EDITORIAL

Hypertension and Analgesic Intake: Light and Shade on an Old Problem

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Given that pain is probably the most common symptomatic manifestation of most human ailments, it is not surprising that the use of painkillers is so widespread in the general population. In fact, painkillers are the most widely used group of drugs in the world. This is shown by pharmacoepidemiological studies both in countries with publically-funded health care and in countries such as the USA where health care is predominantly private and where non-subsidized prescriptions might be expected to result in lower drug consumption.[1]

Transient elevation of blood pressure (BP) is one of the known side effects of non-opioid analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs), paracetamol, and acetylsalicylic acid (ASA). It has been suggested that this undesirable effect is associated with the pathophysiological mechanisms by which these analgesics produce salt and water retention and vasoconstriction.[2]

It has been known for years that ASA and NSAIDs act as inhibitors of cyclooxygenase 2 (COX-2). This inhibition results in decreased renal plasma flow which in turn causes a reduction in renal glomerular filtration, increased Na^+ reabsorption in the proximal tubule, and increased reabsorption of Na^+ and Cl^- in the loop of Henle. At the same time, reduced production of different prostaglandins —such as prostaglandin E-2 (PGE_2) and prostacyclin— conditions other renal effects such as increased synthesis of vasopressin and endothelin,[1] which also have vasopressor effects. These effects have been reported with both COX-2 selective and non-selective NSAIDs.[3-5] Therefore, although beneficial effects on endothelial dysfunction in patients with peripheral arterial disease have been reported for selective COX-2 NSAIDs, there is growing concern about the potentially harmful effects of painkillers on the cardiovascular system.[6]

Clearly, any consistent effect leading to increased BP values —and thus to increased risk of vascular complications— must be taken into account when prescribing pain medications in subjects with established cardiovascular disease, particularly when chronic painful conditions require continuous treatment. Nevertheless, it is also interesting to know what the consequences of analgesic use are on cardiovascular risk in healthy populations. Could the pathogenic mechanisms described above lead to increased incidence of hypertension in these populations? Data available from different observational studies and meta-analysis are contradictory. In a cohort of 51 630 healthy women aged 44 to 69 years included in the Nurses Health Study I, an increased risk of hypertension associated with the prescription and use of NSAIDs, aspirin, and paracetamol was observed after 8 years of follow-up, and risk correlated directly with frequency of use.[7] In the Nurses Health Study II, Forman et al[8] observed an increased risk of hypertension among those taking NSAIDs and paracetamol when compared with those who were not taking analgesics, but no increased risk was observed in those taking ASA. On the other hand, the Physicians Health Study,[9] which followed a cohort of 8229 men for 5.8 years, was unable to show an increased risk of hypertension associated with consumption of NSAIDs, aspirin or paracetamol.

Solomon et al[10] evaluated the possible relationship between COX-2 selective inhibitors and new-onset hypertension and found the highest incidence of hypertension in those receiving treatment with this type of NSAID. The finding was particularly pronounced in subjects with underlying disease (patients with a history of chronic renal failure, liver disease or heart failure). These observational studies showed that both COX-2 specific inhibitors and non-selective NSAIDs may be associated with increases in BP. However, as in all observational

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studies, biases and confounding factors such as age and significant comorbidity may explain some of the observed effects.

Published meta-analysis of randomized clinical trials which assessed the effect of painkillers on the emergence of newly-diagnosed hypertension reported a significant correlation with the use of NSAIDs (indomethacin, sulindac, naproxen, piroxicam, or ibuprofen) but not with ASA.[11] The meta-analysis by Aw et al sought to determine whether COX-2 specific inhibitors were associated with an increased risk of hypertension. The analysis included 19 randomized controlled trials with a total of 45 451 participants, most of whom had arthritis (29 824 with osteoarthritis, 15 627 with rheumatoid arthritis). Drugs evaluated were celecoxib, rofecoxib, and etoricoxib, and a non-significant increase in the risk of hypertension was observed with their use. However, in general, these studies were not designed to evaluate the effects of NSAIDs on BP or on the hypertension incidence.[12]

In this edition of *Revista Española de Cardiología*, Beunza et al[13] present the results of more than 4 years of follow-up of the SUN (Seguimiento de la Universidad de Navarra [University of Navarra Follow-up]) cohort. The cohort consisted of 9986 individuals (mean age, 36 years) without significant comorbidities. Follow-up indicated a greater risk of incident hypertension in regular users of aspirin and other painkillers. Regular use of aspirin 2 or more days per week was associated with an increased risk of incident hypertension, independently of other cardiovascular risk factors. Regular consumption of other analgesics was also associated with an increased risk of hypertension. The fact that the cohort consisted of young individuals from Spain without significant comorbidities gives added value to the observed association between analgesic consumption and increased incidence of hypertension.

One limitation of the study was that diagnosis of hypertension was patient-reported. Nevertheless, the authors had previously validated the method by comparing it with a diagnosis based on clinical measurement of BP.[14] However, there is increasing evidence that masked hypertension is quite prevalent in younger populations, with normal BP figures recorded during medical visits contrasting with raised BP when ambulatory blood pressure monitoring (ABPM) is used; prevalence rates using ABPM can reach 33%.[15] Moreover, data from other studies in Spain suggest that the hypertensive effect of NSAIDs may depend on the time of day they are taken. Hermida et al[16] found a significant decrease in the BP of normotensive subjects when they were given low doses of aspirin at night. In this study, BP was measured using ABPM. To date, however, no prospective studies have analyzed the incidence of hypertension in relation to the time at which the painkiller was taken.

Although it does not affect the validity of the results, another limitation of the study is that information on the dosage forms of the analgesics administered was not provided. This is not a trivial issue, as formulations which use soluble granules to facilitate analgesic uptake can contain significant doses of Na^+. The sodium content of painkillers available in Spain is usually small, with amounts ranging from 2.5 to 20 mg per dosage unit. However, effervescent excipients containing sodium salts, such as bicarbonate, carbonate, or sodium citrate, contain substantial amounts of sodium.[17] In Spain, for example, most effervescent paracetamol formulations are given in doses of 1 g, either as tablets or granules in sachets. The sodium content of these preparations varies between 376 and 567 mg which, for subjects taking 1 g of the painkiller every 8 or 12 h, represents an intake of between 750 and 1700 mg of Na^+ and can exceed 2000 mg if taken four times a day. These amounts of sodium are equivalent to a daily salt intake of between 2 and 5.75 g. Given the well-established hypertensive effect of excessive salt intake in the general population, this may well be one of the mechanisms underlying hypertension incidence in heavy users of painkillers employing these formulations.

In conclusion, the available data suggest that there is a significant correlation between regular consumption of painkillers and incidence of hypertension in healthy populations, and that the correlation strengthens with more frequent use. The results of the SUN study in Spain also confirm observations from other European and North American cohorts. It would be recommendable to further test these observations in prospective studies employing more precise measurement of BP, such as 24 hour ABPM or self-measurement of BP at home, rather than patient self-report. This would allow more definitive conclusions to be drawn. Issues such as whether all analgesics or their formulations have the same effect, or whether the time they are taken is relevant, also await definitive answers. Given the volume of analgesic use in Spain, such studies become imperative from a public health perspective.

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