METABOLISM OF GOLD IN THE RAT FOLLOWING A SINGLE ADMINISTRATION OF SODIUM AUROTHIOMALATE: MATHEMATICAL ANALYSIS OF SERUM AND ORGAN CONCENTRATIONS

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Abstract—The distribution of gold in the male rat following a single s.c. injection of sodium aurothiomalate (1 mg Au/kg body wt) was determined. Serum gold concentration–time data were fitted to the three compartment open model consisting of shallow and deep peripheral compartments connected reversibly and in series with the central compartment. The model indicated that the gold was lost rapidly from the central compartment by elimination and by transport to the shallow peripheral compartment. The gold was released slowly from the deep peripheral compartment producing a biological half-time of 26.5 days. The highest organ concentrations and relatively slow initial rate of clearance was observed in the adrenals, kidneys, liver, lymph nodes, pancreas, parotid, spleen and thymus whilst generally lower concentrations and more rapid initial rate of clearance was observed in bone, heart, lung and submaxillary. When the tissue concentration data were fitted to the three compartment open model the tissue metabolism of gold correlated best with the gold content of both peripheral compartments. The data for bone, heart and lung suggested that these organs contribute predominantly to the shallow peripheral compartment. The organ data were therefore consistent with the rate of disappearance of gold from the serum and the model defines adequately the relationship between serum and organ gold concentrations.

Sodium aurothiomalate has been used for many years in the treatment of rheumatoid arthritis [1, 2]. The fate of gold following its administration to experimental animals and man has been widely studied [e.g. refs. 3, 4] but little information derived from the pharmacokinetic analysis of serum concentration data is available. Also the relationship of serum gold levels to clinical response and toxicity has been a subject of much controversy. The failure of investigators to show a simple relationship illustrates the complexities of gold kinetics and the importance of defining metabolic models capable of relating gold concentrations in the serum to those in other compartments of the body where effector sites are believed to be located [2]. No attempts to determine the relationships between serum and organ gold concentrations have been reported.

In the present study we have investigated the distribution of gold in the rat for up to 48 days after a single exposure to sodium aurothiomalate and have elaborated a metabolic model to describe its distribution characteristics and the relationships between the serum and organ concentrations.

METHODS

Experimental. Random bred male Wistar rats (240–400 g body wt) were used in the study. The animals were grouped in order to minimise weight changes occurring during the investigation.

Sodium [¹⁹⁵Au]aurothiomalate was purchased from The Radiochemical Centre, Amersham, U.K.

and unlabelled sodium aurothiomalate was provided by May and Baker Ltd. Each animal was injected with a single s.c. dose of sodium aurothiomalate (1 mg Au/kg body wt) of specific activity 5.41 μCi/mg Au in isotonic saline. In separate experiments with four groups each of five animals samples of blood were obtained by cardiac puncture at regular intervals up to 15 min, 1 hr, 1 day or 50 days after the injection. A fifth group of 36 rats were killed in groups of three or four at various times up to 48 days after receiving the gold. The adrenals, heart, kidneys, lymph nodes, parotid, spleen, submaxillary and thymus organs and portions of bone (right femur), liver, lung and pancreas were removed, placed immediately in tared polyethylene tubes which were reweighed and sealed. Radioactivity was measured in a gamma counter and all measurements were corrected for background emission and physical decay.

Pharmacokinetic analysis. Using the method of residuals and a programmed electronic calculator the serum gold concentration (C_s) as a function of time (t) was fitted to the equation:

$$C_s = \sum_{i=1}^{n} A_i e^{-L_i t}.$$

The coefficients and exponents were then used as the preliminary estimates for the SAAM 25 program [5] to obtain the optimum fit of the data to this equation. The curve fit equation was then fitted to the series form of the three compartment open model

(Fig. 2) with first order absorption and elimination from the central compartment. The time course of gold in the individual peripheral compartments was then calculated by substituting the model parameters into the appropriate equations [6].

