Aspirin and Analgesic Nephropathy

A. F. MACKLON, A. W. CRAFT, MALCOLM THOMPSON, DAVID N. S. KERR

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Summary

Renal function was studied in 17 patients with rheumatoid arthritis who had each consumed between 5 and 20 kg of aspirin. After an interval of two years 14 of these patients—seven of whom had consumed a further mean of 2 kg of aspirin—had their renal function retested. No relation was found between total dose, rate, or duration of ingestion and any aspect of renal function that was studied. All patients had plasma creatinine levels within the normal range, though slight depression in creatinine clearance was not uncommon.

From this study and other published data we conclude that aspirin rarely if ever causes analgesic nephropathy when prescribed alone in doses appropriate to the treatment of rheumatoid arthritis.

Introduction

Though a few investigations have failed to show any connexion between analgesic intake and renal disease (Lawson, 1973; Waters *et al.*, 1973) most nephrologists accept analgesic nephropathy as an established entity (Abel, 1971; Burry, 1971; Clarkson and Lawrence, 1971; Gault *et al.*, 1971; Murray *et al.*, 1971; Kingsley *et al.*, 1972; Linton, 1972; Wilson, 1972; Cove-Smith and Knapp, 1973). In contrast to this near unanimity on the nature of the disease is a continuing dispute about its cause. After Spühler and Zollinger's (1953) description phenacetin emerged as the one common ingredient in the varied mixtures of analgesic, sedative, opiate, and stimulant drugs incriminated. Most workers regarded it as the major or only cause of the disease (see Lawson and Maclean, 1966; Shelley, 1967, for review). The epidemiological evidence has continued to impress some authors, who have retained the name "phenacetin" in their descriptions of the disease or recommended restrictions on the sale of the drug (Bell *et al.*, 1969; Bengsston, 1969; Raaflaub and Dubach, 1969, 1972; Koutsaimanis and de Wardener, 1970; de Wardener and Koutsaimanis, 1971; Dubach, 1971; Sanerkin, 1971).

Phenacetin is not an indispensable drug; its withdrawal from one British hospital caused no regrets (Hart *et al.*, 1970). In Sweden sales of phenacetin over the counter were banned in 1961 while aspirin and phenazone remained on free sale; the incidence of the disease fell (Bengsston, 1969; Nordenfelt, 1972). A similar decline in the incidence of analgesic nephropathy resulted from the replacement of phenacetin by other analgesics in proprietary mixtures popular in South West Scotland (Murray, 1972 a). Several other countries have restricted or discouraged the sale of phenacetin (Bishop *et al.*, 1972).

On the other hand there is a strong body of opinion that phenacetin has been singled out prematurely (Gilman, 1964; Shelley, 1967; Gault *et al.*, 1968; Prescott, 1969, 1970, 1971; Kincaid-Smith, 1970 a, b; Abel, 1971; Gault, 1972). It is rarely taken alone and many of the drugs with which it is commonly combined, or their metabolites, are nephrotoxic to some animals under some circumstances (Saker and Kincaid-Smith, 1969; Nanra and Kincaid-Smith, 1970; Calder *et al.*, 1971, 1972; Nanra *et al.*, 1971). Consequently "analgesic nephropathy" has replaced "phenacetin kidney" as the common title for the disease (*British Medical Journal*, 1965, 1970) and some workers regard other analgesics, particularly aspirin, with such grave suspicion that they call for restrictions on the sale of all common analgesics (Nanra *et al.*, 1971). This would be a much greater curtailment of personal convenience than merely the withdrawal of a single drug, however, and rigid restrictions on the sale of aspirin would be particularly troublesome to rheumatologists (Scott, 1966), who often prescribe aspirin alone in total doses of many kilograms for the treatment of rheumatoid arthritis.

We therefore looked for evidence of chronic renal disease in patients attending a rheumatology clinic who had taken large quantities of aspirin without also taking appreciable quantities of any other drugs suspected of causing renal damage. We defined "heavy aspirin consumption" as a total intake of 5 kg or more since the patients in three reported series who developed analgesic nephropathy from aspirin-phenacetin mixtures had typically consumed at least this amount of aspirin (Gault *et al.*, 1968; range 3-27 kg, mean 8 kg; Bell *et al.*, 1969; range 2-12 kg, mean 6 kg; Murray *et al.*, 1971; range 2-69 kg, mean 17 kg).

