Over-the-Counter Cough and Cold Medication Use and Risk of Stroke

To the Editor:

I read with great interest the study by Cantu et al. in Stroke that evaluated the association between over-the-counter cough and cold medications containing sympathomimetics and stroke risk. Their study covers an important topic—risk factor assessment of acute stroke and, in particular, drug-induced stroke. The authors use data from a stroke registry including 2500 patients with a diagnosis of acute stroke in Tlahtapan, Mexico. The study related 22 cases of stroke with over-the-counter cough and cold medication use, when such medications were taken within 24 hours prior to the stroke and other known causes of stroke were excluded by appropriate diagnostic tests.

There are several issues that should be taken into account when assessing the association between over-the-counter cough and cold medication use and stroke risk described in the study by Cantu et al. This study is technically a case series in which outcome and exposure were assessed at the same time. To evaluate an apparent association between over-the-counter cough and cold medication use and stroke, a comparison group is essential to determine if the risk of stroke is increased or decreased when using such medications. The study, however, does not provide information regarding over-the-counter cough and cold medication use in the remaining patients from the stroke registry and, more important, in the general population. The use of a case-crossover design would allow a comparison of short-term exposures and stroke risk in a series of cases only and might have been applicable to the data of Cantu et al.

Because over-the-counter drugs are available without prescriptions, they tend to be widely used in the general population. It is thus not entirely surprising that in a series of cases some individuals without obvious other reasons for stroke are using such medications even shortly before to a stroke.

In comparison to the extensive diagnostic work-up of stroke cases, the classification of over-the-counter cough and cold medication use is puzzling. The authors report that these data were collected prospectively, and that stroke patients were considered to have used cough or cold medications when such medications were used 24 hours before the stroke event. However, the authors do not specifically mention how this information was collected. The stroke registry that Cantu et al used followed patients prospectively after a stroke had already occurred. The time interval of interest—the time between over-the-counter cough and cold medication use and the development of stroke—however, lies before the stroke occurrence. There are 2 main ways that such information could have been collected. First, the patients could have been asked about over-the-counter drug use prior to their stroke after the stroke occurred. Second, the information could have been collected using patient-independent documentation. Both scenarios are prone to substantial bias in exposure classification. If the stroke patients were asked about medication use, then the exposure information was not collected prospectively but retrospectively. Patients with no obvious major risk factors for stroke might have been interviewed in greater depth than those with obvious risk factors, and they may have recalled drug use prior to the stroke differently. It is then also unclear how information about drug use prior to the stroke event was gathered from patients with severe aphasia, and whether standardized questionnaires were used. In addition, a retrospective exposure assessment would question the proposed potential biological cascade by which sympathomimetics might relate to stroke in this study because increased blood pressure may also be the result of the stroke event. Patient-independent documentation, such as prescription databases or medical records, is unlikely to contain appropriate information about over-the-counter drug use. Although the authors provide detailed information on the brand and dosage of the cold and cough medications that were used prior to stroke events, such information does not overcome the potential initial bias in the main classification of the exposure.

Another potential bias may also have been present in the study—confounding by indication. The study does not provide information about the reasons for using cough and cold medications. If, for example, headache was one of the reasons for using these medications, there exist several scenarios that can lead to an apparent association between cough and cold medication use and risk of stroke. Of the 18 patients with cerebral angiography, 7 had signs of diffuse narrowing of brain arteries. Besides cerebral vasculitis, such narrowing has been described in patients with migraine headache, which also has been associated with stroke. Another potential scenario would be headaches caused by smaller bleeds prior to subarachnoid hemorrhage, which might play a role in the indication for over-the-counter cough and cold medication use in patients with subarachnoid hemorrhage. Also, headache is a symptom of hypertension, a strong risk factor for stroke. It is possible that hypertension, described in the study as potentially being induced by over-the-counter sympathomimetics, may have been present before the use of these medications. Although such scenarios might or might not be likely in this particular study, it emphasizes the importance of incorporating information regarding the indication of drug use in observational studies.

In summary, in addition to the limitations that apply to case series, the description of the methods used to classify patients with respect to over-the-counter cough and cold medication use in the study by Cantu et al. lacks important information. In pharmacoepidemiologic studies, such information is essential to provide evidence for a direct or causal association between drug use and the outcome of interest.

