INTERACTION BETWEEN BENZOTHIADIAZINES AND TOLBUTAMIDE ON URIC ACID METABOLISM*

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Wales *et al* (15) reported that short-term administration of tolbutamide reverses diazoxide induced hyperglycaemia, hypotension and antidiuresis. This was suggested by the authors as due to the two drugs acting on a common receptor site. They even went on to suggest that tolbutamide and diazoxide have the same receptor for both carbohydrate metabolism and cardiovascular changes. Grant *et al* (5) while commenting on the interference by tolbutamide of the hyperglycaemic and hypotensive actions of benzothiadiazines have stated that there is competitive antagonism between these types of drugs. However, Johnson (7) has studied the effect of orally administered tolbutamide on a benzothiadiazine diuretic hypotensive, viz., hydrochlorothiazide and concluded that tolbutamide does not interfere with the antihypertensive action of benzothiadiazines.

A well recognised action of benzothiadiazine derivatives is an elevation of blood uric acid level, decreased urinary uric acid excretion and precipitation of attacks of gout (2,10,1). Benzothiadiazine-induced hyperuricaemia is not related to the inhibitory effect on uric acid excretion, indicating yet another mechanism for hyperuricaemia besides diminished excretion. No report is available on the antagnonism between tolbutamide and benzothiadiazines on uric acid metabolism. The present study was undertaken to examine the influence of tolbutamide on benzothiadiazine induced changes in blood and urine uric acid levels.

MATERIALS AND METHODS

Urine Uric Acid

Experiments were carried out in rabbits weighing approximately 1.5 *kg*. A group of twelve rabbits was used for each drug or combination. Twentyfour hr uric acid excretion rate was determined in each group before the drug administration. All drugs were administered daily for a period of seven days. The 24 hr uric acid excretion was determined after the following drugs alone or in combination as indicated :—cyclopenthiazide 1.25 *mg/kg*; hydrochlorothiazide 5 *mg/kg*; tolbutamide 40 *mg/kg*; cyclopenthiazide 1.25 *mg/kg* and tolbutamide 40 *mg/kg*; and hydrochlorothiazide 5 *mg/kg* and tolbutamide 40 *gm/kg*. The animals were given no food from the day previous to the collection of 24 hr urine sample but were given water *ad lib*. The animals were hydrated by the administration of 0.85% NaCl in doses of 25 *ml/kg* orally and immediately thereafter were fed 10 *ml* of the drug suspension or alkalinised saline in the case of controls and kept in metabolism cages. Urine was collected by placing a urine glass underneath the funnel attached to the cage. At the end of the experiment, the lower

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portion of the rabbit's abdomen was firmly pressed to express residual urine from the rabbit's bladder. All experiments were made at room temperature (22°-33°C).

Blood Uric Acid

Blood uric acid analysis was undertaken in the animals employed for the urinary uric acid investigation. Blood was withdrawn from the ear vein of the rabbit before the administration of the drugs. Blood was again withdrawn at the end of the drug schedule, before the animals were put up for the 24 hr urine studies.

Uric acid in blood and urine was estimated by the method described by King(9).

RESULTS

Table I gives data on the 24 hr urinary uric acid excretion before and after the administration of drugs.

TABLE I

Effect of benzothiadiazines, tolbutamide and benzothiadiazines in combination with tolbutamide on the urinary uric acid excretion in rabbits

Drug (s)	*Dose(mg/Kg/day)*	*Mean urinary uric acid level (mg%) 1 kg ± S.E.*	
		After 7 days of drug administration	*Probability of difference between control and test*
Control	..	15.36±0.95	..
Cyclopenthiazide	1.25	11.18±0.57	<0.01
Hydrochlorothiazide	5.00	10.11±0.64	<0.01
Tolbutamide	40.00	23.70±0.77	<0.01
Cyclopenthiazide & Tolbutamide	1.25 & 40.00	16.08±0.57	<0.2
Hydrochlorothiazide & Tolbutamide	5.00 & 40.00	16.14±0.60	<0.5

The data on the effect of drugs on blood uric acid level are given in Table II.

