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Excretion of tolbutamide metabolites in young and old subjects

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Summary. Tolbutamide (1 g/70 kg) was administered as a single intravenous dose to 31 healthy, non-smoking, drug-free males between 23 and 87 years old and the total amounts of hydroxy and carboxytolbutamide excreted in 24 h were measured.

There was a significant decrease in the urinary recovery of both metabolites with age.

The reason for these findings is not known at the present time and may be associated with the decrease in creatinine clearance observed in these subjects or other changes in the pharmacokinetics of tolbutamide which are currently being investigated.

Key words: tolbutamide; hydroxytolbutamide, carboxytolbutamide, urinary excretion, age, pharmacokinetics

Tolbutamide is a sulfonylurea which has been used as an oral hypoglycemic agent in non-insulin-dependent diabetes mellitus of middle-aged or elderly patients for three decades. It is well-documented that renal function [1] and plasma albumin concentrations decrease with age [2, 3] and there is some evidence for reduced microsomal oxidative enzyme activity in the liver in the elderly [4]. These physiological changes are likely to affect the pharmacokinetics and/or pharmacodynamics tolbutamide. The drug is eliminated primarily by oxidative metabolism in the liver as two major metabolites, hydroxy and carboxytolbutamide, which are excreted by the kidneys. The formation and urinary excretion of these metabolites in healthy subjects has been previously studied [5]; however, no information is available regarding possible differences in its biotransformation in elderly. The purpose of this report is to show the effect of age on the urinary excretion of tolbutamide metabolites in man.

Materials and methods

Thirty-one healthy, non-smoking, drug-free males 23 to 87 years of age (between 3 and 6 subjects per decade) participated in this study. They were volunteers in the Baltimore Longitudinal Study of Aging (BLSA) at the Gerontology Research Center, National Institute of Aging, National Institutes of Health, Baltimore, Maryland[1]. Prior to the initiation of the study, renal function of each subject was determined by measuring the 24 h creatinine clearance [1]. Subjects fasted overnight before receiving a single intravenous dose (1 g/70 kg) of tolbutamide (Orinase Diagnostic, The Upjohn Co., Kalamazoo, MI) infused over a 2 min period via an antecubital intravenous catheter. Complete urine samples were collected *ad libitum* over a 24 h period. Total urine volumes were measured, pooled and aliquots frozen until the time of assay.

The pooled urine samples were analyzed for both hydroxy and carboxytolbutamide using the method of Matin and Rowland [6]. For the standard curves, blank urine was spiked in the concentration range of 20 to 500 $\mu g \cdot ml^{-1}$ for both metabolites. Hydroxytolbutamide (lot no. RW 1889) and carboxytolbutamide (lot no. RW 1888) were kindly provided by Hoechst Pharmaceuticals, Inc., Somerville, N. J. Since there was a small carry-over of each metabolite into the extraction phase of the other metabolite, standard curves were prepared for each metabolite independently. An average of 9% of the hydroxy metabolite was found in the carboxy metabolite phase, and 4% of the carboxy metabolite was found in the hydroxy metabolite phase at all concentrations studied. Therefore, an adjustment was made in the appropriate standard curve for calculating the final amounts of each metabolite in the urine samples. Interference by unmetabolized tolbutamide was assumed to be negligible as less than 2% is excreted unchanged in man [6]. The recovery data were analyzed by least squares regression analysis as a function of age and creatinine clearance of the subjects.

Results and discussion

The total amount of both hydroxy or carboxytolbutamide excreted in urine in 24 h correlated inversely with age (Fig. 1). Similarly, the sum of these metabolites as the percent of the administered dose (Table 1) decreased significantly with increasing age ($r = 0.530$, $P < 0.01$). These age-related decreases in urinary recoveries of tolbutamide metabolites could be due to alterations in the excretion, metabolism and/or distribution of the parent drug or its metabolites. It is well-established that renal function declines with increasing age [1, 7]. This study also indicated that the true creatinine clearance (normalized to the body surface area) decreased significantly with increasing age

Table 1. Percent of dose excreted as hydroxy- and carboxy-tolbutamide in 24 h

Subject	%	Subject	%	Subject	%
1	73.2	2	75.3	3	83.0
4	52.9	5	59.4	6	70.8
7	75.6	8	74.2	9	51.4
10	78.5	11	74.7	12	72.9
13	63.0	14	69.8	15	71.4
16	58.2	17	71.9	18	80.2
19	76.8	20	68.6	21	95.8
22	79.6	23	73.9	24	74.6
25	59.4	26	81.3	27	54.8
28	69.8	29	74.2	30	65.6
31	70.4				

