PART XXXV

GUEST LECTURE

Chairmen:  J Botella
           I Bcaus
ANALGESIC NEPHROPATHY

U C Dubach

Medizinische Universitäts-Poliklinik, Kantonsspital, Basle, Switzerland

Introduction

Spuhler and Zollinger [1] reported in 1950 a group of patients with the clinical-pathological syndrome of interstitial nephritis and suggested that these patients' renal disease might be caused by excessive ingestion of analgesic drugs. They noted that phenacetin was a common ingredient of the mixtures taken by these patients and they raised the possibility that phenacetin might be the agent responsible for this nephropathy. These initial observations stimulated numerous studies, symposia, controversies and, finally, public health regulatory measures in many nations throughout the world [2–8]. Although much new information and many new insights and details of the disease have been provided by the published information on this subject, there remain still many unanswered questions.

What is analgesic nephropathy?

Analgesic nephropathy is a chronic tubulo-interstitial nephropathy seen in patients who have consumed large quantities of compound analgesic mixtures, usually containing phenacetin, often plus salicylate or chemically related substances, such as paracetamol. Heavy drug consumers are more likely to manifest renal insufficiency than lower dose consumers. The disease progresses slowly and is commonly asymptomatic until severe renal failure occurs. Renal damage is often discovered by laboratory tests revealing azotaemia or impaired renal concentrating capacity. Papillary necrosis and associated interstitial nephritis are characteristic, but only occasionally may this clinically manifest itself by the urinary passage of necrotic tissue or following intravenous urography. The condition is seen mainly in women who take these drugs. They ingest these medications for headaches and for other conditions; they show a relatively high incidence of gastrointestinal disorders, anaemia, ischaemic heart disease and psychiatric disturbances. Through the years this has led to the
description of a so-called analgesic syndrome. If patients with this condition can be convinced to stop the ingestion of compound analgesic mixtures, the progression of the kidney deterioration may be retarded, arrested or even reversed.

What are the more recent and important developments made in recent years?

Pathogenesis [5] Anti-inflammatory drugs are thought to reduce renal blood flow and glomerular filtration rate as well as sodium and water excretion through inhibition of prostaglandin synthesis. In addition, medullary ischaemia by reduction of blood flow through the vasa recta has been suggested. Ischaemic papillary necrosis is thought to be the result of inhibition of synthesis of prostaglandin E, a potent medullary vasodilator. An additional factor is that long-term heavy consumption of acidic anti-inflammatory drugs causes toxic tubular injury. Sclerosis of small vessels in the medulla is a recent discovery, which may be an additional factor in papillary necrosis. Whereas the proximal tubule has a remarkable power of regeneration, damage to the loops of Henle, to the medullary tubules and collecting ducts may lead early to irreversible papillary necrosis.

Biochemical events that could lead to papillary necrosis are thought to be as follows [5,6]: paracetamol undergoes glomerular filtration and is passively reabsorbed by the tubules. It is concentrated in the medulla during anti-diuresis, achieving a concentration of about five to seven times that of the cortex or plasma. However, phenacetin does not reach a concentration in the medulla greater than that in the cortex or in plasma. Aspirin and salicylate undergo proximal tubular secretion. Both are reabsorbed by the distal nephron and become concentrated in the medulla during anti-diuresis. Paracetamol, aspirin and salicylate in addition are distributed within the intracellular compartment of the medullary region. Salicylate depletes cellular glutathione in the kidney. Paracetamol becomes metabolized to a highly reactive intermediate by an NADPH-dependent and -independent mechanism; this intermediate(s) binds covalently to tissue proteins, when glutathione concentrations are reduced [7]. In addition, aspirin directly acetylates kidney proteins and may be nephrotoxic. Thus, combination of salicylate and paracetamol may be synergistic in increasing covalent binding, which, through daily repetition, may produce cell death and eventually the full picture of analgesic nephropathy.

A curious expansion of analgesic nephropathy to an analgesic syndrome was proposed in 1978 [5] which includes gastrointestinal, haematological, cardiovascular, psychological and psychiatric, as well as pregnancy and gonadal manifestations, where premature ageing may also be a feature. Its proposition may help to give new impetus to clinical recognition of analgesic nephropathy and to broaden basic research interests.

Important questions and issues still unsolved

This meeting is especially interested in the importance of analgesic nephropathy as a cause of chronic renal failure and of end-stage renal disease. Furthermore,
the question of the agent responsible for nephrotoxicity remains under debate. The question of malignancy through long-term ingestion of analgesics has been recognized [9-11]. Whatever the specific cause of analgesic nephropathy, retrospective and prospective epidemiological studies from Switzerland and other countries indicate strongly that patients with analgesic nephropathy may have a markedly higher risk of developing transitional cell tumours of the urinary tract, especially of the renal pelvis and the ureter as compared to a control population (in 8%). The basis for the production of urinary tract tumours is well established by experimental ingestion of aniline derivatives: this additional potential risk from analgesic overuse cannot be ignored and makes mandatory eventual public health measures in the various countries.

