Volume 1 Issue 12

December 2007

Misr University for Science & Technology
College of Pharmacy

DRUG INFORMATION CENTER

PHARMA INFO-LINE

Varenicline, smoking cessation updates

Cigarette smoking and its consequences represent a major global public health problem. For instance mortality estimates suggest that 30% of smokers in the 35 to 69 years of age cohort die from smoking-related diseases[1]. Overall estimates predicted that 21 million people in industrialized nations would die from tobacco-related diseases during the 1990 to 1999 decade. Moreover, there are proven benefits of smoking cessation; former smokers were found to live longer than those individuals who continue to smoke, for instance smokers who quit smoking before age 50 years reduce the risk of dying in the next 15 years by 50% compared with those individuals who continue to smoke[2].

It is interesting to note that nicotine abuse was mistakenly believed to be only a habituation although it represents the perfect example of an addictive disorder[3].

Helping smokers to quit smoking have included different approaches such as acupuncture[4], hypnotherapy[5], exercise[6], anxiolytics[7], selective serotonin reuptake inhibitors[8], and herbal products such as lobeline[9]. Among different approaches only evidence of significant benefits were obtained with nicotine replacement therapy NRT (patches, gum or inhalers), and the antidepressants (nortriptyline and bupropion) as shown in Cochrane reviews [8, 10]. Despite the efficacy of both bupripion and NRT in promoting cessation, the vast majority of smokers that used these two agents failed to quit smoking[11]. Therefore there is still compelling needs for new approaches or medications to improve and maintain smoking cessation.

Recently in May 2006 the FDA had approved a novel medication for smoking cessation; Chantix ® (varenicline tartrate) in tablet form. The drug acts at sites in the brain affected by nicotine and may help those who wish to give up smoking in two ways: by providing some nicotine effects (partial agonist) to ease the withdrawal symptoms and by blocking the effects of nicotine from cigarettes if they resume smoking[12]. Historically during World War II, the leaves of the golden rain tree were substituted for tobacco, as they were found to reduce the craving for nicotine, the alkaloid extracted from this plant called cytisine was found to be a partial agonist of α4β2 nicotinic acetylcholine receptors, this is the prototype and the vehicle for the discovery and development of varenicline[13].

Varenicline has three randomized, double blind, placebo- controlled trials, all were published in JAMA 2006; two of them are identically designed and compared varenicline 1 mg twice daily with sustained release (SR) bupropion 150 mg twice daily and with placebo. At 12 weeks, continuous smoking cessation rates in both studies were about 17% and 18% with placebo in the first and second study respectively, while they were 30% with bupropion SR (in both studies) and 44% with varenicline (in both studies),

INSIDE THIS ISSUE:

Article summary

- 21 million people in industrialized nation would die from tobacco related diseases between 1990-1999.
- Quitting before the age of 50 decrease the risk of death by 50% in the following 15 years.
- Varenicline is chemically related to an alkaloid called cytosine that is extracted from the golden rain tree.
- Varenicline is a partial agonist of nicotine receptors, therefore prevent withdrawal effect with smoke cessation and block these receptors towards external nicotine from smoking.

which represented statistically significant differences. In addition, nine months after treatment had stopped, continuous smoking cessation rates in the 2 studies were 8% and 10% with placebo, 15% and 16% with buproprion SR, and 22% and 23% with varenicline [14, 15].

The third trial evaluated whether an additional 12 weeks of treatment with varenicline was beneficial for those who had stopped smoking during the first 12 weeks of treatment. A total of 1,928 subjects initially received open-label varenicline 1 mg twice daily. At 12 weeks, those who responded and had not smoked for at least 7 days (63%) were randomly assigned to either continue varenicline or switch to placebo. Continuous smoking cessation rates were significantly better with varenicline than with placebo at the end of the second 12 weeks of treatment (71% vs. 50%) and remained better from weeks 13-52 (44% vs. 37%)[16].

These trials and more recent data made some authority to conclude that varenicline is the most effective drug available in increasing smoking cessation rates, more effective than NRT or bupropion SR[17].

