Gentamicin serum half-life: a comparison between pregnant and non-pregnant women

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Summary: The serum half-life of gentamicin following an intravenous dose was compared between 19 pregnant women (28–34 weeks of pregnancy) with premature rupture of the membranes and 17 non-pregnant women with pelvic inflammatory disease, the groups being age and weight matched. A significant reduction of gentamicin half-life was found in the pregnant group.

Introduction

Gentamicin is an effective and widely used aminoglycoside antibiotic that is particularly useful in the treatment of Gram-negative bacillary infections. As gentamicin is removed from body fluids principally by renal excretion, its plasma half-life is highly dependent on renal function (Jackson, 1977). The rate of plasma elimination of gentamicin correlates with the serum creatinine concentration, glomerular filtration rate and creatinine clearance (McHenry *et al.*, 1971). During pregnancy glomerular filtration rate increases and we therefore suspected that gentamicin half-life is decreased during pregnancy.

Patients and methods

Two groups of hospitalized women of the same mean age and weight were selected. Group A consisted of 19 pregnant women at 28–34 weeks of gestation – one fetus, 20–30 years old, 62 ± 5 kg in weight, who had premature rupture of the membranes. In group B there were 17 non-pregnant women of the same age range, 55 ± 5 kg in weight who were diagnosed as suffering from pelvic inflammatory disease. Both groups were given 4 mg/kg gentamicin per day, one third being given every 8 h concomitantly with cefazolin 3.0 g/d.

The reason for treating gravid patients in group A was to prevent amniotic infection while awaiting fetal lung maturation following betamethasone injection. No woman in either group had suffered from any previous renal or other systemic disease. All had their

renal function tested upon admission to the hospital and before any medication was given. Those who had any dysfunction were excluded from the study.

Intravenous fluids, 2500 ml/24 h of Hartman's solution, were administered equally to both groups upon admission to the hospital and this was continued as long as the medications were given.

Blood samples were taken at 15 min intervals during the first hour and then at hourly intervals for 8 h.

The EMIT quantitative enzyme immunoassay of gentamicin in human serum was employed to measure total drug concentration in the serum. This assay is designed to quantitate serum gentamicin concentrations accurately within the range 1.0 to 16.0 µg/ml. Optimal precision (coefficient of variation less than 10%) is obtained in the range of 2.0 to 10.1 µg/ml.

Gentamicin half-life was calculated according to its elimination curve (Mayer *et al.*, 1980). The concentration fell rapidly initially, as distribution occurred. First order elimination kinetics were followed. By extrapolation of this line, the serum concentration for every minute could be determined. The half-life of the drug elimination could then be estimated from the graph.

Statistical analysis was made by BMDP Statistical Software Inc., University of California.

Results

Serum creatinine and creatinine clearance of both groups are given in Table I. Gentamicin mean half-life in group A was 93.5 ± 13.5 min, compared to 158.9 ± 14.1 min in group B ($P < 0.0001$). Mean serum concentration of gentamicin in group A was

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Table I Comparison of serum creatinine clearance between pregnant (Group a) and non-pregnant (group B) women

	Group A	Normal value	Group B	Normal value
Serum creatinine (μmol/l)	56.6 ± 8.8	40.7 ± 53.0	74.25 ± 17.7	76.9 ± 150.3
Creatinine clearance (ml/min)	144.78 ± 4.0	132 – 164	96.29 ± 4.1	90 – 130

The values given are mean ± s.d.

1.9 μg/ml after 5 h and 4.1 μg/ml in group B ($P < 0.0001$). Eight hours following intravenous injection there were only traces of the drug in the serum in group A while mean serum concentration in group B was 1.6 μg/ml ($P < 0.0001$).

Discussion

A linear relationship exists between the concentration of creatinine in the serum and the half-life of all aminoglycosides in patients with normal and moderately compromised renal function (Cutler *et al.*, 1972).

The physiological changes that accompany pregnancy may alter the pharmacokinetics of the

antibiotics and also enhance toxic effects. The changes in plasma protein concentration during pregnancy may affect the degree of binding, and thus the amount of unbound drug available (Landers *et al.*, 1983).

The volume increase in the vascular compartment during pregnancy influences the concentration of antibiotic agents, generally resulting in lower serum levels of the drug. The increase in cardiac output and renal blood flow, which results in augmented glomerular filtration rate and creatinine clearance, increases antibiotic clearance and lowers serum level of renally excreted antibiotics (Landers *et al.*, 1983).

We found a negative linear correlation between serum gentamicin half-life and creatinine clearance (Figure 1). This means that due to physiological changes in renal function in normal pregnancy, the

Figure 1 Demonstration of a linear negative correlation between serum gentamicin half-life and creatinine clearance. (N) Pregnant women; (O) non-pregnant women.

half-life of gentamicin is considerably shorter. Thus we might have considered increasing the dosage or shortening the interval between dosages. However, serum levels in both groups for the first 4 h were higher than the minimal inhibitory concentrations for *Staphylococcus aureus*, *Escherichia coli*, *Proteus mirabilis*,

Pseudomonas aeruginosa, *Klebsiella*, *Enterobacter* and *Serratia* (Korzeniowski & Hook, 1979).

Bearing in mind the fact that gentamicin is an antimicrobial with narrow margins of safety we would thus advise giving gentamicin to pregnant women every 8 h in the dosage of 4 mg/kg.

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