**The importance of analgesic nephropathy as a cause of chronic renal failure**

There exist very few prospective longitudinal studies in regard to the unravelling of the question “how analgesic nephropathy develops over time as an important cause of chronic renal failure?” [12-14]. But in the last two decades it could be shown that a significant fraction of patients with chronic renal failure, not only in Switzerland, but also in Australia, Canada, South Africa, Belgium, Denmark and other nations are due to uncontrolled ingestion of analgesics [5]. Unexplained today, are the large variations in prevalence of analgesic nephropathy from one country to the next, even in the same continent and from one region to the other in the same country. In the United States up to 1968, analgesic nephropathy was considered to be extremely uncommon, whereas in Canada many cases were reported comprising 25 per cent of patients with end-stage renal disease. In 1969, however, several patients were reported from Atlanta and a study from Philadelphia performed from 1968 to 1972 suggested that 20 per cent of cases of interstitial nephritis with renal insufficiency might be sick from analgesic nephropathy, a percentage which comprised five to seven per cent of patients with chronic renal failure [5]. Only a few years later, a survey of 30 renal disease centres in the United States indicated that analgesic nephropathy occurred throughout this country with nine or more new cases being diagnosed a year in over half of the centres, which included a mean of 20 per cent of the new cases of interstitial nephritis [14].

The prevalence in Philadelphia, however, did not reach the striking numbers in Switzerland or Australia. In the south eastern region of the United States nearly one-third of new cases of renal disease were diagnosed as analgesic nephropathy. Obviously, the variations in apparent prevalence of analgesic nephropathy relate to differences in regional consumption of analgesic drugs both quantitatively and qualitatively, a fact that has also been shown for Belgium.

**Epidemiological study in Switzerland 1968–1984**

There have been several retrospective, or cross-sectional studies conducted up to 1968 in Switzerland [13,15-17]. These studies mainly were based on history taking. With the help of WHO, the Swiss National Foundation for Scientific
Research and with the aid of the pharmaceutical industry we designed a longitudinal, prospective study on abuse of analgesics containing phenacetin based on urinary controls for analgesic intake lasting from 1968 to 1984. The results of this study have been partially published [13].

The study group of 623 working women 30 to 49 years old with objective evidence of intake of phenacetin-containing analgesics and a matched control group of 621 women without such intake in 1968, living in the north western part of Switzerland and working in 88 enterprises were assessed six times from 1969 to 1978 for laboratory evidence of urinary tract disorders. The two groups did not differ in development of bacteriuria, haematuria or proteinuria after a decade; however, a low urinary specific gravity (study group versus control group, 23 versus 7%) and a raised serum creatinine (6.7 versus 0.9%) were significantly more frequent in the study group (p<0.001).

There was a total of 52 deaths. A life-table analysis adjusted for year of birth, length of follow-up and cigarette smoking was performed. The control group was compared with the total study group, which was broken down for the purpose of analysis in a so-called high-NAPAP (N-acetyl-p-aminophenol, the main metabolite of phenacetin) subgroup and a low-NAPAP subgroup, obtained by averaging the NAPAP concentrations in six urine specimens collected from each subject at the beginning of the study.

The specific causes for death were as follows: renal or urogenital disorders, 12; cancer, 26; cardiovascular diseases, 18; and miscellaneous or unknown causes, 5.

If multiple causes of death were listed for a particular woman, she was counted once for each cause of death. Therefore, the total number of deaths ascribed to the four specific causes is higher than the total number. A life-table analysis adjusted for length of follow-up for overall mortality and for specific causes of death revealed the death rate over the years, which was similar in the high- and low-NAPAP subgroups (6.5 versus 6.9%), but was lower in the control group (2.3%). The relative risk of death in the entire study group in comparison with the control group was 2.7 (p<0.001). The findings for cause-specific mortality made it apparent that for the category of renal or urogenital causes, the study group as compared with the control group, had a relative risk of 4.3 (p=0.033); the high-NAPAP subgroup had a relative risk of 5.9 (p=0.006), and the low-NAPAP subgroup had a relative risk of 1.6 (p not significant).

For mortality due to cancer there was no significant difference between the total study group and the control group (relative risk=2.0, p not significant). Similarly, there was no significant difference in cancer mortality between the high-NAPAP subgroup and the control group (relative risk = 1.7), although significant differences were found between the low-NAPAP subgroup and the control group (relative risk = 2.4, p=0.049). There was one death only with cancer of the bladder in 1970 in the study group. In general the study group had more deaths than expected, while the control group had fewer deaths. To our surprise, no differences were found in the rates for overall mortality or cardiovascular mortality between the high-NAPAP and low-NAPAP study subgroups. No explanation is possible at the present time. However, for death
due to renal or urogenital causes the relative risk was 5.9 in the high-NAPAP subgroup, as compared with the control group (p=0.006), and 1.6 in the low-
NAPAP subgroup, as compared with the controls (p not significant).

Our study does not establish a causal relationship between ingestion of phenacetin and subsequent development of renal disorders. The results indicate
that heavy users of analgesic mixtures over 10 years have a higher incidence of both abnormal kidney function and kidney-related mortality than to casual
users or non-users, but that the absolute incidence over 10 years remains rela-
tively small even among heavy users. In addition we have suggestive evidence
that an overall protective effect of salicylates on mortality may become evident
in the follow-up of the population over the years to come [13].