RESULTS

Pharmacokinetic analysis

The serum gold concentration–time curve shows that the absorption of the gold was rapid with the peak concentration occurring after about 1 hr (Fig. 1). The preliminary estimates of the coefficients and exponents ($A_1 = -9.94$, $A_2 = 8.39$, $A_3 = 1.89$, $A_4 = 0.132$ μg/ml, $L_1 = 82$, $L_2 = 1.106$, $L_3 = 0.318$, $L_4 = 0.029$ day^{-1}) suggested that the gold was distributed from a central compartment into two distinguishable peripheral compartments. Also when the SAAM 25 program was used to obtain the optimum values the change in the residual sum of weighted least squares on going from a three to a four exponential expression was significant at the 1 per cent level ($F_{23,21} = 8.76$) and therefore justified the use of a four-termed equation (Table 1). When the data were fitted to the three compartment open model, negative rate constants were obtained and since such values have no physical reality it was assumed that this was due to a biased time scale. Accordingly a new time scale was defined by $t' = t - t_0$ and t_0 (-0.00084 day) was estimated by setting the curve fit equation equal to zero. The new equation was then fitted to the proposed model (Fig. 2). The estimates of the model parameters and their S.D. indicate that a good fit of the data was obtained (Table 1).

The time course of gold in the total peripheral compartment is particularly influenced by the rate of uptake of gold into the deep peripheral com-
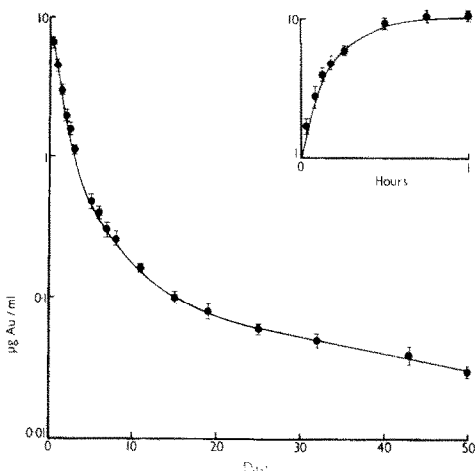

Fig. 1. Mean serum gold concentration (C_s) as a function of time (t) following a single s.c. injection of sodium [^{195}Au]aurothiomalate (1 mg Au/kg body wt) into male rats. The insert shows the time course in the first hour and the bars indicate the S.D. of the mean concentration. The curve is based on the equation $C_s = 9.06e^{-1.038t'} + 1.35e^{-0.268t'} + 0.115e^{-0.0262t'} - 10.53e^{-80t'}$ with $t' = t + 0.00084$ day.

partment. In the shallow peripheral compartment the maximum gold content was reached after 2 days followed by a rather rapid decline. In the deep peripheral compartment, on the other hand, the peak amount occurred after 10 days and was maintained for several days (Fig. 3).

Organ metabolism

The highest gold concentrations were found in the kidney. In this organ and also in the adrenals, liver,

Table 1. Curve-fit and model parameters from nonlinear least-squares fitting of serum gold concentration data

Curve-fit parameter	Parameter value ± S.D.	
	N = 3	N = 4
A_1 (μg ml^{-1})	-8.23 ± 0.13	$-9.85 + 0.30$
A_2 (μg ml^{-1})	8.58 ± 0.15	$9.06 + 0.32$
A_3 (μg ml^{-1})	0.209 ± 0.008	1.35 ± 0.25
A_4 (μg ml^{-1})		$0.115 + 0.012$
L_1 (day^{-1})	107 ± 7.7	80.1 ± 5.8
L_2 (day^{-1})	0.677 ± 0.12	$1.038 + 0.056$
L_3 (day^{-1})	0.0420 ± 0.0015	0.268 ± 0.028
L_4 (day^{-1})		$0.0262 + 0.0026$
Residual sum of squares	6.0×10^{-3}	6.9×10^{-4}

Model parameter	Parameter estimate ±S.D.
k_a (day^{-1})	135 ± 14
k_{el} (day^{-1})	0.549 ± 0.012
k_{12} (day^{-1})	0.326 ± 0.018
k_{23} (day^{-1})	0.129 ± 0.013
K_{21} (day^{-1})	0.201 ± 0.019
k_{32} (day^{-1})	0.059 ± 0.006
V_1 (1 kg^{-1})	0.102 ± 0.008
Residual sum of squares	5.9×10^{-3}

