

Iatrogenic, mainly drug-induced nephropathies

Ph. D. theses

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1. SUMMARY

The rapid rise in the prevalence of chronic renal diseases has turned one of the major healthcare problems. These diseases are hard to be diagnosed in the initial phase, they lead to an impaired quality of life, and more than 50% of the patients die of cardiovascular disease before the onset of renal impairment. Therefore, their prevention is of great importance.

I have chosen iatrogenic renal diseases as the topic of my doctoral theses. In my work, I have focused mainly on the role of drugs, paramedical products, herb extracts and contrast materials.

Out of the drug-induced nephropathies, I have concentrated on analgesic nephropathy induced by the use of combined analgesics. The main cause for this was, that according to a report sent in the first half of the 1990's, this disease was supposed to be rare in Hungary. On the other hand, by the start of my work, many phenacetin-containing drugs were sold in an over-the-counter manner. In other countries with similar marketing strategies, a marked prevalence of analgesic nephropathy has been reported. Thus, we have conducted a national survey with support of the Hungarian Society of Nephrology to evaluate the prevalence of analgesic nephropathy.

According to our results, there was a 14.8% prevalence of analgesic nephropathy in patients with end-stage renal diseases with unknown diagnosis in the background of renal failure. Majority of the patients were females, who have consumed phenacetin-containing analgesic mixtures due to diseases leading to chronic pain, mainly headache. The prevalence of myocardial infarction was significantly higher in patients consuming combined analgesics than in those not taking this type of drugs.

We have also evaluated the psychiatric personality characteristics of patients with analgesic nephropathy, to screen for alterations predisposing to the abuse of analgesics. According to our results, these patients show a higher rate of unrecognized and untreated depression than other patients with renal disease. The patients received mainly psychofarmacos (sedatives and anxiolytics), that did not improve the abuse of analgesics.

Finally, we demonstrate the potential nephrotoxic effect of herb products by reporting the case of a woman consuming Guarana extract presenting with a renal failure.

With my work, I would like to draw attention to the frequency and the prevention of iatrogenic renal diseases.

2. INTRODUCTION

A fast rise in the number of patients with renal diseases has been observed in the last decade. The renal damage developed in relation with medical activity is called iatrogenic renal damage. In the background of acute iatrogenic renal damage we may find diagnostic procedures (e.g. abdominal angiography), numerous medications (e.g. non-steroid anti-inflammatory drugs – NSAID –, angiotensin-converting enzyme inhibitors – ACEI –, antibiotics, analgesics, diuretics), diagnostics (e.g. X-ray contrast materials) and therapeutic interventions (e.g. methods of interventional radiology, vascular operations. Iatrogenic renal damage may develop in 2-5% of patients treated for another disease and in up to 23% of patients treated on an Intensive Care Unit. The rise in chronic renal failure may be accounted for by the rise in life expectancy, the rise in the prevalence of diabetes mellitus and hypertension as well as iatrogenic damages due to medical interventions. As a consequence of a much wider availability of diagnostic and therapeutic procedures, renal damage may develop, that may be preventable. If we take the high cost of renal replacement therapies into consideration, then besides the frequent diseases that predispose to end-stage renal failure (diabetes mellitus, hypertension, polycystic kidney diseases, chronic glomerulonephritis etc.), also iatrogenic effects, especially those caused by drugs (analgesic nephropathy etc.), paramedical preparations, herb extracts and radiocontrast materials deserve special attention. Recently, in the last years it has been recognized that in patients with chronic renal failure gadolinium may lead to a preventable disease, the so-called nephrogenic systemic fibrosis (NSF).

3. HYPOTHESES AND AIMS

Hypotheses:

1. As a consequence of the domestic characteristics of analgesic supply (a high number of phenacetin-containing medications) and the easy availability of the drugs, it is probable, that also in Hungary a lot of patients suffer from analgesic nephropathy and a part of these patients may eventually require renal replacement therapy.
2. We assume that a part of the Hungarian patients with analgesic nephropathy present signs of an impaired personality that may predispose them to the chronic consumption of (combined) analgesics.
3. A lot of herb products are marketed in Hungary for the improvement of performance and preservation of health that may in fact have a potentially nephrotoxic effect.

Aims:

1. Measurement of the prevalence of analgesic nephropathy among patients initiating renal replacement therapy in Hungary.
2. Analysis of markers of personality among patients with analgesic nephropathy in collaboration with psychiatrists.
3. To find a subject in our nephrological medical care, whose renal disease was associated with a herbal product and present his/her case.