Unfortunately, this benefit is not devoid of adverse effects, the drug has been reported to cause nausea in up to 40% of the patients who received 1 mg twice daily compared with only 8 % in placebo group in one study[17]. Furthermore the FDA has recently issued preliminary information for healthcare professionals regarding post-marketing reports of suicidal thoughts and erratic/aggressive behavior in patients who have taken varenicline (Chantix™). Many cases suggest new-onset depression, suicidal ideation, and emotion/ behavioral changes within days to weeks after treatment initiation. Because smoking cessation (with or without treatment) is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness, the role of varenicline in these events is unclear. Some of the cases described above occurred in patients without a history of psychiatric disease and in patients who had not discontinued smoking. The FDA also has reports of excessive drowsiness which may impair the ability to perform tasks requiring mental alertness, therefore patients should be informed by pharmacists to report any behavioral and/or mood changes to their healthcare provider and to use caution when performing tasks requiring mental alertness.

For more data on this new alert please follow the link;

http://www.fda.gov.libauth.mskcc.org:2048/medwatch/safety/2007/safety07.htm#Chantix

References:

1. Peto R, L.A., Boreham J, et al. , *Mortality from tobacco in developed countries: indirect estimation from national vital statistics.* . Lancet 1992. **339** (8804): p. 1268-78.
2. United States Department of Health and Human Services. Washington, D.C.f.D.C., Center for Chronic Disease Prevention and Health Promotion,Office of Smoking and Health, The health benefits of smoking cessation. DHHS Publication No. (CDC), 1990. 90(8416).
3. Hyman, S.E., Addiction: A Disease of Learning and Memory. Am J Psychiatry, 2005. 162(8): p. 1414-1422.
4. White AR, R.H., Campbell JL. , Acupuncture and related interventions for smoking cessation, in Cochrane Database of Systematic Reviews. 2006, John Wiley & Sons, Ltd Chichester, UK.
5. Abbot NC, S.L., White AR, Barnes J, Hypnotherapy for smoking cessation, in Cochrane Database of Systematic Reviews. 1998, John Wiley & Sons, Ltd Chichester, UK.
6. Shraim M, P.A., Aveyard P, Hajek P, Interventions for preventing weight gain after smoking cessation, in Cochrane Database of Systematic Reviews. 2006, John Wiley & Sons, Ltd.
7. Hughes JR, S.L., Lancaster T, Anxiolytics for smoking cessation, in Cochrane Database of Systematic Reviews. 2000, John Wiley & Sons, Ltd Chichester, UK.
8. Hughes JR, S.L., Lancaster T, Antidepressants for smoking cessation, in Cochrane Database of Systematic Reviews. 2007, John Wiley & Sons, Ltd.
9. Stead LF, H.J., Lobeline for smoking cessation, in Cochrane Database of Systematic Reviews. 1997, John Wiley & Sons, Ltd Chichester, UK.
10. Silagy C, L.T., Stead L, Mant D, Fowler G, Nicotine replacement therapy for smoking cessation, in Cochrane Database of Systematic Reviews. 2004, John Wiley & Sons, Ltd Chichester, UK.
11. LeSage MG, K.D., Pentel PR, Current Status of Immunologic Approaches to Treating Tobacco Dependence: Vaccines and Nicotine-specific Antibodies. AAPS Journal, 2006. 8(1): p. E65-E75.
12. FDA Approves Novel Medication for Smoking Cessation, U.S.D.o.H.a.H. Services, Editor. 2006.
13. Potts, L.A. and C.L. Garwood, Varenicline: The newest agent for smoking cessation. American Journal of Health-System Pharmacy, 2007. 64(13): p. 1381-1384.
14. Gonzales, D., et al., Varenicline, an {alpha}4beta2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Sustained-Release Bupropion and Placebo for Smoking Cessation: A Randomized Controlled Trial. JAMA, 2006. 296(1): p. 47-55.
15. Jorenby, D.E., et al., Efficacy of Varenicline, an {alpha}4beta2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomized Controlled Trial. JAMA, 2006. 296(1): p. 56-63.
16. Tonstad, S., et al., Effect of Maintenance Therapy With Varenicline on Smoking Cessation: A Randomized Controlled Trial. JAMA, 2006. 296(1): p. 64-71.
17. varenecline (Chantix) revisited. Med Lett Drugs Ther., 2006. 49(1247): p. 96.

