Effect of Changes in Intercompartment Rate Constants on Drug Removal during Hemoperfusion

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Abstract □ A computer simulation of the effect of changing intercompartment clearance rates on drug removal during hemoperfusion was undertaken. As intercompartment clearance slowed, the fall in plasma levels increased and postperfusion rebound increased, but the total drug removed decreased.

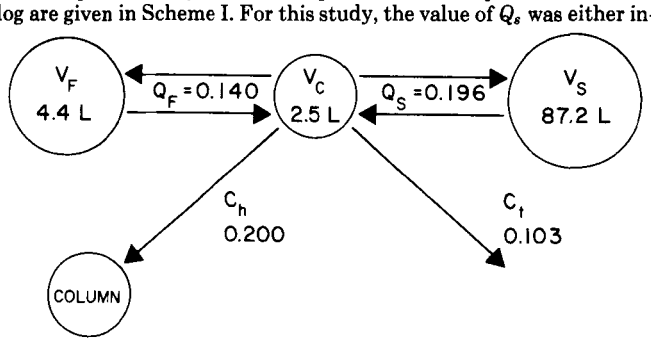
Keyphrases □ Drug removal—during hemoperfusion, effect of changing intercompartment clearance rates, computer simulation □ Clearance rates, intercompartment—effect of changing on drug removal during hemoperfusion, computer simulation □ Pharmacokinetic models—drug removal during hemoperfusion, effect of changing intercompartment clearance rates, computer simulation □ Models, pharmacokinetic—drug removal during hemoperfusion, effect of changing intercompartment clearance rates, computer simulation

Recently (1), the kinetics of intravenous digoxin in dogs before, during, and after resin hemoperfusion were described. There was a rapid curvilinear decline in serum digoxin levels during resin hemoperfusion; but, when hemoperfusion was stopped, serum digoxin levels increased. By 4 hr after hemoperfusion, the increase in digoxin levels was complete. Thereafter, the slope of elimination paralleled the preperfusion slope. A three-compartment open mammillary model (Scheme I) adequately described the kinetics of digoxin distribution and elimination before perfusion, the decline of serum levels during perfusion, and the rebound of digoxin levels after perfusion.

The average volume of distribution, V_d, of digoxin in dogs was found to be 4.3 ± 0.7 liters/kg, most of which (85%) was included in the slowly equilibrating peripheral compartment of the model, V_s (Scheme I). Because the bulk of the body burden of digoxin was sequestered in this large compartment, the effect of changes in the rate of movement of drug from this large compartment, Q_s, to the central compartment, V_c, on the effectiveness of hemodialysis or hemoperfusion was investigated.

EXPERIMENTAL

The experimentally determined pharmacokinetic parameters of one dog are given in Scheme I. For this study, the value of Q_s was either increased or decreased by a factor of 10 from that experimentally observed. Values of V_c, V_s, V_f, Q_F= AND C_h were kept constant, and a simulated perfusion was carried out for 5 hr. For simplicity, C_t was set equal to zero so that concentrations in all model compartments would be equal (18.6 ng/ml) when the distribution equilibrium was reached. All calculations were done with the SAAM 23 program for multicompartment analysis (2).



Scheme I—Multicompartment model used to analyze pharmacokinetics of digoxin in dogs. Key: V, volume; Q, intercompartment clearance rate (liters per minute); C, clearance (liters per minute); f, fast; s, slow; c, central; h, hemoperfusion; and t, nonperfusion.

Table I—Changes in Compartment Content of Digoxin with Alterations of Q_s

Parameter	Q_s Fast	Q_s Intermediate	Q_s Slow
Amount removed, μg	777.2	518.9	204.8
Amoung in V_c, μg			
Start	46.5	46.5	46.5
Lowest point	23.8	17.0	4.0
Reequilibration	25.8	32.5	40.5
Amount in V_s, μg			
Start	1621.7	1621.7	1621.7
End	904.7	1182.6	1533.6
Reequilibration	901.4	1140.8	1433.5
Time to 90% reequilibration, min	3	75	705

RESULTS

Results are shown in Fig. 1 and Table I.

In Fig. 1A, Q_s was increased 10-fold over that observed experimentally. With perfusion, there was a linear and concordant fall in digoxin levels in all compartments, much as in a one-compartment model. Although serum digoxin levels only fell from 18.5 to 9.5 ng/ml, 777.2 μg of digoxin was removed (Table I). The postperfusion rebound was 90% complete within 3 min, and levels in V_c reequilibrated at 10.3 ng/ml.

Figure 1B shows the results with the value of Q_s found experimentally. With hemoperfusion, there was a curvilinear decline in serum levels to 6.8 ng/ml. Digoxin levels in V_s and V_f lagged behind the level in V_c, and

