A kinetic mass balance model for 1,5-anhydroglucitol: applications to monitoring of glycemic control

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Stickle, Douglas, and John Turk. A kinetic mass balance model for 1,5-anhydroglucitol: applications to monitoring of glycemic control. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E821–E830, 1997.—The polyol 1,5-anhydroglucitol (AG) present in human plasma is derived largely from ingestion and is excreted unmetabolized. Reduction of plasma [AG] has been noted in diabetics and is due to accelerated excretion of AG during hyperglycemia. Plasma [AG] has therefore been proposed as a marker for glycemic control. A precise understanding of its utility relies on a quantitative understanding of the mass balance for AG. In this study, non-steady-state data from the literature were analyzed to develop a dynamic mass balance model for AG that is based on the two-compartment model proposed by Yamanouchi et al. [T. Yamanouchi, Y. Tachibana, H. Akanuma, S. Minoda, T. Shinohara, H. Moromizato, H. Miyashita, and I. Akaoka. Am. J. Physiol. 263 (Endocrinol. Metab. 26): E268—E273, 1992]. The data are consistent with a model in which exchange between tissue and plasma pools is rapid and in which the tissue compartment mass is two to three times the mass of the plasma compartment. According to model estimates, accelerated excretion of AG due to hyperglycemia can cause marked net depletion of total AG over a time scale of days. Recovery from a depleted state is slow because the total body capacity represents >5 wk of normal intake. Accordingly, AG monitoring should be able to indicate the presence of past glucosuric hyperglycemic episodes during a period of days to weeks, as well as provide information on the extent to which high deviations from the average plasma glucose concentration are operative.

1,5-ANHYDROGLUCITOL (AG, 1-deoxyglucose) is a polyol present in human plasma and cerebrospinal fluid (11, 17, 23). It is derived largely from ingestion (~5 mg/day), and its major route of elimination is urinary excretion as the unmetabolized substance (38). The plasma concentration of AG (~20 μg/ml or ~130 μM) is essentially stable in the normal population (17). A diminished plasma [AG] has been noted in diabetics (2, 16, 23, 24, 29, 32, 40). The reduction in [AG] appears to be due to accelerated urinary excretion of AG in parallel with urinary excretion of glucose during hyperglycemia (1, 8, 17, 20, 36) and is likely attributable to competition between glucose and AG for tubular reabsorption (16).

For these reasons, plasma AG monitoring has been suggested and/or advocated as a marker for glycemic control (3, 17, 29, 40). At present, however, the interpretation of serial AG measurements has been based more on a qualitative than a quantitative understanding of the data regarding the relationship between hyperglycemia and AG excretion (38). The purpose of this study was to characterize quantitatively the mass balance for AG and the kinetics of AG disposal by use of data existing in the literature to define more precisely the information that might be derived from monitoring of AG.

A steady-state two-compartment mass balance model for AG has previously been proposed by Yamanouchi et al. (38). In this model (Fig. 1), the ingestion rate (k1) and a modest rate of endogenous production (k5) are balanced in the steady state by the excretion rate (k4), with steady-state exchange between plasma [A, within volume of distribution (plasma volume) Vp] and tissue pools [B, within volume of distribution (Vt)] occurring with rate constants k2 and k3. The effect of high glucose to inhibit reabsorption of AG increases the excretion rate and can lead to a net depletion of AG. Unknowns in this system are 1) the mass within the tissue pool, B, and its volume of distribution, Vt; 2) the rate constants k2 and k3 for exchange between the plasma and tissue pools; and 3) the functional dependence of the AG excretion rate k4 on plasma glucose. As will be shown, the steady-state mass balance model proposed by Yamanouchi et al. (38) can be expanded to include the kinetic characteristics of AG disposal by an evaluation of these unknowns with use of data from published studies. The implications of the kinetic model for the use of AG monitoring in the evaluation of glycemic control are discussed.

