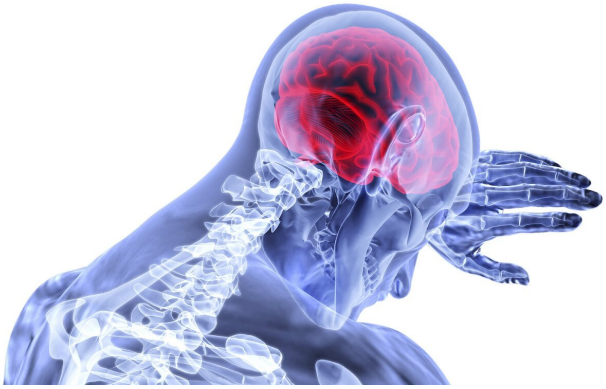
Widely used nausea drugs linked to heightened risk of stroke

23 March 2022



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Drugs known as antidopaminergic antiemetics (ADAs) that are widely used to relieve nausea and vomiting caused, for instance, by migraine, chemotherapy or radiotherapy, and after surgery are associated with an increased risk of ischaemic stroke, finds a study published by *The BMJ* today.

The results show that all three ADAs studied (domperidone, metopimazine, and metoclopramide) were associated with an increased risk, especially in the first days of use, but the highest increase was found for metopimazine and metoclopramide. The researchers suggest that the potential action of ADAs on blood flow to the brain could explain this higher risk.

Like antipsychotics, ADAs are antidopaminergic drugs—they work by blocking dopamine activity in the brain. Antipsychotics have been associated with an increased risk of ischaemic stroke, but whether this risk could extend to other antidopaminergics including ADAs is not known.

To address this gap, a team of researchers in France from Inserm and Bordeaux University (Bordeaux Population Health Centre) and Bordeaux CHU, set out to estimate the risk of ischaemic stroke associated with ADA use in a real world setting.

They identified 2,612 patients from the nationwide French reimbursement healthcare system database (SNDS) with a first ischaemic stroke between 2012 and 2016 and at least one reimbursement for domperidone, metopimazine or metoclopramide in the 70 days before their stroke. Patients had an average age of 72 years and 34% were men.

They compared frequencies of these ADA reimbursements between a risk period (days -14 to -1 before stroke) and three matched reference periods (days -70 to -57, -56 to -43, and -42 to -29 before stroke).

Patients with stroke were then matched by age, sex, and stroke risk factors to a healthy control group of 21,859 randomly selected people who also received an ADA in the same time period.

Among patients with stroke, 1,250 received an ADA at least once in the risk period and 1,060 in the reference periods. Among the control group, 5,128 and 13,165 received an ADA at least once in the risk and reference periods, respectively.

After taking account of potentially influential factors, the researchers found that new users of ADA could be at a 3-fold increased risk of stroke shortly after treatment started.

Further analyses by age, sex, and history of dementia showed similar results, with men at highest (a 3.59-fold increased) risk.

The risk appeared to increase for all ADAs, the highest increase being found for metopimazine (a 3.62-fold increase) and metoclopramide (a 3.53-fold increase), both of which are drugs that cross the blood-brain barrier.

This is an observational study, and as such, can't establish cause, and the researchers point to some limitations that are inherent in database studies, such as a lack of information on prescribed daily dose or duration of ADAs and ischaemic stroke subtypes.

Nevertheless, they say their results show that the risk of ischaemic stroke appears to be associated with ADA use.

And although further causal inference research is needed to confirm this association in other settings, they suggest that "the higher risk found for drugs crossing the blood-brain barrier suggests a potential central effect, possibly through an action on cerebral blood flow."

More information: Risk of first ischaemic stroke and use of antidopaminergic antiemetics: nationwide case-time-control study, *BMJ* (2022). www.bmj.com/content/376/bmj-2021-066192

Provided by British Medical Journal