Before drugs are launched on the market, studies should have already proven that these drugs are efficient in treatment of specific conditions, by trials in vivo, on experimental animals and then finally on humans.

However, premarketing clinical trials are limited and not necessarily homogenous. Limitations, such as the short period of drug administration, or emphasis only in the efficiency of the drug may have caused less attention to be paid towards patient safety or potentially undesirable side effects, such as water retention or worsening of patients’ cardiovascular condition. These drugs have been popularly prescribed to many patients, especially in the premarketing period. However, sometimes, unexpected and undesirable symptoms arise, and increase in number, to the point where the drug may be disapproved by the FDA or similar agency. Some studies illustrate the undesirable side effects of drugs, whereby increased numbers of cardiovascular complications are occurring to people taking the drug. This report will collate some of the data relating to two drugs which are facing controversy in the market recently, namely Sibutramine and Rosiglitazone.

Sibutramine

Sibutramine, an anti-obesity agent, has a dual effect, inhibiting norepinephrine and serotonin reuptake. These reduce appetite and promote weight loss. Sibutramine improves insulin resistance, glucose metabolism, dyslipidemia, and inflammatory markers. Moreover, Sibutramine exerts a favorable effect on some surrogate cardiovascular endpoints, such as reduction of left ventricular hypertrophy and improvement of endothelial dysfunction. In some studies, Sibutramine has been shown to decrease uric acid level and reduce high-sensitivity C-reactive protein (hs-CRP).

A good cardiovascular safety profile was shown in controlled trials over 1-2 years as well as in several observation studies. However, since 2002, several cardiovascular adverse effects have been reported. Sibutramine Cardiovascular and Diabetes Outcome Study (SCOUT) was a randomized, double-blind, placebo-controlled, multicenter trial that was conducted from 2003 through 2009. The objective of this study was to evaluate the long-term effects of Sibutramine treatment, combined with diet and exercise on the rates of cardiovascular events and cardiovascular death among subjects who were at high cardiovascular risk.
All the subjects received Sibutramine during a 6-week, single-blind, lead-in period, then underwent random assignment in a double-blind to Sibutramine or placebo. Subjects who were enrolled in the study were classified into their appropriate cardiovascular risk groups: diabetes only (DM-only group), cardiovascular disease only (CV-only group), or both (CV-DM group). The primary outcome was the time from randomization to the first occurrence of a primary outcome event. The primary outcome events were nonfatal myocardial infarction, nonfatal stroke, cardiac arrest, and cardiovascular death.

The result showed that Sibutramine group had a 16% increased risk, relative to the placebo group (HR=1.16; 95% CI 1.03, 1.31; p=0.02). The individual rates of nonfatal myocardial infarction and stroke were also increased in the Sibutramine group (HR for nonfatal MI, 1.28; 95% CI, 1.04 to 1.57; p=0.02, HR for nonfatal stroke, 1.36; 95% CI, 1.04 to 1.77; p=0.03). The rates of cardiovascular death and death from any cause were not significantly different. An analysis of the three cardiovascular-risk groups showed the increases in nonfatal primary outcome events were seen in the CV-only and CV-DM groups but not in the DM-only group. The result of this and other studies study encouraged the manufacturer to voluntarily withdraw Sibutramine from the Australia, Canada and the U.S. market in October 2010.

Rosiglitazone

Rosiglitazone is an oral antidiabetic agent and a member of the group of drugs known as thiazolidinediones. Rosiglitazone specifically targets insulin resistance, which is thought to be central to the development of type 2 diabetes as well as dyslipidemia and hypertension in patients with diabetes mellitus. The first indications that of rosiglitazone increased the risk of myocardial infarction and cardiovascular death were published in 2007. The trials were divided between 3 categories. The first group included five of the studies submitted to the US FDA for the March 22, 1999. The second group included 35 studies, primarily identified from the GlaxoSmithKline clinical trial registry. And the last group included two studies from large, recently published trials, namely the Diabetes Outcome Prevention trial (ADOPT) and Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM). The results showed that the odds ratio for myocardial infarction was 1.43 (95% CI1.03, 1.98; p=0.03) and the odds ratio for cardiovascular death was 1.64 (95% CI0.98, 2.74; p=0.06). The result of this study raised questions concerning the safety of thiazolidinedione group of drugs, especially rosiglitazone.

