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Paracetamol and Renal Damage

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Summary

Renal function was assessed in 18 patients who had consumed 2 to 30 kg of paracetamol. No relationship was found between the total amount of paracetamol taken and any aspect of renal function studied. No patient had clinically significant renal impairment. Thirteen of the patients showed no significant deterioration of renal function over a period of about one year during which they consumed an additional mean 2 kg of paracetamol.

Introduction

In recent years it has become clear that renal damage may be caused by consuming large amounts of analgesic mixtures. Because most of the affected patients have taken preparations containing phenacetin, this substance has been particularly implicated. Suspicion has also fallen on paracetamol, because it is a metabolic product of phenacetin. Two cases of nephropathy associated with paracetamol consumption have been reported (Krikler, 1967; Kerr, 1970). Kincaid-Smith (1969) noted that patients with analgesic nephropathy, which she attributed to phenacetin, failed to improve as expected

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when analgesic treatment was continued with paracetamol and aspirin in combination. On the basis of this evidence Koutsaimanis and de Wardener (1970) suggested that the use of paracetamol should be restricted by making it available only on prescription.

Paracetamol is widely used, low toxicity and absence of gastric irritation making it particularly suitable for patients with rheumatic diseases. A number of patients attending the rheumatism clinic at Westminster Hospital have consumed large amounts of paracetamol regularly; renal function has been studied in these patients to determine whether or not there is evidence of renal damage resulting from prolonged ingestion of paracetamol.

Patients and Methods

The 18 patients studied had all consumed at least 1 g of paracetamol daily for at least a year. Total drug consumption was determined from the patient's history with the aid of prescribing records. Schirmer's (1903) test of lachrymal secretion was performed, a value of less than 5 mm being taken as positive and indicative of Sjögren's syndrome.

During admission to hospital for 36 hours three blood samples were taken for estimation of urea and the mean value was calculated. Haemoglobin and bicarbonate levels were measured on the first sample. Two midstream specimens of urine were collected and cultured for organisms; the centrifuged deposit was examined for white cells and casts. Urine was collected during the first 24 hours for measurement of protein and creatinine excretion. During the first six hours a urinary acidification test was performed. Gelatin-coated ammonium chloride capsules (0·1 g/kg body weight) were given with water during the first hour, and pH, total acidity, titratable acidity, and ammonium excretion were determined in the urine sample collected between the fourth and sixth

hours (Edwards *et al.*, 1964). Serum and urinary creatinine levels were measured by the method of Wootton (1964). On the second day a urine concentration test was carried out. Pitressin tannate 5 IU in oil was given by subcutaneous injection. An Advanced osmometer was used to measure the osmolality of urine samples taken two-hourly either for eight hours or until the value exceeded 800 mOsm/kg.

In 13 patients the blood urea, serum creatinine, and creatinine clearance were determined on two occasions separated by a mean interval of 13·3 months.

Results

Clinical details and total quantities of analgesics consumed are shown in Table I. Results of the renal function tests are shown in Table II. Two patients vomited after taking ammonium chloride and the acidification test was discontinued. In one patient there was insufficient urine to measure ammonium excretion. One patient was found to have pyuria and bacteriuria, two had bacteriuria without pyuria, and in the remaining 15 the midstream specimens of urine were normal.

A correlation was sought between the total amount of paracetamol ingested and creatinine clearance, titratable acidity, and ammonium excretion. The correlation coefficients, + 0·35, + 0·30, and + 0·23 respectively, were not statistically significant (t = 1·6, 1·2 and 0·9; P>0·1). Twelve of the 18 patients concentrated normally to 800 mOsm/kg or more; mean paracetamol consumption in these patients was 10·7 kg compared with 9·3 kg in those who failed to concentrate

normally. Thus no relationship was found between these aspects of renal function and the total amount of paracetamol consumed.

Results in the 13 patients who were investigated twice are shown in Table III, and were analysed by a paired t test.

TABLE III—*Mean Values and Standard Deviations for 13 Patients Tested Twice at a Mean Interval of* 13·3 *Months. Results were analysed by a Paired* t *Test;Values of* t *and Significant Levels are Shown*

	1st Test	2nd Test	t	P
Paracetamol consumption (kg) ..	8·7	10·7		
Urea (mg 100 ml)	34·6 11·3	38·0 7·5	1·0	0·1
Creatinine clearance (ml min) ..	90·3 17·5	95·7 27·8	0·7	0·1
Serum creatinine (mg 100 ml)	0·70 0·13	0·77 0·20	1·4	0·1

There was no significant deterioration in renal function during a mean period of 13·3 months in which the patients consumed a mean additional 2 kg of paracetamol.

