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Simultaneous ^{51}Cr Edetic Acid, Inulin, and Endogenous Creatinine Clearances in 20 Patients with Renal Disease

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Brit. med. J., 1968, 1, 84–86

^{51}Cr edetic acid, inulin, and endogenous creatinine clearances were studied in 20 patients with renal disease. The group studied includes many subjects in whom the ratio creatinine clearance to inulin clearance was high.

The estimation of endogenous creatinine clearance is the method most widely used to measure the glomerular filtration rate. Unfortunately, in many patients with renal disease this method gives unreliable results, as has been noted by Berlyne *et al.* (1964) in patients with the nephrotic syndrome and by Miller *et al.* (1952) in patients with impaired renal function. The laboriousness of the chemical estimation of inulin inhibits the use of inulin clearance for routine clinical work. For this reason various workers have looked for an alternative method (*Brit. med. J.*, 1967). Nelp *et al.* (1964) reported that ^{57}Co-cyanocobalamin clearance showed good correlation with inulin clearance in man, but Breckenridge and Metcalfe-Gibson (1965) pointed out that it was necessary to give a large dose of the unlabelled vitamin in order to saturate the binding sites of the plasma proteins. Despite adopting this technique, other workers encountered inaccuracies due to protein binding (Foley *et al.*, 1966). In practice it is necessary to estimate the degree of protein binding of the labelled vitamin B_{12} during the midpoint of each clearance period (*Brit. med. J.*, 1967).

Downes and McDonald (1964) described the preparation of ^{51}Cr complexed with edetic acid, and Stacy and Thorburn (1966) compared the renal clearance of this substance with that of inulin in sheep. They found a ratio ^{51}Cr edetic acid clearance to inulin clearance of 0.95. Garnett *et al.* (1967) studied patients with a wide range of clearances and found a correlation coefficient between ^{51}Cr edetic acid clearance and inulin clearance of 0.995. These authors have not reported simultaneous creatinine clearances on their patients.

This paper describes experiments in dogs in which the clearance of ^{51}Cr edetic acid was compared with the simultaneous clearance of inulin over a wide range of plasma concentrations of Cr edetic acid. In addition, simultaneous ^{51}Cr edetic acid, inulin, and endogenous creatinine clearances were studied in 20 patients with renal disease. The group studied includes many subjects in whom the ratio creatinine clearance to inulin clearance was high.

Material and Method

Dog Experiments.—Six dogs weighing from 8 to 25 kg. anaesthetized with pentobarbitone sodium (20 mg./kg.) were used. A bladder catheter was inserted and 0.9% saline infused to establish a high urine flow. Arterial blood samples were collected by a catheter in the femoral artery. Each dog received a loading dose of ^{51}Cr edetic acid (20 μCi) and of inulin (60 mg./kg.). A solution containing ^{51}Cr edetic acid and inulin diluted in saline (0.9%) was then given at a rate of 0.5 ml./min. After 30 minutes for equilibration urine was collected for two clearance periods of 10 minutes. In order to increase the plasma level of Cr edetic acid, a further loading dose of 20 ml. of a second solution containing a higher concentration of ^{51}Cr edetic acid but the same concentration of inulin was then given quickly, and after a further equilibration period with this more concentrated solution two further clearance periods were carried out. Each dog underwent two to four stepwise increments in this way. In order to get a high edetic acid blood level without an excessive increase in radioactivity, ^{51}Cr edetic acid (approximately 300 μCi) was mixed with a concentrated unlabelled Cr edetic acid solution. Thus blood levels of Cr edetic acid from 0.02 up to 2.9 mg./100 ml. were obtained.

Studies in Patients.—Twenty patients were studied. The diagnosis of each of these patients is given in the Table. In each patient simultaneous ^{51}Cr edetic acid, inulin, and endogenous creatinine clearances were estimated. A priming dose of 40 μCi of ^{51}Cr edetic acid and of 60 mg. of inulin per kg. was given, followed by the infusion of a solution containing 40 μCi of ^{51}Cr edetic acid and 6 g. of inulin diluted in 120 ml. of either 0.9% saline or 5% dextrose. The speed of the

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infusion was related to a previously estimated 24-hour creatinine clearance. When the patient's renal function permitted, a large intake of water was given to promote a diuresis. After 30 to 40 minutes for equilibration, two or three clearance periods of 30 minutes were carried out. In one oedematous patient the equilibration time was prolonged up to two hours. The urine was collected by voiding. ^{51}Cr edetic acid was counted in an autoscintillation counter. Inulin was estimated by the anthrone method of Führ *et al.* (1955) and creatinine by Technicon AutoAnalyzer. Each measurement was carried out in duplicate. The clearances were calculated from the formula $C=\frac{U\times V}{P}$, where C=clearance of substance in ml./min., U=urinary concentration per ml., V=urinary volume in ml./min., and P=plasma concentration per ml.