Patients and Methods

All patients attending the rheumatology clinic and seen by two of us (A.F.M. and A.W.C.) were questioned about drug consumption and their answers were checked against the case notes and information from their family doctor. Seventeen patients, 15 women and two men, all with classical rheumatoid arthritis by American Rheumatism Association criteria (Ropes *et al.*, 1959), had taken more than 5 kg of aspirin and all were investigated since none had any appreciable intake of other potentially nephrotoxic drugs.

Since we intended to follow this group of patients we performed only those tests which could be carried out without discomfort or hospital admission. In every patient plasma urea, plasma creatinine, and 24-hour creatinine clearance were measured by standard AutoAnalyzer techniques. Proteinuria was sought by Albustix and white cell excretion rate in a fresh four-hour non-catheter urine sample concentrated by centrifugation was counted in a Fuchs-Rosenthal chamber. Intravenous pyelography was performed in five patients. Fourteen patients were reinvestigated after two years, during which seven of them had consumed an average of 2 kg of additional aspirin.

Results

Details of age, drug consumption, blood pressure, and renal function tests are shown in table I. Creatinine clearance was corrected for surface area and then converted into a percentage of the mean normal for the patients' age, estimated from the collected data of Wesson (1969). Among the original 17 patients correlations were sought between the plasma creatinine and the

Department of Rheumatology, Royal Victoria Infirmary, Newcastle upon Tyne

A. F. MACKLON, M.B., B.S., Research Fellow (Present appointment: Registrar, Department of Medicine, Royal Victoria Infirmary)
A. W. CRAFT, M.B., M.R.C.P., Senior House Officer (Present appointment: Registrar, Department of Child Health, Royal Victoria Infirmary)
MALCOLM THOMPSON, M.D., F.R.C.P., Consultant Rheumatologist

Department of Medicine, University of Newcastle upon Tyne

DAVID N. S. KERR, M.Sc., F.R.C.P., Professor

TABLE I—Aspirin Consumption and Results of Renal Function Tests in 17 Patients with Rheumatoid Arthritis

Case No.	Age (yr)	Total Dose of Aspirin (kg)	Duration of Consumption (yr)	Overall Rate of Consumption (g/Day)	Blood Pressure (mm Hg)		Plasma Creatinine (mg/100 ml)	Corrected Creatinine Clearance (ml/min/1.73 m ²)	W.B.C. Excretion Rate ($\times 10^3$ /hr)
					Systolic	Diastolic			
1	42	7.0	4	4.8	130	80	1.0	82	45
2	70	7.0	8	2.4	150	85	0.9	64	475
3	62	7.2	9	2.2	170	100	0.95	68	149
4	56	7.6	9	2.3	140	90	1.2	61	38
5	34	8.0	6	2.7	130	80	0.6	100	230
6*	54	8.3	6	3.8	130	80	0.85	106	42
7	50	8.7	10	2.4	110	60	0.7	111	101
8	69	10.0	5	5.5	165	90	0.8	119	38
9	67	10.4	7	4.1	140	95	0.9	104	20
10	60	11.4	7	4.5	150	90	0.9	40	210
11	26	11.6	14	2.3	120	75	0.6	124	24
12	47	12.2	15	2.2	140	90	0.6	57	189
13*	55	12.2	7	4.8	130	90	1.2	55	53
14	62	13.0	20	1.8	190	130	0.8	74	182
15	65	14.8	8	5.1	180	110	1.0	71	1,340
16	41	15.7	12	3.6	120	85	0.5	113	364
17	68	19.2	19	2.8	140	80	0.9	75	134

*Male patients.

endogenous creatinine clearance—uncorrected, corrected for surface area, and expressed as an age-related percentage—on the one hand and the total dose, period of ingestion, and average rate of ingestion of aspirin on the other. None of the correlations was significant ($P > 0.1$ in all cases; table II).

The results of the renal function tests of those patients who were investigated on two occasions are shown in table III. They were divided into two groups—those who had continued taking aspirin and those who had not. In each group the plasma creatinine and creatinine clearance results (uncorrected) were compared within the group, using a paired *t* test. The change within one group was then compared with the change in the other group, using a *t* test (table IV). There were no significant differences within the groups or between groups.

