Effect of Bed Rest on Distribution and Elimination of Drugs

Sir:

Most pharmacokinetic studies are conducted on healthy ambulatory subjects. It is recognized, however, that many of these investigations should be carried out also on sick patients in order to assess the effect of various pathological conditions on the kinetics of drug absorption, distribution, and elimination. Such comparative studies will ordinarily involve bedridden patients and a control group of healthy ambulatory subjects (or the same patients upon complete restoration of health). It is the purpose of this communication to point out that bed rest *per se* can have an appreciable effect on drug distribution and elimination. This effect, if unrecognized, can cause considerable errors in the interpretation of pharmacokinetic data.

Schmidt and Roholt (1) have recently determined serum levels and urinary excretion of benzylpenicillin after intramuscular injection of 5 million units of benzylpenicillin sodium in six subjects while these were in bed and, subsequently, while they were ambulatory. For the purpose of this report, data for 5 of these subjects have been subjected to pharmacokinetic analysis. (Data for subject *3* were incomplete and had to be excluded.) It was found that penicillin concentrations in the plasma declined exponentially with time over a concentration range of three orders of magnitude. Half-life values ($t_{1/2}$) were determined graphically and were used to calculate apparent first-order rate constants for elimination (k). Apparent first-order rate constants for excretion of unchanged drug (k_e) were obtained from fk, where f is the fraction of the dose excreted unchanged. Rate constants for metabolism (k_m) were determined by subtracting k_e from k. The apparent volume of distribution (V_d) was calculated on the basis of the relationship A = dose $k^{-1}V_d^{-1}$, with the area (A) under the serum level *versus* time curve obtained by planimetry. Renal clearance was calculated as the product of k_e and V_d. Mathematical derivations for these equations may be found in the review by Nelson (2).

The pharmacokinetic constants for five subjects while ambulatory and during bed rest are listed in Table I. The fraction of the administered dose excreted unchanged and the renal clearance of benzylpenicillin were significantly increased and k_m was significantly decreased during bed rest ($p < 0.05$ by t-test, paired comparisons). The average V_d was increased during bed rest; this effect was not quite statistically significant, but it occurred in all five subjects.

The most interesting effect of bed rest is the apparent decrease in the first-order rate constant for metabolism (and possibly extra-renal excretion) of benzylpenicillin (k_m) to one-half the value observed while the subjects were ambulatory. It is conceivable that similar results, if obtained in the course of a comparative study of ambulatory normal subjects and bedridden patients suffering from certain disease(s), would be interpreted as being indicative of impaired drug metabolizing capacity due to the disease. In fact, it appears that bed rest *per se* can bring about pronounced changes in the distribution, metabolism, and excretion of drugs relative to values obtained in ambulatory subjects. This may be due to the higher metabolic rate of ambulatory subjects (1), or to the marked circulatory and plasma volume differences found in upright and recumbent subjects, respectively. These latter differences are due to the increased hydrostatic pressure of plasma associated with an upright as opposed to a recumbent posture (3). The increased hydrostatic pressure in the lower parts of the upright body causes plasma water to enter the interstitial space and leads to an increase in the concentration of plasma proteins (4). Similar effects are observed following physical exercise (5). This in turn results in higher plasma concentrations of plasma protein-bound drugs, although the total amount of drug in the plasma may be decreased due to the smaller plasma volume. A remarkable example of this effect and the type of artifact it can produce have been described recently by Dettli and Spring (4). These investigators determined plasma levels of sulfasymazine in hospitalized patients at 12-hr. intervals; apparent $t_{1/2}$ values calculated for any given 12-hr. period were much higher if the patient left the bed prior to removal of the second blood sample. In some instances the plasma obtained from a patient who had left the bed before the blood sample was drawn had a higher sulfonamide concentration than the plasma obtained 12 hr. earlier while the patient was in bed!

Pharmacokinetic models in current use do not provide for variations in plasma volume, variable blood flow rates through organs, and other region- or organ-specific circulatory changes. The effects of such variations will appear in the V_d and rate constants of presently used pharma-

TABLE I—PHARMACOKINETIC CONSTANTS FOR BENZYLPENICILLIN IN ADULT HUMAN MALES WHILE AMBULATORY AND DURING BED REST[a]

Subject	$t_{1/2}$, hr.	k, hr $^{-1}$	f	k_e, hr.$^{-1}$	k_m, hr.$^{-1}$	V_d, L.	V_dk_e, ml. min.$^{-1}$
			Ambulatory				
1	.85	.82	.54	.44	.38	45	330
2	.90	.77	.74	.57	.20	47	440
4	.85	.82	.78	.64	.18	35	370
5	.70	.99	.58	.57	.42	28	270
6	.90	.77	.70	.54	.23	33	290
Mean[b]	.84	.83	.67	.55	.27	37	340
			Bed Rest				
1	.75	.92	.76	.70	.22	47	550
2	1.1	.63	.88	.55	.076	51	470
4	1.1	.63	.98	.62	.013	53	550
5	.70	.99	.84	.83	.16	29	410
6	1.0	.69	.64	.44	.25	55	410
Mean[c]	.93	.75	.82[c]	.61	.13[c]	47	480[c]

[a] Based on data from *Reference 1*. All data are expressed in two significant figures based on the results of calculations carried out to three significant figures. [b] All mean values are based on the arithmetic mean half-life. [c] Significantly different ($p < 0.05$) from values obtained while the subjects were ambulatory.

cokinetic models. Thus, the pronounced difference in the k_m values for benzylpenicillin during the ambulatory state and during bed rest, respectively, is probably only an apparent one which is not necessarily indicative of an intrinsically impaired capacity for drug biotransformation during bed rest.

A review of general physiology (3) and particularly of renal physiology (6) suggests to this author that the circulatory and distributive changes in man due to changes in posture [or due to physical exercise (5, 7)] may be too complex to incorporate in pharmacokinetic models. It appears therefore that comparative pharmacokinetic studies on sick, bedridden patients and healthy controls require that the latter be in bed also. An additional complication arises from the fact that prolonged bed rest causes a gradual deterioration of cardiovascular function which is associated with a *decrease* of plasma volume (8). Such selective effects of bed rest give rise to potentially formidable problems in the pharmacokinetic interpretation of drug disposition during disease.

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Received April 3, 1967.
Accepted for publication May 17, 1967.