Discussion

Though we cannot positively exclude the existence of analgesic nephropathy in every patient in this series, none had severe impairment of renal function and those tested twice showed no evidence of renal deterioration. None of our patients had sterile pyuria. Impairment of concentrating ability, the commonest functional abnormality in patients with

TABLE I—*Clinical Details of Patients studied, with Total Quantities of Drugs Consumed*

Case No.	Age	Sex	Diagnosis	Schirmer Test	Analgesic (kg)			Gold Therapy	Past Urinary Infection	Peptic Ulcer	Blood Pressure	
					Paracetamol	Phenacetin	Aspirin				Systolic	Diastolic
1 ..	69	M.	RA	—	2·7	1·7	1·7	—	—	—	160	100
2 ..	62	M.	RA	—	2·8	—	—	—	—	+	120	80
3 ..	62	F.	AS	—	4·3	—	2·0	—	+	—	140	80
4 ..	64	F.	RA	—	4·4	1·8	2·9	—	—	—	170	100
5 ..	64	F.	RA	+	4·5	—	—	—	+	—	190	110
6 ..	75	F.	OA	—	5·3	—	—	—	—	—	150	90
7 ..	61	F.	RA	+	6·1	—	—	—	—	—	180	90
8 ..	50	F.	RA	—	6·6	—	0·4	—	—	—	130	90
9 ..	72	F.	PsA	+	7·5	—	5·3	—	+	—	200	100
10 ..	52	F.	RA	+	7·7	—	1·5	—	—	—	140	80
11 ..	54	M.	RA	—	7·9	—	—	+	—	+	160	80
12 ..	72	F.	RA	+	10·0	—	—	+	+	—	200	140
13 ..	48	M.	RA	+	10·1	—	—	—	—	+	130	80
14 ..	67	F.	RA	—	11·8	—	3·0	+	+	—	160	90
15 ..	62	F.	RA	—	17·1	3·6	3·6	—	—	—	140	90
16 ..	70	M.	RA	+	20·8	—	—	+	—	—	120	80
17 ..	65	M.	RA	+	25·5	—	—	—	—	—	120	80
18 ..	46	F.	RA	—	29·6	—	3·5	—	—	—	140	90

RA = Rheumatoid arthritis. OA = Osteoarthritis. PsA = Psoriatic arthropathy. AS = Ankylosing spondylitis.

TABLE II—*Results of Renal Function Tests*

Case No.	Haemoglobin (g/100 ml)	Urea (mg/100 ml)	Bicarbonate (mEq/l.)	Serum Creatinine (mg/100 ml)	Creatinine Clearance (ml/min)	Urine Protein (mg/24 hr)	Osmolality (mOsm/kg)	pH	Titratable Acidity (μEq/min)	Ammonium Excretion (μEq/min)
1	15·0	56	22·5	0·72	66	6	709	5·2	37·0	45·5
2	10·7	33	26·5	0·85	78	10	940	5·6	86·0	94·0
3	13·6	37	24·0	0·77	75	700	824	4·8	26·2	44·8
4	13·0	61	35·0	0·85	78	400	969	6·35	12·5	110·2
5	14·2	30	27·0	0·62	67	100	766	6·8	3·6	20·8
6	12·0	34	28·0	0·92	64	40	736	4·9	22·7	32·3
7	10·9	28	25·0	0·46	66	20	562	5·4	7·9	—
8	11·2	34	22·0	0·67	110	0	826	5·7	24·9	44·7
9	14·7	35	24·5	0·85	79	50	823	4·9	17·8	34·4
10	13·2	40	24·5	1·32	62	200	788	4·7	32·7	30·6
11	14·4	48	27·0	0·85	107	3	866	5·2	34·4	38·4
12	12·8	56	22·0	0·88	49	100	824	—	—	—
13	12·8	28	28·5	0·54	158	30	900	4·8	47·7	66·0
14	11·7	36	24·5	0·69	117	60	860	4·8	39·5	67·8
15	14·0	38	28·0	0·56	108	60	926	—	—	—
16	13·4	57	19·5	0·77	63	30	845	4·9	30·3	46·6
17	15·0	31	25·0	0·69	113	10	867	5·25	37·8	72·8
18	12·7	44	25·5	0·69	106	170	699	5·5	29·6	79·2
Mean (S.D.)	13·1 ±1·4	40·3 ±10·7	25·5 ±3·4	0·76 ±0·19	87·2 ±27·9	110 ±177	818 ±99	5·3 ±0·6	27·5 ±12·1	55·2 ±25·5
Normal	>12·0	<42	19–30	<1·0	>80	0	>800	<5·3	>24	>33

analgesic nephropathy (Steele et al., 1969), was present in six patients but was of minor degree. Neither the incidence nor the severity of this abnormality was related to the total amount of paracetamol consumed.