4. STUDY DETAILS

4.1. The prevalence of analgesic nephropathy

In 1997, we have conducted a national survey; the study was named Hungarian Analgesic Nephropathy Study (HANS). The aim was to measure the nation-wide prevalence, causes, clinical characteristics of analgesic nephropathy among patients initiating renal replacement therapy, and the composition of drugs. Without such data, we were unable to initiate the withdrawal of phenacetin from marketing, and to make a part of the analgesics prescription-bound. Only in possession of the results could we hope to protect the Hungarian society from a preventable disease.

Patients and methods

The study has been carried out according to the criteria of the earlier Belgium-centered European multicentre study, the Analgesic Nephropathy Network Europe (ANNE). Twenty-two of the eligible 52 dialysis units in Hungary have participated in the study. Over 3 years (January 1st 1995. – January 1st 1998.) all adult patients over the age of 20 years initiating dialysis have been included to study the prevalence of analgesic nephropathy in the background of the development of chronic renal failure. Dialysis units from all parts of the country – also three of the four units located at university centers – were included to make sure that our results are representative for the entire country. Large cities were represented by Budapest and three cities with 100,000 - 200,000 inhabitants, while all other units represented larger cities and rural regions. The study was initiated after the permission of the local Ethical Board and on the basis of written informed consent.

Patients with established glomerulonephritis, polycystic kidney disease, diabetic nephropathy and other systemic diseases (SLE, Henoch-Schönlein syndrome, vasculitis) or hypertensive nephrosclerosis or those with a kidney disease diagnosed upon a renal biopsy were excluded from the study. Those patients who had lacking or incomplete data or who have died prior to the collection of all required data were also excluded from the statistical analysis, i.e. only patients initiating renal replacement therapy because of an unknown kidney disease have only been enrolled into the study.

The *diagnosis of analgesic nephropathy* was established upon the criteria used in the ANNE study.

1. Medication history

We have used following methods to detect abuse of analgesics:

a) An interview based on a questionnaire including potential complaints (frequent headache and pain on menstruation, chronic joint pain, chronic inflammatory bowel diseases, or any type of long-lasting or recurring pain) and medication taking habits (type of medication, dose and duration).

b) All patients were asked to read through a booklet containing images of the package of all „suspicious” analgesic and NSAID drugs sold between 1970 and 1995, asking them to select the drugs that he/she was taking.

c) Finally, in case of suspect, when the patient himself was denying taking such medications, also relatives were asked on the medication-taking habits of the patients.

We defined chronic analgesic abuse as a regular, daily consumption of 1-25 tablets or powder containing (combined) analgesics for at least 5 years. Combined analgesics contained at least two sorts of analgesics (phenacetin/paracetamol and pyrasolon-derivatives or aspirin) and one agent inducing dependence (caffeine and/or codein).

2. Imaging techniques

Patients enrolled in the study underwent ultrasound investigation and/or a CT-scan without contrast-material. Using the criteria of the ANNE (Analgesic Nephropathy Network Europe) study, we suspected analgesic nephropathy, if:

- a.) the sum of the horizontal and vertical diameters of the kidney were <103mm in males or <96 mm in females;
- b.) if the contour of the kidney was irregular, wavy and at least 3 retractions could be seen on the surface;
- c.) we could observe calcification of renal papillae.

To establish the diagnosis, the presence of alterations listed in a+b *or* a+c was required.

We have also collected data on smoking habits and serum lipid and blood pressure values of the patients positive upon the criteria, and we also recorded cardiovascular and cerebrovascular events (acute myocardial infarct, stroke) in their history.

Statistical analysis of the data

Statistical evaluation of the data has been carried out using SPSS 8.0 for Windows, using standard statistical procedures.

Results

HANS was the first study in Hungary to analyse the prevalence of analgesic nephropathy in a representative sample using uniform, objective criteria. Using the diagnostic criteria of the former European ANNE study (chronic analgesics abuse and positive renal imaging), 3.3% of patients initiating dialysis had analgesic nephropathy in this period. This data is approximately three times higher than the number reported from Hungary in the ERA-EDTA registry. The proportion was markedly higher (14.8%) in patients initiating dialysis upon an unknown diagnosis. Patients were taking mainly phenacetine-containing combined analgesics, mainly for chronic headache. The prevalence of acute myocardial infarction was significantly higher in patients regularly consuming combined analgesics compared to patients not receiving these drugs (15 vs. 5%, $p < 0.01$).

4. 2 Psychiatric study of patients with analgesic nephropathy

In our study, we have intended to find some sort of psychic alteration in the background of chronic drug consumption leading to analgesic nephropathy. On the other hand, we planned to characterize the personality of the patients. As chronic somatic diseases may present a high risk for the development of secondary psychiatric symptoms, patients having chronic renal failure for at least 10 years served as controls.

