Hotline Editorial

Diuretic therapy and renal cell carcinoma — another controversy?

What are the facts?
Over the past decade, an association between renal cell carcinoma and diuretic therapy has been documented in nine case control studies (odds ratio 1·55, confidence interval 1·42–1·71, $P<0·00001$). In three cohort studies scrutinizing a total study population in excess of one million subjects, diuretic therapy was associated with a more than twofold risk of renal cell carcinoma[1]. In most studies, women were at a higher risk of diuretic associated renal cell carcinoma than men (odds ratio 2·01 vs 1·69). In three studies, the risk of renal cell carcinoma increased with the duration of diuretic therapy (cumulative dose). The relationship was also present in normotensive patients who took diuretics for another reason, and it persisted even when corrected for the presence of hypertension (which may, by itself, be a low-grade risk factor for malignancies, including renal cell carcinoma[2]).

What is the putative carcinogenic mechanism?
Renal cell carcinoma arises from the renal tubular cell, the very cell that is the main target of the diuretic’s pharmacological effect. Conceivably, chronic chemical bombardment of this cell over years and decades has a low-grade carcinogenic effect. Diuretics have been associated with both nephropathy and renal cell tumours in animals. Hydrochlorothiazide as a cyclic imide can be converted in the stomach to a mutagenic nitroso derivative. The thiazide diuretics cause massive degenerative changes and cell death in the distal tubule in rats[3]. After thiazide exposure these cells looked like tumour cells and exhibited markers of tumour cells[3].

Why are women at higher risk than men?
Renal cell carcinoma is a rare malignancy that occurs two to three times more commonly in men than women. The fact that most studies document women to be at higher risk than men with regard to diuretic-induced renal cell carcinoma indicates a specific cause. Although the use of diuretics has declined over the past decade, women still use two to three times more diuretic therapy than men, possibly because women have a greater tendency for oedema than men[4]. Also it is probably the total chemical burden to the tubular cell that will determine carcinogenicity. Compared with men, women more often abuse analgesics, which also are risk factors for renal cell carcinoma. Also, oestrogens have been shown to enhance the thiazide effect in the distal tubule of ovariectomized rats[5].

What is the true risk/benefit ratio of diuretic therapy?
Several epidemiological studies allow us to estimate the true risk/benefit ratio of diuretic therapy in hypertension. It must be emphasized, however, that these calculations are to be taken with a good grain of salt. While causing one case of renal cell carcinoma, diuretic therapy will prevent 20 to 40 strokes, 3–28 heart attacks, 3–10 cardiovascular deaths, and 4–14 total deaths in the general population[6]. In the elderly, the numbers look even better. However, in middle-aged women, per one case of renal cell carcinoma, diuretics only prevent six strokes, no heart attacks and no deaths.

What are the potential weaknesses of the hypothesis?
Case control studies and cohort studies (and meta-analyses derived thereof) are not hypothesis-testing[7]. They are, at best, hypothesis-generating. We cannot rule out any confounding or unknown risk factors for renal cell carcinoma that are shared by both diuretic therapy and hypertension. A statistical fluke is always possible although unlikely in view of the consistency of the findings in all studies.
Why is diuretic-associated renal cell carcinoma surfacing only now after four decades of diuretic therapy?

Diuretics were introduced into medicine in 1958. We suspect that carcinogenicity is low-grade and that it takes a diuretic exposure of more than two decades until the risk of renal cell carcinoma increases. Of note, the incidence of renal cell carcinoma has increased by 43% over the past 15 years[8]. Diuretics, therefore, are unique in that they enjoy an unparalleled track record and, in the absence of an equally long track record, no comparison should be made regarding efficacy and safety of other cardiovascular drugs.

Why was there no evidence of renal cell carcinoma in prospective, randomized trials?

Carcinogenicity of diuretic therapy is probably low grade and certainly less than that of smoking. If one had to design a prospective, randomized trial proving that smoking causes lung cancer, a study duration of at least one if not two decades would be required. Smoking is a much more powerful risk factor for lung cancer than is diuretic therapy for renal cell carcinoma. The increased risk of renal cell carcinoma with diuretic therapy is therefore unlikely to surface in a time period of less than 5 years, as has been customary for most clinical trials.

Do dose and chemical structure of the diuretic matter?

In most studies there has been no distinction between loop diuretics and thiazide diuretics. Since most of the studies were conducted during the past decade reflecting diuretic use during the previous decade, probably a dose of hydrochlorothiazide 50–100 mg was most commonly used. Thus, the bulk of the data comes from a moderately high dose of thiazide diuretics, although loop diuretics cannot be exculated.

How many patients are presently taking diuretics?

In the countries in which this information is accessible (Spain, Italy, Germany, France, United Kingdom, Belgium, Greece, Japan, Mexico, Australia, and South Africa), a total of 15.2 million patients were on diuretics in 1997. Women accounted for 62% and men for 38% of the patients on diuretics. In the United States until September 1998, 24.5 million patients were taking diuretics.

What should I tell my patients?

Low dose thiazide diuretics probably remain a good choice for initial antihypertensive therapy in the elderly. Similarly, in patients with congestive heart failure, the low-grade carcinogenicity of diuretic therapy can possibly be disregarded because life expectancy is relatively short, and the patient is unlikely to live long enough to reach the threshold of carcinogenicity. However, middle-aged women should probably no longer be treated with diuretics because (1) they have a tendency to overuse diuretics, (2) they are less protected by diuretics against heart attacks and strokes than men, (3) their risk of renal cell carcinoma is higher than in men, and (4) they potentially will be exposed to these drugs for several decades. We are reluctant to recommend imaging procedures in patients who have been exposed to diuretic therapy for longer than two decades. Conceivably, some early and curable stages of renal cell carcinoma could be detected by sonographic screening, but the true cost/benefit ratio of such an approach remains unknown.

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References