Ascorbic Acid Elimination in Humans after Intravenous Administration

Keyphrases □ Ascorbic acid—elimination in humans after intravenous administration□ Elimination—ascorbic acid in humans after intravenous administration □ Vitamins—ascorbic acid, elimination in humans after intravenous administration

To the Editor:

Relatively few studies have examined the disposition kinetics of ascorbic acid in humans after administration of exogenous doses. The elimination half-life of the ascorbate pool in humans is approximately 16 days (1–3). In contrast to this relatively slow turnover time, exogenous ascorbic acid, in excess of the body store, appears to be eliminated rapidly. In human subjects whose body stores have been "saturated" with the vitamin, the elimination half-life was reported to be 2–3 hr (4–6). Recently, however, Zetler *et al.* (7) estimated the elimination half-life as 13–29 hr, values considerably greater than those previously reported.

As part of a study to determine factors influencing ascorbic acid absorption in humans[1], the elimination of ascorbic acid was evaluated after intravenous administration to five healthy normal volunteers (four males and one female; age of 25–32 years). All subjects had their body stores saturated with ascorbic acid by receiving 1 g of the vitamin daily for several weeks. After this dosing period, saturation was assumed when urinary recoveries of ascorbic acid (during 24 hr) on two occasions, separated by 3–7 days, were within ±10% of each other. One gram of ascorbic acid[2] was then administered intravenously into an arm vein over 3–4 min.

Subjects voided their bladders immediately prior to dosing, and frequent urine samples were collected thereafter at known time intervals for 24 hr. The total volume of each collection was recorded, and a 15-ml aliquot was taken and placed into a vial containing sufficient metaphosphoric acid to produce a 4% solution with this volume of urine. All samples were stored in a refrigerator and assayed within 4 days of collection.

Two days prior to and during the experimental period, the subjects avoided the ingestion of ascorbic acid either in vitamin preparations or in foods known to be high in ascorbic acid content. One day prior to the experiment, "blank" urine samples were obtained by collecting total urine for 1–2 hr during two collection periods (one in the morning and one in the afternoon). Urine was assayed to determine the concentrations of ascorbic acid, dehydroascorbic acid, and diketogulonic acid by the 2,4-dinitrophenylhydrazine method as outlined by Pelletier (8).

Urinary excretion data were corrected for blank ascorbic acid excretion. Semilogarithmic plots of excretion rate *versus* time were prepared to obtain initial estimates of the coefficients and exponents of the equation by the method of residuals. The data were fitted by nonlinear regression analysis to an equation appropriate for a two-compartment model, and the parameters of this equation were determined by conventional methods (9).

Table I—Pharmacokinetic Parameters Determined from Intravenous Ascorbic Acid Administration

Parameter[a]	Subject 1	2	3	4	5	Mean (±*SD*)
α, hr^{-1}	1.21	1.16	1.08	0.75	0.78	1.00 (0.22)
β, hr^{-1}	0.23	0.25	0.26	0.16	0.17	0.21 (0.05)
$t_{1/2\beta}$, hr	3.01	2.77	2.67	4.33	4.08	3.37 (0.78)
K_e, hr^{-1}	0.54	0.76	0.67	0.45	0.49	0.58 (0.13)
K_{10}, hr^{-1}	0.70	0.85	0.80	0.51	0.61	0.69 (0.14)
K_{12}, hr^{-1}	0.34	0.22	0.23	0.17	0.12	0.22 (0.08)
K_{21}, hr^{-1}	0.40	0.34	0.40	0.24	0.21	0.32 (0.09)
Percent dose recovered	74.0	86.7	87.3	84.6	81.3	82.6 (5.3)

[a] The α and β are hybrid first-order rate constants, $t_{1/2\beta}$, is the half-life associated with the terminal exponential process (*i.e.*, $t_{1/2\beta} = 0.693/\beta$), K_{10} is the first-order elimination rate constant from the central compartment, K_e is the first-order urinary excretion rate constant, and K_{12} and K_{21} are intercompartmental first-order transfer rate constants.