**KINETIC MODEL ANALYSIS OF AG MASS BALANCE**

**Two-Compartment Mass Balance Model for AG**

To begin a more detailed analysis of the steady-state two-compartment mass balance model for AG of Yamanouchi et al. (38), the model was expanded to include kidney function to account explicitly for filtration, reabsorption, and excretion of plasma AG, as shown in Fig. 1. In this scheme, the fractional reabsor-
tion, \(r\), represents the fraction of AG that is reabsorbed after filtration (i.e., \(r\) is the fraction of the amount that is filtered but is not excreted). The rate of AG excretion is given by the product of the glomerular filtration rate (\(F\)), the plasma AG concentration ([AG]), and the fraction of AG that is not reabsorbed (1 – \(r\)).

\[
k_4 = F[A](1 - r)
\]

(1)

where \(r\) is a variable that is presumed to depend on the plasma glucose concentration, [Glc]. In this model the instantaneous rates of change of masses A and B are given by

\[
\frac{dA}{dt} = k_1 - k_2 \frac{A}{V_A} + k_3 \frac{B}{V_B} - k_4
\]

(2)

\[
\frac{dB}{dt} = k_5 - k_2 \frac{A}{V_A} + k_3 \frac{B}{V_B}
\]

(3)

For the case of constant coefficients (\(k_1 - k_5\)), the mass balance Eqs. 2 and 3 for the model shown in Fig. 2 have simple analytic solutions for \(A(t)\) and \(B(t)\) of the form

\[
A(t) = \alpha_1 e^{k_1 t} + \alpha_2 e^{k_2 t} + \alpha_3, \quad B(t) = \beta_1 e^{k_1 t} + \beta_2 e^{k_2 t} + \beta_3.
\]

Such an analytic solution enables evaluation of the instantaneous rates of change for A and B and the overall kinetics of AG disposal if all coefficients are known for all conditions. The rate constants \(k_2\) and \(k_3\), the volume of distribution \(V_b\), and the rate \(k_4\) are all unknown. As will be shown below, existing data enable a condition-dependent determination of the excretion rate \(k_4\) by characterization of the dependence of \(r\) on [Glc]. In addition, the data suggest a rapid exchange of AG between A and B, leading to a simpler form of the mass balance model for which \(k_2\), \(k_3\), and \(V_b\) are not explicit variables.

Characterization of Fractional Reabsorption of AG as a Function of Plasma Glucose

The relationship between \(r\) and [Glc] can be characterized empirically by analysis of data from a study by Akanuma et al. (1), in which plasma and urine AG were measured during the oral glucose tolerance test (OGTT) (Fig. 2). On the basis of the temporal measurements of blood glucose (Fig. 2A), subjects in this study were classified within three groups according to World Health Organization standards: normal (N), impaired glucose tolerance (I), and diabetic (D) subjects. As shown in Fig. 2B, zero-time plasma AG concentrations were distinct for each group, conforming to the expectation that their expected pattern for the three groups (Fig. 2C), in which glucose was excreted during the test period in both I and D groups but not for the N group. The patterns for excretion of AG were distinct for each group (Fig. 2D), and these patterns were in qualitative accord with the schematic model expectation: for N subjects, there was a constant and low excretion rate derived from a fixed plasma AG in the absence of hyperglycemia; for I and D subjects, excretion from lower plasma AG concentrations was increased during periods of hyperglycemia and exceeded the excretion observed in N subjects.

The AG data from the OGTTs do not directly constitute a mass balance, because urine concentration of AG was measured rather than urine output of AG. However, the data can be analyzed to obtain an estimate of \(r\) as a function of [Glc], with the assumptions of a normal value for urine output rate (\(v\), ml/min) and an average
and equivalent normal glomerular filtration rate \( F \), ml/min) among the three groups. First, AG clearance \( h \) can be calculated according to

\[
\eta = \frac{[U]}{[A]} = \text{volume/time}
\]

where \([U]\) is urine concentration (mass/volume) and \([A]\) is the plasma concentration of AG. Second, \( r \) can be calculated from \( \eta \) given \( F \) according to

\[
r = 1 - \frac{\eta}{F}
\]

when clearance is assumed to involve filtration and reabsorption with no intervening secretion of AG.

