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Medicine Correspondence Blog

The Medicine Correspondence Blog allows authors to post Letters to the Editors, Reviews, and other editorial writings that are not considered original research.

Saturday, January 9, 2016

Letter to the Editor: Using Taiwanese National Health Insurance Database

As specialists in carbon monoxide (CO) poisoning, we noted with interest the three papers in *Medicine* this year by Kao and co-workers examining the diagnosis of other diseases following an episode of CO poisoning (1-3). All were described as retrospective, population-based, cohort studies utilizing the Taiwanese National Health Insurance Database. In essence, patients experiencing CO poisoning during a 13-year period were identified, matched to controls, and the database searched for subsequent new diagnoses that occurred in the CO-poisoned population in excess to those seen in the cohort. One *Medicine* paper reported an increased risk of cardiac arrhythmias following CO poisoning, one Parkinson disease, and one peripheral artery disease.

We subsequently identified two more CO publications from Kao's group in other journals published in 2015, using the same research model and database (4,5). One reported increased risk of ischemic stroke following CO poisoning and one deep vein thrombosis. All of the papers had similar formatting.

It seemed unusual that one would query the same database in the same way, find five conditions associated with CO poisoning and report them in five individual manuscripts. We expected that the findings would be combined in one paper. The senior author, Dr. Chia-Hung Kao, is the same on all papers but the primary authors are different, coming from institutional departments as diverse as Health Services Administration, Emergency Medicine, Hematology/Oncology, and Internal Medicine.

A PubMed search performed December 31, 2015 revealed that Dr. Kao published at least 151 papers in 2015 from the same database analysis, each describing the association of two different conditions. Examples of the associations include gall bladder polyp/stroke, irritable bowel syndrome/erectile dysfunction, neonatal urinary tract infection/childhood allergic rhinitis, COPD/dementia, and allergic rhinitis/intracranial hemorrhage. Kao served as senior author to sixty different primary authors in 2015, each of whom published from one to twelve papers. The primary author's departmental affiliation was often unrelated to the organ system discussed.

This research appears to be templated and not hypothesis-driven. It seems unhelpful to the clinician trying to read the literature to have an investigator publish 150 manuscripts from one study model, each describing two conditions that were associated in an insurance database, often with no apparent connection. Across all of these CO association papers noted, we are wary of the data supporting these specific conclusions.

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Tom Pacific

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Carbon Monoxide Poisoning and Subsequent Cardiovascular Disease Risk: A Nationwide Population-based Cohort Study

Increased Risk of Parkinson Disease in Patients With Carbon Monoxide Intoxication: A Population-Based Cohort Study

Risk of Peripheral Artery Disease in Patients With Carbon Monoxide Poisoning: A Population-Based Retrospective Cohort Study

Posted by Tom Pacific at 3:21 PM

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Friday, January 8, 2016

Acute and Chronic Pheochromocytoma-Induced Cardiomyopathies: Takotsubo Syndrome can provide explanation for both phases

I read with great interest the excellent systematic analytical review by Batisee-Lignier et al¹ on “acute and chronic pheochromocytoma-induced cardiomyopathies”, published ahead of print on Dec 2015 in the journal *Medicine* (Baltimore). The authors have reported on 145 published cases with “pheochromocytoma-induced cardiomyopathies (PIC)” and divided them into two types of pheochromocytoma-induced myocardial disease, the first one is takotsubo syndrome (TS) and the second one is “catecholamine cardiomyopathy”(CC). Both types had similar brutal clinical presentation but different prognosis. The authors believe that the two types of PIC appear to have different pathophysiological pathways. However, it is justified to ask: Could the “TS” and “CC” types represent different levels of disease severity caused by the same disease with the same pathogenesis that is TS?² In the “CC” group, 31/76 (40.8) had complete left ventricular recovery before surgery and 55/75 (73.3%) had complete recovery of left ventricular function after tumor resection with no difference in the median recovery time between “CC” and TS groups. For this author, these 31 and 55 patients had also features consistent with TS. It will be interesting if the authors demonstrate the differences in the pattern of left ventricular wall motion abnormality (LVWMA) between “TS” and “CC” groups. Global left ventricular dysfunction, which I assume that the “CC” group had” does not exclude TS. The LVWMA in TS may be localized to the apical, mid-apical, mid-ventricular, basal; focal and global TS have also been described. The LVWMA may change during the course of the disease from regional to global or vice versa. Such change have been well-demonstrated in the case reported by Flam et al³ where the patient had mid-basal pheochromocytoma-induced TS during the first admission day and this progressed very rapidly to severe biventricular failure with pulmonary edema and cardiogenic shock during the following day. The brutal clinical presentation and the complete left ventricular recovery in “TS” group and the majority of patients in “CC” group challenges the blood-borne catecholamine caused wide-spread myocardial cell destruction. Both groups are most probably caused by the severe myocardial stunning, which was reversible, induced by the local cardiac sympathetic disruption and norepinephrine spillover.²

