CASE REPORT

Applied Pharmacokinetics in a Case of *Vibrio Vulnificus* Induced Anuria

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INTRODUCTION

Vibrio vulnificus is a motile, halophilic, gram negative, marine, bacillus that is associated with high mortality (greater than 50%) in individuals with an underlying chronic disease such as cirrhosis, diabetes or leukemia. Such patients handling or consuming raw, filter-feeding mollusks and crustaceans (oysters, crabs and clams) are at risk for developing a primary septicemia syndrome.[1,2]

Initially, patients present with cellulitis, often displaying distinctive bullae. Coagulopathies are common; one third of the patients become severely hypotensive within 12 hours of admission. The skin lesions rapidly progress to gangrene often with concomitant fever and chills. The primary septicemic syndrome heralds the onset of multiorgan system failure, with death an inevitable outcome.[3]

Vibrio species are highly susceptible in *vitro* to a number of antimicrobials, including ampicillin or alternatively chloramphenicol in combination with an aminoglycoside, with the drug of choice being tetracycline.[2] We report a fatal case of *Vibrio vulnificus* infection, the result of raw oyster consumption by a patient with pre-existing hepatic cirrhosis who required continuous arteriovenous hemofiltration (CAVH) to support his failing kidneys.

CASE REPORT

A thirty-nine year old white male presented to the Emergency Department complaining of pain in both legs, malaise and general weakness. On physical examination, blistered, blue, necrotic haemorrhagic lesions were evident on the lower extremeties. In addition, it was learned that this patient had a history of alcohol abuse, had recently returned from vacationing in Florida where he had been drinking heavily and consuming raw oysters. A provisional diagnosis of streptococcal sepsis was made. The patient was started on penicillin G 1 million units IV every four hours and gentamicin 75 mg IV every eight hours. Shortly thereafter, while still in the Emergency Room, the patient experienced an episode of severe hypotension. Large doses of dopamine and norepinephrine were administered in an effort to stabilize his hemodynamic system. The admitting physician began to fear that multiorgan failure was imminent. On the basis of gram stain obtained from necrotic areas of the skin and reported history of heavy alcohol consumption, a preliminary diagnosis of septic shock due to *Klebsiella* was suggested.

Upon transfer to the intensive care unit, antibiotic therapy was changed to piperacillin 2.5 gm IV every four hours and tobramycin 100 mg IV loading and 80 mg IV every eight hours with levels to be drawn. The patient was given platelets for elevated PTT and fresh frozen plasma to help correct a coagulopathy. The pharmacist attached to the unit calculated a more appropriate dose of tobramycin 150 mg IV every eighteen hours with the aid of Simkin™ computer program.[4] (Figure 1) Isolation of *Vibrio vulnificus* from blood and skin cultures was accomplished by day three of hospitalization and then doxycycline 100 mg IV every twelve hours was added to the regimen. The serum creatinine continued to climb and when it reached 307 μmol/L continuous arteriovenous hemofiltration (CAVH) was instituted.

The steady-state conditions and pharmacokinetic parameters assumed by the Simkin™[4] program

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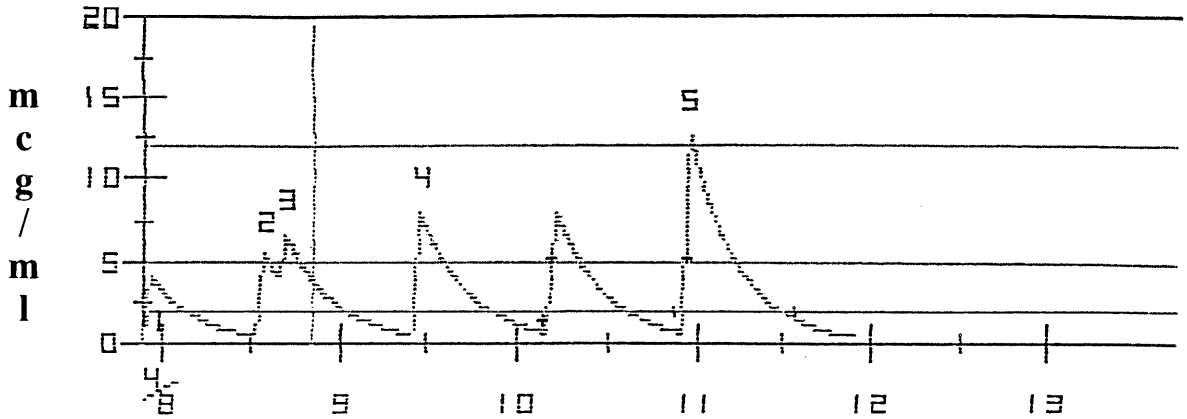
Figure 1: Pharmacokinetic consult generated by Simkin™ using our patient specific parameters

St. Joseph's Health Centre
Pharmacokinetics Consult Service



39 year old male who weighs 68 kg and is 181 cm tall
His current serum creatinine was measured at 160 μmol/L
Dx: septic shock

BLOOD SAMPLING

Point=	Date	Time Drawn	X-Axis Hour	Hours Post-Dose	Conc. Simulated	Thera. Actual	Window
1	10-04-1991	03:50	54.3	17.8	0.00	1.40	Inside
2	10-04-1991	05:15	55.8	1.3	0.00	5.10	Inside
3	10-04-1991	21:50	72.3	17.8	3.37	1.90	Inside
4	10-04-1991	23:15	73.8	1.3	12.38	5.30	Inside
5	11-04-1991	14:10	88.7	16.2	1.35	1.90	Inapp.*

OTHER PHARMACOKINETIC PARAMETERS
Rx 1 - 5: Vd (L/Kg) = 0.27 T 1/2 (Hr) = 4.71
Dosing wt. = 68 Kg.
RECOMMENDATIONS

	Rx#	SIMULATED PEAK (mg/ml)	SIMULATED TROUGH (mg/ml)	TIME TO Cpss*a* (hours)
TOBRAMYCIN 150 mg IVB Q18 h	4	8.1	0.6	23.5

* "Cpss" denotes drug concentration in plasma at steady-state.