The glomerular filtration rate \( F \) was assumed to be a normal value of 100 ml/min, and a normal value for urine output rate, \( \nu = 51 \text{ ml/h} \), was assumed for use in the calculations. On this basis the urine excretion rate for N subjects was equal to the designated net intake rate of 5 mg/day. According to the calculations, when these values are used, AG clearance in N subjects was small compared with \( F \) \((\eta < 1 \text{ ml/min})\) and was increased in I and D groups in rough proportion to glucose excretion (Fig. 3), where glucose excretion occurred for plasma glucose \( >8 \text{ mM} \) (also shown in Fig. 3). Acute urinary excretion of AG accompanying and in proportion to glucosuria is in general accordance with data obtained in previous studies on longer time scales in humans (1, 14, 35) and in rats (8, 33, 36, 39). The relationship of \( r \) to glucose excretion is not of signal importance with respect to the kinetic mass balance for AG except as a rough confirmation of the validity of the assumptions used in the calculation by the correspondence of the results to those observed in previous studies.
studies. Of greater importance is the relationship of r to [Glc] that can be obtained from the data in Fig. 2. As is shown in Fig. 4, r as a function of [Glc] decreased in rough proportion to [Glc] when [Glc] exceeded a threshold of [Glc] > 8 mM, from an apparently constant value of >0.99 below the threshold to <0.97 for [Glc] = 20 mM. The AG reabsorption data for the N, I, and D groups appear to be connected by a continuous function of plasma glucose alone, despite the fact that each condition involved widely different but essentially constant values of [A]. The reduction in r is significant in terms of clearance of AG and the kinetics of excretion, because it represents a fourfold increase in the clearance rate (i.e., a 4-fold increase in the excretion fraction, 1 – r) compared with the N group over the range of values for [Glc] observed for the D group.

Fig. 4. Fractional reabsorption of AG vs. plasma [Glc]. Fractional reabsorption (r) was calculated assuming a constant glomerular filtration rate (F = 100 ml/min), given AG clearance in Fig. 3, and with assumption of no tubular secretion of AG. •, N; □, I; and ○, D glucose tolerance groups. Lines shown connect constant r in normal range (r = 0.9984, [Glc] < 7.4 mM) and as a function of [Glc] for hyperglycemia (r = -0.0026 M⁻¹ [Glc] + 1.018, [Glc] > 7.4 mM) obtained from a linear regression of data points for I and D groups.

Simplification of the Model, Assuming Rapid Exchange Between Pools A and B

The data in Fig. 2 also provide some information about the kinetics of the exchange of AG between the tissue and plasma pools in the two-compartment model. Although the total excretion for the D group over this time represented ~10% of the total mass within the plasma pool for these subjects, the plasma level of AG did not change on the time scale of the glucose tolerance test for this group (or for the I or N groups). Despite the variabilty in the data in Fig. 2B, they suggest that loss of mass from the plasma pool via excretion can be rapidly replaced, as would occur with relatively rapid exchange between tissue and plasma AG pools, such that the mass available for excretion is drawn from both pools even within a short time frame. The interpretation of relatively rapid redistribution and availability to plasma of the majority of the total body AG mass is broadly consistent with the high flux of AG into urine during the major, rapid phase of plasma AG depletion and accompanying tissue AG depletion that occur in glucose-overloaded or streptozotocin-treated rats (8, 33) and with the observation of rapid plasma-erythrocyte exchange of AG (17). In glucose-overloaded rats, an estimate of the average tissue content (mass/volume) decreased to 66% of control within a 2-h period, during which plasma [AG] decreased to 49% of control (33), indicating coupling of the masses within the two pools on a relatively short time scale. The supposition that the total AG mass partitions rapidly between plasma and tissue pools leads to a simplification of the mass balance model, as shown in Fig. 5. In the revised model, the mass of the tissue pool is proportional at all times to
the mass in the plasma pool, according to the relationship

\[ k_2 \frac{A}{V_A} = k_3 \frac{B}{V_B} \]  

(6)

such that \( B = KA \), where \( K = k_2/k_3 \), \( V_B/V_A \). According to this model, the instantaneous rate of change of the total body mass of AG (C, where \( C = A + B \)) is given by

\[ \frac{dC}{dt} = k_i - F(1 - r) \frac{A}{V_A} \]  

(7)

where \( k_i = k_1 + k_3 \). Because the plasma pool mass \( A \) is proportional to the total mass \( C \) by the relation \( A = C/(1 + K) \), Eq. 7 can be written in terms of \( C \) only

\[ \frac{dC}{dt} = k_i - \frac{F(1 - r)}{V_A(1 + K)} C \]  

(8)

This equation has a simple analytic solution for constant coefficients

\[ C(t) = k_i \tau - [C(0) - k_i \tau] e^{-t/\tau} \]  

(9)

where \( \tau = V_A(1 + K)/[F(1 - r)] \) is the time constant for changes in \( C \), and where \( \tau \) is dependent on \( r \) as a function of [Glc]. The steady-state value for \( C \) is given by the product \( k_i \). From the standpoint of data analysis, because \( r \) is a function of [Glc] is not constant in hyperglycemia unless [Glc] is constant, the utility of Eq. 9 is the provision of an explicit function for the rate of change of \( C \) that is calculable given the known dependence of \( r \) on [Glc].

\[ \frac{dC}{dt} = \frac{[C(0) - k_i \tau]}{\tau} e^{-t/\tau} \]  

(10)

A(t) and B(t) are calculable from C(t) by the relations \( A = C/(1 + K) \) and \( B = CK/(1 + K) \) if \( K \) is known. At this stage, then, a complete specification of the kinetic mass balance model lacks only a value for \( K \).

