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BULLETIN ON ADVERSE DRUG REACTIONS

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Department of Pharmacology

LTMMC & LTMGH, Sion, Mumbai - 22

Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk . . . . ✍

Dear Friends and Colleagues

It gives me great pleasure to present to you yet another issue of Bulletin on Adverse Drug Reactions.

Acute pancreatitis is a severe condition with a high mortality and morbidity. Under this broader topic a special mention has to be made about Drug induced pancreatitis which is a rare adverse reaction. Due to the less information available on this topic, the true epidemiology and risk factors are not extensively available and thus it poses a big challenge to the clinicians. The first article deals with this topic of drug induced pancreatitis and gives an overview of the drugs causing it, its pathology and preventive and therapeutic measures.

The second article deals with one of the adverse effects seen with a popular group of drugs called as statins. Under this heading the current controversies over statins and their related cognitive impairment is discussed. Some basic measures for the preventions and identification of this ADR has been highlighted.

Other features in this issue include analysis of the ADRs from our institute for your quick review, an interesting case series and current news related to drug regulatory.

I hope the readers find all the sections of this bulletin interesting and informative.

Finally, I would like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance, to all the authors for contributing in the bulletin and to all the members of Department of Pharmacology for their efforts in bringing out the current issue of this bulletin.

Thank you.

Dr. Sudhir Pawar

DRUG INDUCED PANCREATITIS

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Introduction

Pancreatitis is inflammation of the pancreas with acinic cell injury. It is classified into acute and chronic forms. The incidence of acute pancreatitis is about 5-35/100,000 new cases per year worldwide, with a mortality rate of approximately 3%. The number of hospitalizations for acute pancreatitis in the United States is increasing and is now approximated to be 274,119.[1] Among the various etiologic factors, drugs are often overlooked as a causative agent. Drugs are responsible for 0.1 to 2% cases of drug induced acute pancreatitis. However, no prevalence data is available from India. Only some idea about incidence can be obtained from patients admitted in tertiary care centers. At the All India Institute of Medical Sciences (AIIMS), New Delhi, 276 patients with acute pancreatitis (AP) were hospitalized from January 1997 to June 2002, i.e. about 55 patients per year.[2]

Etiology

The various etiologic factors are responsible for acute pancreatitis are given in the table 1, of which alcoholism and cholelithiasis the leading causes.[1]

Table 1: Etiologic Factors Associated with Acute Pancreatitis

Structural	Gallstone disease, sphincter of Oddi dysfunction, pancreas divisum, pancreatic tumors
Toxins	Alcohol (Ethanol) consumption, scorpion bite, organophosphate insecticides
Infectious	Bacterial, viral (including HIV and H1N1 influenza), parasitic
Metabolic	Hypertriglyceridemia, chronic hypercalcaemia
Genetic	Cystic fibrosis, α1-antitrypsin deficiency, hereditary (trypsinogen gene mutation)
Medications	See Table 3
Iatrogenic	Abdominal Surgery, Endoscopic retrograde cholangiopancreatography (ERCP)
Kidney disease	Chronic kidney disease, dialysis related
Trauma	Blunt abdominal trauma
Vascular	Vasculitis, atherosclerosis, cholesterol emboli, coronary artery bypass surgery
Other etiologies	Congenital Crohn's disease, autoimmune, tropical solid organ transplantation, (e.g. Liver, kidney, heart), refeeding syndrome
Idiopathic	Undetermined cause

The information on drug-induced pancreatitis (DIP) is very less. Most data is obtained from case reports, which do not provide reliable information on the incidence.[3] Badalov et al (2007) suggested a classification system for drug-induced pancreatitis which gives an indication of the association of the drug with DIP. In this classification, the drugs causing pancreatitis are divided into five categories: Ia, Ib, II, III and IV (Table 2).

Table 2: Badalov Classification of Drug-induced Pancreatitis

Category	Criteria
Class Ia	• At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class Ib	• At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class II	• At least 4 cases in the literature • Consistent latency (75% of cases)
Class III	• At least 2 cases in the literature • No consistent latency among cases • No rechallenge
Class IV	• Drugs not fitting in the earlier-described classes, single case report published in medical literature, without rechallenge

Mechanism of drug-induced pancreatitis:[3,4]

The mechanism of action of drug induced pancreatitis is speculative. The various case reports, case-control studies, experimental studies and animal studies helped to extract potential mechanism of action of drug induced pancreatitis. Drug-induced acute pancreatitis has also been associated with adverse effects of the drugs like hypertriglyceridemia, hypercalcaemia, which are the risk factors for acute pancreatitis. (Table 3)

Table 3: Commonly used drugs causing Drug-induced pancreatitis and their proposed mechanism of action

Drug/Drug Class causing acute pancreatitis	Proposed mechanism of action	Badalov Class
ACE inhibitors	• Local angioedema of pancreatic duct due to decreased degradation of bradykinin	• Class Ia, III, IV
Statins	• Direct toxic effect to pancreas • Accumulation of toxic metabolite	• Class Ia, Ib, III, IV

	• Secondary of rhabdomyolysis • Immune mediated inflammatory response	
Anti-HIV Drugs	• HIV infection itself	
	• Direct inflammation of pancreas • Secondary to metabolic disturbances - Protease inhibitors (Insulin resistance, hyperglycemias, hypercholesterolemia, hypertriglyceridemia)	• Lamivudine and Nelfinavir - Class Ib • Didanosine - Class II • Ritonavir - Class IV
Oral contraceptives	• OC induced Hypertriglyceridemia (Risk factor) • OC induced hypercoagulable state leading to pancreatic necrosis	• Class Ib, II
Azathioprine and 6-Mercaptopurine	• Allergic or idiosyncratic	• Class Ib
Antidiabetic drugs (Metformin)	• Drug overdose • Drug accumulation • Acute renal failure triggered by vomiting	• Class III
Mesalamine	• Hypersensitivity reactions	• Class Ia, Ib
Metronidazole	• Free radical production • Immune-mediated inflammatory response • Metabolic effects • Concomitant use with other drugs used in H. pylori infection	• Class Ia
Tetracycline	• Secondary to drug-induced fatty degeneration	• Class Ia
Valproic acid	• Direct toxic effect of free radicals on the pancreatic tissue • Depletion of superoxide dismutase, catalase, glutathione peroxidase • Idiosyncratic reaction	• Class Ia
Diuretics (Loop diuretics, Hydro-chlorothiazide)	• Direct toxic effects to pancreas • Diuretic induced stimulation of pancreatic secretion and ischemia • Hydrochlorothiazide induced hypercalcaemia and hyperlipidemia	• Class II, III, IV

Clinical presentation:[5]

The onset of acute pancreatitis is sudden. The patient presents with epigastric abdominal pain, vomiting and collapse. The pain is steady, boring and severe and often made worse by walking and lying supine

and better by sitting and leaning forward. The pain usually radiates to back, but may radiate to the right or left. The pain is often associated with nausea and vomiting. Marked epigastric or diffuse tenderness on palpation with rebound tenderness and guarding is present in severe cases. The abdomen is often distended and tympanic, with bowel sounds decreased or absent in severe disease. The vital signs may be normal, but hypotension, tachycardia and low grade fever are often observed, especially with widespread pancreatic inflammation and necrosis.[3]

The condition has to be differentiated from other diseases producing acute abdomen such as acute appendicitis, perforated peptic ulcer, acute cholecystitis and infarction of intestine following sudden occlusion of the mesenteric vessels.