TABLE II—Correlation between Aspirin Intake and Renal Function. Results expressed as Correlation Coefficients

	Plasma Creatinine	Creatinine Clearance		
		Uncorrected	Corrected	Age-related
Total dose	-0.154	-0.036	-0.039	-0.004
Duration	-0.270	-0.064	-0.060	-0.070
Average dose	+0.246	+0.080	+0.048	+0.134

The skew distribution of the white cell excretion rates rendered them unsuitable for a *t* test so a non-parametric analysis was used. A Wilcoxon matched-pairs signed rank test was used to compare the changes in leucocyturia within each group. No significant change was found (continued aspirin,

TABLE IV—Analysis of Changes in Renal Function of Two Groups of Patient after Two Years

	<i>t</i> -Test		P
	Within-Group Comparison	Between-Group Comparison	
Plasma creatinine:			
Patients who continued aspirin ..	1.513	} 0.194	>0.8
Patients who discontinued aspirin ..	1.759		
Uncorrected creatinine clearance:			
Patients who continued aspirin ..	0.093	} 0.049	>0.8
Patients who discontinued aspirin ..	0.094		

T = 8; discontinued aspirin, T = 4; $P > 0.1$). A Mann-Whitney U test was used to compare the groups and again there was no significant difference ($U = 23$; $P > 0.3$).

None of our patients had a history of renal colic. None had more than a trace of proteinuria. Three had white cell excretion rates above the upper limit of normal suggested by Little (1962) of 574,000 per hour. White cell excretion rate did not correlate with other tests of renal function or aspirin intake. The results of the five intravenous pyelograms (in cases 2, 4, 6, 10, and 13) were all normal.

Discussion

None of our patients had clinically important impairment of renal function and there was no significant change in function during the two years of continuing aspirin ingestion. The slight reductions in creatinine clearance, even after correction for size

TABLE III—Aspirin Consumption and Results of Renal Function Tests before and after a Two-year Interval in 14 Patients with Rheumatoid Arthritis

Case No.	Aspirin Consumption (kg)		Extra Aspirin Between Tests (kg)	Plasma Creatinine (mg/100 ml)		Uncorrected Creatinine Clearance (ml/min)		W.B.C. Excretion (× 10 ³ /hr)	
	1st Test	2nd Test		1st Test	2nd Test	1st Test	2nd Test	1st Test	2nd Test
Patients who Continued to take Aspirin during Interval									
2	5.5	7.0	1.5	1.15	0.9	49	59	120	475
5	6.0	8.0	2.0	0.7	0.6	110	109	570	230
11	9.6	11.6	2.0	0.7	0.6	103	115	103	24
12	10.5	12.2	1.7	0.8	0.9	64	54	50	189
13*	8.7	12.2	3.5	1.15	1.2	104	61	71	53
15	12.8	14.8	2.0	1.25	1.0	52	66	720	1,340
17	17.0	19.2	2.2	0.9	0.9	56	78	21	134
Patients who did not continue to take Aspirin during Interval									
1	7.0	7.0	Nil	1.0	0.8	78	92	45	74
3	7.2	7.2	Nil	0.95	0.8	55	51	149	738
4	7.6	7.6	Nil	1.2	0.9	58	76	38	729
6*	8.3	8.3	Nil	0.85	0.9	103	75	42	32
8	10.0	10.0	Nil	0.8	0.7	120	115	38	132
10	11.4	11.4	Nil	0.9	0.85	37	43	210	285
14	13.0	13.0	Nil	0.8	0.9	72	70	182	117

*Male patients.

and age, were not unexpected. Burry (1970) found a creatinine clearance below 80 ml/min in 49 out of 97 unselected patients with rheumatoid arthritis and he showed a correlation between reduction in glomerular filtration rate and severity of articular erosions on radiographs. All our patients had radiological evidence of severe rheumatoid arthritis. There is no accepted renal lesion of rheumatoid arthritis, however, so these observed depressions of filtration rate may reflect early involvement of the kidneys by amyloidosis, glomerulonephritis, or analgesic nephropathy. None of our patients had features of amyloidosis or glomerulonephritis but these cannot be totally excluded without renal biopsy, which in our cases was not justified. Equally, we cannot exclude the possibility that some had very early analgesic nephropathy. Nevertheless, our inability to show any correlation between aspirin dose and renal function and the absence of any significant decline in function with continuing aspirin intake are against this suggestion. Bulger *et al.* (1968) studied 42 patients who had taken an average of 8.4 kg of aspirin without phenacetin (except in two patients) and found some correlation between depression of creatinine clearance and total dose of aspirin. Their clearances were not corrected for age, however, and the patients with depressed renal function were slightly older, had a longer duration of arthritis, and a stronger history of receiving other nephrotoxic drugs (notably gold salts) than those with normal renal function. Moreover, none of their patients had a creatinine clearance below 50 ml/min in spite of an aspirin intake of up to 40 kg.

