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Renal excretion of metolazone, a new diuretic

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Summary

1. Metolazone, a new diuretic, was found to be excreted by glomerular filtration and renal tubular secretion.

2. The secretory mechanism was antagonized by probenecid but this did not affect the diuretic action of metolazone.

Introduction

Metolazone*, 2-methyl-3-*o*-tolyl-5-sulphamyl-7-chloro-1,2,3,4-tetrahydro-4-quinazolinone, is a new diuretic being developed for use in man (Belair, Kaiser, Van Denburg, Borrelli, Lawlor, Panasevich & Yelnosky, 1969; Belair, 1970; Cohen & Hinsvark, 1970). The compound is about 10 times more potent, on a weight basis as a natriuretic agent in rats, than quinethazone to which it is chemically related (Belair *et al.*, 1969). Natriuresis is due to a direct action on the kidney (Belair *et al.*, 1969). Studies in rats, dogs and man indicate that the kidney is the major route of excretion of metolazone (Hinsvark & Cohen, 1970; Cohen & Hinsvark, 1970). This paper describes studies undertaken to determine the mechanism by which metolazone is excreted by the kidney.

Methods

Pure bred beagle dogs of either sex were used. The dogs were anaesthetized with sodium pentobarbitone (30 mg/kg, i.v.). The ureters were cannulated for urine collection. A 5% dextrose solution was infused throughout the experiment, beginning 90 min before the first control period. Thirty minutes after starting the dextrose infusion, creatinine (1·2 mg/kg)/h, was added to the infusate following a priming dose of 200 mg/kg, intravenously. When probenecid was used, it was added to the dextrose-creatinine infusate to provide (35 mg/kg)/h immediately following an intravenous dose of 25 mg/kg.

Control creatinine clearances were determined during two 20 min periods; ^{14}C labelled metolazone (0·1 mg/kg, i.v.) was then injected followed by an infusion of (0·15 mg/kg)/hour. In three experiments, probenecid was given after two post-drug periods, followed by three clearance periods.

Creatinine in blood and urine was determined by the method of Folin & Wu (1919). Metolazone clearance, for comparison with reported clearances of other diuretics, was calculated on the basis of the concentration of the drug in the plasma. In addition, metolazone clearance was corrected for drug bound to red blood cells and plasma proteins and was calculated on the basis of the concentration of the unbound drug in the plasma.

*Zaroxolyn® is the registered trademark of the Pennwalt Corporation for metolazone.

The radioactive drug (synthesized in the Department of Organic Chemistry at the Pharmaceutical Division of the Pennwalt Corporation by Drs. T. A. Davidson and B. V. Shetty) was labelled with ^{14}C at the number 2 carbon atom in the ring of metolazone and had a specific activity of 0·97 mCi/mM.

The concentration of ^{14}C-metolazone was determined in the blood and plasma by the method of Mahin & Lofberg (1966) assuming that all radioactivity was due to metolazone. Plasma ultrafiltrates were prepared by centrifugation through dialysis tubing supported by a sintered glass filter funnel (Taylor, Richards, Davin & Asher, 1954). Duplicate samples were estimated by liquid scintillation counting at 2° C using external standard correction for quenching. The values for the erythrocyte fractions were determined as the difference in count between the whole blood and the plasma.

Results

A priming dose of 0·1 mg/kg of metolazone followed by an infusion of (0·15 mg/kg)/h resulted in a marked diuretic effect in dogs (Table 1). The uncorrected renal clearance rate of metolazone in these experiments was approximately equal to the renal clearance rate of creatinine. However, a high degree of binding of metolazone to red blood cells and plasma proteins was found; only about 10% of the whole blood concentration of metolazone was in the free form (Table 2). The clearance rate of metolazone corrected for drug bound to plasma proteins and red blood cells was over three times greater than the clearance rate for creatinine (Table 3).

TABLE 1. *Diuretic effects of metolazone and the interaction with probenecid in anaesthetized dogs*

No. of dogs	No. of periods*	Urinary excretion: Volume ml/min Mean±S.E.		Sodium μeq/min Mean±S.E.		Potassium μeq/min Mean±S.E.		Chloride μeq/min Mean±S.E.		Glomerular filtration rate ml/min Mean±S.E.		Urinary pH Mean±S.E.	
8	16	0·39	0·04	33·9	9·8	15·3	2·3	40·7	9·1	36·9	1·1	6·5	0·11
Metolazone 0·1 mg/kg, i.v. followed by an infusion of (0·15 mg/kg)/hour													
8	22	1·28†	0·06	230·5†	15·5	43·9†	1·6	255·7†	13·5	40·0	2·4	6·2	0·10
Probenecid 25 mg/kg, i.v. followed by an infusion of (35 mg/kg)/hour													
3	9	1·54	0·25	214·3	20·4	50·1	3·3	264·4	18·1	45·5	3·1	6·3	0·17

* Urine was collected from each dog for 2 control periods and for a minimum of 2 periods after the priming dose of metolazone. Three of the 8 dogs were given probenecid following metolazone. († $P<0·01$).

