

Dextropropoxyphene ban in India: Is there a case for reconsideration?

Yatan Pal Singh Balhara

Department of Psychiatry, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India

INTRODUCTION

Dextropropoxyphene is a synthetic weak opioid used as analgesic both as standalone as well as in combination with acetaminophen for more than 50 years. Ministry of Health and Family Welfare, Government of India has issued a gazette notification (dated May 23, 2013) suspending the manufacture, sale, and distribution of dextropropoxyphene and formulations containing dextropropoxyphene in the country.^[1]

This suspension has led to debate about the reasons behind this decision and its implications. India is not the first country to withdraw dextropropoxyphene as it has already been withdrawn from various countries including Australia, Canada, European Union, New Zealand, UK, and USA.^[2-4] UK was probably the first to issue a notification regarding its withdrawal in January 2005. Later on it was withdrawn across the European Union in 2009. Subsequently, recommendations against its use were issued by the US Food and Drug Administration (FDA), New Zealand, and Canada in the year 2010. Australia issued a notification recommending against its use in 2012. All preparation containing dextropropoxyphene (including combinations with acetaminophen) have been withdrawn in these countries. Notably the withdrawal of dextropropoxyphene/acetaminophen combination containing preparations in Australia has been withheld pending a review sought by a pharmaceutical company in the court.

REASONS FOR WITHDRAWAL OF DEXTROPROPOXYPHENE

The reasons cited for its withdrawal from these countries include its implication in overdose related deaths and its impact on cardiovascular electrophysiology even within therapeutic dose range. Additionally, concerns have been expressed about its utility as an analgesic.

Overdose related deaths including suicide

Concerns have been expressed regarding the extent of fatal self-poisoning with dextropropoxyphene/acetaminophen combination in some countries including England and USA.^[5,6] A combination of dextropropoxyphene/acetaminophen was reported to be single drug used most frequently for suicide in England and Wales for the period 1997-1999. It was responsible for 766 deaths over the 3-year period.^[7] Additionally, it was implicated in a fifth of all drug poisoning suicides. Reports of concern about dextropropoxyphene poisoning have been cited as a matter of concern from other nations including Australia,^[8] New Zealand,^[9] Sweden,^[10] and the USA.^[11]

Death following overdose due to this combination has been attributed to the toxic effects of high levels of dextropropoxyphene on respiration and cardiac conduction.^[12] It has been stated that there is a relatively narrow margin between therapeutic and potentially lethal concentrations for this drug.^[13] Also, concerns have been raised about possible underestimation of accidental deaths due to dextropropoxyphene.^[14]

Impact on cardiac electrophysiology

A multiple ascending dose study was conducted in USA on recommendation of FDA to evaluate the effects of propoxyphene on cardiac electrophysiology among healthy volunteers.^[4] Both 600 and 900 mg doses of propoxyphene

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Address for correspondence:

Yatan Pal Singh Balhara, Department of Psychiatry, Room No. 4096, 4th Floor, Teaching Block, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. E-mail: ypsbalhara@gmail.com

were associated with significant QTc interval prolongation that were greater than that recommended in guidelines. In addition, a dose-dependent prolongation of PR and QRS intervals was observed in the study. The study was placed on clinical hold due to safety concerns and hence higher doses could not be tested for these effects. Based on these findings, US FDA recommended against continued prescribing and use of propoxyphene in 2010.

Interestingly, the FDA advisory committee voted by a narrow margin (14 to 12) against the continued marketing of propoxyphene products.^[15]

Concerns regarding utility as an analgesic

Concerns have also been expressed about the utility of dextropropoxyphene as an analgesic. It has been stated that there is no evidence that dextropropoxyphene in combination with acetaminophen is any more effective than acetaminophen alone.^[16-18]

Arguments criticizing withdrawal of dextropropoxyphene

However, the decision to withdraw dextropropoxyphene containing formulations has received some criticism.^[19] It has been argued that there is limited evidence to support withdrawal of dextropropoxyphene on safety grounds. The impact of withdrawal of dextropropoxyphene on overdose related deaths has not been studied extensively. The published literature is limited to a handful of studies.^[20,21] One study from UK reported that following dextropropoxyphene/acetaminophen combination ban there was a major reduction in poisoning deaths involving this drug, without apparent significant increase in deaths involving other analgesics over a 6 year period.^[20] Another study from Scotland also reported a major reduction in the number of deaths associated with dextropropoxyphene/acetaminophen combination poisoning, with no compensatory rise in mortality from poisonings from other common analgesics.^[21]

Even these studies have certain methodological limitations. For example, Hawton *et al.*,^[20] failed to report the impact of dextropropoxyphene withdrawal from UK on deaths involving morphine. Sandilands and Bateman^[21] failed to include a control group in their study. Also the choice of fatal toxicity index has been reported to be an inappropriate parameter.^[19]

Additionally, withdrawal of dextropropoxyphene/acetaminophen combination from certain markets failed to lower overall mortality due to suicides in spite of a reduction of dextropropoxyphene related suicide rate.^[22,23]

Evidence for effectiveness of dextropropoxyphene as analgesic

While there is literature that fails to establish analgesic superiority of dextropropoxyphene (especially when used in fixed dose combination with acetaminophen),^[17,18] evidence

to the contrary also exists. Reviews (including one published by Cochrane) have found dextropropoxyphene as well as combination of dextropropoxyphene/acetaminophen 650 to be comparable to tramadol in efficacy for nociceptive pain.^[24,25] Studies have also found dextropropoxyphene to be an effective and well tolerated analgesic during induction of opioid therapy among opioid-naïve cancer patients.^[26]