Figure 1 is a representative graph of the ascorbic acid excretion rate *versus* time for one subject. The data appear to be consistent with a two-compartment model. The solid line represents the best fit of the data. Table I summarizes the pharmacokinetic parameters generated from the analysis of the data. The urinary recovery values were corrected for the content of ascorbic acid determined from the assay of three vials of the parenteral solution (108.7% of the label claim). The values of urinary recovery represent total vitamin (*i.e.*, the sum of ascorbic, dehydroascorbic, and diketogulonic acids).

Ascorbic acid was eliminated relatively rapidly in these subjects, with an average half-life of 3.37 hr. This value is similar to some results reported previously (4, 6) but is considerably smaller than the values suggested by Zetler *et al.* (7). The degree of saturation of ascorbic acid body stores may partially explain this discrepancy. While the total urinary recoveries of the vitamin in these subjects were virtually identical, only about 83% of the dose ulti-

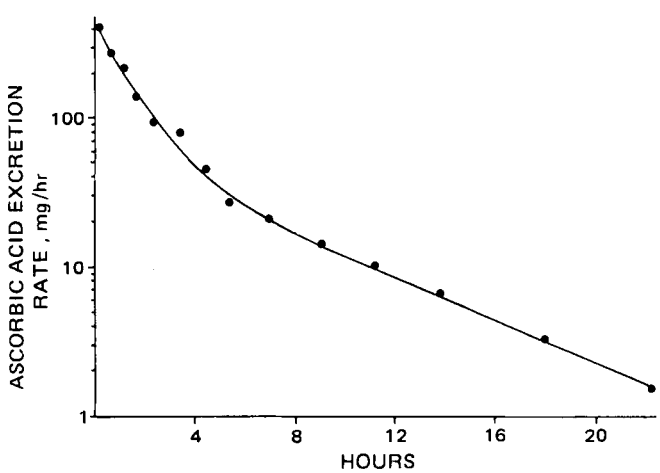

Figure 1—*Semilogarithmic plot of the ascorbic acid excretion rate as a function of time in one subject after the intravenous administration of 1 g of ascorbic acid. The solid line represents the best fit of the data obtained from nonlinear regression analysis.*

[1] Unpublished data.
[2] Lot 7509-1, Sterilab Corp. Ltd., Downsview, Ontario, Canada.

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mately was excreted. The remainder of the dose may be accounted for by other minor metabolites (*e.g.*, oxalic acid and ascorbate 2-sulfate) (10–12), or a portion of the dose may remain in the ascorbate body pool. Approximately 84% of the recovered vitamin was excreted in the form of ascorbic acid.

(1) L. Hellman and J. J. Burns, *J. Biol. Chem.*, **230**, 923 (1958).

(2) E. M. Baker, H. E. Sauberlich, S. J. Wolfskill, W. T. Wallace, and E. E. Dean, *Proc. Soc. Exp. Biol. Med.*, **109**, 737 (1962).

(3) G. L. Atkins, B. M. Dean, W. J. Griffin, and R. W. E. Watts, *J. Biol. Chem.*, **239**, 2975 (1964).

(4) J. S. Stewart and C. C. Booth, *Clin. Sci.*, **27**, 15 (1964).

(5) W. Kubler and J. Gehler, *Int. Z. Vit. Forsch.*, **40**, 442 (1970).

(6) J. Gehler and W. Kubler, *ibid.*, **40**, 454 (1970).

(7) G. Zetler, G. Siedel, C. P. Siegers, and H. Iven, *Eur. J. Clin. Pharmacol.*, **10**, 273 (1976).

(8) O. Pelletier, *J. Lab. Clin. Med.*, **72**, 674 (1968).

(9) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1975.

(10) M. Banay and E. Dimant, *Biochim. Biophys. Acta*, **59**, 313 (1962).

(11) B. M. Tolbert, M. Downing, R. W. Carlson, M. K. Knight, and E. M. Baker, *Ann. N.Y. Acad. Sci.*, **258**, 48 (1975).

(12) E. M. Baker, D. C. Hammer, S. C. March, B. M. Tolbert, and J. E. Canham, *Science*, **173**, 826 (1971).

