily diffuse from blood to lung. Also, lower concentrations in tissues may be in part caused by antibiotic binding to plasma proteins. The mean value for vancomycin binding to plasma protein is approximately 45–55% (Lamer *et al.*, 1993; Sun, Maderazo & Krusell, 1993). Penetration of vancomycin into lung tissue (obtained post-mortem) has been reported for a patient who received 500 mg iv qds (Torres *et al.* 1979). The single concentration of vancomycin in lung tissue determined by bioassay was 13 mg/kg and tissue:serum antibiotic concentration ratio was 2.45. This very high ratio may be

an artifact caused by the discrepancy between the times of blood and tissue sampling. The concentration in lung tissue, detected at steady-state, is near the upper limit of the concentrations we found 1 h following the end of a single dose infusion.

The concentrations of vancomycin that we observed in lung tissue were above the MIC breakpoint of 4 mg/L (Acar & Goldstein, 1991) for susceptible staphylococci in all the patients studied at 1 and 2 h following vancomycin administration. However, a substantial percentage of patients observed at sampling times after 3 h post infusion had sub-MICs of vancomycin in lung tissue. With the known limitations underlying the interpretation of tissue concentration data, our study indicates that administration of 1 g vancomycin as a 1 h iv infusion does not allow the maintenance of adequate antibiotic concentrations in lung tissue for 12 h. A dosage approach allowing sustained inhibitory concentrations of vancomycin in lung tissue, such as constant iv infusion, may be more appropriate.

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