TABLE 2. *Distribution of ^{14}C-metolazone* in dog blood*

No. of dogs	No. of determinations	Metolazone concentration in whole blood ng/ml Mean±S.E.		Percentage of metolazone in blood fractions: Erythrocytes Mean±S.E.		Plasma bound Mean±S.E.		Plasma free Mean±S.E.	
8	16	248·3	19·1	61·1	1·04	28·9	1·01	10·0	0·37

* A priming dose of 0·1 mg/kg, i.v. was followed by an infusion of (0·15 mg/kg)/hour.

Probenecid markedly reduced the renal clearance of metolazone. The average ratio, drug clearance/creatinine clearance, was 0·81 with a standard error of 0·12 ($n=6$) before probenecid and $0·27 \pm 0·04$ ($n=6$) after probenecid (Table 3). Interference with the renal excretion of metolazone did not produce any significant changes in the diuretic effects of the drug (Table 1).

Discussion

The ratio, drug clearance/creatinine clearance, has been reported for other diuretics (Scriabine, 1962; Rennick, 1960). The ratio for metolazone (0·81) was considerably lower than the ratios for hydrochlorothiazide (4), flumethiazide (3·5) and chlorothiazide (3·0). It was slightly lower than the ratio for dihydroflumethiazide (1·6), about equal to the ratio for benzhydroflumethiazide (0·7) and trichloromethiazide (1·0) and considerably higher than the ratio for polythiazide (0·14).

One factor accounting for the relatively low estimated clearance rate of metolazone was the high proportion of the drug which binds to plasma proteins and red blood cells leaving only a small fraction available for glomerular filtration.

The renal clearance of metolazone, however, cannot be explained solely on the basis of glomerular filtration. Since drug bound to red blood cells and plasma proteins would normally not be filtered to any great extent the metolazone appearing in the urine would be expected to represent the unbound form. The clearance rate for metolazone calculated on the basis of the concentration of free drug in the plasma was more than three times greater than the clearance rate for creatinine. Furthermore, probenecid markedly reduced the renal clearance of metolazone. It is likely, therefore, that metolazone, like some thiazides and ethacrynic acid, was secreted into the tubular urine by the same mechanism as probenecid (Scriabine, 1962; Rennick, 1960; Beyer, Baer, Michaelson & Russo, 1965). Since the binding of metolazone was found to be reversible, all of the drug, bound as well as free, was available for active secretion (Cohen & Hinsvark, 1970; Goldstein, Aronow & Kalman, 1969).

Presumably some tubular reabsorption of metolazone also occurs but the extent of this has not yet been estimated.

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TABLE 3. *Effect of probenecid on renal clearance of ^{14}C-metolazone in three anaesthetized dogs*

	Creatinine clearance ml/min	Metolazone concentration: Plasma ng/ml	Metolazone concentration: Ultrafiltrate ng/ml	Metolazone clearance: $*C_{drug}$ ml/min	Metolazone clearance: $\dagger C_{drug}$ ml/min	$*C_{drug}/C_{cr}$	$\dagger C_{drug}/C_{cr}$
	Metolazone 0·1 mg/kg, i.v. followed by an infusion of (0·15 mg/kg)/hour						
Mean±S.E. ($n=6$)	44·1±2·6	178·1±18·7	44·6±6·5	35·0±4·1	142·2±15·1	0·81±0·12	3·2±0·04
	Probenecid 25 mg/kg, i.v. followed by an infusion of (35 mg/kg)/hour						
Mean±S.E. ($n=9$)	45·5±3·1	199·0±10·1	57·1±2·9	13·7±1·4	48·4± 5·8	0·27±0·04	1·1±0·16
P value	0·76	0·30	0·07	0·01	0·01	0·01	0·01

* Based on plasma concentration. † Based on concentration in ultrafiltrate. Clearance periods were of 20 min duration.

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