N = number of exponential terms. V_1 = apparent volume of central compartment.
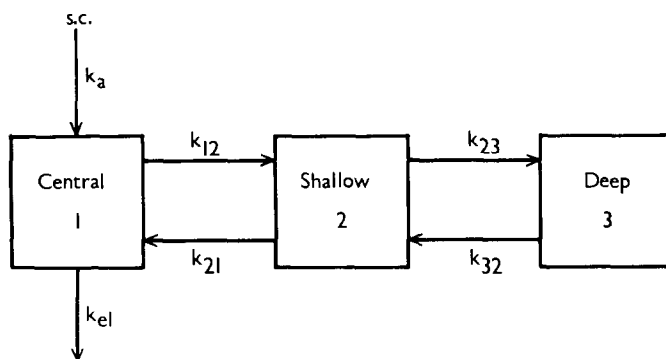
Fig. 2. Three compartment open model describing the metabolism of gold following a single s.c. injection of sodium [^{195}Au]aurothiomalate into male rats.

lymph nodes, pancreas, parotid, spleen and thymus, gold concentrations were generally higher than in bone, heart, lung and submaxillary. The initial rate of decline in concentration seemed to be more rapid in the latter group of tissues. Thus in bone, heart, lung and submaxillary the gold concentration fell by 68, 72, 54 and 56 per cent respectively between days 2 and 9. In the other organs, on the other hand, the fall in gold concentration ranged from 7 per cent in the kidney to 52 per cent in the thymus during the same period (Fig. 4).
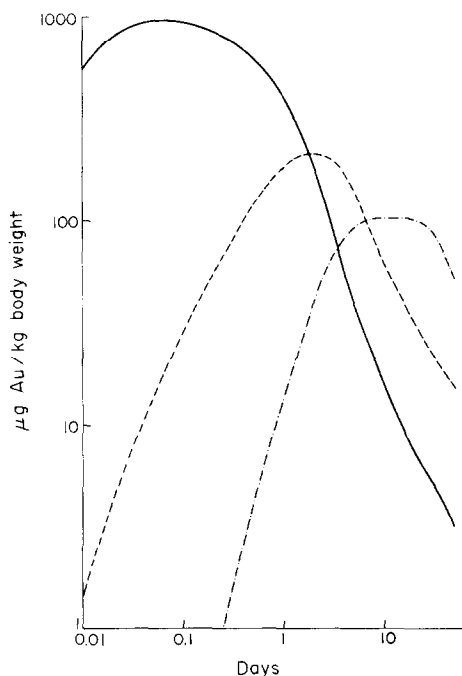

Fig. 3. Simulated amounts of gold (μg Au/kg body wt) as a function of time (t) in the individual compartments of the three compartment open model describing the metabolism of gold. The curves were calculated by substituting the model parameters into the appropriate equations. ———, central compartment (A_1 = 924e$^{-1.038t}$ + 138e$^{-0.268t}$ + 12e$^{-0.0262t}$ — 1074e^{-80t}); ———, shallow compartment (A_2 = 2.44e^{-135t} — 442e$^{-0.978t}$ + 391e$^{-0.261t}$ + 48.7e$^{-0.0255t}$); ·—·—·, deep compartment (A_3 = 62.1e$^{-0.978t}$ — 250e$^{-0.261t}$ + 188e$^{-0.0255t}$ — 0.0023e^{-135t}).

Each organ was then assumed to consist of two distinguishable metabolic compartments (analogous to the peripheral compartments of the model) connected to the serum compartment of the organ. The experimental organ gold concentrations were then correlated separately with the corresponding simulated amount of gold in the shallow peripheral compartment (one compartment regression—OCR) and in both peripheral compartments (two compartment regression—TCR) and the linear least squares regression equations used to calculate predicted organ gold concentrations (T_{calc}) as a function of time. Using the F statistic [7] the goodness of fit of the experimental data (T_{exp}) to the alternative compartments was determined by comparing the ratios of the respective variances (Table 2). The kidney, liver, lymph node and parotid data demonstrated a superior TCR (F test). Of the other organs, the adrenals (OCR) and submaxillary (OCR) showed negative trends when the residuals ($T_{exp} - T_{calc}$) were plotted against time for times greater than 8 days. The 9 day result for the spleen appeared to be anomalous and was omitted for a further pair of regressions. This caused no significant improvement in the OCR but a highly significant improvement in the TCR ($F_{5,4}$ = 15.9, P < 0.01). The curves in Fig. 4 were calculated using the appropriate TCR based on the full data set from 2 to 48 days.