Fig. 5. Simplified kinetic mass balance model assuming rapid partitioning between pools A and B. Production and ingestion rates have been combined to form a single constant input rate, \( k_i = 5 \) mg/day. \( K \) is proportionality constant for partitioning of mass between pools, \( K = B/A \).

Fig. 6. Recovery of depleted plasma AG after initiation of “glycemic control” in type II diabetics. Data were redrawn from original study by Yamanouchi et al. (35). Line, fit of data to Eq. 9, with assumption of a constant fractional reabsorption, \( r \), for normoglycemic state, namely, \( r = 0 \). For [AG] = [AG], \( 1 - e^{-t/\tau(r)} \), steady-state value for plasma AG ([AG]) = 20.4 \mu g/ml, \( \tau = 5.6 \) wk. Initial condition was assumed to be \( [AG] = 0 \), and effective time 0 point \( (t_0 = 1.1 \) wk) was allowed to shift in fit to accommodate a period of establishment of glycemic control; first 2 data points were excluded from fit.

Estimation of the Mass of AG in Pools A and B and of the Proportionality Constant \( K \)

An estimation for the proportionality constant \( K \) can be obtained in two ways by using Eq. 9 when any value for \( \tau \) is given that was obtained under conditions in which \( r \) is constant and known. First, a value for \( \tau \) specifies the mass of AG in the total body pool (C), given a known value for the overall input rate, \( k_i \), because steady-state C is equal to the product \( k_i \). Because the steady-state amount of AG in the plasma pool A is known directly by measurement, the size of the B pool is known by the difference between C and A, and from this distribution a value for the proportionality constant, \( K \), is obtained by \( K = B/A \). Second, because \( \tau \) is an explicit function of \( V_A \), \( F \), and \( K \), then by rearrangement, \( K = \tau F(1 - r)/V_A \). Thus an estimation for the proportionality constant \( K \) can be obtained from a value for \( \tau \), obtained under conditions of known \( r \) and known \( F \).

The recovery of plasma AG from a depleted state to a normal state after initiation of “glycemic control” in type II diabetic subjects [Fig. 6; data from the study of Akanuma et al. (1)] is an example of data demonstrating changes in plasma AG under conditions of a relatively constant \( r \) associated with normoglycemia. Such data are suitable for determination of \( \tau \) for the estimation of \( K \). In these data, plasma AG demonstrated an increase to a steady state of \( 20 \mu g/ml \) after 10 wk, and the time course of the increase is well characterized by a single time constant, \( \tau = 5.6 \) wk. The recovery data thus are compatible with the analytic
solution to the simplified mass balance model for \( A(t) \) with a constant \( r \). As described above, \( K \) can now be computed in two ways.

1) \( K \) computed from \( r \) given \( k_i \). According to Eq. 9, the steady-state value for the total body content \( C \) is the product \( K \cdot r \). Given \( r = 5.6 \) wk and \( k_i = 5 \) mg/day, then \( C \) is calculated to be 196 mg. The mass of AG within the tissue pool can be calculated as the difference between the total mass, \( C \), and the mass within the plasma pool: \( B = C - A \), where \( A \) is known (calculated as \( [A] V_A \), where \( V_A \) is assumed to be a round value for normal subjects of 3,000 ml). Given the steady-state value for \( A \), \( \sim 21 \) mg/ml, then \( A \), the mass of AG present in the plasma pool, is \( \sim 63 \) mg. The tissue pool \( B \) is thus \((196 - 64) = 132 \) mg, approximately two times the mass of AG within the plasma pool. Given that \( K = B/A \), then \( K = 2.1 \). This value is sensitive to the precision used for the calculated values for \( A \) and \( C \); with use of round numbers, \( C = 200 \) mg and \( A = 60 \) mg, and then \( K = 2.3 \).