The obvious conclusion from our study and that of Bulger *et al.* (1968) is that aspirin given alone in the doses commonly prescribed for rheumatoid arthritis rarely if ever causes serious renal disease. There is, however, an objection to such point-in-time studies. Possibly analgesic nephropathy affects only a small minority of the population who are unduly sensitive because of slow hepatic inactivation of the causative drug or some other factor. Such patients would be eliminated from the rheumatology clinic by early death from analgesic nephropathy and would be under-represented in a cross sectional study. As a partial check on the possibility that Newcastle patients are dying early from aspirin nephropathy we examined the case notes of all patients who had died in the Royal Victoria Infirmary in the last five years with a clinical or pathological diagnosis of both rheumatoid arthritis and renal failure. There is a high probability that any patient attending our rheumatology clinic who had died in hospital would have done so in the Royal Victoria Infirmary. Of the six patients who met these criteria only one had analgesic nephropathy; he had consumed between 3 and 6 kg of phenacetin as Sonalgin. One patient had died in uraemia without a primary diagnosis. There was no necropsy, but there was no history of heavy analgesic intake. The four other patients had firm pathological evidence of unrelated renal disease. Ideally this evidence for the lack of aspirin nephrotoxicity should be tested by a prospective trial of aspirin takers as planned in New Zealand (Wigley, 1971). Decades of observation will probably be needed, however, to provide a firm answer in a population of 3 million.

It would be unsafe to extrapolate our results to patients taking aspirin in drug mixtures, in climates hotter than those of England or the State of Washington (Bulger *et al.*, 1968), or in the very high dosage (up to 30 g/day) sometimes adopted by drug habitues (Kincaid-Smith *et al.*, 1971). So far as they go, however, our results contradict the growing belief that aspirin is the most nephrotoxic of the common analgesics. The following evidence has been given for this belief.

Firstly, animal studies, reviewed by Nanra *et al.* (1971), which suggested that aspirin, alone or in combination with phenacetin, is more nephrotoxic than phenacetin alone. Though important these studies can be applied to man only with great reserve.

Secondly, the occurrence of analgesic nephropathy in seven patients who gave no history of taking phenacetin and whose major drug consumption was of aspirin (Harvald, 1963; Lawson and MacLean, 1966; Olafsson *et al.*, 1966; Prescott, 1969;

Murray *et al.*, 1971). An eighth case was withdrawn after the discovery of methaemoglobinemia (A. A. H. Lawson, personal communication to J. T. Scott). These cases have to be set against the massive international consumption of aspirin, which, unlike phenacetin, is often prescribed alone; against the far more numerous cases associated with phenacetin; and against the formidable difficulty of excluding forgotten drug consumption. It must be admitted, however, that drug abusers usually choose drug mixtures (Murray, 1972 b).

Thirdly, the high incidence of papillary necrosis at necropsy in rheumatoid patients at certain centres. Papillary necrosis was found in 17 consecutive necropsies by Nanra and colleagues (1970, 1971) and aspirin was blamed by implication. The drug histories of these 17 patients have never been published, however, and the high incidence of papillary necrosis has been reported only from centres where aspirin-phenacetin mixtures have been popular (Clausen and Pedersen, 1961; Lawson and MacLean, 1966; Nanra *et al.*, 1971). The disease is relatively rare in Newcastle and the State of Washington (Bulger *et al.*, 1968) where rheumatologists have never been in the habit of prescribing such mixtures. The differences may have other explanations but climate is unlikely to enter into a contrast between Edinburgh and Newcastle.

Lastly, relapses in patients with analgesic nephropathy when they consumed aspirin-containing mixtures without phenacetin (Kincaid-Smith *et al.*, 1971; Murray *et al.*, 1971). Such reports are not easy to evaluate. In all the six cases reported in detail by Kincaid-Smith *et al.* (1971) the deterioration in renal function was associated with urinary obstruction by sloughed papillae; this might have been a sign of renewed activity of the disease but it is also an accident that could have occurred in the absence of analgesic intake.