Diagnosis:[5,6]

The main objective in the diagnosis of drug-induced pancreatitis is to first diagnose it as acute pancreatitis using defined criteria. The diagnosis should be within 48 hours based on the characteristic abdominal pain and elevation of several markers which includes serum amylase and lipase. Lipase is more sensitive and specific than amylase.[3] Other tests which are useful in diagnosis are serum trypsinogen, pancreatic proteases, C-reactive protein, interleukin-6, and interleukin-8, leucocyte count, urine tests for casts, proteins and glucose, blood glucose levels, blood urea nitrogen and serum bilirubin levels. Lipid profile, serum calcium levels also assist in the diagnosis, since elevated lipid levels and calcium levels considered as risk factors for acute pancreatitis.

While diagnosing drug-induced pancreatitis a detailed medical and medication history should be recorded. The onset of drug-induced pancreatitis after initiation of medications ranges from a few months to several years, with a median of 5 weeks; onset after rechallenge can occur within hours. Drug-induced acute pancreatitis should be suspected in high risk patients, such as those receiving immunomodulating drugs or who have HIV infection, the elderly, or those with diabetes mellitus.[3] Trivedi and Pichumoni (2005)[7] provided an algorithm to diagnose Drug-induced pancreatitis (DIP) (Figure 1).

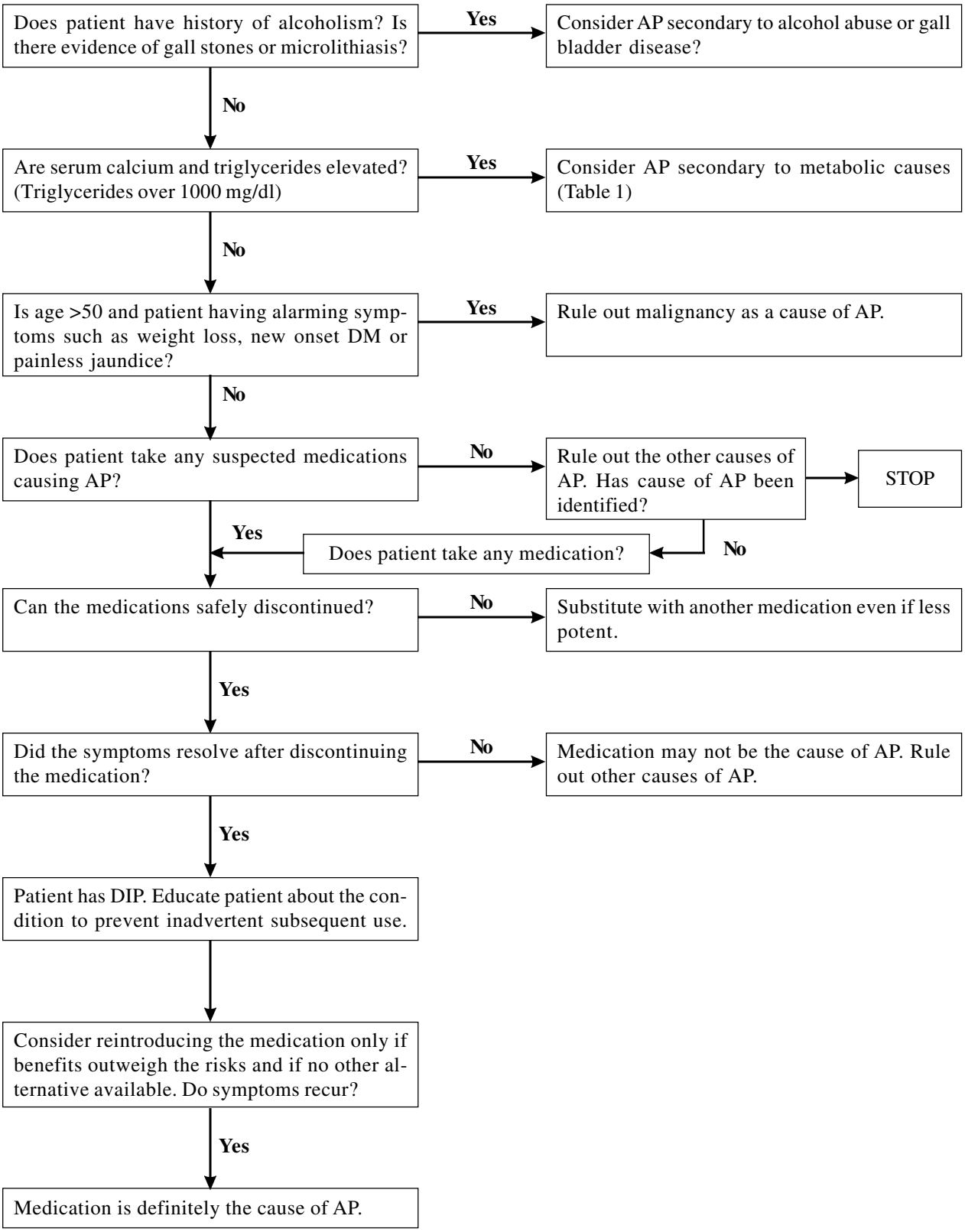

Figure 1 : Algorithm to diagnose DIP

Management:

One of the most important strategies to manage drug-induced pancreatitis is the withdrawal of the offending agent to prevent further pancreatic injury. The offending drug may be substituted for a drug from a different class.

Management of drug-induced acute pancreatitis is similar to that of acute pancreatitis due to other causes. The aims of treatment of acute pancreatitis are:

- To relieve abdominal pain and nausea
- To provide fluid replacement therapy
- To correct electrolyte, glucose and lipid abnormalities
- To minimize systemic complications
- To prevent pancreatic necrosis and infection

Relief of abdominal pain

Parenteral opioid analgesics are used to control abdominal pain associated with acute pancreatitis. Injection Pethidine 100-150 mg i.m. every 3-4 hours may be used to control pain. In patients with liver or kidney disease, the dose needs to be reduced. Oral intake of fluids and foods can be resumed when the patient is largely free from pain and has bowel sounds however in 20% of patients, pain may recur on refeeding.

Fluid replacement therapy

It has been noted from various observational studies that aggressive fluid administration may lead to benefit like decreased mortality and organ failure as well as harm like abdominal compartment syndrome. Lactated Ringer's solution may be preferred over normal saline for fluid replacement therapy.[8]

Correction of electrolyte, glucose and lipid abnormalities

IV potassium and magnesium are used to correct electrolyte deficiency states. Calcium gluconate must be given intravenously if there is evidence of hypocalcaemia with tetany. Insulin is used to treat hyperglycaemia. Statins may be started to correct abnormal lipid levels.

Prevention of pancreatic necrosis and infection

Necrosectomy may improve survival in patients with necrotizing pancreatitis and is often indicated for infected necrosis, although a select group of relatively stable patients with infected pancreatic necrosis may be managed with antibiotics alone.

Prevention of drug-induced pancreatitis:

Prevention of drug-induced pancreatitis consists largely on recognition of which drug has strongest evidence of being causally associated with pancreatitis, high-risk groups, maintenance of high index of

suspicion. DIP can be prevented by extracting the detailed history like risk factors for pancreatitis, any history of drug intake, any previous such event, history of alcohol intake, gallstone etc. Knowledge of possible mechanisms of drug-induced pancreatitis may be helpful in prevention of this adverse drug reaction. DIP occurring as a result of idiosyncratic drug reaction is difficult to prevent.[9]

Conclusion:

The incidence of drug-induced pancreatitis is increasing globally. There are many drugs reported in literature to be causally associated with acute pancreatitis. Acute pancreatitis due to drug reactions is often overlooked because of difficulty in appreciating a drug as its cause. A careful clinical assessment, history and causality assessment of drug reaction will help in early diagnosis and management. There are many risk factors for drug-induced pancreatitis which should be taken in to consideration for proper diagnosis. Future studies are needed to identify which subset of the population is more prone for this adverse drug reaction.

