

Statement

Analgesic nephropathy

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More than 40 years after the first publication, analgesic nephropathy still remains a controversial issue. During the 60s and 70s, phenacetin was singled out as the nephrotoxic culprit. Some countries reacted early by banning all phenacetin-containing products from the 'over-the-counter' market (Sweden, 1961; Canada, 1973). In other countries phenacetin was removed from analgesic mixtures by the pharmaceutical industry long before legislative measures were taken (Switzerland, Germany, Belgium). By 1996, phenacetin use had ceased for more than 10 years in Western Europe. Analgesic nephropathy however, remains a common disease in several areas. Although a decrease in the national incidence has been observed in several West European countries, in Eastern Europe analgesic nephropathy has gained recognition. Unexpectedly high incidences were recently measured in e.g. Czech and Slovak Republics [1].

During the last decade, scientists demonstrated the renal risk of other analgesic mixtures not containing phenacetin and many clinicians diagnosed analgesic nephropathy in patients who never consumed phenacetin. The recent publications investigating the nephrotoxic potential of paracetamol [2], the recommendations of the National Kidney Foundation of the United States [3] and the recent legislative actions in Belgium focused on all analgesic mixtures revived the discussion concerning the nephrotoxicity of the many analgesic combinations currently available.

The fact that analgesic nephropathy is one of the few preventable renal diseases, makes worthy the investment to establish clear statements regarding this issue. The statements presented here deal with and are limited to 'classic' analgesic nephropathy. This particular form of renal disease is characterized by renal papillary necrosis and chronic interstitial nephritis associated with prolonged and excessive consumption of analgesic mixtures containing addictive substances.

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NSAID-related renal toxicity, mainly presented as acute renal failure and serious fluid and electrolyte disorders, is excluded from the discussion.

The following statements represent our opinion concerning the current status of analgesic nephropathy:

1. Attempts to evaluate the nephrotoxicity of different analgesics using **experimental animal models** have yielded conflicting results. Experimental analgesic nephropathy and renal papillary necrosis can be induced in animals with different kinds of analgesics. Moreover, the experimental data provide a biochemical and pathological basis for the enhanced renal toxicity of analgesic mixtures compared with that of single agents. The use of extremely high doses and the aggravation of the renal effects by dehydration or by introducing bacteria, however makes the extrapolation from the experimental data to analgesic nephropathy observed in humans difficult [4].
2. In humans, there is overwhelming clinical **evidence linking analgesic abuse with a particular form of chronic renal damage** evolving towards end-stage renal failure. The association between analgesic consumption and the development of renal impairment was further investigated in the case-control studies published during the last decade [2,5,6,7]. The strongest proof of causality came from the two prospective studies published following the renal function of healthy abusers and controls during a period of several years [8,9].
3. The long-standing **excessive use** of analgesics observed in patients with analgesic nephropathy is **concentrated on combination analgesics**. Abusers prefer analgesic mixtures rather than single analgesics, taking these products rather than their mood-altering effects than for the relief of physical complaints. Hence, all these mixtures contain caffeine and/or codeine and it is clearly established that the addition of these substances can create a psychological dependence towards these drugs [10].
4. Analgesic nephropathy is caused by the abuse of **analgesic mixtures containing two analgesic components combined with potentially addictive substances**

- (2+ analgesics). Evidence came in the first place from the clinicians confronted with the history of abuse obtained from their patients with analgesic nephropathy. Further evidence came from the case control study of Pommer *et al.* showing an increased odds ratio for all combined analgesics but not for the single ones [6]. Moreover, Elseviers and De Broe reported that in 219 out of 226 patients with analgesic nephropathy diagnosed according to objective renal imaging criteria, the abuse was concentrated on analgesic mixtures [11].
5. Last year the ad hoc committee of the National Kidney Foundation in the US examined data available from the peer-review medical literature in forming opinions regarding analgesic nephropathy [3]. The available information, gathered from hundreds of peer-reviewed articles, suggests that habitual consumption of **both phenacetin-containing mixtures and non-phenacetin-containing mixtures is associated with analgesic nephropathy. Phenacetin can no longer be considered as the only nephrotoxic culprit in analgesic mixtures.** Clinical observations in countries where analgesics without phenacetin are on the market for a period of more than 20 years (e.g. Australia, Belgium, Germany) learned that identical renal pathology is observed in patients abusing analgesic mixtures which never contained phenacetin. The diagnostic criteria studies documented the nephrotoxicity of the combinations of salicylic acid-paracetamol, salicylic acid-pyrazolones, paracetamol-pyrazolones, and two pyrazolones [11].
 6. The problem of chronic analgesic toxicity can be prevented efficaciously by curtailing heavy consumption. That educational and voluntary restraint alike should have but little effect on analgesic abuse is understandable, even predictable, given the addictive nature of analgesic mixtures. The most rational approach to prevention of classical analgesic nephropathy is the prohibition of 'over-the-counter' sales of any analgesic mixture containing two analgesic components combined with caffeine and/or codeine. The Australian experience learned that by

limiting the 'over-the-counter' availability of analgesic mixtures, the disease almost disappeared [12].

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Editor's note

Please see also the letter to the Editor by Fox (pp. 2519-2520 in this issue).