We conclude that the case against aspirin is very weak and that there is no need to restrict its sale on the basis of nephrotoxicity. Is there indeed any need to restrict the sale of any analgesic? The studies of Sørensen (1966), Lawson (1973), and Waters *et al.* (1973) which showed a low prevalence of renal disease in subjects who had consumed several kilograms of analgesic mixtures—usually containing both aspirin and phenacetin—suggest that there is not. These mixtures, however, do play a key role in analgesic abuse (Murray and Smith, 1972), possibly because of the uplift provided by other ingredients such as caffeine. It would seem reasonable to provide at least a "Government health warning" on each packet (Bishop *et al.*, 1972).

We still feel that the most likely culprit in analgesic nephropathy is phenacetin. Since it is so rarely consumed alone direct prospective studies of its role are impracticable and it must be judged on indirect evidence. In view of the encouraging results from Scandinavia (Nordenfelt, 1972) and South-west Scotland (Murray, 1972 a) a national experiment on a larger scale on its restriction seems to us justifiable and we would welcome moves to limit its sale to "prescription only" in Britain, provided we can first arrange adequate data collection to ensure that the experiment really gives an answer.

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Ventilation-Perfusion Lung Scanning for Pulmonary Emboli

OLWEN WILLIAMS, JAMES LYALL, MARIAN VERNON, D. N. CROFT

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Summary

The conventional method of lung scanning detects defects of pulmonary artery perfusion. False positive results occur because regions of hypoventilation, such as are present in obstructive airways disease, also cause defects of perfusion. The converse is not true, however, as defects of perfusion continue to be ventilated. Thus in pulmonary embolism ventilation-perfusion discrepancy (normal ventilation and impaired perfusion) occurs.

We have assessed the clinical value of this discrepancy. Out of 18 patients with ventilation-perfusion discrepancy 14 had a final diagnosis of pulmonary emboli, whereas in none of the 34 patients without the discrepancy was this final diagnosis made. We conclude that combined ventilation-perfusion lung scanning distinguishes pulmonary emboli from other lung conditions such as asthma and bronchitis which cause impaired pulmonary perfusion. The false positive rate was only 4% overall and 7.7% in patients with perfusion defects.

Introduction

Lung perfusion scanning is of value in the diagnosis of pulmonary embolism and is a simple and safe screening procedure.

Interpretation of lung scans, however, creates a problem in some patients because abnormal perfusion is not peculiar to pulmonary embolism but can appear in a variety of lung diseases, including bronchitis and asthma (Lopez-Majano *et al.*, 1966; Mishkin and Wagner, 1968). There is a need for a reliable method of diagnosing emboli in patients with asthma, bronchitis, and other conditions with impaired pulmonary perfusion.

Animal studies show that a reduction in lung ventilation such as occurs in man with chronic obstructive airways diseases leads rapidly to a corresponding reduction in lung perfusion. On the other hand, reduction in lung perfusion, as in pulmonary embolism, does not lead to a correspondingly marked and sustained reduction in ventilation. With this in mind several workers have suggested that combined ventilation-perfusion lung scans might aid more specific diagnosis of pulmonary embolism (De Nardo *et al.*, 1970; Farmelant and Trainor, 1971). Their studies were made on a total of 57 patients and the results justified a clinical trial with a larger series. We have therefore performed 100 combined ventilation-perfusion lung scans on patients with pulmonary problems and have assessed the results in relation to the final diagnosis.

Patients and Methods

The patients had been routinely referred by clinicians in the hospital. Both scans were performed at the same session, ventilation scanning always preceding perfusion scanning. The combined scans took 20 minutes. Perfusion images were obtained by using macroaggregated albumin (MAA) labelled with ^{99m}Tc. Gaseous ¹³³Xe was used for ventilation imaging. All the images were recorded on Polaroid film by means of a Nuclear Enterprises mark III gamma camera with a diverg-

Isotope Department, St. Thomas's Hospital, London SE1 7EH
 OLWEN WILLIAMS, M.Sc., M.R.C.P., Senior Medical Registrar
 JAMES LYALL, M.Sc., M.R.C.P., Lecturer in Medicine
 MARIAN VERNON, B.Sc., Physicist
 D. N. CROFT, D.M., M.R.C.P., Consultant Physician