Comparison of Clearances of ^{51}Cr Edetic Acid, Inulin, and Endogenous Creatinine in 20 Patients

Case No.	Age	Description	Proteinuria (g./day)	^{51}Cr Edetic Acid Cl. (ml./min.) A	Inulin Cl. (ml./min.) B	Creatinine Cl. (ml./min.) C	A/B*	C/B†
1	35	Orthostatic albuminuria	±	129·6	116	144·5	1·12	1·23
2	31	" "	±	61·1	57·5	64·0	1·06	1·15
3	57	Hypertension	0	99·2	97·5	131·9	1·01	1·28
4	52	"	0	102·3	99·0	103·3	1·04	1·04
5	47	"	0	40·14	39·7	39·9	1·01	1·0
6	73	Congestive cardiac failure	0	71·9	68·6	77·7	1·05	1·14
7	52	Membranous glomerulonephritis	0	109·8	129·5	127·5	0·84	0·98
8	39	Chronic glomerulonephritis	0·5	134·0	147·0	185·5	0·91	1·26
9	37	" "	0	6·18	6·38	8·77	1·01	1·44
10	23	Glomerulonephritis	1	137·7	126·1	194·6	1·08	1·53
11	49	Chronic pyelonephritis	0	85·6	77·6	143·2	1·09	1·86
12	19	" "	0	65·15	57·5	85	1·13	1·32
13	45	" "	0	2·04	1·97	4·23	1·02	2·13
14	21	Nephrotic syndrome	6	123·4	119·6	160·5	1·02	1·34
15	20	" "	16·4	98·68	110·7	132·4	0·93	1·25
16	62	" "	8	90·1	90·8	145·4	1·0	1·57
17	54	" "	18	148	146·3	161·12	1·01	1·13
18	31	" "	6·4	21·6	21·3	31	1·01	1·44
19	38	Urate nephropathy	2	5·28	4·47	7·5	1·17	1·78
20	16	Diabetes	1	119·8	102·8	139·4	1·16	1·36

* Mean ± S.D. = 1·02 ± 0·14. † Mean + S.D. = 1·36 ± 0·20.

Results

Dog Experiments.—Fig. 1 shows that the ratio between ^{51}Cr edetic acid U/P and inulin U/P did not change over a range of plasma concentrations of edetic acid of from 0.02 to 2.9 mg./100 ml. In individual experiments a change in plasma concentration of up to sixtyfold did not alter the clearance of edetic acid.

Studies in Patients.—The Table records some clinical details and the ratios of ^{51}Cr edetic acid clearance to inulin clearance and creatinine clearance to inulin clearance. Each value is the average of two or three clearance periods. The average ratio ^{51}Cr edetic acid clearance to inulin clearance is 1.02; the average ratio creatinine clearance to inulin clearance is 1.36. Figs. 2 and 3 show the relation between the same pairs of clearance estimations. The coefficient of correlation between ^{51}Cr edetic acid clearance and inulin clearance is 0.992 and between creatinine clearance and inulin clearance 0.908. Since the urine volume is the same for each substance, errors in collection do not enter into the calculation. The clearances have not been corrected to standard body-surface area.

Discussion

Garnett *et al.* (1967) have demonstrated that ^{51}Cr edetic acid is not significantly bound to plasma proteins and is not taken up by the red cells. In dogs, our results show that the ratio U/P for ^{51}Cr edetic acid to U/P for inulin remains constant over a wide range (0.02 to 2.9 mg./100 ml.) of edetic acid plasma concentrations (Fig. 1). Also, the clearance of ^{51}Cr edetic acid stays constant when the edetic acid blood level is increased by up to 60 times in any one dog. The clearance of ^{51}Cr edetic acid is therefore independent of plasma concentration, and remains identical with simultaneous inulin clearances over a wide range of edetic acid plasma concentrations. The measurement of ^{51}Cr edetic acid clearance therefore gives a reliable estimate of the inulin clearance.