DISCUSSION

The exponents of the serum concentration–time curve fit equation are hybrid rate constants and functions of the individual rate constants of the model. The smallest value (L_4 = 0.0262 day^{-1}) reflects the overall rate of elimination of gold from the body and corresponds to an elimination half-time of 26.5 days. The individual rate constants of the model characterise the transport of the gold to and from the compartments. Thus the gold was apparently lost rapidly from the central compartment by elimination (k_{el} = 0.549 day^{-1}) and by transport to a shallow peripheral compartment (k_{12} = 0.326 day^{-1}). The small value of k_{32} indicates that the rate of release of gold from the deep peripheral compartment was the rate controlling step in the elimination of gold from the body and is responsible for the relatively long biological half-time. The pharmacokinetics of
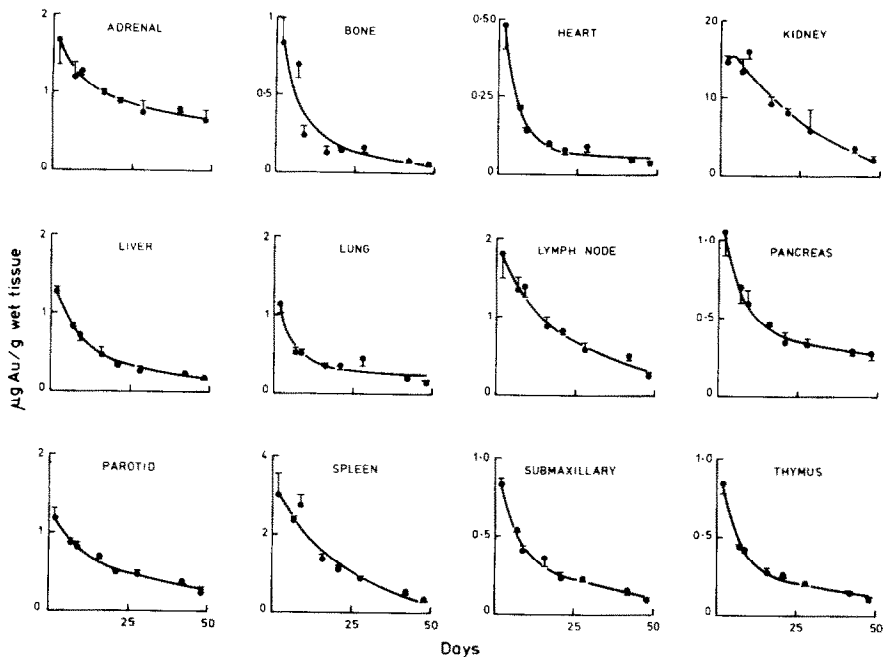
Fig. 4. Organ gold concentrations as a function of time following a single s.c. injection of sodium [195Au]aurothiomalate (1 mg Au/kg body wt) into male rats. The solid circles indicate the mean values of the experimental data and each line was calculated using the two compartment least squares regression equation (see Table 2). The bars indicate the S.E. of the mean concentration.

gold in man has been described using the simpler two compartment open model and data which indicated that the gold was transported rapidly from the central to a deep peripheral compartment with a slow rate of return to the central compartment and a rapid rate of excretion from the central compartment [8]. The interpretation of the present data is consistent with these observations.

The serum half-life (26.5 days) found in the present study is significantly longer than that found in humans. It has been reported for example that the decline in serum gold concentrations conformed to first order kinetics with serum half-lives ranging from

4.6 to 5.6 days during the period from 1 to 7 days after the administration of sodium [195Au] aurothiomalate to human subjects [9]. These findings are substantiated by the observation that serum gold concentrations declined rapidly during the first 36 hr after the administration of sodium aurothiomalate to human subjects, followed by a slower decline during the following 6 days [10]. The differences in serum half-life may have been a result of a species difference in the distribution and elimination of gold but it seems equally likely that the blood level measurements were not made for long enough to establish the log-linear line.