References:

1. Conwell DL, Greenberger NJ, Banks PA. Approach to the patient with pancreatic disease. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, et al., editors. Harrison's principles of internal medicine. 19th ed. New York: McGraw Hill; 2016. p. 2086-2090
2. Shinde J.V., Shinde V.C. Acute pancreatis: Demographics, aetiological factors and outcomes. Indian Journal of Applied Research. 2015;5(4):440-443
3. Conti Bellocchi, Maria Cristina. Campagnola, Pietro. Frulloni, Luca. (2015). Drug - induced acute pancreatitis. Pancreapedia: Exocrine Pancreas Knowledge Base, DOI: 10.3998/panc.2015.32
4. Kaurich T. Drug-induced acute pancreatitis. Proceedings (Baylor University Medical Center). 2008;21(1):77-81.
5. Friedman LS. Liver, biliary tract and pancreas disorders. In: Papadakis MA, McPhee SJ, editors. Current Medical Diagnosis and Treatment 2016. 55th Edition. New York: McGraw Hill; 2016. p. 663-720.
6. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: a review. Ochsner J. 2015 Spring;15(1):45-51
7. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005 Sep;39(8):709-16.
8. Wu Bu, Hwag JQ, Gardner TH, et al. Lactated Ringer's solution in patient with acute Pancreatitis. Clin Gastroenterol Hepatol 2011;9(8):710-717.
9. Balani AR, Grendell JH. Drug-induced pancreatitis : incidence, management and prevention. Drug Saf. 2008;31(10):823-37.

CONTROVERSIES OVER STATINS RELATED COGNITIVE IMPAIRMENT

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Introduction

HMG coenzyme A reductase inhibitors - 'Statins' have become the most commonly prescribed hypolidemic agents since their introduction in 1987.[1] Statins are the most effective and widely used hypolipidemic agents to reduce low-density lipoprotein cholesterol and reduce cardiovascular morbidity and mortality.[2] Statins are well tolerated and have minimal adverse effects, most commonly myopathies, effects on liver enzymes, diarrhoea, and rarely rhabdomyolysis.[3] However, some adverse effects do not become evident in clinical trials but become apparent after use in real world clinical practice and use in broader patient populations. On similar lines, several case reports and case series have suggested a budding association between statins and cognitive impairment.[4]-9 However, because this probable adverse event is conflicting with findings of several studies that demonstrate a potential benefit on cognition with the use of statins, it merits further analysis to clear the confusion.[10-13]

This article is in fact prompted by the U.S. Food and Drug Administration (FDA) statement on cognitive impairment with statins, which came as a bolt from the blue to many physicians.[14] Many practitioners really wondered what was the body of evidence and what was the rationale for that decision. The suggested label revision may have important public health consequences, such as limiting the use of statins, or doses of statins, in patients with established cardiovascular diseases and thereby depriving them the cardiovascular benefits. Despite the US FDA warning regarding cognitive impairment, the relationship between statins and cognition remains unknown.

The US FDA Warning:

The US FDA in 2012 released a safety announcement of risk of cognitive impairment. Explicitly, the US FDA stated that "ill-defined memory loss" and "confusion" were among the cognitive effects eminent in statin users.[14]

To further provide the rationale on the warning, the US FDA in its report says that it had been investigating reports of cognitive impairment with statin use for several years. It has reviewed databases that reported this adverse reaction to statins and also some clinical trials that assessed the effects of statins on cognition.

The US FDA cited certain observational studies[8,9,15-20] and randomized controlled trials,[21-23] for the cognitive impairment risk with statins use and highlighted that these effects were not associated with "fixed or progressive dementias" such as Alzheimer disease.

The statins affected by this warning include lovastatin, rosuvastatin, fluvastatin, atorvastatin, pitavastatin, pravastatin and simvastatin.[14] However, what is more important here is that while releasing this warning, the US FDA has also underlined that "The value of statins in preventing heart disease has been clearly established" and "Their benefit is indisputable, but they need to be taken with care and knowledge of their side effects."

What does the data suggest? Heart Saviour coming at the price of Brain?

Reports of statin-associated cognitive impairment were found principally in few observational studies (e.g., case reports/series) and occasionally in few randomised trials. On the contrary, in the majority of randomized controlled trials and observational studies, statins were found to have either a neutral or beneficial effect on cognition.[24] In a narrative overview of statin safety, it was concluded that there is no increased risk of cognitive decline with statin use and that the FDA label changes should not change clinical practice.[25]

Various level 3 /level 4 evidences suggested that there was no increased incidence of Alzheimer disease and no difference in cognitive performance related to procedural memory, attention, or motor speed with statin therapy. Similarly, level 2 evidences found that statin therapy did not result in higher incidence of cognitive impairment or dementia. Also, very few reports of cognitive impairment with statin were observed in FDA post-marketing surveillance databases, incidence of which was almost similar to that is usually observed with other cardiovascular drugs.[26]

Various short-term trials suggest no consistent effect of statin therapy on cognitive end points. The most common short-term end point used was Digit Symbol Substitution Testing (a well-validated measure of cognitive function) which showed no significant differences in the mean change from baseline to follow-up between the statin and placebo groups (296 total exposures in 3 trials).[27] Long-term cognition studies included 23,443 patients with mean exposure duration of 3 to 24.9 years. Three studies found no association between statin use and incident dementia, and 5 found a favourable effect. Pooled results revealed a 29% reduction in incident dementia in statin-treated patients (hazard ratio, 0.71; 95% CI, 0.61-0.82).[27]

On the other hand, statins for the prevention and treatment of dementia first created attention in 2000 when 2 epidemiologic studies reported a lower risk of dementia in those using statins. Several publications that followed reported mixed results. Two more recently published meta-analyses found a potential benefits on cognition.[27]

Recognition of cognitive impairment

As highlighted by the US FDA statement, the reports about memory loss, forgetfulness and confusion span all statins and all age groups. Patients affected by cognitive impairment with statin often report feeling "fuzzy" or unfocused in their thinking. In general, the symptoms were not serious and were reversible within a few weeks after the patient stopped using the statin.[14]

Largely, cognition may be subdivided under 4 domains: executive function, memory, language and visuospatial ability. Cognitive impairment can therefore be defined as a decline from baseline in any of the 4 domains, sometimes overlapping one another.[28]

Cognition Tests[28]

	MMSE	3MS Test	ADAS-Cog	DSST
Goal	To evaluate orientation (time, place), registration, attention and calculation, recall, language, ability to follow commands			To evaluate attention, short-term memory, processing speed
Description	11 questions (10-min test)	24 questions (15-min test) As the MMSE but more comprehensive with different levels of difficulties	11 blocks of different tasks to do (30- to 45-min test). More in-depth test	Consists of 9 digits and symbols to pair. Under each digit, the subject writes down the corresponding symbol, pairing as many as possible in 90s.
Score range	0-30	0-100	0-70	0-76* (number of correct pairs of symbols/digits)
Threshold for diagnosis	>26: no or questionable impairment 21-25: mild 11-20: moderate 0-10: severe	<79 suggests cognitive impairment <48 suggests severe impairment	Score <18 suggests greater cognitive impairment. A 4-point change in 6 months is a clinically significant difference.	A low score indicates cognitive impairment but no specific threshold defined.