Is there any evidence for the use of mepivacaine as a diluent for intramuscular benzathine penicillin injection in order to reduce the pain?

Benzathine penicillin G (BZ penicillin) is recommended for many infectious disease conditions, among which it is used for secondary prophylaxis of rheumatic fever. The drug is available as 1.2 million international units MIU powder, which should be reconstituted with sterile water for injection to form a homogenous suspension then, should only be administered by deep intramuscular IM injection. The dose for children ranges from 25,000-50,000 units/kg up to a maximum of 1.2 million units, given as a single dose every 3-4 weeks[1].

It is available in Egypt with the following names; *Retarpen®, Lastipen®, Durapen-S®, Penicid LA®, and Penadur LA®.* The main disadvantage of BZ penicillin IM injection is the local pain and discomfort at the injection site, particularly in children which was so severe that half of the children that were given the injection could not walk for 2 to 3 days after that [2].

One approach to lessen this pain is by combining BZ penicillin with varied quantities of procaine (PC) penicillin C. This approach has been successful, decreasing the incidence of significant local reactions. Preparations containing 600 000 U BZ penicillin C Plus 600 000 U PC penicillin and containing 900 000 U BZ penicillin G plus 300 000 U PC penicillin G respectively are available in a 2-mL injections, and are marketed in the US and Canada, however they are not available in Egypt[3].

Local anesthetics such as lidocaine has been used successfully to reduce pain in minor surgical procedures, dental manipulation and has also been used as diluent for some antimicrobial agents, such as with IM ceftriaxone, Rocephin ® in order to reduce the pain associated with the injection[3].

There is lacking evidence for the use of mepivacine as diluent for BZ penicillin in the literature, however in one study the administration of BZ penicillin G was compared by using two different diluents; sterile water and lidocaine hydrochloride 1%.for penicillin concentrations and pain of injection[4]. The study which was randomized double blind, crossover trial; involved 18 children, ages 11 to 19 years who required prophylactic treatment for rheumatic fever and were randomly divided into two groups. One received an injection of BZ penicillin G diluted with 3.2 ml of sterile water, that was followed 1 month later by an injection of BZ penicillin G diluted in lidocaine hydrochloride 1%; the second group received the same regimen in the reverse order. Serum penicillin concentrations and subjective pain sensation were determined after each injection. The authors reported similar peak serum penicillin concentrations at 24 h after injection for both preparations (0.100 mcg/ml for water, 0.102 mcg/ml for lidocaine), as were the other serum values measured throughout the month. 28 days later there was no significant difference in the detectable concentrations (>=0.020 mcg/ml) that was seen in 44% of the subjects who received water and 29% of the subjects who received lidocaine (P = 0.4). Urine penicillin concentrations on day 28 were 1.81 ± 0.25 and 2.31 ± 0.25 mcg/ml, respectively.

Most importantly, the pain score immediately after the injection was significantly lower with the lidocaine than with the sterile water dilution. The authors concluded that the use of lidocaine hydrochloride as a diluent for BZ penicillin G does not change the penicillin concentration in body fluids and significantly reduces the pain of injection. They also recommended its use for reconstitution of BZ penicillin injection[4].

Answer Conclusion:

Benzathine penicillin injections are so painful that it may compromise adherence, several approaches were studied in order to reduce this pain, combining BZ penicillin with procaine penicillin is one of them. However, products containing this combination are only available abroad. Concerning the use of mepivacaine as a diluent for BZ penicillinis; although it is a rational approach, it lacks evidences for stability, compatibility and bioavailability. On the other hand, there is one study that had used 3.2 ml lidocaine 1% as a diluent which offered similar bioavailability to that of the water suspension which is routinely used and with better tolerability and less pain.