Table 2. Linear regression parameters for the regression of experimental organ gold concentrations on the amounts of gold in the shallow and deep peripheral compartments

Regression:	Shallow peripheral compartment				Both peripheral compartments					
	a	b	Variance	r	a	b	c	Variance	R	$F_{(}$
Adrenal	0.715	4.734	0.0136	0.949	0.461	5.109	2.546	0.0072	0.978	1.89
Bone	0.033*	4.051	0.0143	0.929	−0.058	4.185	0.910	0.0160	0.934	1.12 [a]
Heart	0.013*	2.094	0.00042	0.991	0.039	2.055	−0.261	0.00040	0.993	1.05
Kidney	5.493	55.566	13.3	0.747	−4.442	70.213	99.570	2.01	0.972	6.33 [c]
Liver	0.188	5.324	0.0072	0.977	−0.038	5.657	2.264	0.0014	0.996	5.14 [c]
Lung	0.178	4.299	0.0089	0.959	0.175	4.304	0.031	0.0106	0.959	1.19 [a]
Lymph node	0.497	6.882	0.0562	0.907	−0.146	7.831	6.450	0.0087	0.988	6.46 [c]
Pancreas	0.256	3.859	0.0019	0.989	0.151	4.015	1.061	0.00069	0.997	2.75
Parotid	0.365	4.204	0.0147	0.932	0.038	4.686	3.278	0.0025	0.991	5.88 [c]
Spleen	0.708*	12.735	0.3314	0.853	−0.778	14.926	14.893	0.0843	0.971	3.93
†	0.582	12.321	0.1371	0.937	−0.464	14.086	10.949	0.0053	0.998	25.87 [b]
Submaxillary	0.131	3.448	0.0040	0.971	−0.026	3.679	1.569	0.0013	0.992	3.08
Thymus	0.116	3.392	0.0016	0.987	0.035	3.513	0.821	0.00098	0.994	1.63

The regressions are $T = a + bX_s$ and $T = a + bX_s + cX_d$ where T = calculated tissue content (μg Au/g wet tissue); X_s and X_d are amounts of gold (μg/g body weight) in the shallow and deep compartments respectively.

Variance is the variance about the regression line, r and R are correlation coefficients. * Not significantly different from zero (P = 0.025); † Omitting the result for t = 9 days. [a] $F_{5,6}$, [b] $F_{5,4}$; P < 0.01, [c] P < 0.05.

In addition to the serum the central compartment probably includes other body fluids not investigated in this study. The similar pharmacokinetics of gold in the serum and synovial fluid of human patients, for example, indicated that the central compartment is almost certainly not limited to the serum [9]. The lean tissues, however, do not appear to make a significant contribution to this compartment and Figs. 3 and 4 show that the kinetics of gold in these tissues are quite different from its kinetics in the serum.

The results of the present study show that the majority of organs yield data which correlate better with the simulated gold content of both peripheral compartments. Nevertheless, Table 2 shows that the data for bone, heart and lung suggest that these organs contribute predominantly to the shallow peripheral compartment. The poorest regressions accounted for 87 per cent (bone) and 92 per cent (lung) of the initial sum of squares. In the case of the other organs the TCR accounted for at least 95 per cent of the initial sum of squares (Table 2). Thus the tissue metabolism of gold is consistent with the rate of disappearance of gold from the serum and the model defines adequately the relationship between serum and organ gold concentrations.

The biochemical interpretation of these results is not yet clear. Gold is localised in the nuclear, mitochondrial, lysosomal, microsomal and cytosolic fractions of liver, kidney and spleen cells of the rhesus monkey. The metabolism of gold in individual subcellular fractions is similar in these organs but there is evidence of differences in the pattern of uptake of gold which may reflect differences in intra-organelle metabolism and therefore compartmentation within the cell [11].

Unlike many pharmacological agents, critical serum gold concentrations related to clinical response and toxicity have not been demonstrated and it is the opinion of many authors that gold response is probably related to organ or subcellular gold concentrations. The present study demonstrates that it is possible to elaborate a metabolic model capable of relating gold concentrations in peripheral compartments of the body where the gold interacts with effector sites to gold concentrations in a convenient biological index medium, the serum. Further work is now needed to determine whether the uptake and metabolism of gold by subcellular particles, particularly at prospective sites of action, can be related to the kinetics of gold in the peripheral compartments of the model.

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