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognition; DSST, Digital Symbol Substitution Test; MMSE, Mini Mental State Examination; 3MS Test, Modified Mini-Mental State Test.

**In theory, the maximum score is 90; in practice, the maximum is set at 76.*

Managing cognitive impairment as a side effect should it happens

Although most of the available data suggest no impairment in cognition with use of statins, based on expert opinion, a series of steps has been recommended by the Statin Cognitive Safety Task Force (SCSTF) should a patient report cognitive impairment after initiation of therapy. It recommends finding out other potential contributors such as anticholinergic medications (e.g., diphenhydramine, tricyclic antidepressants, some antipsychotics), cognitive testing and performing a benefit-risk assessment of

stopping or decreasing the dose versus continuing the statin. Statins have robust evidence supporting their use in secondary prevention of cardiovascular events. Therefore, it becomes vital to discuss the risks of stopping (increased risk of cardiovascular events) or continuing (cognitive impairment) the statin with the patients. It is recommended that a drug-free period of 1 to 2 months can be given prior to a rechallenge if it is suspected that the statin is contributing to the cognitive impairment. Also, expert opinion suggests a switch to a less lipophilic statin such as Rosuvastatin or Pravastatin to diminish the effects on cognition.[28] Preliminary data suggest that statins that are less lipophilic (i.e., pravastatin and Rosuvastatin) may be less likely to contribute to cognitive impairment due to limited penetration across the blood-brain barrier. These drugs would be a reasonable alternative in cases where cognitive impairment secondary to another statin is suspected.[24]

Summary

Overall, the available literature supports the rare occurrence of cognitive impairment with the use of statins in spite of occasional reports of statin-associated cognitive improvement. In patients without baseline cognitive dysfunction, short-term data do not support the association of cognitive impairment and statins. In contrast to this, the long-term data may support a beneficial role for statins in the prevention of dementia. However, to draw unequivocal conclusions about the either effects of statins on cognition, larger and well-designed studies are needed. If cognitive impairment is suspected in a patient taking a statin, it is essential to look at other causes before attributing it to the statin. Should it happens, switching from lipophilic to hydrophilic statins such as rosuvastatin may resolve this issue of cognitive impairment. Also, in case of suspected ADR, it is imperative that the well-established cardiovascular benefits of statins, including stroke reduction, should always be highlighted to the patient before discontinuation of treatment. Probably, there is no need to press the panic button on concerns of cognitive impairment with statins as the evidences suggest that cardiovascular benefits of statins and possible cognitive benefits prevail over the risk of cognitive impairment. Thus, in spite of some concerns of cognitive impairment with statins, the current evidences do not favour the changing practice with respect to statin use, though one needs to be vigilant and address efficiently if it occurs at all.

References:

1. Wang TJ, Stafford RS, Ausiello JC, et al. Randomized clinical trials and recent patterns in the use of statins. Am Heart J 2001;141:957-63.
2. Genest J, McPherson R, Frohlich J, et al. Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult-2009 recommendations. Can J Cardiol 2009;25:567-79.
3. Armitage J. The safety of statins in clinical practice. Lancet 2007;370: 1781-90.
4. Peters JT, Garwood CL, Lepczyk M. Behavioral changes with paranoia in an elderly woman taking atorvastatin. Am J Geriatr Pharmacother 2008;6:28-32.
5. Galatti L, Polimeni G, Salvo F, et al. Short-term memory loss associated with rosuvastatin. Pharmacotherapy 2006;26: 1190-2.
6. Padala KP, Padala PR, Potter JF. Simvastatin-induced decline in cognition. Ann Pharmacother 2006;40:1880-3.

7. King DS, Wilburn AJ, Wofford MR, et al. Cognitive impairment associated with atorvastatin and simvastatin. Pharmacotherapy 2003;23:1663-7.

8. Orsi A, Sherman O, Woldeselassie Z. Simvastatin-associated memory loss. Pharmacotherapy 2001;21:767-9.

9. Wagstaff LR, Mitton MW, Arvik BML, et al. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871-80.

10. Kurata T, Miyazaki K, Kozuki M, et al. Atorvastatin and pitavastatin improve cognitive function and reduce senile plaque and phosphorylated tau in aged APP mice. Brain Res 2011;1371:161-70.

11. Wolozin B, Kellman W, Rousseau P, et al. Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000;57:1439-43.

12. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000;356:1627-31.

13. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002;59:223-7.

14. FDA expands advice on statin risk. FDA Consumer Health Information/ U.S. Food and Drug Administration. January 2014. Available at: http://www.fda.gov/downloads/ForConsumers/ ConsumerUpdates/ UCM293705.pdf. Accessed Mar 22, 2015.

15. Zamrini E, McGwin G, Roseman JM. Association between statin use and Alzheimer's disease. Neuroepidemiology. 2004;23(1-2): 94-98.

16. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? Arch Gen Psychiatry. 2005;62:217-224.

17. Bettermann K, Arnold AM, Williamson J, et al. Statins, risk of dementia, and cognitive function: secondary analysis of the Ginkgo Evaluation of Memory study. J Stroke Cerebrovasc Dis. 2012; 21(6):436-444.

18. Beydoun M, Beason-Held LL, Kitner-Triolo MH, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. J Epidemiol Community Health. 2011;65(11):949-957.

19. Evans M, Golomb B. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy. 2009;29(7): 800-811.

20. Parker BA, Polk DM, Rabdiya V, et al. Changes in memory function and neuronal activation associated with atorvastatin therapy. Pharmacotherapy. 2010;30(6):236e-240e.

21. Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. Am J Med. 2000;108(7):538-546.

22. Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med. 2004; 117(11):823-829.

23. Trompet S, Vliet P, Craen AJM, et al. Pravastatin and cognitive function in the elderly: results of the PROSPER study. J Neurol. 2010;257(1):85-90

24. Carlos H, Jean-Christy F. Is Statin-associated Cognitive Impairment Clinically Relevant? A Narrative Review and Clinical Recommendations. The Annals of Pharmacotherapy. 2012;46(4):549-557.

25. Jukema JW, Cannon CP, De Craen AJM, et al. The controversies of statin therapy: weighing the evidence. J Am Coll Cardiol. 2012;60(10):875-881.

26. Karl Richardson, Marisa Schoen, Benjamin French, et al. Statins and Cognitive Function: A Systematic Review Ann Intern Med. 2013;159(10):688-697

27. Swiger KJ, Manalac RJ, Blumenthal RS, et al. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. Mayo Clin Proc. 2013 Nov;88(11):1213-21.

28. Jérémie MG, Anne Massicotte. Statins and their effect on cognition: Let's clear up the confusion. Can Pharm J (Ott). 2015 May; 148(3): 150-155.

ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED

(November 2015 to February 2016)

Compiled by Dr Swati Patil

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Total Case Reports: 77

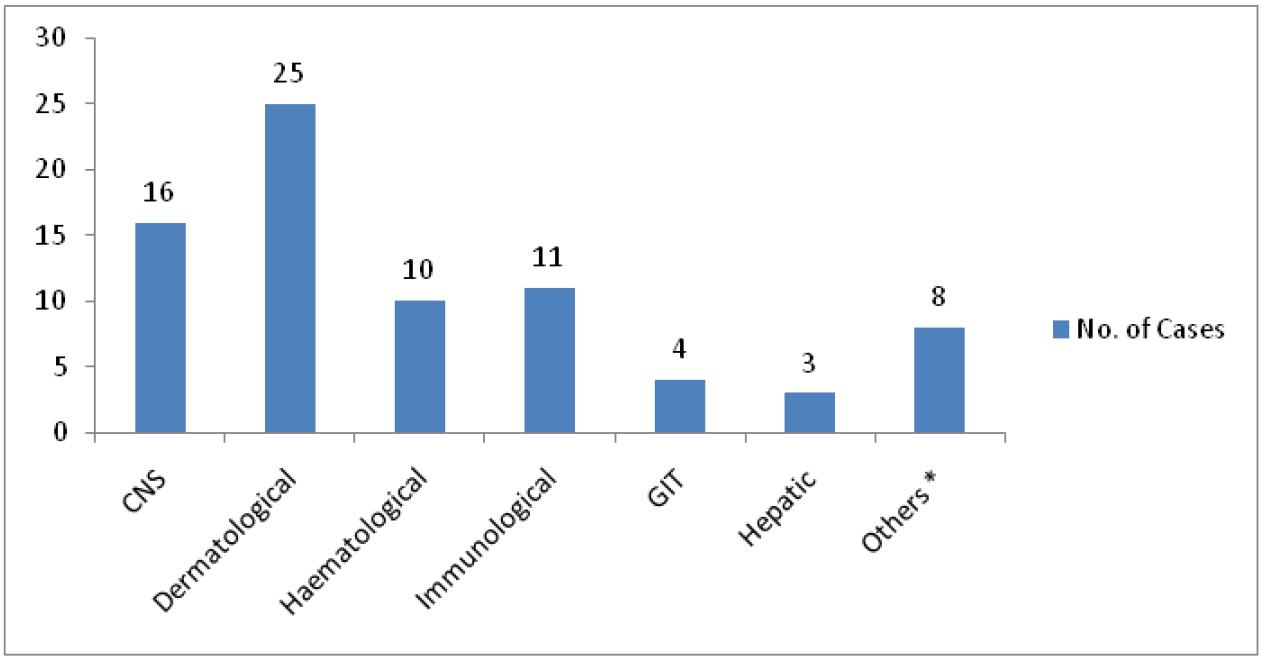
I. Age and Gender distribution:

Age groups	Number of patients	Males	Females
<3 yrs	2	1	1
3 - 17 yrs	19	13	6
18 - 44 yrs	38	18	20
45 - 60 yrs	10	5	5
>60 yrs	8	7	1
Total	77	44	33

II. Seriousness of the reaction:

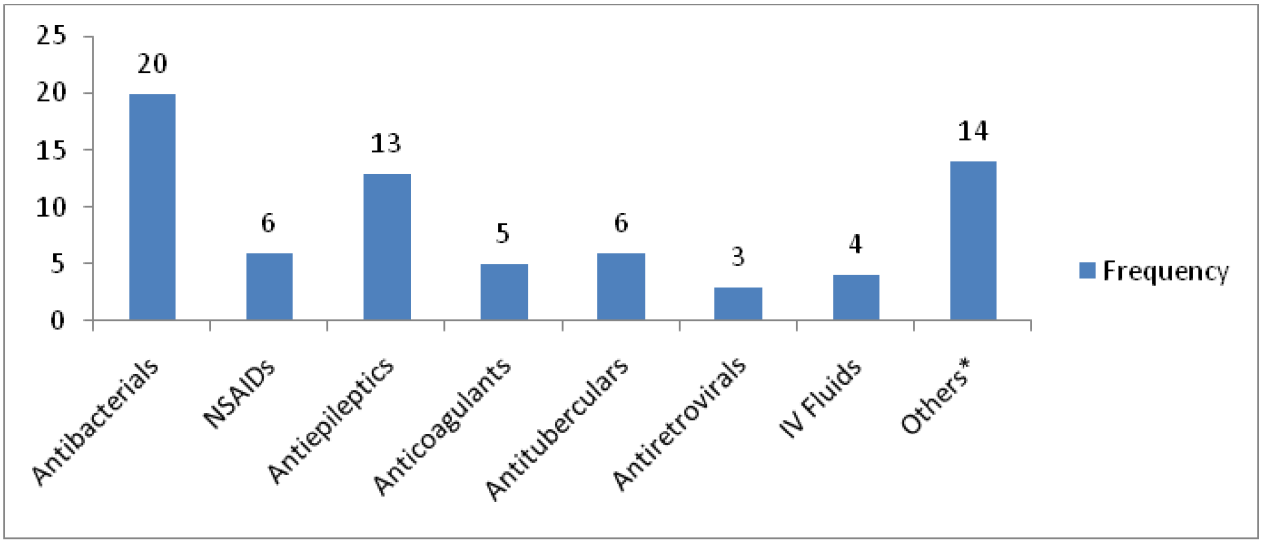
Seriousness of the ADR	No. of Cases (N=77)
Yes	62
No	15

III. System involved in the ADR : N=77



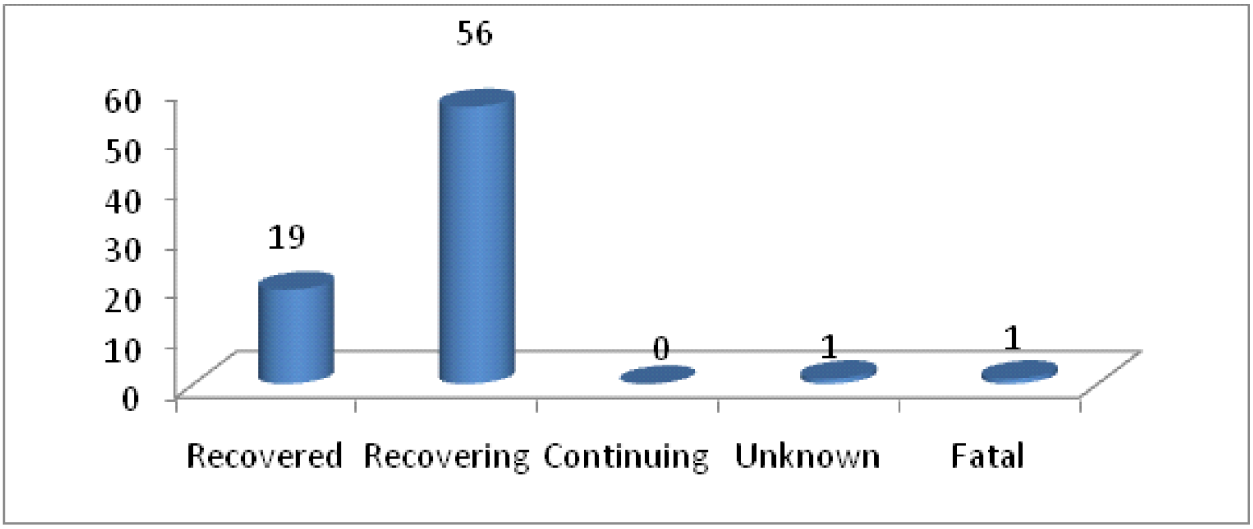
*Others includes cardiovascular, ENT, endocrine, musculoskeletal and renal systems.

