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COMMENTARY

Antihypertensive Drugs, Hypotension, and Ischemic Colitis

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In this issue of the journal, Hines et al. [1] report incidence rates of ischemic colitis in treated hypertensive adults in the USA, with a focus on aliskiren, a direct renin inhibitor. While these investigators are to be commended for assessing such a large dataset (2,356,226 hypertensive patients), they provide no clear explanation for the focus on aliskiren.

The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) trial, which concerned patients with type 2 diabetes and chronic kidney disease or cardiovascular disease, was stopped prematurely because of a slight excess risk of cardiovascular events in patients receiving aliskiren plus an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) compared with those receiving placebo plus an ARB or ACEI. This study also demonstrated a significantly higher risk of renal impairment, hypotension, and hyperkalemia in the aliskiren group [2]. Consequently, the US FDA modified the labeling of aliskiren in April 2012 with a new contraindication against the use of aliskiren with ARBs or ACEIs in patients with diabetes, and a warning to avoid the use of aliskiren with ARBs or ACEIs in patients with moderate to severe renal impairment [3] The European Medicines Agency (EMA) contraindicated aliskiren in both situations [4].

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One and a half years later, the FDA published a new warning and precaution about symptomatic hypotension that may occur after initiation of aliskiren in patients with marked volume depletion, those with salt depletion, or those receiving other agents acting on the renin–angiotensin–aldosterone system [5]. More recently, in light of two other clinical trials and a meta-analysis [6–8], the EMA recommended against the prescription of dual renin-angiotensin system blockade through the combined use of ACEIs, ARBs, or aliskiren [9] because these combinations were associated with an increased risk of hyperkalemia, kidney damage, and hypotension. Furthermore, no significant benefits from dual blockade were seen in patients without heart failure. Benefits were thought to outweigh risks only in a selected group of patients with heart failure in whom other treatments were unsuitable.

Hypotension is a risk factor of ischemic colitis, an uncommon, potentially severe, and sometimes fatal disease caused by a lack of blood flow. It is also a diagnosis of exclusion with no identified cause [10, 11]. The age- and sex-adjusted incidence rate was estimated to be 22.9 per 100,000 patient-years (PYs) (95 % confidence interval [CI] 18.6–27.3) for the period 2006–2009 among unselected subjects in a US county [12]. The incidence was twice as frequent for women and increased strongly with age, from 1.1 per 100,000 PYs before the age of 40 years to 107 per 100,000 PYs for subjects aged 80 years or older [10]. In this study, the main risk factor was a hypotensive episode in the previous month (odds ratio [OR] 33.0, 95 % CI 13.3–80.9) [11]. Other independent risk factors identified were collagen vascular disease (OR 8.0, 95 % CI 2.2–28.3), peripheral vascular disease (OR 7.9, 95 % CI 4.7–13.2), congestive heart failure (OR 4.1, 95 % CI 2.6–6.3), psychotropic medications used in the past

30 days (OR 3.7, 95 % CI 1.3–11.0), digoxin used in the past 30 days (OR 3.6, 95 % CI 2.1–6.2), cerebrovascular disease (OR 3.2, 95 % CI 2.3–4.6), chronic obstructive pulmonary disease (COPD) (OR 3.1, 95 % CI 1.8–5.2), coronary artery disease (OR 2.6, 95 % CI 2.0–3.5), aortic aneurysm or coronary bypass surgery (OR 2.5, 95 % CI 1.5–4.2), hypertension (OR 2.1, 95 % CI 1.6–2.7), diabetes mellitus (OR 2.0, 95 % CI 1.4–2.8), history of thromboembolism (OR 1.9, 95 % CI 1.2–3.3), current smoking (OR 1.9, 95 % CI 1.3–2.7), and diuretic used in the past 30 days (OR 1.6, 95 % CI 1.2–2.1) [12].

Thus, estimation of the incidence rate of ischemic colitis among treated hypertensive adults, with a specific focus on aliskiren, as conducted by Hines et al. [1] is a topic of high interest. Unfortunately, the authors present only crude incidence rates of ischemic colitis for overall, incident, and prevalent patients according to some treatment groups. The lack of adjustment or standardization makes comparisons or even overall medical appreciation between groups complex. Indeed, any lower or greater incidence rate could be due to a small unbalanced distribution of gender, age, or other risk factors [12]. For example, the incidence rate was 34 % higher in the prevalent medication group than in the incident medication group. It could be in relation to an older mean age (+4.5 years), more women, more severe pre- and post-index comorbidities, as well as more frequent antihypertensive drug combinations and longer duration of antihypertensive drug exposure rather than a real difference. Unbalanced risk factor distribution could also explain that the crude incidence rates increased with the number of antihypertensive drugs prescribed. One may agree that the risk factors cited above are likely to increase with the severity of hypertension and the number of antihypertensive therapies needed and therefore lead to a higher incidence rate of ischemic colitis for dual and triple-plus combination therapies. In addition, hypertension per se is a risk factor for colic artery atherosclerosis and therefore lack of blood flow and ischemia: the more severe and chronic the hypertension, the greater the risk of ischemic events, and the greater the risk of using antihypertensive and multiple antihypertensive drugs.