It is recommended that a followup peak (obtained at 30 minutes post infusion) and trough (obtained at 30 minutes pre-infusion) be drawn in no sooner than 24 hours.

The above calculations are based upon literature population averages individualized to your patient and to previously measured concentrations.

were no longer valid and the suggested dose calculated the day before could no longer be used. Using semilog paper, the pharmacist plotted peaks and troughs reported by Clinical Laboratory on a daily basis and extrapolated the time of the next dose of aminoglycoside assuming a desired trough of 1 mcg/mL. The amount of the dose to be administered utilized a theoretical volume of distribution which was calculated by dividing the most recent dose infused by the most recent peak serum concentration reported. (Table I) Levels of drug in CAVH filtrate were also assayed initially as a double check to confirm theory that a fraction of aminoglycoside removed approximated 95%. (Table I) To confirm theoretical filtration rate and achievement of therapeutic levels,[5,6] serum and filtrate samples of doxycycline were sent to Pfizer for analysis as the assay was not performed in-house. (Table II) In the meantime, the physician empirically reduced the doxycycline dose to 100 mg IV every thirty-six hours to accommodate deteriorating hepatic function. Extreme skin sloughing and gangrene of the affected limbs was noted at this point. A plastic surgery consult directed the attending physician to contemplate amputation of both limbs to save the patient's life. Blood

Table I: Tobramycin levels in serum and filtrate as reported by the Clinical Laboratory Department

	Admission Day						
	1	2	3	4	5	6	8
TIME (h)	2130	1300 1600	1000	0400 2200	2200	2000	2400
DOSE (mg)	80	100 60	150	150 150	240	200	200
SERUM PEAK LEVEL (mg/mL)			5.1	10.7	9.3	8.8	7.5
*PREDICTED PEAK LEVEL (mg/L)			5.4	9.0	9.0	9.0	9.0
SERUM TROUGH LEVEL (mg/L)			1.4	1.0	2.5	2.1	2.2
*PREDICTED TROUGH LEVEL (mg/L)			1.6	1.0	1.8	1.5	1.5
FILTRATE PEAK (mg/L)					9.3		
FILTRATE TROUGH (mg/L)				1.7			
ALBUMIN (g/L)		33	35	27	26	25	21

* using Simkin™ or manual calculations.

Table II: Doxycycline levels in serum and filtrate as reported by Pfizer for empirically administered doses

	Admission Day		
	5	6	8
Time (h)	1130 1800	1000 1800	0600
Dose (mg)	100 100	100 100	100
Serum Peak Levels (mg/L)	— 3.46	3.39 4.24	2.7
Serum Trough Levels (mg/L)	— NS	2.70 3.05	NS
Filtrate Peak Levels (mg/L)	— NS	NS 3.43	2.35
Filtrate Trough Levels (mg/L)	— NS	NS 1.96	NS
Albumin (g/L)	26	25	21

NS = no sample.

cultures returned negative for *Vibrio* but positive for *Streptoccocus pneumoniae*. Before any changes to therapy could be made, the patient suffered haemoptysis, internal hemorrhage secondary to DIC and had a cardiac arrest. He expired ten days after admission.

DISCUSSION

CAVH provides an alternative to conventional hemodialysis for the critically ill patient who is in acute renal failure. This simple, relatively safe and cost effective technique simulates the human kidney but in a much less efficient manner, effecting a clearance of about 10 mL/min.[7] It employs a hemofilter, extracorporeally which freely filters water and non-protein bound molecules weighing less than 5200 Daltons. The hemofiltration process is accomplished by convective mass transfer where the solute (drug) dissolved in the plasma water crosses the membrane and may adhere to it depending on such factors as transmembrane pressure, affinity, and volume of distribution of solute. The fraction of drug removed is known as the sieving co-efficient and primarily varies inversely with the amount of drug bound to protein.[6]

We utilized the literature values for protein binding and theoretical sieving co-efficients for tobramycin and doxycycline to estimate doses. Since tobramycin is only 5% protein bound its calculated sieving co-efficient should be high (0.7 - 0.9).

The opposite was true of doxycycline which is highly protein bound and should have a low sieving co-efficient.[6] We attempted to confirm these values by testing a select number of filtrate samples. Once serum and filtrate levels corresponded closely to predicted ones (Table I), we felt there was no further need to do filtrate determinations and that we could continue with our dosing methods. Further serum sampling for the aminoglycoside was paramount however, since the dosing interval was progressively lengthening and it became increasingly more difficult to maintain the trough below 2 mg/L. (Table I) The physician reasoned that as the interval for tobramycin dosing was increased three-fold, he would empirically increase the doxycycline dosing interval from every twelve to every thirty-six hours. This empiric dosing of doxycycline achieved serum levels of 3 mg/L; thus, therapeutic levels for the drug were maintained for a portion of the dosing interval.[10] The physician and pharmacist were both impressed with the close correspondence between actual and predicted serum and filtrate levels for both tobramycin and doxycycline given the patients changing renal function.

This case illustrates in abbreviated

form the use of CAVH as a technique for removing drugs from the plasma of a critically ill patient. Although the patient succumbed as a result of multiple organ system failure, attempts to treat his overwhelming infection were successful to a point, as the *Vibrio* was eradicated. Noteworthy, was the co-operation between physicians, nurses, the laboratory and pharmacists in trying to save the patient's life.

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