IV. Class of the Suspected drug: N=77

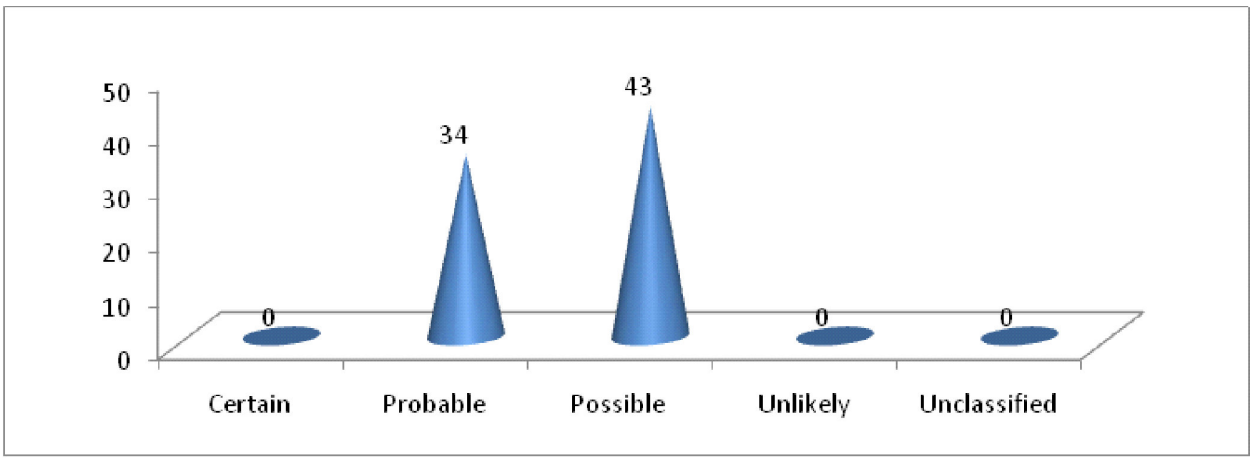


*Other drugs includes Cardiovascular drugs, antivirals, anticancer, antihelminthic, antihistaminic, antipsychotic, antotoxin, vaccines and antispasmodics.

V. Outcome of the reaction : N=77



VI. Causality assessment (WHO UMC Classification) : N = 77



OC PILLS INDUCED CEREBRAL VENOUS SINUS THROMBOSIS: A CASE SERIES

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Introduction

Newer oral contraceptives (OC) afford not only excellent contraception but also provide a variety of non-contraceptive benefits, ranging from regulation and reduction of both menstrual bleeding and dysmenorrhea to treatment of premenstrual syndrome, menstrual migraines, acne and hirsutism. Long-term benefits include reduced rates of endometrial, ovarian, and colorectal cancer. Cerebral venous sinus thrombosis represents a rare disorder usually in middle age group.[1] Independent trials and retrospective data analysis in several countries show markedly increased predisposition in women who are taking oral contraceptives (OC) especially with genetic hypercoagulable disorder.[2] In the present case series, we are presenting two such cases reported to our tertiary care setup.

Case History:

Case 1: 18yrs old unmarried female reported to outpatient department with chief complaints of headache, nausea, vomiting and photophobia since last 5 days. There was no history of fever, trauma, neck stiffness, or any other complaints.There were no significant findings present on general physical and systemic examination.

Patient was suffering from menorrhagia for which she was started on combined oral contraceptive pills containing ethinylestradiol (0.05mg) and norgestrel (0.5mg). The present symptoms reportedly commenced around 20 days after starting with low dose OC pills. In the past, patient had consumed OC pills for a period of about 1year as a treatment for oligo-menorrhoea. Patient was hospitalized and treated symptomatically with intravenous fluids and supportive care. OC pills were discontinued. All routine investigations were within normal limits.Magnetic Resonance Imaging (MRI) brain revealed venous sinus thrombosis in superior sagittal sinus, bilateral transverse sinus and left sigmoid sinus. Patient was not screened for any coagulopathy. Patient was recovering gradually with continued medical care.

Case 2- 23yrs old married female was brought to the hospital by her relatives with the presenting complaints of headache, vomiting, altered sensorium since around 3 days. There was no history of fever, trauma, neck stiffness, or any other complaints. General and systemic examination was

inconclusive. Drug history included consumption of low dose OC pills (ethinylestradiol (0.05mg) and norgestrel (0.5mg) for contraception since last 3 months.

On admission, OC pills were withheld and patient was managed symptomatically. Investigations revealed cerebral venous sinus thrombosis on MRI brain and blood investigations showed protein -C resistance and anti-thrombin III deficiency. Patient improved symptomatically with supportive medical treatment.

Discussion

Cerebral venous sinus thrombosis (CVST) is a relatively rare condition which over the past two decades has been diagnosed more frequently due to greater availability of non-invasive diagnostic methods like MRI and Magnetic resonance venography (MRV). It presents usually in a relatively younger age group than other vascular neurological conditions and can result in a significant morbidity and mortality which ranges from 5 to 30 percent. Though relatively uncommon, CVST is a complex disease due to multitude of etiologies, varying from complex hyper coagulable states to simple physiological states like dehydration, pregnancy and peurperium.[3] Amongst medications oral contraceptives, androgen therapy and L-Asparaginase therapy have been implicated as the causative factors for CVST.[4,5,6]

Epidemiological studies indicate that OC pills use increases the absolute risk of venous thrombosis (VT) from 0.8 per 10,000 women per year among premenopausal women not using OC pills to 3.0 per 10,000 per year among OC pills users.[7] These numbers indicate a low absolute risk even for OC pills users. Nevertheless, because OC pills are so widely used, they are responsible for a large part, if not the majority, of all venous thromboses in young women.

The main cerebral venous sinuses affected by CVST are the superior sagittal sinus (72%) and the lateral sinuses (70%). In about one-third of cases more than one sinus is affected.[8] CVST presents with a wide spectrum of symptoms and signs. Headache is the presenting symptom in 70-90% of cases.[9,10] Focal deficits such as hemiparesis and hemisensory disturbance, seizures, impairment of level of consciousness and papilloedema occur in one-third to three-quarters of cases.[8,9] The onset may be acute, subacute or insidious, most patients presenting with symptoms which have evolved over days or weeks.[9] There are several typical clinical constellations: 18-38% of cases present with a syndrome resembling benign intracranial hypertension with headache, papilloedema and visual disturbances; up to 75% of cases are characterised by a focal neurological deficit and headache; a third group of between 30% and 50% may present with seizures often followed by a Todd's paresis. Rare but classical clinical pictures are that of superior sagittal sinus thrombosis (4%) with bilateral or alternating deficits and/or seizures and cavernous sinus thrombosis (3%) with chemosis, proptosis and painful ophthalmoplegia.[8,9,10] An even less frequent presentation is a rapidly progressive illness with deepening coma, headache, nausea and pyramidal signs, due to extensive involvement of the deep cerebral veins.[11]

The prothrombotic effect of the pill was considered to be not strictly dependent on the dose of estrogen but rather on the "total estrogenicity" of the formulation.[12] The "total estrogenicity" rises with increasing dose of estrogen but decreases with increasing anti-estrogenic activity of progestogen compound. It was suggested that third generation progestogens, as well as drospirenone and cyproteron acetate possess a weaker anti-estrogenic activity than levonorgestrel and, therefore, are less potent in the counterbalancing the prothrombotic effects of estrogen.[12,13] Consequently, OC pills containing third generation progestogens (desogestrel or gestodene), drospirenone or cyproterone acetate have a higher "total estrogenicity" as compared to second generation OC pills which may explain why users of these formulations are exposed to a higher thrombotic risk.[13] However, in the present cases patient was taking OC pills containing levonorgestrel implying that the formulation has lesser total estrogenicity.