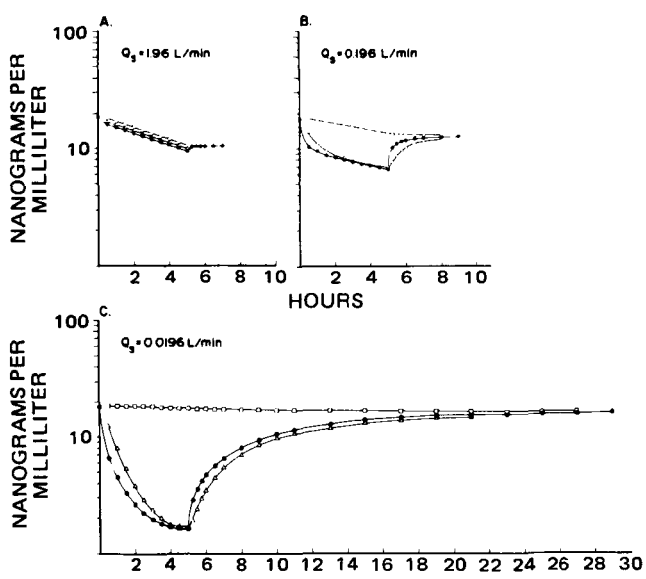


Figure 1—*Effect of altering Q_s on digoxin concentration in V_c (●), V_f (△), and V_s (□) during and after hemoperfusion.*

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only 581.9 μg of digoxin was removed. Seventy-five minutes was required postperfusion before the system reached 90% of equilibration.

In Fig. 1C, Q_s was slowed by a factor of 10. Digoxin levels in V_c and V_f fell rapidly to 1.6 ng/ml, and hemoperfusion in this setting apparently was very effective. However, digoxin levels in V_s fell very slowly, and only 204.8 μg of digoxin was removed. Reequilibration was 90% complete in 705 min.

DISCUSSION

As can be seen in Table I, the amount of digoxin in V_s continued to fall after the completion of perfusion as V_c and V_f were refilled. If the pharmacological effect of digoxin or any other drug takes place in V_s then the adverse effect of those drugs with rapid intercompartment clearances can be rapidly decreased by hemodialysis or hemoperfusion. As Q_s decreases, changes in concentration in V_c will become greater with dialysis or hemoperfusion, but there will be little net reduction in pharmacological effects or total body burden with short perfusion times. However, if the pharmacological effect is in V_c, the toxicity of drugs with slow intercompartment clearances will be rapidly reversed, only to return as this compartment is refilled from V_s.

Schreiner (3) correctly pointed out that the effectiveness of the artificial kidney in removing substances will depend upon the rapid equilibration of the substance with plasma water. However, some nephrologists neglect this fact and feel that V_d *per se* is the rate-limiting factor controlling the effectiveness of drug removal. Clearly, while a large V_d influences the effectiveness of dialysis or hemoperfusion, the rate-limiting step may be the rate of movement of drug from V_s to V_c.

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Factors Affecting Homogeneous Precipitation of Aluminum Hydroxide Gel

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Abstract □ The variables affecting homogeneous precipitation in the hydrolysis of aluminum nitrate by sodium carbonate were studied. Increased temperature, decreased concentration of reactants, and decreased rate of addition of titrant favor conditions that achieve homogeneous precipitation. During acid hydrolysis, the nitrate anion was the major anion associated with the gel and only small amounts of carbonate were observed. It is recommended that homogeneous conditions be achieved during the precipitation of aluminum hydroxide gel to improve reproducibility.

Keyphrases □ Aluminum hydroxide gel—factors affecting homogeneous precipitation in hydrolysis of aluminum nitrate by sodium carbonate □ Antacids—aluminum hydroxide gel, factors affecting homogeneous precipitation in hydrolysis of aluminum nitrate by sodium carbonate

The precipitation of aluminum hydroxide gel through the hydrolysis of an aluminum salt is complex. The precipitation method and subsequent treatment have a great effect on the properties of the product (1–4). This variability has been a problem affecting all areas of research and production of aluminum hydroxide gel.

In the titration of aluminum nitrate with sodium hydroxide, polymerization occurs prior to precipitation under homogeneous conditions (5, 6). This was achieved by precipitation under carefully controlled conditions in a specially designed reaction chamber. Precipitation of aluminum hydroxide gel under homogeneous conditions may be important in reducing the variability in precipitation.

Studies were undertaken to determine if homogeneous precipitation conditions could be achieved using standard precipitation equipment. The effect of precipitation variables was then investigated to determine the contribution of each variable in the achievement of a homogeneous reaction.

The system studied was the precipitation of aluminum hydroxide from acidic media (5, 6). However, sodium carbonate was used as the titrant instead of sodium hydroxide because the aluminum hydroxide gels used as antacids usually contain carbonate (7, 8).

EXPERIMENTAL

Potentiometric titrations were performed by placing 100 ml of solution in a 400-ml jacketed beaker. The temperature was controlled to ±0.1°, and the solution was stirred[2] at 2000 rpm. Titrant was added at a controlled rate[3]; the standard rate of addition was 2 ml/min. The solution pH was monitored continuously and recorded. Exact replication of titration curves was obtained when conditions producing homogeneous precipitation were used.

IR analysis[4] (9) was performed on a portion of the aluminum hydroxide, which was washed with three volumes of water to remove excess salts prior to drying under vacuum at room temperature. Spectra were obtained using potassium bromide pellets.

RESULTS AND DISCUSSION

Titration of 0.5 *M* aluminum nitrate by 0.5 *N* NaOH at 22° (Fig. 1)

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[2] Stedi-Speed stirrer, Fisher Scientific, Pittsburgh, Pa.

[3] Solution metering pump, model 746, Beckman Instruments, Fullerton, Calif.

[4] Model 180, Perkin-Elmer Corp., Norwalk, Conn.

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