Contribution of Nonsteroidal Anti-inflammatory Drugs to Deaths Associated With Peptic Ulcer Disease

A Prospective Toxicological Analysis of Autopsy Blood Samples

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Context.—Of the side effects occurring in temporal association with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), peptic ulcer disease is reported most often.

Objectives.—To (1) provide information on the temporal association between fatal peptic ulcer presenting as sudden death and NSAID use prior to death, and (2) to examine the diagnostic efficiency of postmortem determination of NSAID levels using high-pressure liquid chromatography.

Design.—Prospective autopsy study of all cases of sudden death associated with peptic ulcer disease from a total of 1139 medicolegal autopsies performed during a 12-month period.

Methods.—Postmortem femoral blood samples were analyzed for NSAIDs using high-pressure liquid chromatography, and specimens of gastric and duodenal mucosa were examined for coexisting pathologic conditions.

Results.—Twelve fatalities that occurred out of hospital as a result of peptic ulcer disease and presented as sudden death were identified. Autopsy blood samples were positive for NSAIDs in 7 cases (ibuprofen in 4 cases, levels 0.8 to 1.4 µg/mL; diclofenac in 2 cases, levels 0.6 and 1.6 µg/mL; and ketoprofen in 1 case, level 0.3 µg/mL). The ages of the affected individuals (3 men, 4 women) ranged from 43 to 60 years. No other drugs, including corticosteroids, anticoagulants, salicylic acid, and salicylates, were present. Microscopic examination revealed no pathologic antemortem mucosal conditions in any of the cases.

Conclusions.—For the postmortem elucidation of etiopathogenetic factors contributing to fatal peptic ulcer disease, high-pressure liquid chromatography to determine NSAID levels in autopsy blood samples is of considerable diagnostic benefit, especially when combined with histology. The number of cases of sudden death involving younger individuals dying as a result of peptic ulcer disease in temporal association with preceding use of NSAIDs seems to be underestimated from the clinical viewpoint due to the underrepresentation of out-of-hospital fatalities in the field of clinical pathology.

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Of the side effects occurring in temporal association with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), peptic ulcer disease is reported most often.1-5 Fatal upper gastrointestinal hemorrhage and perforation complicating the course of peptic ulcer disease may be encountered in autopsy cases of sudden, unexpected, or clinically unexplained death.6,7 The present preliminary study was conducted to (1) provide information on the temporal association between fatal peptic ulcer disease presenting as sudden death and NSAID use prior to death, and (2) to examine the diagnostic efficiency of postmortem determination of NSAID levels using high-pressure liquid chromatography (HPLC) on autopsy blood samples.

MATERIALS AND METHODS

For the prospective analysis, cases were selected from all autopsies performed at the Institute of Legal Medicine, University of Hamburg, Germany, during a 12-month period (May 1999 through April 2000). All cases of sudden death resulting from peptic ulcer disease were selected for the study. A standardized protocol was used to document the ulcer site, morphology, and type of fatal complication (eg, bleeding, perforation with subsequent peritonitis, penetration into adjacent organs). In each case, microscopic examination of the peptic ulcer and various gastric and duodenal mucosa specimens was carried out according to the criteria recently specified by Sipponen10 in order to obtain further information about the presence of Helicobacter pylori- and atrophy-related alterations or intestinal metaplasia. Furthermore, a thorough histologic examination of the relevant internal organs and a complete toxicological analysis were performed to rule out comorbid underlying diseases or intoxication potentially promoting the fatal outcome. In each case, postmortem venous blood samples from the femoral vein were analyzed for NSAIDs by HPLC as described earlier.8

RESULTS

Study Population

A total of 1139 autopsy cases was investigated prospectively during the 12-month study period, and 12 nonconsecutive fatalities resulting from peptic ulcer disease were identified and included in the study. All fatalities occurred out of hospital and presented as sudden death; therefore, data on the previous medical history, clinical symptoms, or medication use prior to death were not available in any...
of the cases. A history of chronic alcohol consumption was reported in 2 cases. Autopsies were performed between 2 and 3 days after death. The male-female ratio was 1:1. The ages of the subjects ranged between 43 and 80 years; 3 subjects were younger than 50 years, 5 subjects were 50 to 60 years old, 2 subjects were 61 to 70 years old, and 2 subjects were older than 70 years.

**Autopsy Findings**

In 8 cases, the ulcer was located in the duodenum. An isolated ulcer ranging between 0.6 and 5 cm in diameter was found in 7 of these 8 cases; an eroded vessel within the ulcer was apparent in 1 case, and the ulcer had penetrated the head of the pancreas in 4 cases. In 1 case, so-called "kissing ulcers" were present in the duodenum. In 4 cases, the ulcers (1–5 cm in diameter) were located in the stomach (in the pyloric region in 3 cases and in the antrum in 1 case, showing an eroded vessel in the depth of the ulcer). The cause of death was acute gastrointestinal bleeding in 7 cases (5 cases of duodenal ulcer, 2 cases of gastric ulcer), peritonitis following ulcer perforation in 4 cases (3 cases of duodenal ulcer, 1 case of gastric ulcer, volume of intra-abdominal fluid between 150 mL and 2500 mL), and coincident bleeding and perforation in 1 case of duodenal ulcer.