The antithrombotic treatment modalities include heparin, thrombolysis and oral anticoagulants. Intravenous heparin should be the first-line treatment, even in the presence of haemorrhagic infarction, provided there are no general contraindications to its use. It is then followed by oral anticoagulants given to all patients. Most investigators suggest oral anticoagulants following the treatment of the acute phase for 3-6 months, except when there is a known prothrombotic condition in which treatment may have to be life-long. Other symptomatic treatments such as antibiotics, anticonvulsants, anti-emetics and analgesia will depend on the circumstances. Whether anti-epileptic treatment should be given to all patients or only to those who present with or develop seizures is controversial. Special interventions to reduce significantly raised intracranial pressure, for example when vision is threatened, include acetazolamide, steroids, repeated lumbar punctures, mannitol, shunt procedures and barbiturate induced coma.[14]

In literature, the use of oral contraceptives seems to be associated with CVST, more strongly in presence of hereditary hypercoaguable disorders, like Factor V leiden deficiency, Protein C or S and anti thrombin deficiency and more recently prothrombin gene mutation at position 20210 (guanine to adenine).[6] However, considering the low prevalence of CVST of around 1 per 1000, it is not thought to be a cost effective for screening all females and there are no recommendations on this. Also there is no clear guidelines regarding withholding oral contraceptives in carriers of hypercoagulable genes, however it is recommended that other methods of contraception should be used in women with previous episodes of thrombosis.[7]

Even though both the patients did not recover completely they showed symptomatic improvement after dechallenge. As the OC pills were given as fixed drug combination, the causality as per WHO causality scale is considered as "Possible" for both the drugs in the above cases.

Conclusion

Thus, OC pill consumption should always be borne in mind as a causative factor, in a young female presenting with cerebral venous sinus thrombosis considering its long term sequel. Though a genetic

testing can be an important tool for preventing such ADR, its feasibility in clinical practice remains doubtful.

References:

1. Strachan R, Hughes D, Cowie R. Thrombosis of the straight sinus complicating hormone replacement therapy. Br J Neurosurg 1995:9:805-8.
2. Sheerani M,Urfy MZS. Oral Contraceptives and Cerebral Venous Thrombosis: case report and a brief review of literature.J Pak Med Assoc 2006;56(11):559-60.
3. Cantu C, Barinagarrementaria F. Cerebral venous thrombosis associated with pregnancy and peurperium. Review of 67 cases. Stroke 1993: 24: 1880-4.
4. Buchanan DS, Brazinsky JH. Dural sinus and cerebral venous thrombosis: incidence in young women receiving oral contraceptives. Arch Neurol 1970:22:440-4.
5. Lanska DJ,Kryscio RJ. Risk factors for puerperium and postpartum stroke and intracranial venous thrombosis. Stroke 2000:31:1274-82.
6. Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood 2003:102:1363-6.
7. Vandenbroucke JP, Koster T, Briet E, et al. Increased risk of venous thrombosis inoral-contraceptive users who are carriers of factor V Leiden mutation. Lancet1994;344:1453-7.
8. Bousser MG, Barnett HJM. Cerebral venous thrombosis. In: Stroke: pathophysiology, diagnosis and management, 2nd edn. New York: Churchill- Livingstone, 1992: pp 517-37.
9. Ameri A, Bousser MG. Cerebral venous thrombosis. NeurolClin1992;10:87-111.
10. Villringer A, Mehraen S, Einhaupl KM. Pathophysiological aspects of cerebral sinus venous thrombosis. J Neuroradiol1994;21:72-80.
11. Crawford SC, Digre KB, Palmer CA, et al. Thrombosis of the deep venous drainage of the brain in adults. Analysis of 7 cases with review of the literature.Arch Neurol1995;52:1101-8.
12. Odlind V, Milsom I, Persson I, et al. Can changes in sex hormone binding globulinpredict the risk of venous thromboembolism with combined oral contraceptivepills? ActaObstetGynecolScand 2002;81:482-90.
13. Kemmeren JM, Algra A, Meijers JC, et al. Effect of second- and third-generation oral contraceptives on the protein C system in the absence or presence of the factor VLeiden mutation: a randomized trial. Blood 2004;103:927-33.
14. Allroggen H, Abbott RJ.Cerebral venous sinus thrombosis.Postgrad Med J 2000;76:12-15.

PUBLISHED CASE REPORTS ON OC PILLS INDUCED CEREBRAL VENOUS SINUS THROMBOSIS

Compiled by Dr Jaisen Lokhande

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The difficulties with the diagnosis of cerebral sinus thrombosis of a young woman - a case report

Merkur Lekarski. 2016 May 26;40(239):314-7

Kaczmarek J, Kozera-Kepniak A, Majos A, Kaczorowska B.

We show the case of a young woman taking the oral contraceptive pill whose only symptom of venous thrombosis for a few days was a strong headache. When the woman was admitted to hospital, she didn't have any other symptoms (in neurology examine, tomography and blood tests). The severity of headache after lumbar puncture (because of suspected subarachnoid bleeding) suggested presented of post-dural-puncture headache, which delayed the correct diagnosis. It was not until after the symptoms of the focal brain damage appeared on the fifth day that we finally made the correct diagnosis confirmed by some additional tests/examinations. Thus we started causal and symptomatic treatment. The difficulties we had with making the correct diagnosis indicate that the recognition of cerebral thrombosis should be taken into account when treating every young woman taking contraceptive pills and suffering from strong headaches. Headaches can be the only symptom of venous stroke in 90% of cases.

Cerebral Venous Sinus Thrombosis in a Woman Using the Etonogestrel-Ethinyl Estradiol Vaginal Contraceptive Ring: A Case Report

J Obstet Gynaecol Can 2010;32(3):270-273

Dunne C, Malyuk D, Firoz T.

The vaginal contraceptive ring is a hormonal contraceptive that releases etonogestrel and ethinyl estradiol. Cerebral venous sinus thrombosis (CVST) is a rare but serious complication of hormonal contraceptive use. Case: We present a case of CVST in a 33-year-old nulligravid woman who was using a vaginal contraceptive ring. At the time of presentation, she had been using the ring for 18 months, having previously used oral contraceptives for 13 years. She had no additional risk factors for thrombosis apart from cigarette smoking. Despite vigorous management, the patient died from the effects of the CVST. Conclusion: The serious adverse effects of the vaginal contraceptive ring are not well known, although deep vein thrombosis, pulmonary embolism, and aortic thrombosis in association with use of the ring have been reported to Health Canada. Continuing post-market surveillance of thrombotic risk in users of the vaginal contraceptive ring is critical.

Norethisterone induced cerebral venous sinus thrombosis (CVST): a rare case report and review of literature

Int J Reprod Contracept Obstet Gynecol. 2014; 3(1): 231-235

Ramya T, Prakash B, Devi B.

The association between the progestin only pill used for treatment of menstrual disorders and cerebral venous sinus thrombosis (CVST) has rarely been reported in the literature. This report describes a case of cerebral venous thrombosis following intake of norethisterone for menorrhagia secondary to polycystic ovary syndrome in a young woman with undiagnosed underlying hyperhomocysteinemia. A 24 year old married woman presented with acute onset of headache, vomiting and right focal seizures. MRI Cerebral venogram and CT Brain revealed thrombosed anterosuperior segment of superior sagittal sinus and haemorrhagic infarct in right frontoparietal region. The risk factors were acquired hyperhomocysteinemia, polycystic ovary syndrome and norethisterone for menorrhagia. The patient was treated with low molecular weight heparin, followed by warfarin, vitamin B12, vitamin B6 and folic acid. She made a total recovery. Although venous thrombosis is usually linked to the ingestion of estrogen, rather than progestogen, this case illustrates that patients who are prescribed progestogen only pills for gynaecological disorders may develop thrombosis, especially if they have predisposing metabolic disorders.