[1] At the time of the study, R. E. V. was affiliated with this institution

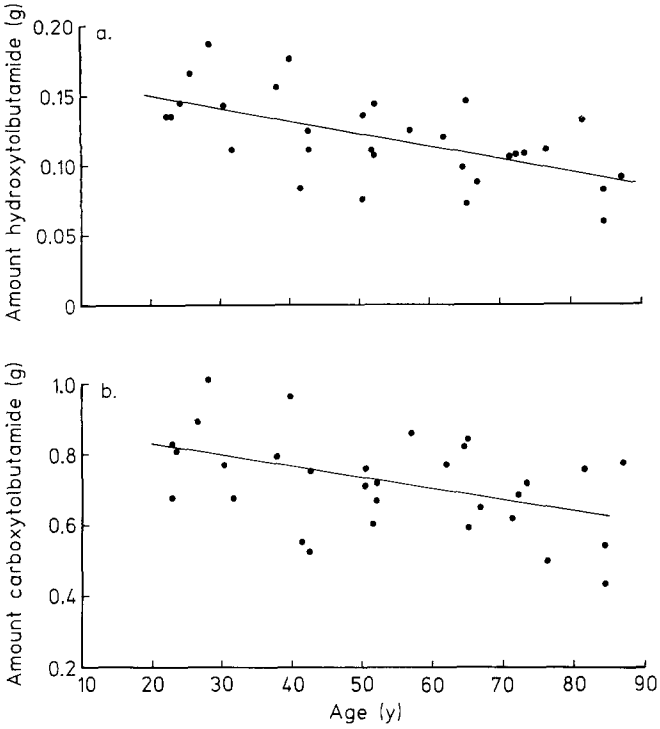

Fig. 1 a, b. Plot of amounts of tolbutamide metabolites excreted in urine in 24 h as a function of age. **a** hydroxytolbutamide ($r = 0.610$, $P < 0.001$); **b** carboxytolbutamide ($r = 0.435$, $P < 0.05$)

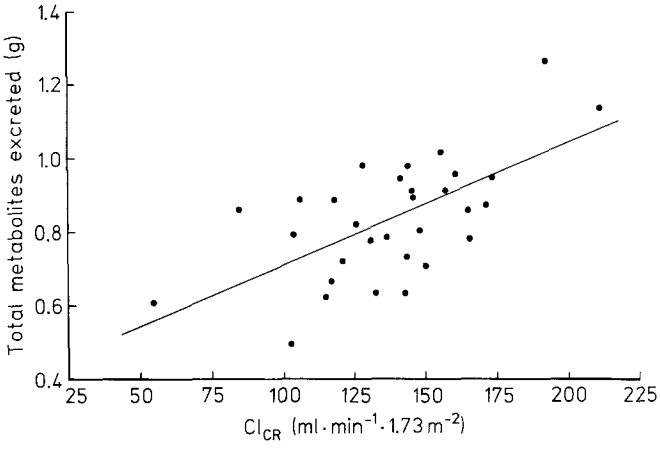

Fig. 2. Plot of total amount of tolbutamide metabolites excreted in urine in 24 h as a function of creatinine clearance ($r = 0.630$, $P < 0.001$)

($r = 0.672$, $P < 0.001$). Therefore, the relationship between renal function and excretion of these metabolites in the subjects was examined. Fig. 2 shows that the total amount of metabolites excreted correlated positively with creatinine clearance ($r = 0.630$; $P < 0.001$). These data indicate that the age-related decrease in the 24 h recovery of the total metabolites may be related, at least in part, to the decrease in glomerular filtration rate. Confirmation of this observation was obtained by partial correlation analysis of the data. Holding age constant, excretion of the metabolites correlated positively with creatinine clearance ($r = 0.436$, $P < 0.05$); however, when creatinine clearance was held constant, the partial correlation between the metabolites recovery and age was not significant.

We also found a significant decrease in the ratio of hydroxytolbutamide to the total amount of metabolites excreted as a function of age ($r = 0.429$, $P < 0.05$), suggesting that there might be an alteration in the oxidation of the parent drug and/or in the further conversion of hydroxy to carboxytolbutamide. Changes in drug metabolism are generally reflected in the urinary excretion of unchanged drug when the latter represents a significant route of elimination. However, since tolbutamide is predominantly excreted as metabolites, this method is not useful for this purpose.

The half-lifes of tolbutamide and its hydroxy and carboxy metabolites have been reported to be 6.3 h, 35 min, and 20 min respectively [8]. Therefore, the rate-limiting step in tolbutamide elimination appears to be hydroxylation. Thomas and Ikeda [5] showed in their study of orally administered tritiated tolbutamide in 8 normal male subjects that on the average about 84% of the dose was excreted in the urine as the two metabolites within 48 h. Nine % of the dose was eliminated in the feces, but was not identified [5]. Our study showed that between 71.4 (9.4)% of the dose was recovered in the urine of all subjects in 24 h (Table 1). Thus, although the 24 h period of urine collection encompassed about three half-lifes of tolbutamide, it is still possible that its excretion was not complete. Unfortunately, the one-day visit schedule of the BLSA subjects precluded urine collections for longer than 24 h.

Finally, changes in tolbutamide's pharmacokinetics with age may provide further explanations for the decreased excretion of its metabolites as a function of age. We have previously reported that protein binding of this drug decreases significantly with age [9, 10] and are currently investigating its plasma profile in the elderly population.

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