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Comparative Pharmacokinetics of Coumarin Anticoagulants XXXVII: Simultaneous *In Vivo* Displacement of Dicumarol from Serum Protein and Tissue Binding Sites by Tolbutamide in Rats

Keyphrases □ Dicumarol—*in vivo* binding to serum proteins and tissues, effect of tolbutamide in rats □ Tolbutamide—effect on *in vivo* binding of dicumarol to serum proteins and tissues in rats □ Binding, serum protein and tissue—dicumarol *in vivo*, effect of tolbutamide in rats □ Anticoagulants, coumarin—dicumarol, *in vivo* binding to serum proteins and tissues, effect of tolbutamide in rats □ Antidiabetic agents—tolbutamide, effect on *in vivo* binding of dicumarol to serum proteins and tissues in rats

To the Editor:

The ability of some drugs and endogenous substances to displace other drugs or endogenous substances from serum or plasma protein binding sites has been studied extensively. However, there is only very limited information on such displacement effects in various organs and tissues, probably because of the technical difficulties of such investigations, which must be carried out *in vivo* (1). Recently developed pharmacokinetic theory indicates that a full appreciation of the pharmacokinetic implications of changes in drug binding can only be obtained by assessing the magnitude of such changes in serum as well as in tissues (2). During a study of pharmacokinetic and pharmacodynamic interactions between dicumarol and tolbutamide, we have found evidence that tolbutamide administration causes a displacement of dicumarol not only from serum proteins but also from binding sites in the liver.

Thirty adult male Sprague–Dawley rats, 250–350 g, received ^{14}C-dicumarol, 8 mg/kg iv, and the pharmacokinetics of this drug were determined by methods described previously (3) (Experiment I). Twenty of these animals were matched into pairs with nearly identical total clearance values. One month later, these rats again received a dicumarol injection (Experiment II), but one member of each pair also received tolbutamide, 125 mg/kg ip at the time of dicumarol administration and 62.5 mg/kg every 3–4 hr thereafter while the other member received saline injections at these times. The animals were killed when serum dicumarol concentrations were expected, by extrapolation of earlier concentrations (determined during the experiment), to have declined to about 7 μg/ml. The liver was removed and blood was expressed from it; it was homogenized, and the homogenate was assayed for dicumarol.

Another six pairs of rats (not from the original group of 30) with nearly identical dicumarol clearance received only tolbutamide (125 mg/kg for the first dose and then 62.5 mg/kg every 3–4 hr for 30 hr) or saline, but no dicumarol, one month after Experiment I. They were killed 3 hr after the last dose of tolbutamide; plasma was obtained from blood withdrawn from the abdominal aorta and diluted 1:10 with pH 7.4 isotonic sodium phosphate buffer. The liver was excised and homogenized with three volumes of ice-cold phosphate buffer. ^{14}C-Dicumarol, 10 μg/ml final concentration, was added to both plasma and liver homogenate, and the samples were dialyzed at 25° against an equal volume of phosphate buffer to equilibrium (4).

The effects of tolbutamide on the pharmacokinetics of dicumarol when both drugs were administered *in vivo* are summarized in Table I. Intentionally, animals with widely different total clearance values were selected for the study (range in Experiment I: 3.33–16.8 ml/hr/kg), so standard deviations are reported only for the mean of the individual ratios of various parameter values. The average total clearance, the volume of distribution, and the β value of the control and tolbutamide groups were almost identical in Experiment I; these values were also nearly identical in Experiments I and II of the control group. These results reflect the excellent matching of the two groups and the reproducibility of the pharmacokinetic parameter values in repeated experiments.

Concomitant administration of tolbutamide caused a pronounced increase in the total clearance and β and a smaller, but still statistically significant, increase in the volume of distribution (Experiment II, tolbutamide group). The free fraction of dicumarol in diluted plasma (mean ± *SD*, $n = 6$) was 0.000754 ± 0.000156 for control animals and 0.00213 ± 0.00095 for tolbutamide-treated animals ($p < 0.01$). A method to determine protein binding of dicumarol in undiluted plasma was not available when these studies were done.

Since tolbutamide administration was acute, it is unlikely to have caused enzyme induction. This conclusion

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