Cerebral Venous Sinus Thrombosis: A Rare Presentation Of Headache Mimicking Subarachnoid Hemorrhage

J Medicine. 2009;10:115-118

Sultana N, Chowdhury MH, Mahbub MS, Alam MB

Cerebral venous sinus thrombosis is a rare disorder accounting for less than 1% of all strokes. It is more common in children and young adults. Here we report a rare and interesting case of cerebral venous l sinus thrombosis mimicking subarachnoid hemorrhage. A 40 years old women, presented with sudden onset of headache, vomiting and unconsciousness associated with convulsions. She had a history of taking oral contraceptives for the last 12 years. Clinical examinations showed ill-looking women with Glasgow Coma Scale of 12 along with neck rigidity and bilateral papilloedema. Although initially we suspected her as a case of subarachnoid hemorrhage, subsequent investigations with MRI and MRV showed to be a case of superior sagittal and transverse sinus thrombosis. Treatment with anticoagulation recovered her from headache and papilloedema. Serum levels of thrombophilic factors were within the normal physiological limits. Thus we concluded that although cerebral venous thrombosis is 100 times less than the cerebral arterial disease, a women presented with sudden onset of headache and vomiting with long term use of oral contraceptives, cerebral thrombosis should be considered as a differential.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr Jaisen Lokhande

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Fluoroquinolone Antibacterial Drugs for Systemic Use: Drug Safety Communication - Warnings Updated Due to Disabling Side Effects

The FDA approved label change for systemically used fluoroquinolones (i.e., taken by mouth or by injection). These drugs are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system and as a result, the FDA has revised the Boxed Warning, to address these serious safety issues.

FDA recommends that fluoroquinolones should be reserved for patients who have no other treatment options for acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and uncomplicated urinary tract infections. Fluoroquinolones should remain available as a therapeutic option for serious bacterial infections where the benefits outweigh the risks. FDA is continuing to assess safety issues with fluoroquinolones as part of FDA's usual ongoing review of drugs and will update the public if additional actions are needed.

Reference: *FDA Drug Safety Communication: Fluoroquinolone Antibacterial Drugs for Systemic Use: Drug Safety Communication - Warnings Updated Due to Disabling Side Effects.[Internet]. [Cited 2016 August 10]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm513065.htm*

Febuxostat - Risk of heart failure Canada.

Health Canada has requested manufacturers of febuxostat to revise the prescribing information to include a statement regarding the potential increased risk factors of heart failure in patients with pre-existing cardiovascular disease and/or risk factors. As of March 2015, there were 32 cases of heart failure suspected to be linked to use of febuxostat reported in the WHO global database of Individual Case Safety Reports, VigiBase®. This triggered Health Canada to conduct a safety review and advice for the change in prescribing information.

Reference: Who Pharmaceuticals Newsletter. [homepage on the Internet]. 2016 [cited 2016 Aug 10]. Available from: http://www.who.int/medicines/publications/PharmaNewsletter3_16.pdf

Aripiprazole : Risk of impulse-control problems

The US Food and Drug Administration (FDA) have issued a safety warning and drug lable change

about the association of impulse-control problems and use of aripiprazole. Pathological gambling is already listed as an adverse effect. However, the FDA is now aware of other compulsive behaviours which have been reported with aripiprazole use such as: eating, shopping and sexual actions. A review of the FDA Adverse Event Reporting System (FAERS) and literature identified 184 cases of impulse-control problems reported with use of aripiprazole. In the majority of cases there were no prior histories of compulsive behaviours and the uncontrollable urges stopped once doses were reduced or medication discontinued.

Reference: *Who Pharmaceuticals Newsletter. [homepage on the Internet]. 2016 [cited 2016 Aug 10]. Available from: http://www.who.int/medicines/publications/PharmaNewsletter3_16.pdf*

Saxagliptin and Alogliptin containing products : Risk of heart failure USA.

The US FDA has requested that a new safety warning is added to the product labels of saxagliptin- and alogliptin-containing products to advice on the risk of heart failure. The warning was issued following the evaluation of two clinical trials conducted in patients with heart disease. The trials showed a higher number of hospitalization in patients who were exposed to saxagliptin- or alogliptin-containing medicines compared to placebo group.

The recommendations advise health-care professionals to consider discontinuing saxagliptin- and alogliptin-containing products in patients who develop heart failure and monitor their diabetes control. If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.

Reference: *Who Pharmaceuticals Newsletter. [homepage on the Internet]. 2016 [cited 2016 Aug 10]. Available from: http://www.who.int/medicines/publications/PharmaNewsletter3_16.pdf*

MATCH THE ADVERSE EFFECT WITH THE DRUG

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1	Sitagliptin	A	Fulminant hepatitis in children
2	Flutamide	B	Nephrolithiasis
3	Sildenafil	C	Joint Pain is common
4	Raloxifene	D	Livedo reticularis
5	Alendronate	E	Severe Rash
6	Midazolam	F	Nasopharyngitis
7	Valproic acid	G	May precipitate hepatic coma
8	Amantadine	H	Deep vein Thrombosis and pulmonary embolism.
9	Thioridazine	I	Abdominal syndrome
10	Gossypol	J	Eye Damage limits long term use.
11	Lamotrigine	K	Affects color vision
12	Acetazolamide	L	Ataxia in the elderly
13	Rifampin	M	Esophagitis
14	Topiramate	N	Gynaecomastia
15	Letrozole	O	Hypokalaemia

1 _____
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12 _____
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14 _____
15 _____

ANSWERS

1 - F; 2 - N; 3 - K; 4 - H; 5 - M; 6 - L; 7 - A; 8 - D; 9 - J; 10 - O; 11 - E; 12 - G; 13 - I; 14 - B; 15 - C

ALPHABET 'L' PUZZLE

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1 L									
2	L								
3		L							
4			L						
5				L					
6					L				
7						L			
8							L		
9								L	
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1. Post-treatment elevation of aminotransferase (>500IU/ml) occurs in about 15% patients of chronic HBV hepatitis after cessation of therapy with this reverse transcriptase inhibitor.
2. Weight gain and its associated long term complications are especially prominent with long term treatment of antipsychotics like Clozapine and _____.
3. Vomiting, diarrhea and abdominal pain are the earliest signs of impending acute toxicity of this anti-gout drug, after which the drug should be discontinued.
4. Severe CNS toxicity like seizures, confusion, altered sensorium and acute psychosis are seen in 0.5% cases of drug resistant malaria receiving this antimalarial drug.
5. This drug should never be administered until the patient has abstained from alcohol for at least 12 hours, or else, it can lead to signs and symptoms of acetaldehyde poisoning.
6. Therapy with amphetamines is complicated by the risk of abuse, depression, irritability, paranoia and disturbances in night sleep when given to a patient of _____.
7. Apart from cessation of the antipsychotic drug and giving supportive care, _____ is helpful for treatment of Neuroleptic Malignant Syndrome caused by antipsychotic drugs.
8. Along with all other common side effects seen with beta blockers, insomnia and visual disturbances are also seen in 1-3% of patients receiving this drug.
9. Though this antifungal drug is considered safe for topical use in vagina in pregnancy, adverse effects like pelvic cramps are seen in 0.2% of recipients.
10. The administration of this benzodiazepine antagonist is not only ineffective in TCA/Barbiturate poisoning, on the contrary, it can also cause seizures.

ALPHABET 'L' PUZZLE:

1. LAMIVUDINE, 2. OLANZAPINE, 3. COLCHICINE, 4. MEFLOQUINE, 5. DISULFIRAM, 6. NARCOLEPSY, 7. DANTROLENE, 8. CARVEDILOL, 9. MICONAZOLE, 10. FLUMAZENIL

NOTES

NOTES

We would like to request all the clinical departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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