Later rosiglitazone was evaluated for Cardiac Outcome and Regulation of Glycemia in Diabetes (RECORD which was an open-label, randomized non-inferiority trial. The primary endpoint was unconventional, cardiovascular hospitalization or cardiovascular death. That study was limited by low event rates, which resulted in insufficient statistical powers of detection The majority of results were concordant with the first meta-analysis study; the rosiglitazone group demonstrated increased risk for myocardial infarction but not cardiovascular or all-cause mortality. The US FDA did not withdraw rosiglitazone from the market but it has cancelled ongoing phase clinical IV trials of Thiazolidinedione Intervention (00879970) at the present time. The phase II and phase III study indicated increased cardiovascular mortality, myocardial infarction and stroke including hospitalization for acute coronary syndrome and urgent revascularization procedures as a result of taking the drug. The US FDA ordered the manufacturer to demonstrate that the antidiabetic drugs therapy to treat type 2 diabetes will not increase cardiovascular risk. The European Union recommended that rosiglitazone be withdrawn from the EU market in September 2010.

Summary

Nowadays, we have many new drugs in the market; despite their apparent efficacy in treatment management, however, side effects have not necessarily been seriously investigated during premarketing. Serious reactions to the drug appear later on, which sometimes results in the drugs being withdrawn. Sibutramine was available for prescription since more than 10 years and has now been withdrawn in Western markets by the manufacturer; unlike the European Medicines Agency, the US FDA has not yet withdrawn Rosiglitazone from the market but the present clinical applications have shown it to increase the risk of cardiovascular events.

New antidiabetic agents need to be demonstrably free of causing patients increased risk of cardiovascular events.
Drug Induced Cardio-vascular Events

References

Autism and Epilepsy: Practical points that clinicians should aware of

Typical Clinical Scenarios

Case 1: A 15-year-old high functioning autistic boy with normal IQ was found to have episode of eyes rolling upwards followed by rhythmic body shaking and was unresponsive for 2 minutes. Ten hours after symptom onset, EEG study was performed and reported as normal. One week later, during playing soccer, he had another attack with similar pattern. Physical examination was unremarkable. Second EEG study was normal. He has no history of head injury. Family history was negative for seizure disorder. No developmental regression is mentioned. Should we prescribe antiepileptic drugs for this child?

Case 2: A 7-year 2-month-old autistic girl with severe developmental delays who has developed ‘bizarre behaviors’ described as head nodding and rapid eye blinking during listening to radio over a two week period. During sleep, she sometimes wakes up in the middle of the night and makes loud noises for 10 minutes before falling asleep again. These behaviors are unusual and have never occurred before. Regular medications included risperidone, methylphenidate, and zinc supplements. Are those ‘bizarre, unusual behaviors’ epilepsy or just stereotypic movements that are commonly found in autistic children?

Case 3: A 5-year-old autistic girl with epilepsy. Her seizures (generalized tonic-clonic) are well-controlled by valproic acid. She has had regular rehabilitation and physical therapy for motor and speech delay. Overall milestones are gradually improved. One day after being rebuked by a friend at school, she stopped speaking, not making any sound. However, she is able to follow verbal instruction as usual. Parents are frightened and bring her to pediatrician for proper opinion. Has she developed language regression? Could this symptom be a subclinical seizure or just a behavioral reaction?

Case 4: A 10-year-old high functioning autistic boy is brought to clinic due to excessive drowsiness over two weeks. Actually his sleep duration is usually of 6-8 hours a day but has increased to 12-16 hours a day. Teachers have also reported to parents regarding his frequent falling asleep in the classroom. Normally, he is a good disciplined child and is always admired by parents, teachers and friends. Academic performance is average. He is a school tennis athlete. There is neither fever, history of head injury nor drug use during this episode. Physical examination is normal. Blood tests for CBC, electrolytes, sugar, BUN, Cr, liver function, thyroid function, and ammonia level are normal. CT scan of the brain shows negative study. Shall we consider ‘non-convulsive seizure’ as the cause of excessive sleepiness in this patient?