TABLE II

Effect of benzothiadiazines, tolbutamide and benzothiadiazines in combination with tolbutamide on the blood uric acid level of rabbits

Drug (s)	*Dose (mg/Kg/day)*	*Mean blood uric acid level (mg%) ± S.E.*		
		Control I	*After 7 days of drug administration* II	*Probability of difference between I and II*
Cyclopenthiazide	1.25	4.19±0.02	5.70±0.32	<0.01
Hydrochlorothiazide	5.00	4.44±0.18	6.49±0.29	<0.01
Tolbutamide	40.00	4.47±0.16	3.39±0.10	<0.01
Cyclopenthiazide & Tolbutamide	1.25 & 40.00	4.85±0.05	4.77±0.05	>0.5
Hydrochlorothiazide & Tolbutamide	5.00 & 40.00	4.39±0.06	4.40±0.06	>0.5

The benzothiadiazines raised the blood uric acid level and diminished the urinary excretion of uric acid. Tolbutamide lowered blood uric acid level and increased the urinary excretion of uric acid. The changes were statistically significant. Tolbutamide antagonised the effects of benzothiadiazines both on blood uric acid levels and urinary uric acid excretion.

DISCUSSION

The renal handling of uric acid in rabbits is supposed to be a combination of glomerular filtration, tubular reabsorption and tubular secretion(3). However, we have studied the effects of the drugs on the overall excretion of uric acid. Grant *et al* (5) studied the influence of tolbutamide on the diuretic effect of benzothiadiazines and found that tolbutamide antagonised the effect of benzothiadiazines on the kidney. The present study has shown that this antagonism extends to the retention of uric acid also.

Acetohexamide produces an uricosuric effect and a decrease in the serum uric acid level (16). However, tolbutamide in 2.0 *g* doses does not have these effects in patients (16). We found that tolbutamide increased the uric acid excretion and decreased the serum uric acid level.

It has been postulated that insulin produces an uricosuric action. In diabetic keto acidosis there is a retention of uric acid and excretion of uric acid starts when insulin is administered(11). The uricosuric effect of an infusion of glucose may be mediated through a release of insulin by glucose(12). The increased elimination of uric acid by tolbutamide may be mediated through its insulin-releasing action. Benzothiadiazines produce direct inhibitory effect on the production of insulin by the cells of the pancreas (4). The diminished insulin level may be the responsible factor for the uric acid retention by benzothiadiazines. Hence the hyperglycaemia as well as the uric acid retention produced by benzothiadiazines may both be two facets of the same phenomenon, viz., their inhibition of insulin secretion.

The blood acetaldehyde level rises in the tetraethylthiuram disulphide (TETD)-alcohol reaction. The hypoglycaemic sulphonylurea may produce a reaction similar to TETD—ethanol reaction and cause the acetaldehyde concentration to rise (6,14). Since the reaction is the same as seen with TETD, it may be presumed that the biochemical mechanisms involved in both cases my be similar. TETD depresses xanthine oxidase(13). Xanthine oxidase is an essential enzyme in the synthesis of uric acid. Allopurinol which depresses this enzyme produces a reduction in blood uric acid(8). The possibility is therefore strong that tolbutamide may contribute to the reduction of blood uric acid level by a depression of xanthine oxidase.

SUMMARY

Cyclopenthiazide and hydrochlorothiazide produced a decreased excretion of uric acid and a raised blood uric acid level in rabbits.

Tolbutamide produced an increased uric acid excretion and reduced blood uric acid level.

When tolbutamide was combined with the benzothiadiazines, the actions of benzothiadiazines on blood and urine uric acid were antagonised.

A possible mechanism of action is postulated.

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