Impact of dextropropoxyphene and other opioids on cardiac electrophysiology

Prior to its withdrawal in 2010, dextropropoxyphene was a commonly prescribed analgesic in the USA. No cases of torsades de pointes causally associated with dextropropoxyphene have been reported. Over 33 years of use, 91 deaths were reported in association with use of Darvocet (most commonly dispensed formulation of propoxyphene in USA).^[27] A dominant causal role for dextropropoxyphene containing products could not be established in these deaths based on the presence of underlying medical conditions or multiple co-suspect medications. Additionally, Office of Surveillance and Epidemiology (OSE) failed to find enough evidence to support an association between the therapeutic use of propoxyphene and cardiac-related deaths.^[27]

The reported rate of adverse drug events associated with the use of propoxyphene as reported to the VAMedWatch system as part of the FDA MedWatch Program was no worse than the reported rate associated with the nine comparators in 2004 and 2005. In fact, the rates were lowest among all opioids.^[15] Another study from New Zealand reported that based on prescription frequency, death rate was similar for dextropropoxyphene and methadone. Also this rate was lower than that of morphine. Additionally, analysis based on defined daily doses value also concluded that dispensed dextropropoxyphene had the lowest rate of death as compared to other prescription opioids.^[9]

There is a paucity of available information on the impact on QT interval for most opioids.^[22] Levo-alpha-acetylmethadol (LAAM) and methadone have also been associated with risk of torsade de pointes, especially in high doses.^[28]

Risk of overdosing with dextropropoxyphene

It has been argued that risk of abuse and possible overdosing for a drug is related to its availability. Overrepresentation of dextropropoxyphene in self-inflicted harm in UK has been attributed, at least partially, to its over-the-counter status in the country.^[19] In a study from South Africa (a country where dextropropoxyphene is a prescription-only drug) it was shown incidence of dextropropoxyphene overdose was only 0.6% which was much lower than other drugs such as paracetamol (27%), antihistamines (13%), and nonsteroidal anti-inflammatory drugs.^[29] Also, possible contribution of coingestion of ethanol and other sedative agents along with

dextropropoxyphene needs to be taken into consideration while assessing dextropropoxyphene related deaths.^[30] Coingestion of alcohol has been observed in around 58% of dextropropoxyphene related deaths.^[13]

CONCERNS ABOUT ABUSE

Concerns have been expressed about abuse of dextropropoxyphene. While safety concerns have been cited as reason for dextropropoxyphene withdrawal from India in the gazette notification, 'misuse of the drug by addicts' has been cited as a possible contributor to this decision.^[31] Studies from India have cited an increase in abuse of dextropropoxyphene over the years in certain parts of the country.^[32] Dextropropoxyphene (along with heroin) was found to be the common substance abuse through injecting route from the northeastern states of the country in the National Survey.

Dextropropoxyphene use in India

Dextropropoxyphene has been a commonly prescribed analgesic in India. It has been used for management of pain associated with acute as well as chronic conditions. Additionally, it has been used in palliative care. Easy availability of this medication even in the villages has made it a commonly prescribed medicine. Dextropropoxyphene is the least expensive Step II opioid in the world Health Organization ladder approach for cancer pain management. An equianalgesic dose of tramadol is likely to cost much more than what dextropropoxyphene costs. It has been quoted that "*100 mg of tramadol four times a day would cost twice the daily income that defines the poverty line*".^[31] The cost advantage associated with dextropropoxyphene was supplemented by its easy availability. Most of the other opioids such as morphine are stringently regulated and are not widely available.

Implication of dextropropoxyphene as a common drug associated with suicide in some countries like UK cannot be used as an argument to withdraw this drug from Indian market. Dextropropoxyphene did not even figure in the list of means of suicide in India in a recent publication.^[33] Similarly, the argument focused on limited analgesic utility of dextropropoxyphene has been challenged by findings from various studies and reviews as mentioned above.

Finally, withdrawal of a drug from market is unlikely to be an effective solution to the problem of abuse of the drug. Many illicit drugs continue to be used in the country. Additionally, various prescription drugs are also abused/misused. Dextropropoxyphene is not the only prescription opioid that is being abused in the country. Codeine and pentazocine abuse has also increased in the country over the years.^[32] Which strategy will be used for these medicines?

The cost and adverse consequences of prohibition approach to drug use problem have been realized in various countries including USA.^[34] Drug prohibition has been associated with increase in organized crime, increased prices, illicit trafficking, and increased risk to user due to added impurities due to lack of stringent control. Failed prohibition of alcohol in some states in the past can help understand possible implications of such approach.

Interestingly, dextropropoxyphene has also been used in the management of opioid dependence in the country.^[35] Easy availability and oral route of administration coupled with prohibitive cost and restricted availability of alternatives in the country have guided this approach of using dextropropoxyphene for detoxification as well as short- to medium-term maintenance therapy. Better regulation of its availability can help address the overdose related deaths associated with it as has been the experience in some countries.^[36]

Of course, dextropropoxyphene warrants a close scrutiny in light of available information, evidence, and experience. The decision to withdraw any drug should be guided by the science and needs of society.

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