2) \( K \) computed from \( r \) given \( V_A \), \( F \), and \( r \). By use of \( K = F(1-r)/V_A \), then \( K \) can be obtained, given values for \( r \), \( V_A \), and \( F \) and \( r \) as constants. For \( r = 5.6 \) wk, \( V_A = 3,000 \) ml, \( F = 100 \) ml/min, and \( r = 0.9984 \), then \( K = 2.0 \). This value is obviously most sensitive to the precision of the value used for \( r \). Decreasing \( r \) to three significant figures (to \( r = 0.998 \)) increases \( K \) to \( K = 2.8 \).

Thus two approaches to the calculation of the value of \( K \) result in the range of values \( K = 2.0–2.8 \). These numbers can be compared with an estimated upper bound for \( K \) that can be obtained from the same data. The maximum possible total body content, \( C \), from the recovery data would be the integral of the input rate, \( k_i \), during the recovery period of \( \sim 10 \) wk, by assuming zero excretion; this would lead to a value for \( C \) of \( \sim 300 \) mg, corresponding to an upper bound of \( K = 4 \) [by \( K = B/A = (300 - 60)/60 = 4 \)]. Another way to estimate an upper bound for \( K \) with the assumption of zero excretion is to take the increase per unit time in \( A \) and calculate the partitioning into \( B \) of the mass input rate \( k_i \) that would have to occur to account for the net increase in \( C \) due to \( k_i \). The data in Fig. 6 show a maximum rate of increase in \( [A] \) of \( 1.94 \) µg·ml\(^{-1}\)·wk\(^{-1}\); with the assumption \( V_A = 3,000 \) ml, then this is equal to an increase of \( 5.8 \) mg/wk in \( A \); for \( k_i = 5 \) mg/day (35 mg/wk), then the increase in \( B \) would be equal to \( k_i - 5.8 \) mg/wk = 29.2 mg/wk with the assumption of zero excretion; this partitioning would correspond to \( K = (29.2/5.8) = 5 \). Thus an upper limit for \( K \) is in the range of \( K = 4–5 \), which is a factor of 2 greater than that obtained with the kinetic model equations analysis. This calculation is simply for comparison with the values obtained above, given that there are no data for \( r \) at low \([A]\) in normoglycemia; to say that excretion was insignificant except at near-normal values for \([A]\), then the value of \( K \) would be at most in the range of 4–5. If \( r \) is even greater than 0.998 at low \([A]\), then the value for \( K \) obtained by the analysis using Eq. 9 may be regarded as a lower limit.

From this, the parameters necessary to characterize completely the kinetic mass balance for AG have been defined and evaluated (Table 1): the proportionality constant for the exchange plasma and tissue pools (\( K \)), which gives their relative amounts, and the dependence of the excretion rate on glucose \( (r = f([Glc])) \), which determines the time constant \( (\tau) \) for changes in total AG and the associated steady-state values for \( A \) and \( B \), given a constant input rate, \( k_i \). As a check on the model parameters, the results of model simulations are compared with the OGTT data in Fig. 2. Simulations were performed from the initial conditions \([A](0)\) for each group by successive calculations of Eq. 9 at 1-min simulation intervals for which \([Glc](t)\) was given from the spline interpolation in Fig. 2A, and from which \( r \) was calculated using the correlation given in Fig. 4. The correspondence of simulation results to the urine excretion data in Fig. 2D was inexact only because of the difference between the correlation of \( r \) to \([Glc]\) and the exact values of the small number of measurements for \( r \). For the AG recovery data in Fig. 6, model values of \([A](t)\) can be calculated directly from Eq. 9 by use of the model parameter values in Table 1. Because this is the same equation as that used in fitting the data, the only difference between the model predictions and the data set is a slightly different value for the steady-state \([A]\) between the recovery data fit (20.4 µg/ml) and the value used in Table 1 based on the OGTT data for the N group (21 µg/ml).

