Incidence of analgesic nephropathy in Berlin since 1983

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Abstract

Background. Phenacetin was removed from the German market in 1986 and was replaced mainly in analgesic compounds by acetaminophen. Our objective was to examine the effect of this measure on the incidence of analgesic nephropathy in light of the changes in other end-stage renal diseases.


Results. On the one hand, the proportion of end-stage analgesic nephropathy decreased significantly from 30% in 1981–1982 to 21% in 1991–1992 and 12% in 1995–1997 (P = 0.01). On the other hand, type II diabetes increased significantly from 7% to 22% (P = 0.01) and 29% (P = 0.001). Using the χ² distribution test to analyze the frequencies of seven diseases at three different time intervals, however, showed that the changes in renal-disease proportions between 1982–1983, 1991–1992 and 1995–1997 were not significantly independent. There was a significant median age increase from 52 years (CI 0.95 44–58) in 1982–1983 to 63 (CI 0.95 55–67) in 1991–1992 and 63 (CI 0.95 60–66) in 1995–1997 (P = 0.003) for all patients starting dialysis but not for those with analgesic nephropathy (59 (55–71) vs 64 (53–67) and 61 (50–72); n.s.).

Conclusion. The decrease of end-stage analgesic nephropathy since 1983 may be partially due to the removal of phenacetin from the German market in 1986. However, considering the general increase in numbers of dialysis patients, their higher age and the increased incidence of type II diabetes, the decrease in analgesic nephropathy is not a statistically significant independent variable. Altered admittance policies for dialysis treatment have yielded a new pattern of renal disease proportion which interferes with changes in the incidence of analgesic nephropathy.

Key words: analgesic mixtures; analgesic nephropathy; dialysis treatment; end-stage renal disease; type II diabetes

Introduction

In Germany, phenacetin was removed from the market in 1986 and replaced by acetaminophen in most compound analgesics. However, compound analgesics without phenacetin are also suspected of being nephrotoxic [1–3]. The per capita analgesic consumption increased from 18.2 g in 1983 to 20 g in 1995 [4,5]. It has not yet been properly investigated how the replacement of phenacetin in mixed analgesics by aminophen or other analgesic components has affected the incidence of analgesic nephropathy.

In Scandinavia, both phenacetin and acetaminophen were put under prescription at the same time in 1961, which led to an exemplary reduction in the incidence of analgesic nephropathy [6–9]. However, banning both analgesic components made it impossible to know which of the two had caused nephropathy. In Australia, gradual replacement of phenacetin by acetaminophen was started in 1967 and completed in 1977. This was soon followed (in 1979) by the banning of all compound analgesics. Thus it is difficult to correlate the slow disappearance of analgesic nephropathy since 1984 in Australia with one of these measures [10,11]. In Belgium, phenacetin was put under prescription in 1988 [11,12]. Assessment of the impact of this legislative measure has been contradictory in the country itself. Some authors have stated that patients taking mixed analgesics containing two analgesic compounds with caffeine or codeine continue to have a high risk of developing analgesic nephropathy [13]. Others, however, regard the banning of phenacetin as sufficient to eliminate analgesic nephropathy as proven by the increasing age of analgesic nephropathy patients [11]. The EDTA data show a general decrease of analgesic nephropathy from 3 to 2% in Europe and from 5 to 4% in West Germany without reference to other renal diseases (1981 vs 1990 [14]).

We investigated the incidence of analgesic nephropathy in relation to that of other renal diseases in patients who have begun dialysis at our hospital since
Our aim was to determine the effect of phenacetin being reserved from the German market in 1986 and replaced by acetaminophen in most analgesic mixtures. In particular, we attempted to correlate the changed incidence of analgesic nephropathy and other renal diseases within the context of altered admittance policies for dialysis treatment.

Subjects and methods

We investigated the proportion of analgesic nephropathy and other renal diseases among patients starting dialysis treatment during three 18-month periods: April 1982 to September 1983, January 1991 to June 1992, and October 1995 to March 1997. The renal-disease incidences during these three periods were compared using the $\chi^2$ distribution test for two random samples and additionally using the $\chi^2$ distribution test for independence of different frequencies (seven renal diseases at three different time intervals). To compare the age differences during three time intervals (comparison of several independent random samples), we used the non-parametric $H$-test of Kruskal and Wallis, which is a generalization of Wilcoxon's rank-sum test. In cases of significant differences, multiple tests according to Tukey were performed to determine the time intervals during which the differences occurred. The ages of patients with different renal diseases are given as medians with 0.95 confidence intervals (CI_{0.95}).

The diagnosis of analgesic nephropathy was based on characteristic anamnestic and clinical data [15] and, since 1991–1992, has been verified by computed tomography (CT) scan in cases of unknown kidney disease [16].

The development of the dialysis and transplant population in West Berlin was investigated by questioning all dialysis and transplant centers at different times.

Results

The number of new dialysis patients increased from 57 in 1982–1983 to 81 in 1991–1992 and 76 in 1995–1997. The $\chi^2$ distribution test suggested a significant decrease in the incidence of end-stage analgesic nephropathy: 30% in 1981–1982 vs 21% in 1991–1992 vs 12% in 1995–1997 ($P=0.01$); and a significant increase in incidence of type II diabetes: 7% vs 22% ($P=0.01$) vs 29% ($P=0.001$). However, the $\chi^2$ distribution test for independence or homogeneity of the seven renal diseases within three different time intervals did not disclose a significant time dependence for the seven renal diseases ($P=0.092$). To compare two relative frequencies of diagnosis, an approximation based on the arcsine transformation was used. However, following the $\chi^2$ test, statistically significant differences were found. The frequency of analgesic nephropathy decreased from 1982–1983 to 1996–1997 ($P=0.01$), whereas that of type II diabetes increased from 1982–1983 to 1991–1992 ($P=0.01$) and from 1982–1983 to 1995–1997 ($P=0.001$) (Figure 1).