In comparing simultaneous clearance estimations in patients with a variety of renal disease (see Table), a close relation between ^{51}Cr edetic acid clearance and inulin clearance was demonstrated (r=0.992). This correlation is better than the correlation between creatinine clearance and inulin clearance measured simultaneously (r=0.908). The correlation between ^{51}Cr edetic acid and inulin clearances is in close agreement with the findings of Garnett *et al.* (1967), though we have used different methods of counting ^{51}Cr edetic acid and for the chemical estimation of inulin.

The group of patients studied included many with a high ratio of creatinine clearance to inulin clearance (see Table). In two of our five cases with the nephrotic syndrome this ratio was markedly increased (1.57 and 1.44). We also found high ratios (1.53 and 1.44) in two patients with chronic glomerulonephritis with proteinuria, in one diabetic girl with slight proteinuria (1.36), and in two patients with chronic pyelo-

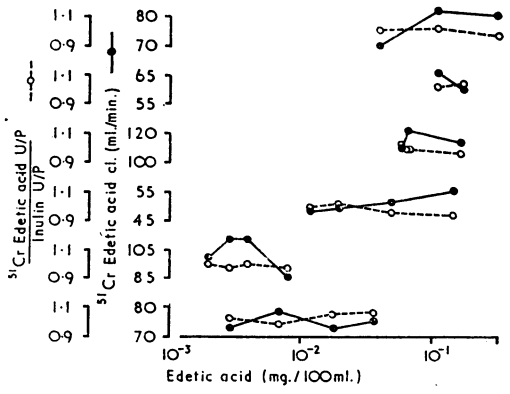

FIG. 1

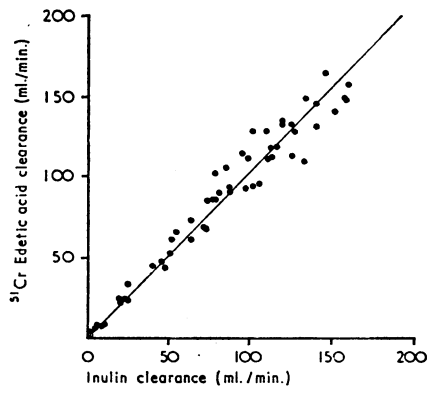

FIG. 2

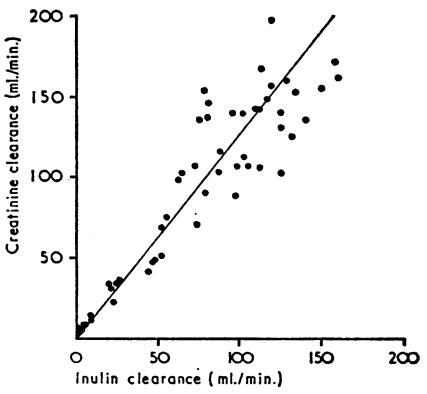

FIG. 3

FIG. 1.—Results of increasing edetic acid blood levels on the clearance of ^{51}Cr edetic acid (continuous line), and on the ratio U/P for ^{51}Cr edetic acid to U/P for inulin (interrupted lines) Each pair of lines records the results of one dog experiment. Each point is the mean of two 10-minute collection periods. N.B.: edetic acid plasma concentration has been plotted on a logarithmic scale. All edetic acid was present as Cr edetic acid. In the high concentration experiments not all the Cr was labelled ^{51}Cr (see text). FIG. 2.—Correlation between ^{51}Cr edetic acid clearance and inulin clearance for 57 collection periods. r=0.992. Linear regression equation: $y=x(1.024)-0.95$. FIG. 3.—Correlation between creatinine clearance and inulin clearance for 56 collection periods. r=0.908. Linear regression equation: $y=x(1.282)-2.49$.

nephritis without proteinuria (1.86 and 1.32). In three patients with low glomerular filtration rate (inulin clearance less than 10 ml./min.) we found ratios of from 1.44 up to 2.13, in agreement with the findings of Miller *et al.* (1952). It is pertinent to note that in all these cases the ratio ^{51}Cr edetic acid clearance to inulin clearance remains close to 1.00. Therefore ^{51}Cr edetic acid clearance gives a reliable estimate of inulin clearance even in the presence of proteinuria and advanced renal failure and in other renal diseases where creatinine clearance is unreliable.