### Table 1. Kinetic mass balance model variables and constants

<table>
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<tr>
<th>Designation</th>
<th>Description</th>
<th>Units</th>
<th>Value</th>
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<tr>
<td>A</td>
<td>AG in plasma compartment</td>
<td>mass</td>
<td>64 mg*</td>
</tr>
<tr>
<td>V_A</td>
<td>Plasma compartment volume</td>
<td>volume</td>
<td>3,000 ml</td>
</tr>
<tr>
<td>B</td>
<td>AG in tissue compartment</td>
<td>mass</td>
<td>132 mg*</td>
</tr>
<tr>
<td>V_B</td>
<td>Tissue compartment volume</td>
<td>volume</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>C</td>
<td>AG total body mass</td>
<td>mass</td>
<td>196 mg*</td>
</tr>
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<td>B/A</td>
<td>dimensionless</td>
<td>2.1</td>
</tr>
<tr>
<td>k_i</td>
<td>Net input rate</td>
<td>mass/time</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>k_2</td>
<td>Rate constant A → B</td>
<td>volume/time</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>k_3</td>
<td>Rate constant B → A</td>
<td>volume/time</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>k_4</td>
<td>Excretion rate</td>
<td>mass/time</td>
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</tr>
<tr>
<td>F</td>
<td>Glomerular filtration rate</td>
<td>uptake</td>
<td>100 ml/min</td>
</tr>
<tr>
<td>r</td>
<td>Urine output rate</td>
<td>volumetime</td>
<td>F[1−r]</td>
</tr>
<tr>
<td>η</td>
<td>Plasma glucose concentration</td>
<td>uptake</td>
<td>Variable</td>
</tr>
<tr>
<td>r</td>
<td>AG reabsorption fraction</td>
<td>Dimensionless</td>
<td>r = f([Glc])‡‡</td>
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<tr>
<td>τ</td>
<td>Time constant</td>
<td>time</td>
<td>V_A(K + 1)/F(1−r)</td>
</tr>
</tbody>
</table>

Values for constants determined by model analysis and used in simulation of AG excretion. *Normal steady-state values; \( r = 0.9984 \), \([Glc]<7.4 \) mM; \( r = -0.0026 \) mM\(^{-1}\) \([Glc] + 1.018 \), \([Glc]>7.4 \) mM.

### Time Constants for Changes in \([A]\) Derived from Changes in \([Glc]\)

Previous studies of long-term profiles for \([Glc]\) and \([A]\) in individuals have shown that episodes of hyperglycemia are tracked by decreases in \([A]\), such that \([A]\) can be used as a monitor of hyperglycemia on a time scale of
days or weeks (31, 33). To examine this potential use from the standpoint of the model calculations, the time constant \( \tau \) for changes in total AG and steady-state values for \([A]\) for constant coefficient conditions of the model were calculated using the parameter values of Table 1 and the function \( r([\text{Glc}]) \) from Fig. 4. As shown in Fig. 7, values for \( \tau \) ranged from months to days for glucose concentration, ranging from 5 to 20 mM, with the corresponding steady-state values for \([A]\) decreasing with glucose concentration from normal to 5% of normal. According to the calculation, marked net depletion of AG via the plasma pool due to hyperglycemia can thus occur relatively quickly depending on the magnitude of hyperglycemia. For instance, a step change to 20 mM glucose produces a steady state in which plasma AG is reduced to \( \sim 5\% \) of its initial value, with a time constant for approach to the steady state of 44 h, or \( \sim 1.8 \) day. Note that the analytic function given by Eq. 9 only gives a time solution for AG mass under the condition of constant coefficients (e.g., for a step change to a different and fixed \([\text{Glc}])\), with an associated step change in \( r \). Although step changes in fixed glucose are not part of normal or disease physiology, the model value for \( \tau \) indicates the instantaneous rate of change that would be operative under specified conditions, and it depicts boundaries on the mass within the system under different steady-state conditions.

Because of the dependence of excretion of AG on both the magnitude and duration of glucosuric hyperglycemic excursions on short time scales, serial measurements of plasma AG probably cannot be used as a retrospective indicator of the sequence of conditions that were operative during the interval between any two measurements. That is to say, AG monitoring on the usual time scale for evaluation of diabetic care will not identify a unique set for the characteristics (frequency, duration, magnitude) of possible intervening hyperglycemic episodes, although serial measurement may place boundaries on estimates of the characteristics of such episodes when they occur. Moreover, because the repletion rate for AG is slow, AG measurement should be able to indicate accurately the occurrence of glycemic episodes during monitoring periods on the scale of days or weeks, as has previously been suggested (38).

