

Analgesics and Kidney Disease

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The National Institutes of Health (NIH) recently issued a report stating that 'combinations of antipyretic analgesics, taken in large doses over a prolonged period, cause a specific form of kidney disease and chronic renal failure.'¹ This hypothesis has been widely held for many years.² The NIH report may faithfully describe the consensus in medicine today, but it is not informative about what is known concerning analgesics and kidney disease. Our purpose here is to provide criticism of some popular ideas presented in the NIH report, and at the same time suggest ways to further our understanding of the possible role of analgesics in the development of kidney disease.

The concerned analgesic-user, clinician or policy-maker will note that the hypothesis in its present form is too imprecise to be useful. The primary questions of interest should be: what types and quantities of analgesics, if any, cause kidney disease? The current hypothesis indicts combination analgesics without specifying which types of analgesics are thought to be involved. All types of analgesics are implicitly alleged to be hazardous, but the evidence differs considerably for individual analgesics. An increased rate of papillary necrosis has been observed among female phenacetin users, most of whom ingested a cumulative dose of more than 2 kg.³ There is little evidence indicating that analgesics not containing phenacetin are associated with kidney disease in humans.^{4,5} Interactive effects of combinations of analgesics as compared to single ingredient preparations have not been studied. In claiming a causal relation for combination analgesics 'taken in large doses over prolonged periods' but not for single ingredient analgesics 'when taken in the smaller doses usually prescribed by physicians,' analgesic type is confounded with dose.¹

The vague nature of the theory reflects severe limita-

tions of the evidence. The major difficulties are that there is discordance between the effects seen in animals and those seen in humans,³ and the evidence in humans is meagre and non-discriminating with respect to several important sources of bias.

A fundamental problem in determining whether an illness is caused by a drug arises in 'circumstances when the drug may be indicated for treatment of the early manifestations of the illness or a predisposing factor'.⁶ This problem of confounding by indication for drug use can produce strong but non-causal associations between a drug and many types of illness. For example, a recent study found that cimetidine users experienced increased mortality from several types of cancer (digestive, lung, lymphatic and haematopoietic), ischaemic heart disease, chronic liver disease and accidents.⁷ Nevertheless, the investigators concluded that 'none of these drug-disease associations represented adverse effects of cimetidine treatment; on the contrary, they resulted from cimetidine being used, knowingly or unknowingly, for treating the symptoms of serious diseases.'

People who take large quantities of analgesics usually have histories of chronic illness.⁸ Heavy users of analgesics have been characterized by 'a striking incidence of migraine headache, musculoskeletal complaints, personality disorders, anemia, arteriosclerotic cardiovascular disease, and peptic ulcer in addition to manifestations of renal disease'.⁹ There is evidence indicating that illnesses seen among analgesic-users are long-term effects of the disease processes that caused patients to take analgesics.

Consider the one prospective study that evaluated the relation between phenacetin-containing analgesics and several health outcomes. The Swiss study reports an association with impaired renal function in women, but also shows among the phenacetin-users a fourfold increase in mortality from renal and urogenital disease, a doubling of overall cancer mortality and more than a fourfold increase in deaths from cardiovascular disease.¹⁰ The causal interpretation that has been offered for the increased rate of kidney disease among phenacetin-users would oblige us to conclude that phenacetin also caused the dramatic increases in the

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death rates from cancer and from cardiovascular disease. Strangely, this implication has not been addressed.

Another study that tried to replicate the result seen in the Swiss study found no association between analgesics (including phenacetin) and impaired renal function.¹¹ The only explanation that has been offered for these seemingly conflicting results is that the increased incidence of adverse outcomes observed in the Swiss study reflects the poor health status of analgesic users rather than causal effects of analgesics.¹¹ Methods to control this source of error in the Swiss study have already been suggested.¹²

Another common misinterpretation concerns the claim that 'analgesic nephropathy, including papillary necrosis, is most common in regions where the consumption and/or sale of analgesic mixtures is high'.¹ Even if this statement were true, it is misleading. When the diagnosis of a particular disease depends on a positive history of exposure, that disease is linked inextricably to the exposure by definition; even in the absence of a causal association, the disease will be diagnosed more frequently in geographical regions where the exposure is more common. There exist no clinical criteria for defining or diagnosing 'analgesic nephropathy,' which is usually defined simply as kidney disease in people using analgesics.⁸ When evaluating aetiological hypotheses, researchers have admonished that the identification of cases 'is valid only if it does not depend on the exposure status itself. . . the use of the drug can influence the detection of cases firstly by influencing the level of medical attention, or, secondly by becoming a partial criterion for the diagnosis (because of its known or suspected aetiological or preventive role in illness)' (emphasis added).¹³ This warning could hardly be more pertinent than for a disease which is referred to as 'analgesic nephropathy.'

The NIH report claims that 'in most of the United States, analgesic nephropathy accounts for about 2% of end-stage renal disease.'¹ This figure is entirely speculative and should be sharply distinguished from an empirical effect estimate. A valid estimate of the proportion of end-stage renal disease that can be attributed to analgesic use requires accurate quantification of the relative magnitude of the difference in the incidence of end-stage renal disease among users and non-users of specific kinds of analgesics, and knowledge about the frequency and dose levels of analgesic use in the United States. The NIH report acknowledges the 'lack of data about the extent of use of these drugs in the general population.'¹ More importantly, however, only one study has attempted to quantify the

relation between analgesics (including phenacetin) and end-stage renal disease; the investigators concluded that 'this study was unable to demonstrate any increased risk of end-stage renal disease associated with use of analgesics either as single compounds or in combinations'.¹⁴

A failure to appreciate the limitations of the evidence prompted the NIH panel to recommend that 'serious consideration be given to the withdrawal of mixed analgesic drugs from over-the-counter use in the United States'.¹ Since phenacetin-containing analgesics have already been withdrawn, this recommendation applies to analgesics that do not contain phenacetin, for which the evidence does not indicate a causal relation. Our concern is that without critical assessment of the effects of specific doses and types of analgesics, any personal, clinical or regulatory decision will not be adequately informed.

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