**Histology**

Apart from mild to moderate autolysis of the mucosa, no pathologic mucosal conditions, such as *H. pylori* infection, atrophy-related alterations, or intestinal metaplasia, could be identified. The possibility of an underlying gastric cancer masquerading as a benign gastric ulcer was also ruled out by microscopic examination.

**Toxicology**

Postmortem venous blood samples revealed NSAIDs in 7 cases; ibuprofen was detected in 4 cases (levels 0.8–1.4 μg/mL), diclofenac was found in 2 cases (levels 0.6 and 1.6 μg/mL), and ketoprofen in 1 case (level 0.3 μg/mL). Among the 7 cases positive for NSAIDs, there were 3 male and 4 female subjects; the ages of these subjects ranged from 43 to 60 years (mean 57 years). In all positive cases, the ulcer was located in the duodenum. Three cases positive for ibuprofen showed a concomitant penetration of the ulcer into the pancreas, whereas none of the remaining NSAID-positive cases were accompanied by penetration in adjacent organs. No other drugs, including corticosteroids, anticoagulants, salicylic acid, and salicylates were found by toxicological analysis, and blood alcohol tests were negative in all cases.

**COMMENT**

In clinical studies, controversy exists about the number of deaths resulting from peptic ulcers that are attributable to the use of NSAIDs. In the current preliminary study, an approach to the subject was undertaken using HPLC on autopsy blood samples to assess the temporal association between fatal peptic ulcer disease presenting as sudden death and the preceding use of NSAIDs in a medicolegal autopsy population during a 12-month period. In 58% of all cases of fatal peptic ulcer disease identified at autopsy, we found toxicological evidence of NSAID use prior to death. We were able to detect ibuprofen in postmortem venous blood samples in 4 cases, diclofenac in 2 cases, and ketoprofen in 1 case. Postmortem NSAID levels (ibuprofen levels 0.8–1.4 μg/mL, diclofenac levels of 0.6 and 1.6 μg/mL, and ketoprofen level of 0.3 μg/mL) were below or within the lower range of therapeutic concentrations.

The presence of histologically normal gastric and duodenal mucosa indicates an extremely low risk of both peptic ulcer disease or gastric cancer and, therefore, is a finding of high clinical relevance. Among patients with normal gastric and duodenal mucosa, the use of NSAIDs or salicylic acid is the cause of peptic ulcer disease in more than two thirds. In none of the 7 cases positive for NSAIDs did microscopic examination reveal coexisting pathologic antemortem mucosal conditions, such as *H. pylori* infection, atrophy-related alterations, intestinal metaplasia, or tumorous lesions of the gastric and duodenal mucosa, thus suggesting NSAIDs to be the most likely cause of peptic ulcer disease.

Regarding the age-specific incidence of fatal ulcer complications in relation to the use of NSAIDs, Guess and coworkers conducted the largest epidemiologic cohort (follow-up) study on the subject until now in a defined population of 1 million residents. Among 111 478 users of NSAIDs younger than 75 years, the authors identified only 1 case of NSAID use associated with a fatal peptic ulcer complication. In contrast to the results of the study by Guess and coworkers, and the prevailing clinical concept of a strong association of NSAID-related ulcer complications and advanced age, as observed in several different clinicopathologic studies, the age of the individuals dying of fatal ulcer complications in temporal association with the use of NSAIDs included in our study ranged between 43 and 60 years. Of course, the number of subjects included in the present study is too small to draw any general epidemiological conclusions, and our observation of considerably younger individuals dying of peptic ulcerations in temporal association with NSAID use prior to death has to be interpreted with considerable caution. However, even though one may suggest that the presence of NSAIDs in autopsy blood samples and fatal peptic ulcerations in the present study may be pure coincidence rather than a categorical relationship in some cases, an explanation for the conflicting results may be the fact that younger people undergo medicolegal autopsies more often than older individuals, and a selection bias could have occurred. A second possibility is that the age difference in the present investigation compared with the results of earlier studies can be ascribed to a recently high prevalence of over-the-counter NSAID sales without previous medical advice and prescription. This situation may be reflected in autopsy cases of sudden death in younger individuals with no obvious previous medical history that are investigated by the forensic pathologist and that are underrepresented in the field of clinical pathology.

Clinical studies indicate that male sex, prior peptic ulcer disease, advanced age, high NSAID dose, and combination of NSAIDs with corticosteroids or anticoagulants are high risk factors for NSAID-related ulcer complications, such as bleeding or perforation. The dose-dependent risk is maintained even after many months of treatment and is thought to disappear completely about 2 months after treatment is stopped. Symptoms such as epigastric pain, nausea, and vomiting are poor predictors of serious lesions and of complications of NSAID-induced peptic ulcers, which may occur without previous symptoms mainly due to the analgesic effects of NSAIDs. Taking the
The employment of HPLC to determine NSAID levels in autopsy blood samples is of considerable diagnostic benefit regarding the postmortem elucidation of death associated with peptic ulcer disease, especially when combined with histology. In our opinion, the presented data are evidence of the importance of sudden death of younger individuals resulting from peptic ulcer disease in temporal association with preceding use of NSAIDs. The number of such fatalities occurring out of hospital seems to be underestimated from the clinical viewpoint, owing to the fact that these cases are underrepresented in the field of clinical pathology.

**References**