**Monitoring of AG Compared With Monitoring of Glycated Hemoglobin**

Measurement of glycated hemoglobin (gHb) assesses the average of blood glucose concentrations on the basis of weeks (12, 26), but it provides essentially no information about the magnitude of short-term glycemic excursions about the average that characterize unstable diabetic control (22). In contrast, because AG excretion is accelerated under conditions of glucosuric hyperglycemia, monitoring of AG can theoretically provide retrospective information on glycemic excursions that would not be apparent from monitoring of gHb alone, as has previously been suggested (9, 31, 35, 37). Specifically, according to the model, AG monitoring should be able to distinguish between conditions in which a set average plasma glucose is accompanied by greater or lesser glucosuric hyperglycemic excursions. A hypothetical example is shown in Fig. 8. Three different glucose profiles, repeating with the same period and with identical average glucose values, were used as inputs to determine \( r \) and to calculate plasma \([A] \) as a function of time according to a 90-day simulation of the AG mass balance model, beginning in each case with the same initial condition for \([A]\). By design, each of these glucose profiles would in principle produce no significant change in gHb concentration during the simulation period, and, in addition, there should be no difference in gHb concentrations among the profiles. In contrast, AG measurements for the two profiles that were designed with excursions of \([\text{Glc}] \) above the glucosuric threshold show continuing changes in AG as well as differing extents of the changes in AG as a function of time. AG depletion is more rapid for greater excursions from the mean and from the glucosuric threshold, and the depletion indicates circumstances that would not be discernible via analysis of gHb measurements alone (37). The results accord with human studies tracking the relationship of \([A]\) to \([\text{Glc}] \) in individuals (31, 33), although the time resolution of the data in those studies is too low to permit a direct comparison of these results with the predictions of the model.

The simulation data illustrate the point that monitoring data will probably be unable to specify uniquely the conditions that generate them. On a long time scale, the simulation data are well characterized by a single exponential with a single time constant (Fig. 8), but this composite time constant greatly underestimates the actual magnitude of the glucose excursions above the mean compared with the relationship of the instantaneous time constants \( \tau \) to glucose concentrations (Fig. 7). Thus weekly or monthly monitoring data that result from fluctuating blood glucose concentrations (the usual case) would be consistent with numerous patterns of
DISCUSSION

Because of the coupling of AG excretion to blood glucose concentrations, the potential use of measuring plasma AG to screen for diabetes or to monitor glycemic control in diabetes has been widely investigated. A two-compartment mass balance model proposed by Yamanouchi et al. (38) has thus far provided the basic framework whereby AG measurement for monitoring has been interpreted. Schematically, the model states that a slow rate of AG ingestion is balanced by a slow rate of excretion in N subjects, whereas in D subjects a decrease in AG results from increased excretion in the presence of acute glucosuric hyperglycemia that is not replaced in balance by ingestion. Thus decreases in plasma AG reflect past glucosuric hyperglycemia on a time scale that is derived from the relative excretion and ingestion rates of AG. The kinetic aspects of the model for the nonsteady state have not heretofore been quantitatively characterized. In this study, the model of Yamanouchi et al. was expanded to attempt to characterize quantitatively the parameters on which dynamic changes in AG depend to better define the basis for the use of AG measurement in monitoring glycemic control.

This analysis relied on relevant data from two previous studies (2, 35). The data are consistent with a two-compartment kinetic mass balance model in which:

1. the distribution between tissue and plasma pools of AG is in the ratio of approximately 2:1;
2. the exchange between tissue and plasma pools is sufficiently rapid to be treated as an equilibrium partitioning between the two pools; and
3. reabsorption of AG is between 99 and 100% in normoglycemia but decreases significantly in hyperglycemia in approximate proportion to the extent of hyperglycemia above the glucosuric threshold.

The conclusions of the model analysis are in accordance with previous interpretations of the relationship of AG to hyperglycemia (see review in Ref. 31). The total body pool of AG can be depleted relatively rapidly by glucosuric hyperglycemia, on the time scale of days in the presence of overt hyperglycemia. Because AG is derived from dietary intake and because the normal daily intake of AG represents a small fraction of the total body pool of AG in the replete normoglycemic steady state, recovery from a significantly depleted state is slow even under continuously normoglycemic conditions. Thus decreased plasma AG reflects glucosuric hyperglycemia within a time scale of days or weeks.

According to the model, depletion of plasma AG depends on both the magnitude and duration of glucosuric hyperglycemia, and measurement of plasma AG will not be attributable to a unique set or sequence of prior episodes of hyperglycemia. AG monitoring may nonetheless be useful to identify episodes of glucosuric hyperglycemia. As in the example given and in accordance with the conclusion from previous studies (33), AG monitoring may provide adjunct information about the characteristics of glycemic episodes that is distinct

![Figure 8](http://ajpendo.physiology.org/)