It is not surprising that some minor renal functional abnormalities were found in our group of elderly patients, most of whom were suffering from rheumatoid arthritis. Burry (1970) showed that impaired glomerular function may be associated with rheumatoid arthritis; he found a creatinine clearance of less than 80 ml/min in 49 out of 97 unselected patients, and showed a correlation between reduction of glomerular filtration and the presence of radiological articular erosions. Patients with Sjögren's syndrome may also be unable to concentrate or acidify their urine (Kahn et al., 1962; Talal et al., 1968). Eight of our patients had a positive Schirmer's test, and urinary concentration or acidification was abnormal in four.

The evidence implicating paracetamol lies in its chemical relationship to phenacetin, in two reported cases of suspected paracetamol nephropathy, and in its effect on the course of established analgesic nephropathy. Prescott (1970) suggested that phenacetin is not the cause of analgesic nephropathy and claimed that salicylates or mixtures containing salicylates are responsible. Animal work cannot necessarily be extrapolated to man, but supports this concept. Aspirin and mixtures containing aspirin cause papillary necrosis in rats but phenacetin alone does not (Saker and Kincaid-Smith, 1969; Nanra and Kincaid-Smith, 1970). Only two cases of analgesic nephropathy attributable to paracetamol abuse have been reported, despite the widespread use of the drug; it is notoriously difficult to be certain that patients have not consumed other drugs, and this is well illustrated by the first case reported by Kerr (1970). Kincaid-Smith (1969)

implicated paracetamol on the basis of its effect on patients with established analgesic nephropathy, but her patients were taking mixtures of paracetamol and salicylates. Our results indicate that paracetamol does not cause significant impairment of renal function, and hence we find no justification to restrict the use of paracetamol by making it available only on prescription.

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MEDICAL MEMORANDA

Idiopathic Steatorrhoea and Idiopathic Pulmonary Haemosiderosis

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The aetiology of idiopathic pulmonary haemosiderosis is unknown. In the present case it was seen in association with idiopathic steatorrhoea.

Case Report

A 23-year-old man had first presented at the age of 9 years with a two-year history of attacks of postprandial epigastric pain. Haemoglobin was 8·1 g/100 ml but occult blood was absent and

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stool faecal fat contents of 3·2 and 3·8 g/24 hours did not suggest malabsorption. Oral iron was given, raising the haemoglobin to 11·9 g/100 ml. At age 12 he was anaemic again (haemoglobin 9·6 g/100 ml) and was below normal height for his age. Barium studies showed appearances compatible with chronic duodenal ulceration. Tests for occult blood were still negative. Over the next four years his condition remained chronically unsatisfactory, with features of intermittent abdominal pain, poor appetite, recurrent mouth ulcers, listlessness, lack of growth, and persistent iron-deficiency anaemia. Further tests for malabsorption (faecal fat and xylose absorption) at age 13 and 16 were again negative and barium studies again suggested a scarred duodenal cap.

When he was aged 18 a febrile respiratory tract illness with severe haemoptysis and changes in both lower lung fields on chest x-ray examination led to a provisional diagnosis of idiopathic pulmonary haemosiderosis. A review of previous radiographs suggested that infiltration had been present for 10 years. Examination showed a small but well-nourished man who shaved little and had an unbroken voice; his pubic hair and external genitalia were normally developed.

Investigation.—Haemoglobin 6·9 g/100 ml; M.C.H.C. 27%; P.C.V. 25%; film, hypochromia with occasional macrocytes; bone marrow, normoblastic haemopoiesis; serum iron 60 μg/100 ml; serum vitamin B_{12} 245 pg/ml. Iron intake was satisfactory in terms of both food and iron preparations: iron loss seemed unlikely since only one out of 10 stool specimens was positive for occult blood. Faecal fat excretion 7·6 g/24 hours; prothrombin to 61% to 72%.

(Owren); total proteins 7·1 g/100 ml (albumin 2·5 g). Barium studies of the small bowel showed dilatation and flocculation compatible with malabsorption. Jejunal biopsy showed sub-total villous atrophy, establishing a diagnosis of idiopathic steatorrhoea (Fig. 1). Sweat sodium concentration was normal. Iron-laden macrophages were