References:

1. *Lexi-Comp online TM*. 2007, Lexi-Comp Inc.
2. VE., K.S.P., *Local tolerance to penicillin: comparison of five intramuscular preparations:comparison of five intramuscular preparations.* J Pediatr. **49**: p. 699-702.
3. *AHFS Drug Information*. 2007, American Society of Health-System Pharmacists.
4. Amir, J., et al., *Lidocaine as a diluent for administration of benzathine penicillin G.* Pediatric Infectious Disease Journal, 1998. **17**(10): p. 890-3.

Three Medical myths

In the latest issue of the BMJ, December 2007, Rachel C Vreeman and Aaron E have edited a very interesting article, that discusses medical myths which are endorsed even by physicians[1].
In the following text we have chosen only 3 of these myths without editing;

People should drink at least eight glasses of water a day: The advice to drink at least eight glasses of water a day can be found throughout the popular press. One origin may be a 1945 recommendation that stated: A suitable allowance of water for adults is 2.5 liters daily in most instances. An ordinary standard for diverse persons is 1 milliliter for each calorie of food. Most of this quantity is contained in prepared foods. If the last, crucial sentence is ignored, the statement could be interpreted as instruction to drink eight glasses of water a day. Another endorsement may have come from a prominent nutritionist, Frederick Stare, who once recommended, without references, the consumption "around 6 to 8 glasses per 24 hours," which could be "in the form of coffee, tea, milk, soft drinks, beer, etc." The complete lack of evidence supporting the recommendation to drink six to eight glasses of water a day is exhaustively catalogued in an invited review by Heinz Valtin in the American Journal of Physiology. Furthermore, existing studies suggest that adequate fluid intake is usually met through typical daily consumption of juice, milk, and even caffeinated drinks. In contrast, drinking excess amounts of water can be dangerous, resulting in water intoxication, hyponatraemia, and even death.

We use only 10% of our brains: The belief that we use only 10% of our brains has persisted for over a century, despite dramatic advances in neuroscience. In another extensive expert literature review, Barry Beyerstein provides a detailed account of the origins of this myth and the evidence disputing it. Some sources attribute this claim to Albert Einstein, but no such reference or statement by Einstein has ever been recorded. This myth arose as early as 1907, propagated by multiple sources advocating the power of self improvement and tapping into each person's unrealized latent abilities. Evidence from studies of brain damage, brain imaging, localization of function, microstructural analysis, and metabolic studies show that people use much more than 10% of their brains. Studies of patients with brain injury suggest that damage to almost any area of the brain has specific and lasting effects on mental, vegetative, and behavioral capabilities. Numerous types of brain imaging studies show that no area of the brain is completely silent or inactive. The many functions of the brain are highly localized, with different tasks allocated to different anatomical regions. Detailed probing of the brain has failed to identify the "non-functioning" 90%. Even micro-level localization, isolating the response of single neurons, reveals no gaps or inactive areas. Metabolic studies, tracking differential rates of cellular metabolism within the brain, reveal no dormant areas.

Shaving hair causes it to grow back faster, darker, or coarser: Another common belief is that shaving hair off will cause it to grow back in a darker or coarser form or to grow back faster. It is often reinforced by popular media sources and perhaps by people contemplating the quick appearance of stubble on their own body. Strong scientific evidence disproves these claims. As early as 1928, a clinical trial showed that shaving had no effect on hair growth. More recent studies confirm that shaving does not affect the thickness or rate of hair re-growth. In addition, shaving removes the dead portion of hair, not the living section lying below the skin's surface, so it is unlikely to affect the rate or type of growth. Shaved hair lacks the finer taper seen at the ends of unshaven hair, giving an impression of coarseness. Similarly, the new hair has not yet been lightened by the sun or other chemical exposures, resulting in an appearance that seems darker than existing hair.

References: **Vreeman, R.C. and A.E. Carroll, *Medical myths.* BMJ, 2007. 335(7633): p. 1288-1289.**

Misr University for Science & Technology
College of Pharmacy

Address
M.U.S.T.
6 October city - Almutamayez area

Fax / Phone: 02/38377643
E-mail: sherifelghandour@yahoo.com

Providing Up-to-date Information