The incidence of other renal diseases remained unchanged: glomerulonephritis, 18% vs 14% vs 14%, n.s.; polycystic kidney disease, 12% vs 4% vs 7%, n.s.; type I diabetes, 5% vs 5% vs 3%, n.s.; various kidney diseases, 19% vs 14% vs 21%, n.s.; unclarified diagnoses, 9% vs 15% vs 14%, n.s.

Discussion

The incidence of analgesic nephropathy must be considered within the context of its social and cultural background. In Germany, the period following the Second World War was characterized by tough competition to create new private and economic structures and the increasing double burden of holding a job and household chores borne by women. This created the basis for overadaptation and analgesic abuse [17,18]. For some time, the correlation between analgesic abuse and interstitial nephritis was doubted [19–21]. However, discussion about the nephrotoxicity of phenacetin-containing drugs was definitely ended by the
Table 1. The age in all patients starting dialysis treatment increases significantly, but not in patients with analgesic nephropathy [medians with 0.95 confidence intervals (CI_0.95)]

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<tbody>
<tr>
<td>All</td>
<td>52 (44–58)</td>
<td>63 (55–67)</td>
<td>63 (60–66)</td>
<td>( P = 0.0031^* )</td>
</tr>
<tr>
<td>Analgesic nephropathy</td>
<td>59 (55–71)</td>
<td>64 (53–67)</td>
<td>61 (50–72)</td>
<td>( P = 0.9655 )</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>37 (17–44)</td>
<td>43 (23–62)</td>
<td>64 (23–74)</td>
<td>( P = 0.0699 )</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>40</td>
<td>53</td>
<td>41</td>
<td>( P = 0.2761 )</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>59</td>
<td>74 (69–78)</td>
<td>65 (61–75)</td>
<td>( P = 0.0279^* )</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>49 (24–75)</td>
<td>50</td>
<td>60</td>
<td>( P = 0.6561 )</td>
</tr>
<tr>
<td>Various</td>
<td>43 (37–56)</td>
<td>60 (44–73)</td>
<td>57 (47–67)</td>
<td>( P = 0.0518 )</td>
</tr>
<tr>
<td>Unknown</td>
<td>65</td>
<td>63 (48–77)</td>
<td>65 (40–84)</td>
<td>( P = 0.6216 )</td>
</tr>
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\*Statistically significant.

Fig. 2. Prevalence of patients with ESRD with dialysis treatment or a functioning graft in West Berlin from 1981 to 1998.

longitudinal study of Dubach et al. [22,23], confirming the increased risk of renal insufficiency in patients with analgesic abuse defined by positive tests for acetaminophen in urine. In his study, however, as in the longitudinal study of Elseviers and De Broe [24], no distinction was made between phenacetin- and acetaminophen-containing drugs. In Germany, after the removal of phenacetin from analgesic mixtures in 1986, we are currently having the same discussion about compound analgesics without phenacetin but often containing acetaminophen with or without another analgesic component and caffeine or codeine.

It takes years to determine the effect of changes in the analgesic market on the incidence of analgesic nephropathy. Over the course of these years, there may be changes in other conditions relating to the incidence of renal diseases. This has happened during the last 15 years. Acceptance of older patients for dialysis, as well as those with more complicated diseases, has increased enormously (Figure 2). There is now hardly any contraindication to chronic dialysis treatment. In addition to the resultant general increase in patient age, type II diabetes has become the leading cause of kidney disease among the dialysis population [25,26].

Our dialysis center reflects this development. Nearly all patients with any renal diseases are accepted for dialysis therapy. Analgesic patients have always been among the oldest, their mean age has not changed significantly. However, the age of the other patients has increased considerably. Diabetic nephropathy has become the leading kidney disease, as in many other dialysis centers (Figure 1).

Since the restriction of phenacetin, there have not been any studies on the development of analgesic nephropathy that take into account the altered incidence of other renal diseases. We consider it dangerous to publish the assertion that analgesic nephropathy has decreased due to the restriction of phenacetin without taking into account the changing policies of
admittance to dialysis treatment and the changing conditions associated with other renal diseases. In our dialysis center, it is true that analgesic nephropathy has decreased considerably from 1983 to the present, however, this was not a statistically independent factor when considering the rapid increase of type II diabetes. Detection of analgesic nephropathy was always problematic in that it lacked a scientific background and was based on the observations of pathologists and clinicians [27,28]. No animal model exists. Epidemiologic studies are criticized and considering the high rate of denial among analgesic abusers, must in deed be regarded with skepticism [29–31]. Nephrotoxicity of phenacetin could hardly be proven by scientific measures. Thus it does not make sense at present to demand scientific proof of nephrotoxicity for other analgesic mixtures without phenacetin. A lack of proof does not imply the absence of analgesic nephropathy without phenacetin, a conclusion which is sometimes drawn [11,32–34].

Nephrologists continue to observe analgesic nephropathy in analgesic abusers who have taken analgesic mixtures without phenacetin [2,35,36]. It is not yet possible to determine whether compound analgesics with components other than phenacetin are less toxic or less addictive. Further studies are required to elucidate this. The assurance that mixed analgesics without phenacetin are now safe with regard to nephrotoxicity, is, in our opinion, far from being justified.

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