Mental health

Antidepressant NSAID combination raises risk of brain haemorrhage

The combination of antidepressants and NSAIDs is associated with an increased risk of intracranial haemorrhage, a retrospective cohort study has found.

Data were obtained from the claims database of the Korean National Health Insurance system which covers almost the entire South Korean population of 50.2 million. Patients were included in the study if they had been newly commenced on antidepressants during the five-year study period (1 January 2009 to 31 December 2013). Patients were excluded if they had been diagnosed with cerebrovascular disease during the 12 months prior to treatment initiation.

The main outcome measure was hospital admission with nontraumatic intracranial haemorrhage within 30 days of starting antidepressant treatment (ICD-10 diagnosis codes I60: subarachnoid haemorrhage, I61: intracranial haemorrhage or I62: subdural or epidural haemorrhage). NSAID use was defined as prescription of at least one NSAID during the 30 day follow-up period.

The propensity score is the probability that a patient with a particular set of baseline characteristics will be given the treatment of interest. In this study, the statistical technique of propensity score matching was used to minimise confounding due to age, gender, comorbid conditions and concomitant medications. Two matched cohorts of 2,072,613 patients were compared. Those prescribed a combination of antidepressants and NSAIDs had a greater 30 day risk of intracranial haemorrhage than those prescribed antidepressants alone hazard ratio 1.6 (95% CI: 1.32-1.85).

This study does not tell us whether antidepressants alone are associated with an increased risk of cerebral haemorrhage. A UK cohort study found that depressed stroke survivors were more likely to die if they were prescribed SSRIs and one possible mechanism for this is an increased risk of cerebral haemorrhage.[1] It is a pity that patients with a recent history of cerebrovascular disease were excluded from the present study rather than treated as a separate and important group.

Selective serotonin reuptake inhibitors (SSRIs) are known to inhibit serotonin uptake into platelets and increase the risk of gastrointestinal haemorrhage.

A recent meta-analysis found only a modest increase in the risk of upper GI bleeding with SSRIs alone odds ratio (OR) 1.66 (95% CI: 1.44-1.92) but a much higher risk with the combination of SSRIs and NSAIDs OR 4.25 (95% CI: 2.82-6.42).[2] NICE recommends consideration of a gastroprotective drug for older patients taking SSRIs with NSAIDs or aspirin.[3]

An alternative strategy to reduce the risk of both GI and intracranial bleeding might be to choose a tricyclic antidepressant e.g. lofepramine. A case control study from the UK General Practice Research Database found a small risk of GI haemorrhage with SSRIs (RR 1.3), a higher risk with venlafaxine (RR 1.9) and no risk at all with tricyclics (RR 1.0).[4]

However, a large UK elderly cohort study found that all classes of antidepressants were associated with significantly increased risks of upper GI bleeding.[5]

The present study found no statistically meaningful differences in the risk of intracranial haemorrhage when comparing the classes of antidepressants.

It is important not to overstate the risk of intracranial haemorrhage. We do not know whether the risk continues beyond the first 30 days of treatment but even if it does the absolute risk is only 4.1 per 1,000 patient-years.

Nevertheless, I think it is wise to avoid prescribing NSAIDs with antidepressants and to caution patients against taking OTC ibuprofen, particularly in older patients and those with cerebrovascular risk factors.

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● **Shin J-Y, Park M-J, Lee SH et al. Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. *BMJ* 2015;351:h3517**

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