Journal of Developing Drugs
ISSN: 2329-6631

Lisberg and Scheinmann, J Develop Drugs 2013, 2:2
DOI: 10.4172/2329-6631.1000109

Letter Open Access

Is it Time to Consider Use of Levo-methadone (R-(-)-Methadone) to Replace Racemic Methadone?

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Racemic methadone, a mixture of its two enantiomeric optically active forms, R-(-)-Methadone and S-(+)-Methadone (also known as levo-methadone and dextro-methadone), was first synthesized in Germany before the outbreak of World War II.

Racemic methadone is now generic and was admitted in 2005 to W.H.O.'s Essential Medicines List [1] and issued in over 70 countries around the world:

1. in the management of chronic pain, and

2. as the gold standard substitution therapy for illicit opioid misuse.

History of Racemic Methadone and its Optical Isomers

By 1945, researchers at Hoechst had isolated levo-methadone (a difficult and costly process), discovering it had a far greater analgesic activity over the racemic form [2]. By the late 1940s, USA-based Eli Lilly (who bought the methadone patent as war reparations for the peppercorn sum of $1) confirmed the analgesic superiority of levo-methadone [3,4]. To date, levo-methadone has never been developed commercially in the U.S.A.

However, events took a different turn in Germany where in 1965 Hoechst discontinued its production of racemic methadone, replacing it with levo-methadone (L-polamidon). In 1992, racemic methadone was re-approved in Germany to fall in line with international standards of MMT (methadone maintenance therapy). To this day in Germany, both racemic methadone and levo-methadone are available. Surprisingly levo-methadone has command of about 25% of the methadone market there in spite of it being up to 3 times more expensive to purchase [5].

The F.D.A. has issued a "Black Box Warning" regarding the use of racemic methadone where life threatening side effects such as cardiac arrhythmias and potassium channel blockage are attributed to S-(+)-methadone [6]. Toxicity problems may also arise from metabolism by Cytochrome P450 enzymes (CYP3A4 and CYP2B6) in the presence of benzodiazapines, tranquilizers and alcohol [7].

Meanwhile in the absence of levo-methadone in most countries, the worldwide manufacture of racemic methadone continues to increase reaching 43.9 tons in 2010 with almost half being used in the U.S.A [8].

Comment

In the U.S.A. there are over 5,000 deaths every year attributed to racemic methadone [9]. Over a million patients are currently being treated with racemic methadone for both pain management and MMT (Methadone Maintenance Treatment). More choice in medication may benefit patients by switching to levo-methadone once market authorization has been obtained. As levo-methadone is used only in German-speaking countries (Germany, Austria & Switzerland), some studies evaluating racemic methadone and levo-methadone safety and efficacy have been published in German [10-12].

Reasons for Switching to Safer Levo-methadone

The preference for stereochemical control and the use of one stereo isomer at a given biological target follows from authoritative recommendations:

a) In 1992, the F.D.A. recommended that the biological active isomer should be used instead of the racemate where possible in medication [13]. To encourage such new drug development in 2007 FDCA s.505 (u) was introduced granting chiral switches five years of market exclusivity [14].

b) Use of levo-methadone instead of racemic methadone allows for half the dose for equipotency in treatment of pain and methadone maintenance therapy [15,16].

c) Studies of chiral isolates of methadone on the cardiac potassium channel IKr and stereoselective block by S-(+)-methadone have been reported [17-19]. Thus, levo-methadone has a greater safety profile.

Although levo-methadone has been licensed for use in Germany, it is not available in the U.S.A. even though senior clinicians have expressed their interest in carrying out further trials to firmly establish the selectivity of the chiral isolates for greater safety and efficacy in the treatment of pain and drug addiction, now that a cost effective method of preparation is available and ready for scale-up for A.P.I manufacture.

Scientific and Commercial Considerations

The resolution of racemic methadone to provide levo-methadone by classical methods is done at the end of the synthesis, or at the penultimate stage, whereby more than half of the material by weight is lost. This extra stage makes levo-methadone more expensive for an equipotent dose and is wasteful on equipment and reagent resources.

This waste can be eliminated by an asymmetric synthesis with a cheap chiral starting material and proving that chirality is not lost during the total synthesis to provide levo-methadone. This has been done and is the subject of a publication [20] and U.S. patent [21].

The prime objective must be to prescribe what is best for the patient and the literature cited indicates that levo-methadone is a safer drug for MMT and treating somatic pain. The asymmetric

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Received July 25, 2013; **Accepted** August 14, 2013; **Published** August 20, 2013

Citation: Lisberg P, Scheinmann F (2013) Is it Time to Consider Use of Levo-methadone (R-(-)-Methadone) to Replace Racemic Methadone? J Develop Drugs 2: 109. doi:10.4172/2329-6631.1000109

synthesis makes better use of the existing equipment and reagents and is more cost effective than classical resolution for synthesizing levo-methadone. Progress in medication, and more choice for professionals in prescribing, justify making changes [22].

Conclusion

Since the article revealing the chiral cardiotoxicity of racemic methadone was published, an increasing number of health professionals worldwide have demanded a better assessment of the risks and chiral R-(-)-methadone prescription [23,24].

Is it now time for the regulatory (FDA in USA and MHRA in the UK) and health authorities to decide what is best for the patient and review the data and subsequent work which shows that it is safe to switch from racemic methadone to levo-methadone [25] and to provide fast track assessment of additional work that may be required for market authorization?

Hopefully this will soon provide medical practitioners more choice of medication in treating somatic pain and for MMT.

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