The “CC” group had more frequently pulmonary edema and worse prognosis possibly due to more severe disease and a longer delay time to the diagnosis of pheochromocytoma. It will be interesting to know the difference in the delay time to diagnosis between the “TS” and the “CC” groups. The patients in the “CC” group may have been exposed to repeated subclinical TS causing with time some permanent myocardial damage. The authors have appropriately mentioned this fact that “evolution of CC was likely longer due to chronic exposure even if the acute initial presentation was quite similar”. Furthermore, the time delay to diagnosis may expose the myocardium to longstanding hypertension which may be caused by pheochromocytoma. The “CC” group patients had significantly more patients with left ventricular hypertrophy, which may be attributed to longstanding hypertension. Another interesting point to know is whether there was difference in the prevalence of “CC” and “TS” before and after 1999 (1961-1999 versus 1999-2012) when the first report on TS was published in English language. Critical review of some cases of PIC published before 1999 and deemed as angina pectoris, myocardial infarction, severe left ventricular dysfunction or transient shock shows that they in fact had clinical features and course consistent with TS.⁴ Shaw et al⁵ in 1987 described a case with pheochromocytoma crisis induced transient shock and “myocardial impairment”; this case had actually clinical features, cardiac image study findings and course consistent with mid-apical takotsubo syndrome.

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Acute and Chronic Pheochromocytoma-Induced Cardiomyopathies: Different Prognoses?: A Systematic Analytical Review

Posted by Tom Pacific at 2:01 PM

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Friday, January 8, 2016

Comment on "Is long-term use of benzodiazepine a risk for cancer?"

Iqbal et al. conducted a longitudinal population-based case-control study on the carcinogenicity of benzodiazepines (BZD) in Taiwan.¹ They found that certain benzodiazepines were associated with a higher risk for cancers. The conclusion raised the concerns even panic of the insomniacs, to whom BZDs were most commonly prescribed, as well as the psychiatrists in Taiwan. However, I think that there was a major confounder missing in the abovementioned study, that is chronic insomnia. Obviously, insomnia would be the very direct cause for the insomniacs to use various BZDs. It is easy for the researchers to include insomnia as the adjusting confounder by means of International Classification of Disease code (ICD-9-CM codes 307.40, 307.42, 307.44, 307.49, and 780.52) from the data of the Bureau National Health Insurance system in Taiwan. Without considering the most common cause for the BZD use, the conclusion of the abovementioned study could be very erroneous.

For example, according to Iqbal et al., while compared with the non-users of BZDs, the users were associated with a higher risk for overall cancers with the adjusted hazard ratio of 1.14. However, as Fang et al. examined the risk of sleep disorder-induced cancers using nationwide population data during 2001-2011 in Taiwan,² they revealed a significantly adjusted hazard ratio (AHR) of 1.71 for overall cancers in the patients with sleep disorders compared with those without sleep disorders. Furthermore, Chen and Hwang explored the risk for primary central nervous system cancers in patients with obstructive sleep apnea (OSA) syndrome, which usually led to insomnia, between 2000 and 2003 in Taiwan.³ They found a significantly higher AHR of 2.20 for developing CNS cancer in the insomnia with OSA group. Both studies by Fang et al. and Chen and Hwang provide the evidence that the insomniacs are at a higher risk of developing cancers. Since the above three studies are all resulted from nationwide population data in Taiwan around relevant time period, the results seem to reveal that the use of BZDs may reduce the risk for developing overall and brain cancers in terms of AHRs, which reduced from 1.71 to 1.14, and from 2.20 to 1.98, respectively. Of course, the statistical analysis cannot be so straightforward since the referential control group in Iqbal's study, the non-users of BZDs, and that in Fang's study, those without sleep disorder, were not exactly the same, yet closely related and grossly overlapped. Nonetheless, the protective effect of certain BZDs was also found in the study by Iqbal et al. Actually, the protective effect of BZD use on cancers is rather manifested according to the dose-dependent trend in Iqbal's study. Their results (Table S4) revealed that a significant higher AHR was associated with less defined daily dose (DDD) of BZD (1.23 for < 0.10 DDD), while lower AHR with higher daily dose (0.95 for >1.00 DDD). The conflicting results justify the inclusion of insomnia as a major confounder while studying the association between BZD use and cancer risk for the future study.