Hines et al. [1] used three methods to calculate incidence rates, with wide variations in the results. In the main method of calculation, patients were classified according to the drugs taken within 30 days after inclusion for hypertension, irrespective of the duration of drug exposure, drug switch, or drug add-on during the follow-up (intent-to-treat analysis). This approach is the gold standard for efficacy in randomized controlled trials and is frequently used in observational cohort studies. However, in terms of harms, especially for an acute or sub-acute event, we should rather investigate drugs used at the time of, or within the days before, the event. From a pharmacovigilance point of view, it is hard to consider that an ischemic colitis can be imputed to a drug not used for a long time rather than to a recently introduced drug. This method of calculation leads to a regression toward the mean of the results and masks differences.

The second calculation method, "end of follow-up assessment" for treatment group classification has also been used in some observational cohort studies. However, if it is adequate for the numerator, it is not for the denominator, which should be the population at risk with the cumulative exposure for the treatment group and not the cumulative time of follow-up. For example, a patient followed-up for 3 years with drug A used for 3 months at the end of the follow-up should be counted only for 0.25 PY in the denominator and not for 3.0 PY as in this analysis. This "end of follow-up assessment" calculation method tends to underestimate the true incidence for the groups with a higher risk.

The third method, using an assessment of cases and populations at risk during exposure to the first treatment, is a more valid methodology for incidence rate calculation. For triple-plus combinations, it shows that the group with ACEI without aliskiren had a significantly higher incidence rate than the group without ACEI or aliskiren (no overlap of 95 % CI and with the assumption that risk factors are well balanced between the two groups), and that the group with aliskiren were close to the group with ACEI and without aliskiren, but with a wider 95 % CI due to the small number of cases observed ($n = 5$). For monotherapy and dual combination therapy groups, no case is observed with aliskiren: is this because there is no risk or just because too few patients were exposed? The number of patients exposed to the drug under study needs to be large enough to assess the incidence rate of the rare event of interest. For example, 15,000 PYs are needed to have at least a 95 % chance of observing at least one case with a true incidence rate of 20 per 100,000 PYs (Poisson distribution). This was probably not reached for the aliskiren monotherapy and dual combination therapy groups. This point is incidentally well underlined by the authors in the discussion: "interpretation of the data is limited by the wide confidence intervals, which resulted from the facts that pIC [probable ischemic colitis] events were rare and the aliskiren-exposed sample was small" [1]. Despite the huge size of the database, with more than 70 million unique patients, 2.3 million in the aggregate hypertensive study cohort, and wider inclusion criteria for aliskiren than for other antihypertensive agents, the authors should not exclude that aliskiren could raise the risk of ischemic colitis compared with other antihypertensive agents, because of a lack of statistical power.

What do we know at this point about antihypertensive drugs, hypotension, and ischemic colitis?

1. Several medical conditions are risk factors, including hypertension, with an OR point estimate of 2.1 in Yadav et al. [12], and gender and age incidence rates are higher by a factor of 2 or 3 for treated hypertensive patients compared with non-hypertensive subjects in Hines et al. [1].
2. A hypotensive episode within 30 days is the most important risk factor identified, with an OR point estimate of 33.0 in Yadav et al. [12].
3. All antihypertensive drugs can be responsible for hypotension episodes, but a higher risk has been identified for some drug combinations [2–9].

Although the paper by Hines et al. [1] brings important information on the general risk of ischemic colitis in treated hypertensive patients, further research is needed to differentiate the attributable risk of hypertension from that of its treatment, which of the available antihypertensive drugs, drug classes, and combinations have a higher risk of ischemic colitis, and whether the higher risk is constant during exposure or mainly at the beginning of exposure (initiation or switch). One of the best designs to address these questions is that used by Yadav et al. [12], applied to a hypertensive population with a cohort to estimate the overall age- and sex-adjusted incidence rate of ischemic colitis in this population, and a nested case–control analysis, or self controlled design [13], to estimate crude and adjusted ORs for risk factors, antihypertensive drugs, classes, and combinations commonly used in medical practice.

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