Patients and methods

The study has been carried out with the permission of the local Ethical Board in 9 Hungarian dialysis units, also participating in HANS. We have analyzed the personality of 47 patients diagnosed with analgesic nephropathy as cases, and 57 patients with more than 10 years established chronic renal disease as controls. Out of the 104 patients, 69 underwent chronic dialysis, while 35 patients were in ambulant patient care, not yet requiring renal replacement therapy.

During the psychiatric and somatic interview, we collected data on the presence of psychiatric diseases in the family or in the patients' case history, and on psychopharmacoans consumed by the patient at the time of analysis or prior to that. We have used a list of symptoms and two tests for the survey of psychological characteristics of the patients. In the list of symptoms, we can find 36 frequent somatisation symptoms (pain, vegetative signs of anxiety etc. and psychic complaints: anxiety, problems with concentration, forgetfulness etc.) were listed, and patients reported prevalence of these symptoms within the past month.

Tests:

1. A Beck Depression Inventory is a self-check multiple-choice test with 22 questions containing the major somatic (weight loss, anorexia, sleep disorder, fatigue, sexual disorders) and psychic components (hopelessness, self-accusation, remorse, sadness, feeling insufficient etc.).
2. We used the Ammon's Ego-Structure test to examine the patients personality traits.

Statistical analysis of the data

Microsoft Excel 7.0 and SPSS for Windows 8.0 were used for the analysis of the test sheets and the statistical analysis, respectively, we used Mann-Whitney u test and crosstabs (χ^2 -test) for the analyses.

Results

Examining the patients' psychiatric characteristics, it was found that psychological problems occurred more frequently in the family histories (14.9 vs. 7.0 %) as well as personal case histories (36.2 vs. 8.8 % $p < 0.001$) than in patients with other renal diseases. Depression was the most frequent among the earlier psychiatric disorders, affecting nearly 30% of patients with analgesic nephropathy compared to other renal diseases (29.8 vs. 7.0%, $p < 0.01$). During their lifetime, nearly two third of the patients has regularly consumed psychopharmacons, while only slightly more than one quarter of the control group. Among the psychopharmacons, sedatohypnotics (mainly benzodiazepines and meprobamate) were the most frequent in both groups, while the proportion of mood stabilizers was markedly lower.

Interestingly, at the time of the study, there was no more significant difference in the use of psychopharmacons, and more than one third of the patients has received psychiatric medication. Distribution of the current drugs was similar to that observed by the previous drugs. Concerning items of the symptom list, patients suffering from analgesic nephropathy reported more somatic (10.80 vs. 7.32 symptoms, $p < 0.01$) and psychological problems (4.53 vs. 3.35 symptoms $p < 0.08$). There was a significantly higher rate of headache, vertigo, weakness, palpitation and digestive problems as well as sleeping disorders, weariness, nervousness, forgetfulness and inability of making decision in cases than in controls.

Patients with analgesic nephropathy also had a higher score in the Beck test (12.6 vs. 10.36; $p < 0.05$). Considering the total score of the test, the number of cases free of symptoms of depression (score < 9) was significantly lower than that for controls (34.0 vs. 54.4 %, $p < 0.05$) We have also found a difference between the two groups in more factors of the Ammon's Ego-Structure-Test. Patients with analgesic nephropathy had lower scores of constructive aggression and anxiety as well as inner and outer self-limitation; while they had

significantly higher scores for destructive anxiety as well as destructive and deficit narcissism compared to controls.

4.3 RENAL DAMAGE INDUCED BY HERB EXTRACTS AND PARAMEDICAL AGENTS

Many plants are known to be able to induce renal damage. The damage may develop upon many ways, most significant of which is an allergic reaction, direct or indirect toxicity or interaction with other paramedical preparations, hormones or heavy metals.

We report the case of a 30-year-old female patient, who was admitted to our department because of acute renal failure and elevated level of liver enzymes. In the background of her symptoms, we have histologically diagnosed acute renal tubular necrosis that may have developed due to the combined intake of Guarana and Allopurinol. After omission of the drugs and transient hemodialysis sessions, the acute renal failure has gone into remission, and the general state of the patient has improved.

Using this case, we would like to draw attention to potential renal damage-inducing ability of widely marketed paramedical preparations, herb extracts. These herb extracts may be purchased in pharmacies or drugstores without a prescription, may be ordered electronically via the internet, and their composition, purity, active substance content are much less controlled and regulated than that of regular medications.