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Resources:

Is Long-term Use of Benzodiazepine a Risk for Cancer?

Posted by Tom Pacific at 1:59 PM

2 comments

Wednesday, December 9, 2015

Letter to the Editor: Using of decision aids and algorithms in reporting adverse drug reactions

A recent manuscript by Li Z *et al* (1) have reported a Piperacillin/Tazobactam administration related fever in a 36-year-old woman. The fever developed after 3 days of the initiation of the above mentioned drug and disappeared at the 4th day of the cessation of it. It is really an interesting and teaching case that guides us in our everyday clinical practice. However, we think that some important issues should be discussed.

They have noted an apparent increase in patient's blood eosinophil count, ESR (erythrocyte sedimentation rate), and C - reactive protein levels after initiation of drug; but they did not mention whether these laboratory parameters have returned to normal levels (or decreased) after stopping of the offending drug and/or after discharge of the patients or during her further follow-up (1).

Adverse Drug Reactions (ADRs) are serious and common conditions that need to be reported to national and/or international authorities. A number of algorithms are used to standardize these ADRs reports and help us in making more objective decision on causality (e.g. the Naranjo algorithm, the Yale algorithm, the Karch algorithm, etc.) (2). One of these algorithms that are widely used in medical literatures is Naranjo ADR probability scale (2-4). It is a questionnaire designed by Naranjo *et al* (2) to better define ADRs and guide us in making objective decision. A score of 9 means definite, 5-8 probable, 1-4 possible, and 0 doubtful ADR (2). Although Li Z *et al* tried to exclude other causes of fever in their patient, they did not mention the patient's Naranjo ADRs probability score (1). According to our evaluation from the published data (1), it seems that the patient's Naranjo score is about 5 (i.e. probable ADR).

So, we think that these algorithms should be borne in mind and be used when reporting such conditions.

Conflict of interest

None to declare

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Resources:

Drug Fever Induced by Piperacillin/Tazobactam in a Scoliosis Patient: A Case Report

Wednesday, November 25, 2015

Letter to the Editor: Atrial Fibrillation and Gastroesophageal Reflux Disease: what about vice-versa? The arrow of time in medicine and biology

I read with great interest the hospital-based, retrospective, case-control observational study pointing out a possible link between Atrial Fibrillation (AF) and Gastroesophageal reflux disease (GERD) recently published in *Medicine*¹. As it is clearly stated by the authors, several studies have shown a correlation between GERD and AF but, interestingly, the present study suggests an inverse relationship between AF and GERD, since it is designed to look at AF as a risk factor for GERD. Indeed, by taking into consideration the possible pathophysiological mechanisms properly listed in the study, it would seem more logical to endorse the inverse association, which is supported by another recently published article², but it is this apparent contradiction that raises an important question on the use of time variable in contemporary medicine that I want to point out.

The availability of comprehensive clinical data, compiled less or more diligently during the hospitalization, allows the clinical researcher to force backward the arrow of time in search of possible causal links. This cheaper approach has often been criticized³ for the possible sources of errors due to bias and confounding that are more common if compared with prospective studies⁴; furthermore, it must be admitted that a positive association between two diseases is more likely among hospitalized patients than in the general population simply because the subjects that require hospitalization have often a combination of clinical issues.

Time is the most intriguing variable in the universe as it affects irreversibly biological life, but, when dealing with diseases that are recurrent during time, as AF and GERD are, with a certain seasonality, any observation, forward or backward, can connect the two diseases according to a timeline that can, inevitably, vary depending on our point of view. For this I have prepared a naïve explanatory drawing ([Figure 1](#)). Possibly we are still looking at the *etiological model* expecting a cause-effect relationship forgetting that we are definitively moving in a *multifactorial context* where the relationship between events is much more fluid and follows *non-linear dynamics*⁵ and, often, misunderstanding the fact that in statistics correlation does not imply causation.

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"...believe the separation between past, present, and future is only an illusion, although a convincing one." Albert Einstein

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Resources:

[Is Atrial Fibrillation a Risk Factor for Gastroesophageal Reflux Disease Occurrence?](#)