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Response
The main purpose of our series of cases was the description of some clinical, neuroimaging, and prognostic observations in patients who developed a stroke after taking a sympathomimetic contained in over-the-counter cough and cold drugs. It is well known that case series studies have important limitations for evaluating associations or cause-effect relationships. As pointed out by Dr Kurth, observational studies and particularly case series concerning the adverse effects of drugs are prone to diverse bias (recall bias, confounding for indication bias, exposure classification bias, etc.) and they should be considered when interpreting our case series. We decided to report our experience once an important publication, based on a case-control trial by Kernan et al, revealed that phenylpropanolamine (PPA) contained in appetite suppressants, and perhaps in cough and cold...
Dr Kurth comments that a comparison group is essential to determine if the risk of stroke is increased when using an over-the-counter cough and cold medication. We did not attempt to demonstrate a risk between stroke and cold remedy medications and then we did not use a comparison group; case series studies are mainly useful for making observations and not for testing associations or risks. We assumed that a risk probably existed based on the study by Kernan et al as previously commented. We did not plan and then do not have enough information from our patients to carry out a case-crossover design as proposed by Dr Kurth, which would allow us a comparison of short-term exposures and stroke risk in a series of cases.

Dr Kurth points out that our study does not provide information regarding over-the-counter cough and cold medication use in the remaining patients from our stroke registry and, more important, in the general population. As pointed out in the introduction of our case series, the first 2 cases of PPA-related hemorrhagic stroke in our hospital were described more than 10 years ago; from then on, information on the intake of sympathomimetic agents has been systematically obtained in all patients with stroke. Detailed information about drug medications (doses, time elapsed between drug ingestion and stroke onset, etc) was obtained only when a strong association with stroke development was evident. We did not obtain additional information from those patients who could have received such medications but did not fulfill our criteria for attributing the ingestion of particular sympathomimetics to the stroke in each case as described in the methods section.

We agree with Dr Kurth that because over-the-counter drugs are available without prescriptions, they tend to be widely used by the general population (probably as much as 40% of our population). Therefore, there is always a possibility that in a series of cases some individuals are using such medications when they develop a stroke for other reasons. This seems to be mainly applicable to ischemic stroke type where we identify only 1 patient among 1586 ischemic stroke cases. However, in comparison to ischemic stroke, the much higher frequency of hemorrhagic stroke cases after taking a sympathomimetic contained in over-the-counter cough and cold drugs (17 out of 678 intracerebral hemorrhages and 4 out of 49 nonaneurysmal subarachnoid hemorrhages) is noteworthy. This observation suggests that these medications could be implicated in the development of hemorrhagic stroke.

Concerning the comment by Dr Kurth about prospective or retrospective collection of data regarding exposure to drugs and stroke, we mentioned that information was prospectively collected because the association with drug ingestion was sought when the acute stroke occurred. Patients, or their relatives when patients were unable to cooperate, were asked about over-the-counter drug use in a retroactive way as it is usually done in clinical practice. When this information was not clear or impossible to be obtained for whatever reason, we assumed that exposure was not present. Indeed, the fact of looking prospectively for the association between drug ingestion and stroke for more than 10 years has allowed us to describe our current series of cases.

Dr Kurth emphasizes that increased blood pressure in our patients may be the result of the stroke event or that hypertension may have been present before the use of over-the-counter cold drugs. However, our patients did not have evidence of long-standing hypertension (retinal changes through ophthalmoscopy, ventricular hypertrophy by ECG, etc). On the other hand, it is well-known that sympathomimetics contained in cold agents are associated with the development of severe hypertensive crisis. In relation to the possibility of stroke associated to migraine in our patients, not one fulfilled established diagnostic criteria for considering this migraine complication; in addition, migraine has been associated with ischemic rather than hemorrhagic stroke. Finally, in the results section of our case series we described how well-known causes of vasculitis were excluded.

In conclusion, considering evidenced-base medicine, case series studies confer a weak level of evidence. Nevertheless, an important part of medical literature consists of reports of case series, and valuable results have sometimes ensued. Case series are useful for making observations that give rise to more decisive studies. Despite its possible limitations, our series of cases allows us to consider that (1) hemorrhagic strokes are much more common after taking a sympathomimetic contained in over-the-counter cough and cold drugs when compared with ischemic strokes; (2) because such medications are available without prescription, their use in the recommended doses should be emphasized; and (3) over-the-counter cough and cold sympathomimetic drugs should be used carefully in hypertensive patients.

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Stroke. 2003;34:e234-e235; originally published online December 1, 2003;
doi: 10.1161/01.STR.0000104161.88050.40

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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