The results substantiate our clinical impression that long-standing analgesic
abuse of at least 10 years’ duration with drugs containing phenacetin is damaging
to the urinary system, sometimes fatally [13]. The question remains, however,
whether abuse of analgesics containing phenacetin causes renal damage, or
whether the subjects who take phenacetin-containing pills do so because of
symptoms that indicate an underlying propensity to renal damage.

The importance of analgesic nephropathy as a cause of end-stage renal disease
must be considered separately, because data suggest that the incidence of anal-
gesic nephropathy as a fraction of the general renal disease population may
be higher than the incidence in patients with end-stage renal disease [18].
In areas where analgesic consumption is extremely high, as for instance in
Switzerland and Belgium, analgesic nephropathy is still responsible for a high
proportion of patients with end-stage renal failure. On the other hand in areas
where compound analgesic overdose is not widespread, as for instance in France
and Italy, the incidence of analgesic nephropathy in dialysis centres is very
low [18]. Obviously, the interpretation of these observations to a general
conclusion, that analgesic nephropathy may not be an important cause of renal
failure or renal disease in general, cannot be drawn. The reasons are the follow-
ing: 1) compound analgesic consumption habits are low in France and Italy;
2) analgesic nephropathy is a very slowly progressive disease, and many patients
may therefore not develop end-stage renal disease or may die of non-renal
causes; 3) the latter possibility is supported by our observations that patients
with analgesic nephropathy had an incidence of ischaemic heart disease that
is significantly higher than that in the general population [3]; 4) finally, there
may have been an important impact of the widespread publicity in regard to
the toxicity of analgesic compounds over the last two decades with a consequent
decrease in the heavy consumption of analgesics.

The agents responsible for nephrotoxicity remains the most controversial
question and is still inconclusively resolved. Prescott [20] has given an overview
to this problem and his paper remains the most important source for the evalua-
tion of this question.

From an epidemiological and clinical perspective the following observations
are of importance: 1) there are no or very few patients reported with chronic
analgesic nephropathy who have ingested only a single drug; 2) the greatest
number of cases has been associated with combinations of phenacetin and
aspirin often combined with caffeine, codeine or pyrazolones, but there are also examples of analgesic nephropathy with different combinations of analgesics. It may be postulated that the mechanisms of renal damage may be the same in all cases, since mixtures may contain one agent with an action similar to aspirin and another agent with an action simulating phenacetin; 3) reports of regulatory removal of phenacetin from analgesic mixtures show a decrease of analgesic nephropathy in Canada, not, however, appreciably in Australia. An explanation for this discrepancy is not available to date, but it should be noted that analgesic mixtures with aspirin and acetaminophene were still available in Australia.

Animals models of analgesic nephropathy simulating the human conditions have been very difficult to produce [21]. Nevertheless, the available data suggest that renal papillary necrosis is produced more readily and is more severe with chronic treatment with mixtures of analgesics than with a single drug alone. Metabolites of both drugs are concentrated in the kidney, especially in the renal papilla, where the site of the presumed primary lesion of analgesic nephropathy lies. There is a biochemical basis for a synergistic action of phenacetin and aspirin in producing tissue damage [22]. Clinical and experimental evidence strongly suggest that combinations of drugs rather than a single agent may be responsible for producing analgesic nephropathy. It is therefore understandable that after Canada, Australia has introduced in 1984 a law that over-the-counter analgesics can only be sold as single-ingredient preparations in order to avoid hopefully analgesic nephropathy and eventually end-stage renal failure.

In an effort to resolve some of the questions about analgesic associated kidney disease, the National Institutes of Health held a Consensus Development Conference on Analgesic-associated Kidney Disease in February 1984. After scientific presentation by experts from all over the world in regard to available data about the problem, the Consensus Panel, including representatives of the fields of nephrology, pathology, internal medicine, family medicine, pharmacology, biostatistics, epidemiology, and the general public, agreed on the following general statement [23]:

"Considerable evidence indicates that combinations of antipyretic analgesics, taken in large doses over a long period of time, can cause kidney disease and chronic renal failure. Persons so exposed may also be more susceptible to the subsequent development of uroepithelial tumours. In contrast, there is little evidence that preparations containing a single analgesic agent are similarly harmful."

"The occurrence of analgesic-associated nephropathy shows striking geographic differences. Such differences may be related, at least in part, to regional variations in the habitual consumption of antipyretic-analgesic mixtures."

"The pathogenesis of the condition is uncertain, but may be a direct cytotoxic effect on the renal papilla, perhaps enhanced by ischaemia."

"The sustained use of mixtures of antipyretic analgesics in large doses is not advisable. Serious consideration should be given to limiting over-the-counter products to those containing a single antipyretic-analgesic agent."
References

2. Ringoir S. Thérapie 1974; 29: 507
10. Landmann-Kolbert Ch, Rutishauser G, Dubach UC. Urologe 1975; 14: 75
20. Prescott LF. Drugs 1982; 23: 75