Cr edetic acid is chemically inactive and has no chelating action. Downes and McDonald (1964), using large doses of Cr edetic acid in the rat, have shown that it does not cause renal damage. The total dose of ^{51}Cr edetic acid given for the purpose of measuring clearance in man is much lower than the dose administered when edetic acid is used as a chelating agent (5 mg. against 2–3,000 mg.). Ninety-eight per cent. of the Cr edetic acid administered is excreted through the kidney. Radiation dosage to the patient's kidney is comparatively trivial (Garnett *et al.*, 1967). ^{51}Cr emits monochromatic gamma radiation of 320 keV and is easily counted with any standard well-type scintillation counter. The ease of manufacture of ^{51}Cr edetic acid is an advantage over other labelled substances such as ^{51}Cr inulin (Johnson *et al.*, 1967). The use of this substance is therefore safe and convenient.

Summary

Experiments in dogs have shown that the clearance of ^{51}Cr edetic acid remains identical with the simultaneous clearance of inulin, and that it is independent of the concentration of Cr edetic acid in the plasma. Simultaneous ^{51}Cr edetic acid, inulin, and endogenous creatinine clearances were measured in 20 patients with renal disease of various origin and a wide range of severity. The correlation between ^{51}Cr edetic acid and inulin clearances (r=0.992) was found to be better than the correlation between creatinine and inulin clearances (r=0.908). ^{51}Cr edetic acid is safe and convenient to use.

We thank Dr. R. F. Jewkes and Miss Barbara Jones, who carried out the isotope measurements ; Dr. Pierre Verroust for help with the dog experiments ; Miss E. M. Clarkson in whose laboratory the creatinine estimations were performed ; and Mr. B. McAuliff for preparing the figures. We are especially grateful to Mr. N. Veall, of Guy's Hospital, who made available the original supplies of ^{51}Cr edetic acid.

Supplies of ^{51}Cr edetic acid were obtained from Dr. D. J. Jenkins, Radiochemical Centre, Amersham, Buckinghamshire, England. A preservative in the form of 1% benzyl alcohol is now added, and in our hands results with this preparation have been identical with those obtained with solutions prepared without this preservative.

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Treatment of Oral Lichen Planus with Betamethasone

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Brit. med. J., 1968, **1**, 86–89

Oral lichen planus is a relatively common form of stomatitis ; it may be symptom-free, but soreness, sometimes severe, is typical of the erosive form. Soreness of the mouth for 10 years or more, with little in the way of remissions, is a particular characteristic of lichen planus, and demands effective treatment. There is also a suspicion that persistent oral lichen planus may be followed by malignant change, as described by Warin (1960) and others. Until recently the usual treatment was hydrocortisone (Corlan) pellets, which seem only occasionally to have any effect, and tetracycline mouth washes, which often seem to expedite healing of erosions.

Betamethasone 17-valerate (Betnovate) is a synthetic corticosteroid with much greater anti-inflammatory effect than cortisone and has been noted by Williams *et al.* (1964) to cause dermal lesions of lichen planus to regress. Betamethasone was prepared in 0.1-mg. pellets with the original purpose of comparing it with hydrocortisone pellets in a double-blind trial in the treatment of recurrent aphthous ulceration. This trial was extended to include lichen planus. Betamethasone pellets were also used in the treatment of oral lesions of mucous membrane pemphigoid as described below.

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Present Investigation

Diagnosis.—This was made on clinical grounds in patients with a pattern of silvery-white striae or papules, with or without erosions, symmetrically distributed on the oral mucosa, especially on the posterior buccal mucosa. Experience has shown that clinical diagnosis of lichen planus is reliable—McCarthy and Shklar (1964)—and biopsy examination was carried out only in cases where lesions were less than typical in character, especially when only one side of the mouth was affected.

Clinical Material and Assessment of Results.—Symptoms were severe enough to require treatment in three cases. These patients were in the first instance given either hydrocortisone (2.5 mg.) or betamethasone (0.1 mg.) pellets at random as part of the double-blind trial. The pellets were allowed to dissolve in the mouth, and were given four times a day. It quickly became apparent that one preparation was outstandingly effective while the other seemed ineffective except on rare occasions. The effectiveness of treatment of oral lichen planus can be readily and objectively assessed by the diminution of size or disappearance of the lesions. Completely objective comparison can be made by means of serial photographs, but it is difficult to obtain an adequate and uniform angle of view. In assessing