**Fig. 8.** A: 3 theoretical time profiles for plasma [Glc] for which mean [Glc] values are equal (6.5 mM) but with varying degrees of excursion from the mean. A variable amplitude sine waveform was chosen for profile of greatest excursion amplitude (profile 1); a simple sine waveform (profile 2) and a constant waveform (profile 3) were chosen to match the same mean as for profile 1. B: time courses of plasma [AG] according to simulations of mass balance model for plasma glucose profiles 1–3 shown in A. For simulation, Eq 9 with constant $k_i$ was used to obtain successive values for $C$, by calculating $C_{i+1} = C_i + dc/dt \Delta t$, with $\Delta t = 5$ min and with $t$ updated for each 5-min interval, using [Glc] from glucose profile to obtain $r$ from correlation of Fig 4 to calculate $r$. Plasma [AG] [A] was calculated from C by [AG] = C/(1 + K/V). Initial condition for C was set equal to steady state for constant plasma glucose profile (corresponding to [A] = 130 µmol/l). C: simulated time courses of plasma [AG] continued from (B) with 3 plasma glucose profiles [profiles 1–3 in (A)] repeated over a period of 90 days.
from that derived from monitoring of gHb. Whether identification of such circumstances would be useful from a clinical standpoint remains to be established. AG monitoring might be useful in diabetes management both to assess fluctuation of blood glucose concentrations and to document the continuous absence of glucosuric hyperglycemia. It is emphasized that the AG mass balance is only significantly affected by excursions of glucose when the renal threshold for glucose reabsorption is exceeded; AG monitoring would not be useful for monitoring of hyperglycemia of patients who are not well controlled but whose glucose levels nonetheless stay below the renal threshold for glucose reabsorption.

Individual variations in glomerular filtration rate would need to be considered in interpretation of AG monitoring results. The fractional reabsorption data shown in Fig. 4 for high glucose concentrations probably represent an upper boundary for r values, because whereas an average and “normal” glomerular filtration rate was assumed for the calculation of r, it is not improbable that F for the D group would be less than average and that due to osmotic diuresis the urine output rate would be greater than average. In this circumstance the calculated fractional reabsorption r would be less than that shown in Fig. 4. A reduction in r would have the net effect of further decreasing the calculated time constants for changes in AG in the D cases.

Kidney function can also affect AG clearance in other ways. Decreases in AG occur in uremia unrelated to diabetes (15, 18). Chronic renal failure alone can lead to decreased plasma [AG], presumably due to tubular damage and ineffective reabsorption (4, 30), and a recent paper discusses the potential use of AG measurement to distinguish chronic from acute renal failure (30). Interindividual variations in F may be part of the reason that AG measurement would appear to be better used in serial measurements for monitoring of diabetic control than as a single measurement to screen for diabetes. Diabetic screening is a complex issue (5, 7, 10), and AG screening studies have yielded differing results (13, 21, 28, 34). Complexities for AG use in screening for diabetes include the observation of a difference in average plasma [AG] among normal subjects (as defined by an OGTT) depending on whether there exists a family history of non-insulin-dependent diabetes mellitus (27). Age is also a factor in defining normal reference values for plasma AG (6, 28), and possible variations in the ingestion rate of AG or factors attributable to ethnic differences may influence plasma [AG] (5).

As with any modeling study, the analysis of the data in terms of the mass balance model is only a demonstration that the model is consistent with the data rather than evidence that the model is correct. There are other, more complicated models that would also be consistent with the data. A more detailed model that includes a physiological rather than an empirical characterization of the dependence of r on [Glc] could accommodate the data by use of a greater number of parameters characterizing binding and transport functions in the way that glucose reabsorption has been characterized (25). The dependence of AG excretion on [Glc] as a function of plasma [AG] also requires better characterization, such as with data obtained from AG clearance during short-term hyperglycemic clamp of N subjects, or measurement of urine output during “recovery” of depleted AG. Another more detailed model might specify a dependence of AG excretion on [AG] itself. For instance, the model does not specify the excretion that would occur on a bolus addition of AG, wherein the fractional reabsorption would be expected to decrease in the presence of overtly high concentrations of AG (19). In normal physiology, however, this would appear to be unimportant (19), because the steady-state excretion in the setting of constant dietary intake results in a constant level of plasma [AG].

In summary, the mass balance for AG has been characterized for both the steady state and the nonsteady state on the basis of a two-compartment model. The study determined the empirical relationship between glucose and the fractional reabsorption of AG, characterized the distribution between plasma and tissue compartments for AG, and determined the functional form of the time constant that characterizes changes in AG in the nonsteady state according to the model formulation. The results of this study may be useful in guiding interpretation of AG monitoring or in suggesting areas for further study of the physiology of AG disposal and of the clinical use of AG measurement.

REFERENCES