5. LIST OF DOCTORAL THESES

1. According to HANS – the national analgesic nephropathy survey –, we can found analgesic nephropathy in the background of end-stage renal disease in 14.8% of patients initiating renal replacement therapy with an unknown renal disease.
2. The patients were mainly consuming phenacetin-containing combined analgesics, mainly due to chronic headache.
3. The prevalence of acute myocardial infarction was significantly higher in patients regularly consuming combined analgesics.
4. Both somatic and psychological symptoms were significantly more prevalent in the personal as well as in the family history of patients with analgesic nephropathy; leading symptoms were depression and anxiety. Patients with analgesic nephropathy treat their problems and symptoms with psychopharmacocons (mainly sedatives and anxiolytics), their depression is rarely recognized and they rarely receive an adequate therapy.

6. CONCLUSIONS, PLANS FOR THE FUTURE

1. Results of the HANS study and data of the literature indicate that phenacetin is harmful for the kidneys and leads to analgesic nephropathy in a marked percent of case in Hungary, as well. Our study conducted with the support of the Hungarian Society of Nephrology has contributed to the fact that phenacetin was replaced by other analgesics in the latest edition of *Formulae Normales*. Only two phenacetin-containing company-products are currently being sold (*Antineuralgica* and *Dolor*), and they may not be marketed over-the-counter. On the other hand – unfortunately – *Algopyrin*, an agent with a less toxic side-effect profile and good painkiller properties has also turned prescription-only. Therefore patients with chronic pain syndroms consume prescription-free marketed NSAIDs at even larger proportions (thanks to a great contribution of TV-commercial spots, too), which are well-known to be nephrotoxic. As the major cause for taking analgesics is headache from the chronic pain syndromes, we plan to screen patients of „headache patient care units” beside pain- and rheumatologic outpatient units for analgesic nephropathy.
2. The anxiety-depression syndrome observed in our patients with analgesic nephropathy may contribute to the abuse of analgesics. Therefore we plan to treat these patients in collaborations with our psychiatrist colleagues. In a further step, we plan to evaluate analgesic abuse and to perform nephrological screening of patients presenting with anxiety-depression symptoms at psychiatric outpatient units.

3. As a consequence of the widening field of diagnostic and therapeutic possibilities as well as that of complimentary medicine, there is an increasing prevalence of iatrogenic renal damage, the prevention of which should be focused more on. We would like to draw attention to the prevention of iatrogenic renal damage with the inclusion of colleagues from other fields such as rheumatology, neurology, radiology, psychiatry as well as presenting lectures for general practitioners and writing papers published in national medical educational journals.

7. PUBLICATIONS FOR THE PH.D. THESES

I. Pintér I, Degrell P, Nagy J: Kontrasztanyag okozta nephropathia. Orv Hetil 2005; 146 (48): 2451-2456.

II. Pintér I, Vágási K, Wittmann I, Nagy J: Nefrogén szisztémás fibrosis. Orv Hetil 2007; 148 (38): 1805-1807.

III. Pintér I, Nagy J: Analgetikum-nephropathia. Orv Hetil 1998; 139: 2839-2843.

IV. Pintér I, Mátyus J, Czégány Z, Harsányi J, Homoki M, Kassai M, Kiss É, Kiss I, Ladányi E, Lócsey L, Major L, Misz M, Nagy L, Polner K, Rédl J, Solt I, Tichy B, Török M, Varga G, Wagner Gy, Wórum I, Zsoldos B, Pótó L, Dérczy K, Wittmann I, Nagy J : Analgesic nephropathy in Hungary: the HANS study. Nephrol Dial Transplant 2004; 4: 840-843.

Impact factor: 2.84

V. Dérczy K, Pintér I, Nagy J, Vadon G: Analgetikum nephropathia képalkotó diagnosztikája. Hypertonia és Nephrológia 2002; 6 (4-5): 250-254.

VI. Kátai J, Trinn Cs, Pintér I, Nagy J: Veseelégtelenség és paracetamol. Kórház 1998; 6: 38-40.

VII. Pintér I, Osváth P, Amma Z, Czégány Z, Kassai M, Ladányi E, Lócsey L, Misz M, Rédl J, Török M, Nagy J: Analgeticum-nephropathiában szenvedők pszichés jellemzőinek vizsgálata. Hypertónia és Nephrologia, 2002; 6 (4-5): 269-272.

VIII. Vágási K, Degrell P, Késői I, Kovács T, Pintér I, Molnár B, Cseh J, Nagy J, Wittmann I: Növényi kivonat okozta akut veseelégtelenség. Orv Hetil 2007; 148 (9): 421-424.

BOOK CHAPTER

Nagy J, **Pintér I**.

Analgesic Nephropathy In: Nephrology, Hypertension, Dialysis, Transplantation. Eds: T. E. Andreoli, E. Ritz, L. Rosivall, Hungarian Kidney Foundation, 2006, 327-333.

Nagy J, **Pintér I**.

Analgetikum nephropathia. In: Belgyógyászat alapjai. Szerk: Tulassay Zsolt, Medicina Budapest, 2007, 1122-1123.